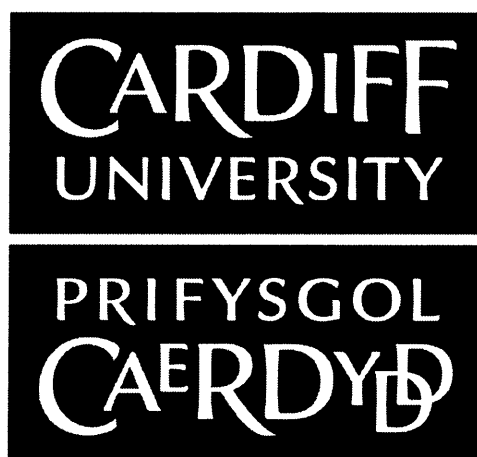


NEW INEXPENSIVE POLYMER SUPPORTED REAGENTS BASED ON POLYSILOXANES

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**A THESIS SUBMITTED AS PART
REQUIREMENT FOR THE DEGREE
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To My Family

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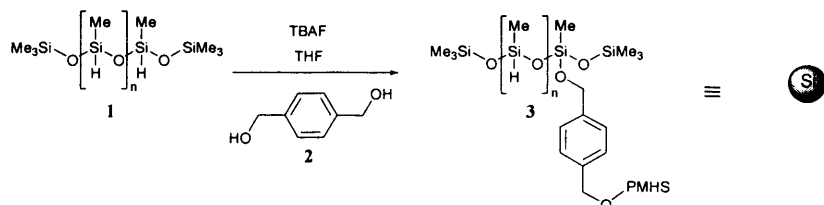
- The late Mr. Donald Summers, who lost his battle with cancer in July 2004 for being not only my landlord but like family here in Cardiff he will be sorely missed
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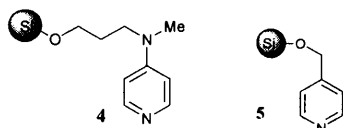
Last but by no means least I wish to thank my family without whose generous support, encouragement and tolerance I would not have been able to cope these last few years.

Abstract.

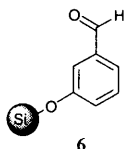
Using polymethylhydrosiloxane (PMHS) **1**, a commercially available free flowing liquid, the formation of crosslinked polymers **3** using a crosslinker **2** and a variety of catalysts such as Wilkinson's, TBAF and diethylhydroxylamine to aid this process are reported. The application of these polymers to the reduction of acetophenone is also discussed.



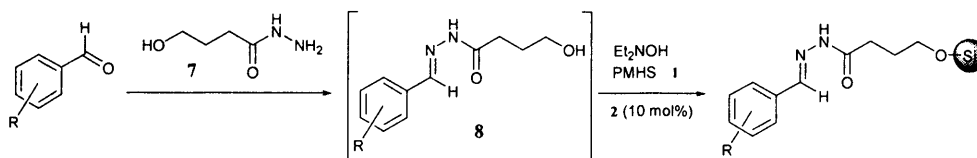
Secondly, crosslinked PMHS resins incorporating DMAP **4** and pyridine derivatives **5** were developed as scavengers.



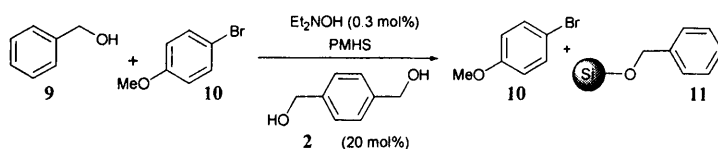
Both resins were found to successfully scavenge benzyl bromide. Studies using various substrates are discussed along with resin compositions giving indications of loading. The resins were found to be active towards benzyl halides and cinnamyl halides. A comparison is also made between the resins made in house and those available commercially. Aldehyde resins **6** were also developed to scavenge amines. This was found to be successful in scavenging benzylamine and other amine derivatives.



An *in situ* method to scavenge aldehydes is also described. Using the substrate and the scavenging hydrazine **7** in solution, crosslinked PMHS was then used to remove the imine intermediate **8** successfully from solution.



Finally, studies were performed using an *in situ* polymerisation method to scavenge for alcohols **9** and other substrates from solution along with a 3 component scavenging study. PMHS was used to successfully scavenge various alcohols from 1:1 standard solutions in the presence of 1,4-benzenedimethanol **2** and diethylhydroxylamine catalyst giving species such as **11**.



Tzu-hsia said, A man who

Treats his betters as betters

Wears an air of respect,

Who into serving father and mother

Knows how to put his whole strength,

Who in the service of the prince will lay down his life,

Who in interaction with friends is true to his word -

others may say of him that he still lacks education, but I for my part should certainly call him an
educated man.

Confucius

Abbreviations.

Ac	acetyl
Aq	aqueous
Ar	aromatic
Bn	benzyl
b.p.	boiling point
Br	bromide
^t Bu	<i>tert</i> -butyl
°C	degrees centigrade
cat.	catalyst
Cl	chloride
Conc.	concentrated
d	doublet
DBATO	bis(dibutylacetoxytin)oxide
DMAP	dimethylaminopyridine
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
g	gram
h	hour
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
Hz	Hertz
IR	infra red
lit.	literature
m	multiplet
Me	methyl
min.	minute
mmol	millimole
mol	Mole
m.p.	melting point
NMR	nuclear magnetic resonance
PEG	polyethylene glycol

Ph	phenyl
PMHS	Polymethylhydrosiloxane
ppm	parts per million
PS	polymer supported
PVP	polyvinylpyridine
s	singlet
SPOS	Solid phase organic synthesis
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet
w/w	weight for weight

1. INTRODUCTION

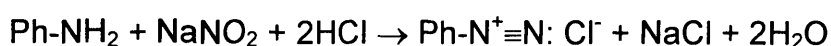
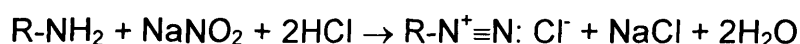
1.1 Evolution of supported reagents

Man has constantly attempted to find new ways to reduce his workload and increase his proficiency. In terms of chemistry, scientists are constantly trying to find new ways to increase their productivity in order to synthesise many hundreds of thousands of compounds. To find a few biologically *active* compounds, libraries of many thousands of chemical entities must be generated.¹ Such library synthesis can be highly problematic, particularly from the process of purification. If, for example, a library of a hundred thousand compounds were created, it would not be feasible to attempt their synthesis in a singular fashion as synthesis would take a long time. Secondly, purification of this number of new entities using conventional chromatographic techniques would be an even more time consuming process. But as will be seen from this introduction solid supported reagents and associated technologies provide a very attractive tool for reducing the time scale for library production.^{2,3,4,5}

As an introduction to the work of the author described in Chapter 2, several aspects of supported chemistry will be described.

Worldwide pressure for the development of 'green chemistry' from environmental groups has paved the way for the development of many new technologies. One solution is the use of combinatorial methods.⁶ Combinatorial technologies have the beauty of allowing large numbers of molecules to be prepared, purified and tested rapidly. This comprises an integrated approach of high throughput screening and combinatorial chemistry. An example of this is a recent development by Ley *et al.* for the synthesis of azo dyes using polymer supports.⁷ In solution phase synthesis, azo dyes are produced by diazotisation of a primary amine and following this, the coupling of the resulting diazonium salt with either a phenol or an aromatic amine. However, this produces large amounts of waste with repercussions on the environment.

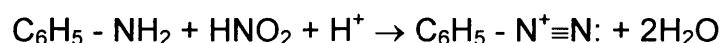
Scheme 1



Both aliphatic and aromatic primary amines can be used to form diazonium salts. This can be done by reacting the amine with nitrous acid (HNO₂), at a temperature of 0 - 5 °C

(Scheme 1). Owing to the instability of nitrous acid, it is always generated during a reaction, usually by the action of dilute sulphuric acid or hydrochloric acid on sodium nitrite (NaNO_2). The acid used to generate nitrous acid provides the anion of the diazonium salt.⁸ However, alkyl diazonium salts are extremely unstable and always decompose to evolve the colourless unreactive nitrogen gas, amongst other products. The diazonium cations of aromatic diazonium salts are somewhat more stable than their aliphatic counterparts. With aniline the benzene diazonium ion is formed (Scheme 2):

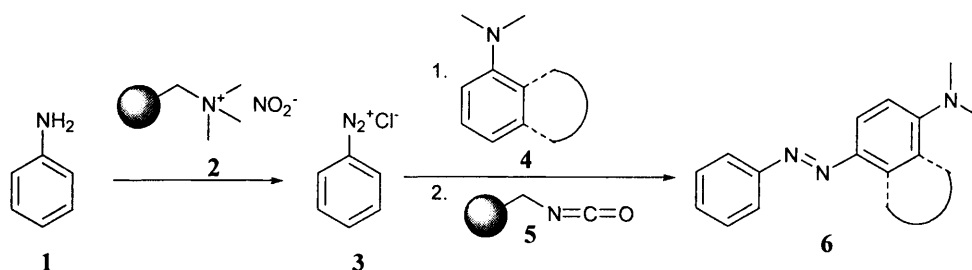
Scheme 2



Although benzene diazonium salts can be isolated in the crystalline form, they are usually retained in solution and used immediately as they decompose on standing even in the cold. In the solid state the salts are explosive and can be easily detonated by a slight shock or on mild warming.

The method shown below (Scheme 3) was used by Ley and his co-workers to produce several azo dyes in high yield.⁷ Starting with aniline (**1**), the supported ammonium nitrite **2** was used to produce the diazonium salt **3**. This was then reacted with the aryl amine **4** which undergoes an electrophilic attack on the aromatic ring to give the azo dye **6** in high yield and purity. The isocyanate resin **5** was used as an electrophilic scavenger.

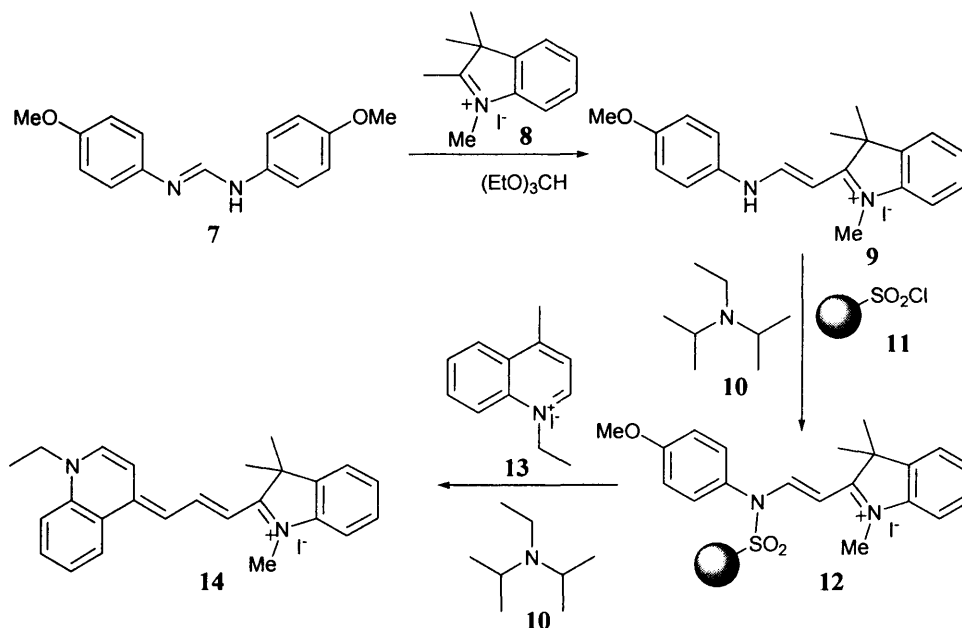
Scheme 3



Another group to work on synthesis of dyes is Balasubramanian *et al.* (Scheme 4). They have described the synthesis of cyanine dyes using solid phase “catch, activate and release” methods (Scheme 4).⁹ The cyanine dye **14** was synthesised by capture and activation of a hemicyanine intermediate on sulfonyl chloride resin. This was followed by reaction and subsequent cleavage by a nucleophile. Again a number of dyes were synthesised in high yield. Reaction of the amidine **7** with the indolenium salt **8** leads to substitution of 4-methoxyaniline to give cyanine **9**. This is then subsequently tethered on sulfonyl resin **11** through the amine moiety on **9**, in the presence of Hunig’s base **10** to give the resin bound cyanine **12**. The final step is cleavage of **12** from sulfonyl resin and substitution by

indolenium salt **13** in the presence of Hunig's base to give the cyanine dye **14**. This demonstrates the versatility of combinatorial synthesis using polymer supported reagents.

Scheme 4

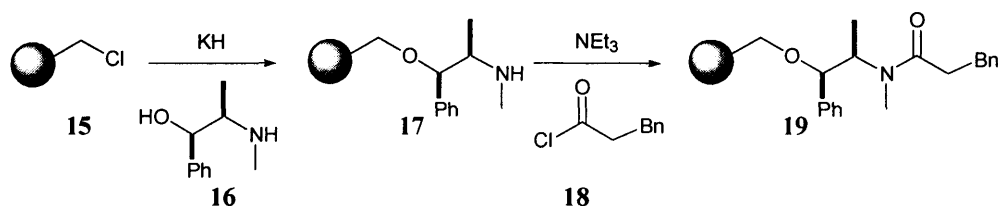


Although polymer supports have been used in organic synthesis for many decades, only recently have they received recognition through their application in combinatorial chemistry. Since the advent of *Merrifield* resin,¹⁰ many libraries of peptides and oligosaccharides have been synthesised in a stepwise manner. Some areas of the use of polymer supports remain problematic. This includes choosing a linker and cleaving the product from the support. The number of techniques that can be used to monitor reactions is also limited in contrast to solution phase counterparts. However, the big advantage of solid phase synthesis combines the ease of work up and purification *via* simple filtration.¹¹

After detailed development, solid phase organic synthesis (SPOS) is now used on a regular basis within organic chemistry programmes to generate low molecular weight molecules.¹² Much of this work has been geared toward discovery of lead compounds for medical research. One clear advantage of this technique, already mentioned is the ease of product purification, as well as the high product purity obtained.¹³ However, this technique does have its limits. Excess reagent is often needed to drive the reaction to completion and though excess reagent can usually be easily removed during purification by filtration, reaction times tend to be significantly slower than its solution phase counterparts due to the heterogenous nature of reactions. Despite this, much effort has been directed towards development of new techniques to ensure rapid purification in solution phase chemistry.¹⁴

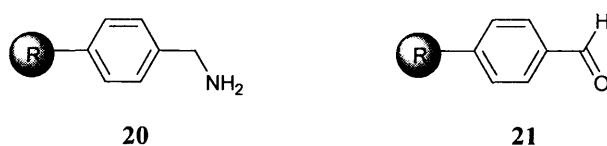
Considerable work has been carried out to develop different kinds of resins for solid phase synthesis; an example of this is the development of a pseudoephedrine resin for use in asymmetric alkylations by Procter and co-workers (Scheme 5).¹⁵ This is achieved through the attachment of pseudoephedrine **16** to Merrifield resin **15** through the hydroxyl group to give the resin bound species **17** and subsequent acylation with **18** on the nitrogen, thus producing immobilised pseudoephedrine amides such as **19**.

Scheme 5



A polymeric reagent, by definition, is one which has a low molecular weight molecule imbedded in a polymer backbone, thus allowing many useful organic synthetic steps to take place. Besides the advantages of filtration for purification as well as functional groups which would normally be incompatible due to side reactions, can be used. This is yet to be fully investigated. The theory is that if two crosslinked polymers are ‘stirred’ together the active moieties should not come into contact, except for the few that are exposed at the surface of the beads (**20** and **21**) (Figure 1). Ideally this allows mutually incompatible reagents to be used in the same reaction vessel.¹⁶

Figure 1



Generally, polymers are produced from monomers in a polymerisation reaction where all the bond-forming reactions take place in one reaction.¹⁷ This unfortunately leads to molecular weight variation and therefore polymer molecular weights are expressed in terms of averages.¹⁸ Variations in structure are also paramount in functional polymers and it is generally not possible to know exactly the structure of each polymer molecule.¹⁹ A polymeric reagent is aptly defined as a functional material that can effect the transformation of a low molecular weight substrate into a product.^{15,16,17} A significant role is played by the support material in the direction of the course of reactions with soluble substrates. Porosity and size of the material affects the reactivity of the material used for the support. A change in the reactivity and specificity of a functionalised polymer is due to various physicochemical effects arising from intrinsic polymeric properties.²⁰ Other factors such as

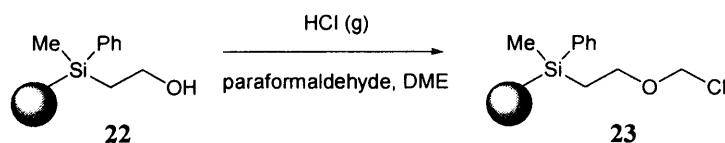
polarity of the support, degree of crosslinking, and the topographical nature of the gel network can affect the overall reactivity of a functional polymer. The straight forward removal of the insoluble spent resin by simple filtration, regeneration and recycling all contribute to the increased popularity of supported reagents. In the past few decades a considerable amount of research has been aimed at gaining a better understanding of the structure-reactivity correlation of polymers.²¹

Despite the success and advantages of solid phase organic synthesis, there are also severe limitations to this approach that are worth noting. Firstly, the reactions can be slow relative to their solution phase counterparts and it can be difficult to monitor reaction progress. Despite the much needed development of methods in recent years (e.g. FTIR, MALDI-MS, Gelphase and MAS NMR *etc.*)²² to monitor progress of reactions, these techniques still do not provide the same quality of analysis as rapidly and conveniently as conventional solution phase techniques (e.g. TLC, GC-MS, LC-MS, SFC-MS, NMR *etc.*).^{23,24}

1.2 Library generation

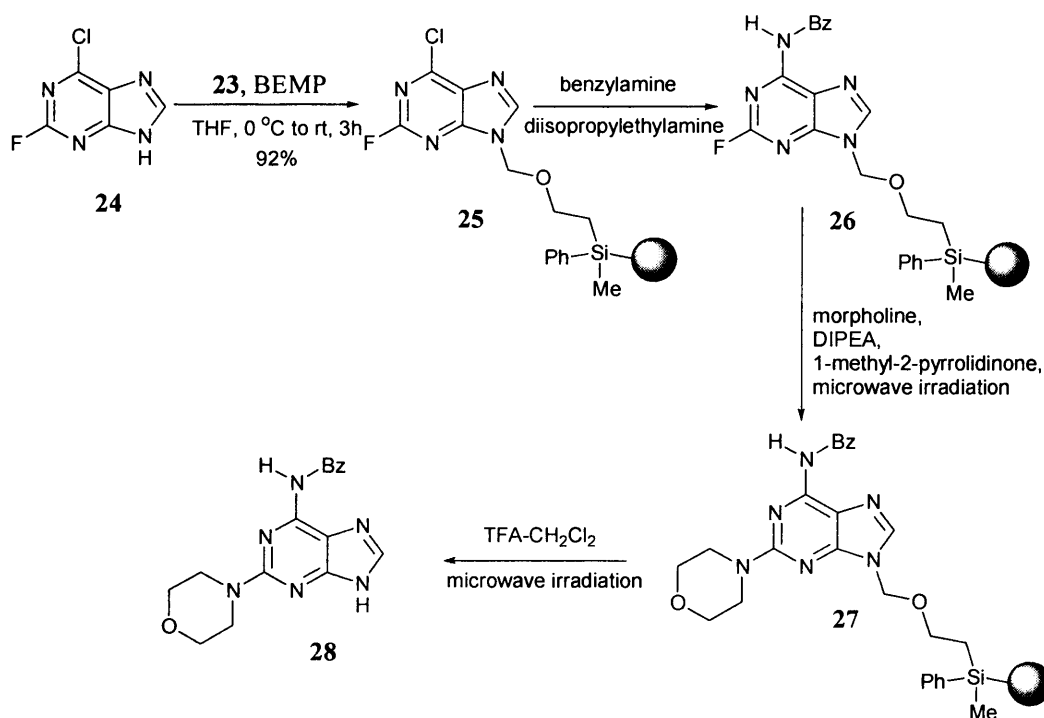
Combinatorial chemistry is an umbrella term under which several recent breakthroughs are placed collectively.^{25,26} Linear syntheses are very time consuming when it comes to generating compound libraries, hence parallel methods must be used to produce these compounds in as efficient manner as possible.^{27,28} However, to counteract some of the problems associated with traditional multi-step synthesis in solution and to produce large numbers of compounds in a multiparallel fashion, a modification of the techniques introduced by Merrifield¹⁰ and Letsinger²⁹ have been extensively developed. A substrate is supported on a backbone of solid material allowing transformations to take place when in the presence of excess of reagents and coupling components, hence driving the reaction to completion. The desired molecule is then detached from the support material and isolated following a simple filtration. This general process has become the backbone of modern combinatorial chemistry and is now a widely used technique. One example of this is demonstrated by Kim and co-workers in using a novel polymer supported (diphenylmethylsilyl)ethoxymethyl chloride (DSEM-Cl) linker the synthesis is shown in Scheme 6 from polymer supported 2-(trialkylsilyl)ethanol linker **22** using paraformaldehyde and hydrochloride gas to give **23**.³⁰ Subsequent use of this linker is shown in Scheme 7.

Scheme 6



Polymeric DSEM-supported 2-fluoro-6-chloropurine **25** was then utilised to synthesise a number of 2,6-disubstituted purines on solid phase (Scheme 7). Nucleophilic amination of **25** with benzylamine proceeded successfully under the conditions shown to provide **26**. Subsequent amination at C2 has been reported to require longer reaction time and higher temperature due to decreased reactivity at C2. Therefore Kim and co-workers applied microwave-assisted heating to enhance reaction rates to give **27**. Microwave radiation in 1-methyl-2-pyrrolidinone at 180 °C followed by sequential microwave-assisted linker cleavage provided a good yield of **28** with high purity.

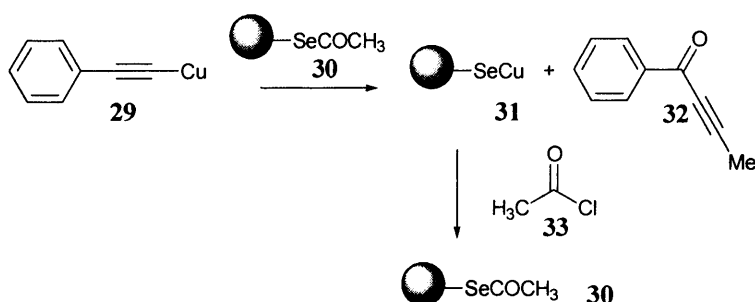
Scheme 7



Another method exploited by Huang and co-workers is the use of polymer supported selenol esters in acylation to synthesise β -acetylenic ketones (Scheme 7).³¹ Selenol esters exhibit high selectivity towards nucleophiles, and this effect is enhanced further by activation with heavy ions or oxidizing agents. However, organic selenium always has a foul smell and reagents of this type are quite toxic. A solid supported reagent is much more easily handled is usually odourless compared to the non-supported counterpart. The alkyne substrate **29** undergoes transmetalation with the resin bound acetyl selenium **30** to give the acetylenic

ketone **32** and the selenium-copper complex **31**. The resin bound selenium **30** can be regenerated by acetylating the selenium-copper byproduct **31** with acetyl chloride **33**.

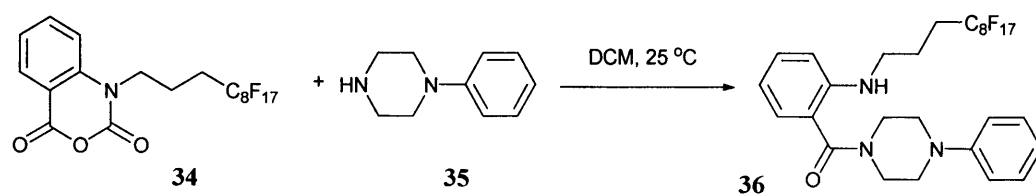
Scheme 8



A fundamental feature of solid-phase synthesis is that additional steps are required to bind to and remove products from the resins, the drawback being often that traces of the linker unit are found in the final product and linker compatibility with the reagents used can be a source of problems or limitations. It is also not possible to satisfactorily undertake a convergent synthesis using this methodology and the resin loading and swelling characteristics can be poor, necessitating the use of solvents that are sometimes not optimal for the chemistry being carried out.³² However, the most frustrating aspect of this type of chemistry is usually the time consuming process of attempting to optimise solution phase chemistry on a polymer supported substrate, particularly where a long synthesis is required.

Owing to these problems, a number of alternative and innovative approaches have also been developed for chemical library generation, some of which are now beginning to show tremendous potential. The use of fluorous molecules such as **34**³³ as reagents (shown in Scheme 9) and scavengers in conjunction with fluorous solvents, for example, is an attractive concept designed to exploit multi-reaction and separation phases.^{34,35} In the scavenging reaction shown below, *N*-phenylpiperazine (**35**) was reacted with isatoic anhydride **34**. After 60 min., the fluorous isatoic anhydride reaction indicated less than 10% of amine **35** remained demonstrating the superior reactivity of the fluorous scavenger. In another example comparing fluorous thiols to silica supported thiols, the fluorous scavenger was found to be about 10 times more efficient, once again due to the complete solution phase chemistry involved.

Scheme 9



Many believe that the advantages of solution-phase chemistry heavily outweigh disadvantages,³⁶ so much so that their efforts focus around improved high-throughput purification technology to clean-up the products from complex reaction streams. Others have concentrated their efforts on using insoluble polymer and other solid supported agents to scavenge by-products and excess starting materials thereby purifying reaction products produced in solution. The notion that a suitably functionalised polymer-support can be used to selectively capture the required product away from any contaminating impurities, be filtered and then re-release the required material (catch and release) in a pure form is also an important purification concept.³⁷ Perhaps most significant is that both hetero- and homogeneous polymer-supported reagents, including immobilised enzymes, which have been known and used for a long time, are making a noticeable comeback and are likely to have a crucial impact in the future on the development of this entire area.³⁸

There are few explanations as to why the technique of solid-phase chemistry has been unpopular for nearly three decades. One of these reasons might be that only through the recent needs in production have medicinal chemists been challenged by developments in automation and biology, allowing the screening of a large number of compounds.^{39,40,41}

Considerable work has been carried out to optimise solid-phase oligomer synthesis, more specifically peptide analogues.⁴² However, obviously no single class of compounds will cover the structural diversity required for all drug compounds to be produced in the future. Through the development of a broad array of organic reactions on solid support, the scope of combinatorial chemistry will increase, albeit this being only one step in a compound library.⁴³

1.3.1 Types of available resins and supports

The foundation of all solid phase synthesis is found in the polymeric core. Polystyrene is the most common core resin. Other core matrices are also available such as polyacrylate, polyethylene glycol (PEG) and polyacrylamide. The most important factors to consider when utilising these resins in organic synthesis are swelling and the bead size of the resin used. The swelling characteristics are affected by degree of crosslinking, hydrophobicity of substrate, and the nature of the core matrix. This section will discuss a few of the different types of supports available and their characteristics.^{38,39,44}

Polystyrene itself is very hydrophobic and either swells or dissolves in aprotic solvents such as toluene, DCM and DMF.^{38,45} Usually when used in organic synthesis, polystyrene is

crosslinked with divinylbenzene producing a mechanical gel-like consistency when in the presence of swelling solvents. Uncrosslinked or linear polystyrene dissolves in hydrophobic solvents, and precipitates in protic solvents. Lightly crosslinked, approximately 1-2%, polystyrene resins are the most commonly used for solid phase synthesis. Crosslinking does not occur uniformly because of the higher reactivity of divinylbenzene relative to styrene, forming local regions of higher crosslink density, which in turn affects neighbouring group reactivity. Functional groups are introduced with either functional styrene monomers or in a post-functionalisation step.

The most fundamental substituted polystyrene core is chloromethylated and hydroxymethylated polystyrene, more commonly known as *Merrifield* resin (**37** and **38**) (Figure 2) after the Nobel Laureate who pioneered its use in the synthesis of peptides. Many nucleophilic substrates such as carboxylic acids can be attached to this resin in different ways.¹⁰

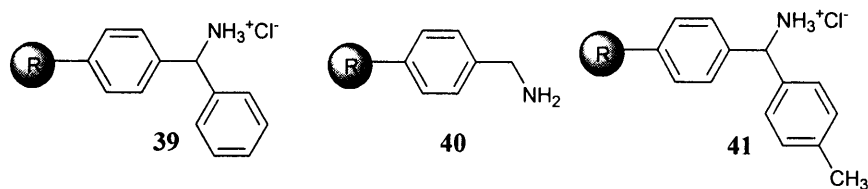
Figure 2



The resin itself can be generated, like other substituted resins, by one of two methods: direct incorporation of substrate onto the polymer core through an electrophilic aromatic substitution reaction or copolymerisation of the substituted monomer with styrene. A hydroxymethylated form (**38**) is also available for application within chemistry where the chloride form is inappropriate.^{38,46}

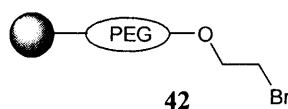
Nitrogen containing resins (Figure 3) such as benzhydrylamine (BHA)⁴⁷ **39**, aminomethyl (AM)⁴⁸ **40** and 4-methylbenzhydrylamine (MBHA)⁴⁹ **41**, were originally developed for peptide amide synthesis using *N*-Boc protection/TFA deprotection procedures. These resins form very stable amide or amine linkages to either carboxylic or electrophilic alkyl substrates. Generally, very acidic conditions are required to cleave substrates from these base resins, therefore primarily their application was as a basic resin for the more easily cleaved first order resins.

Figure 3



As the polystyrene support does not swell well in solvents such as methanol, ether or water, it causes a problem with using this support in these common reaction solvents. Another problem is caused by the hydrophobic environment of the polymer matrix that repels charged ionic species which are common reaction intermediates in organic synthesis. To counteract this problem a resin has been developed, namely polyethylene glycol (PEG) grafted onto the polystyrene core.⁵⁰ The resulting combined resin **42** (Figure 4) has both hydrophobic and hydrophilic character and therefore swells well in both solvents such as water and methanol, but poorly in ether and ethanol. As a result a broader spectrum of chemistry becomes available through this modification. Sometimes referred to also as poly(ethylene oxide) (PEO), poly(oxyethylene) (POE)⁵¹ and polyoxirane, it is effectively a linear polymer formed from the polymerisation of ethylene oxide. PEG by convention indicates the polyether of molecular weight less than 20000; PEO designates polymers of higher molecular weights, and PEO and polyoxirane have been applied to polymers of a wide range of molecular weights. An alternative synthetic approach has utilised the coupling of acid functional PEG oligomers with aminomethyl polystyrenes, however, these types of resin have not found wide usage in SPOS, possibly because of the presence of the amide linkage.

Figure 4

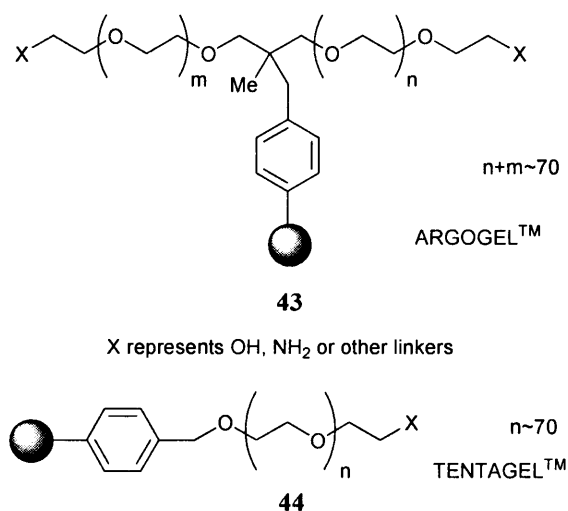


The reason for selecting a PEG graft resin for use in solid phase organic synthesis (SPOS) is usually because of the high compatibility the resin has in polar protic solvents and the ability to obtain high quality ^1H and ^{13}C NMR spectra on bound molecules.⁵² Reaction monitoring on single beads by NMR has been shown with large macrobeads.⁵³ Linkers can be attached either through an ether linkage, which is more stable than the analogous polystyrene system because of the absence of a benzylic ether linkage.⁵⁴

There are occasional problems arising from the differences in composition between the PEG graft resins and polystyrene itself, and this may affect reactions, such as those requiring Lewis acids that may have a strong effect with the PEG. Nevertheless there have been a number of examples where SPOS reactions on PEG graft resins proceeded in higher yield or selectivity or both, than reactions on polystyrene resins. The improved solvent compatibility of PEG-grafted resins can also be advantageous for reaction purification.⁵⁵

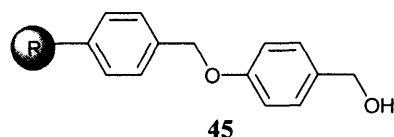
There are many advantages brought about by the PEG graft, however these are countered by the fact that the increased mass associated with the PEG, which comprises up to 70% of the bead mass, unfortunately leads to a lower loading resin ($\sim 0.2\text{--}0.3$ mmol/g) and the presence of the benzylic graft-polystyrene attachment results in instability to commonly used trifluoroacetic acid cleavage conditions. However these problems have been addressed in the form of a new graft resin, known as ArgoGel™ **43**, which is designed with a bifurcation at the polystyrene-graft linkage through the use of a polystyrene diol as the base resin for grafting.⁵⁶ The diol linkage serves to increase the stability of the resin to acids and to provide materials with higher loading capacities.

Figure 5

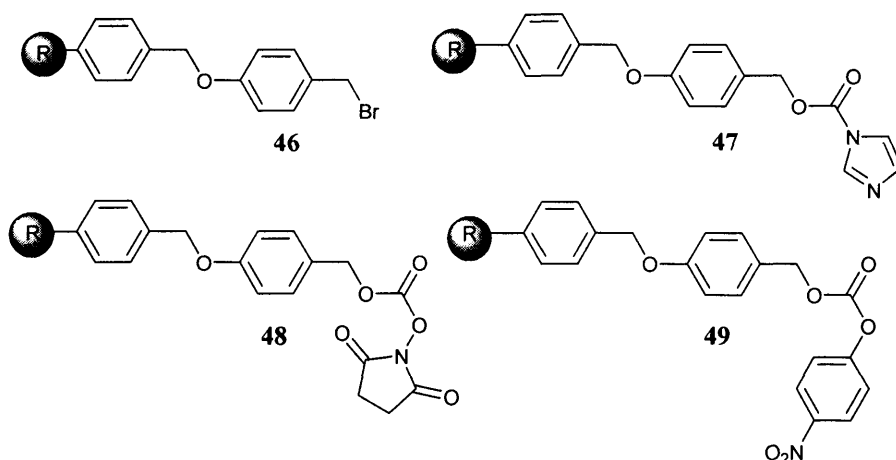


The improved stability was demonstrated in synthesis involving secondary amide-based linkers, where no PEG side product was observed under extended acidic cleavage conditions. The use of a 1-methyl-2-hydroxyethyl derivative as a polymer matrix for grafting has also been observed to afford more acid stable PEG-polystyrene resins. This is found in Tentagel™ resin **44** shown in Figure 5.⁵⁷

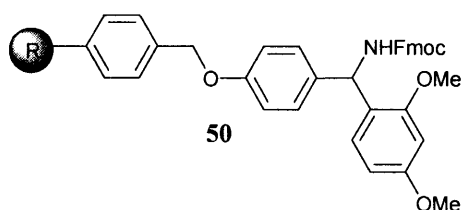
An example of an acid labile resin is Wang resin **45** (Figure 6).⁵⁸ It is the most widely used of all resins for acid substrates bound to a solid support. The linkage between the substrate and the support is through a 4-hydroxybenzyl alcohol moiety.^{59,60} The linker is bound to the resin through a phenyl ether linkage. The ester linkage is resilient to a variety of reaction conditions but can be readily removed using moderately acidic conditions, generally using trifluoroacetic acid.⁶¹

Figure 6

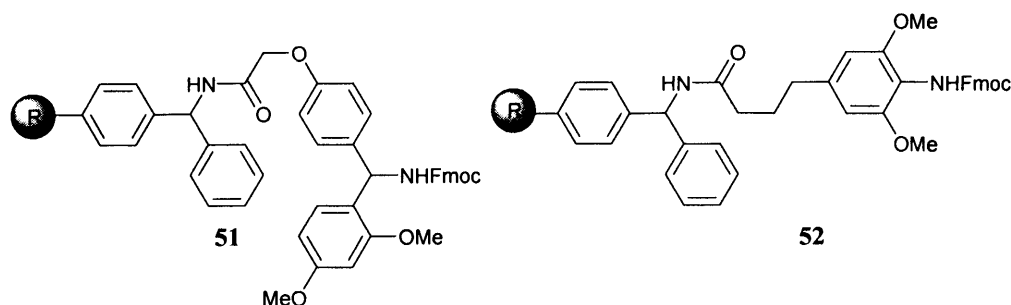
Wang resin is also available in electrophilic forms, such as benzyloxybenzyl bromide resin **46** and the carbonate resins with imidazole **47**, succinimidyl **48** or 4-nitrophenyl **49** as leaving groups to the incoming substrate (Figure 7).

Figure 7

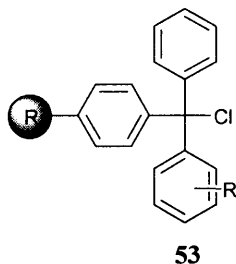
The most popular solid phase supports for the formation of amide products include Rink,⁶² Knorr and PAL resins. All of these were initially developed for peptide synthesis using the Fmoc protection strategy. These resins are favoured due to their higher acid lability allowing cleavage to be performed in as low as 1% TFA to produce the amide of the carboxylic acid substrate attached to it.

Figure 8

Like the *Wang* linker, the Rink linker in resin **50** (Figure 8) is bonded to the core polystyrene matrix through an ether linkage. The Knorr resin **51** (Figure 9) possesses the same terminal functionality as Rink resin, but its linker is bonded to the core through an amide linkage. Rink and Knorr resins exhibit similar characteristics with respect to type and cleavage conditions. Rink resin however, has been more widely utilised. PAL resin⁶³ **52** requires similar cleavage conditions to both Rink and Knorr, but it is somewhat more acid labile.

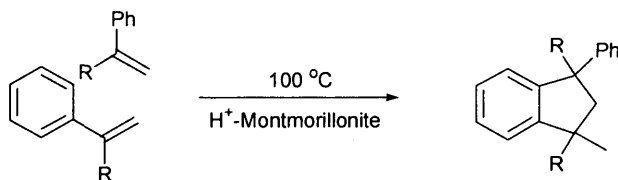
Figure 9

Trityl resins such as **53** (Figure 10) have been widely used in both solid phase organic and peptide chemistry⁶⁴. The bulky triphenylmethyl group prevents undesired reactions of the linker through steric hindrance. This resin is available in a variety of different forms with different labilities. The 2-chlorotrityl resin is slightly more acid labile than the trityl resin.

Figure 10

There are also other types of supports available, including silica, macroporous silica and clay.^{23,65} Varma and others have pioneered the use of these materials in various organic transformations such as Diels-Alder⁶⁶, Heck⁶⁷ and Suzuki⁶⁸ reactions as well as simpler conversions such as aromatic substitution reactions such as Friedel-Crafts acylation.⁶⁹

Similar to silica, clays are made up of layered silicates. The particle size of these crystalline materials are very fine ranging from 150 to less than 1 micron.^{70,71} These materials undergo efficient swelling as water is drawn in between the layers. An example can be seen below of using acid treated Montmorillonite to catalyse a cyclisation reaction²³ (Scheme 9).

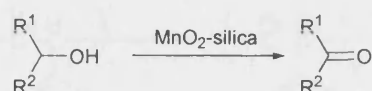
Scheme 9

Porous silica gels are now widely used in various areas of modern science and technology in various capacities, for example, adsorbents, catalyst supports, fillers, and chromatographic column packings.⁷² This range of uses is continuously growing owing to their unique

properties; high specific area, large pore volume, precisely specified size of pore and particles, large mechanical and thermal stability, and finally simple surface modification.

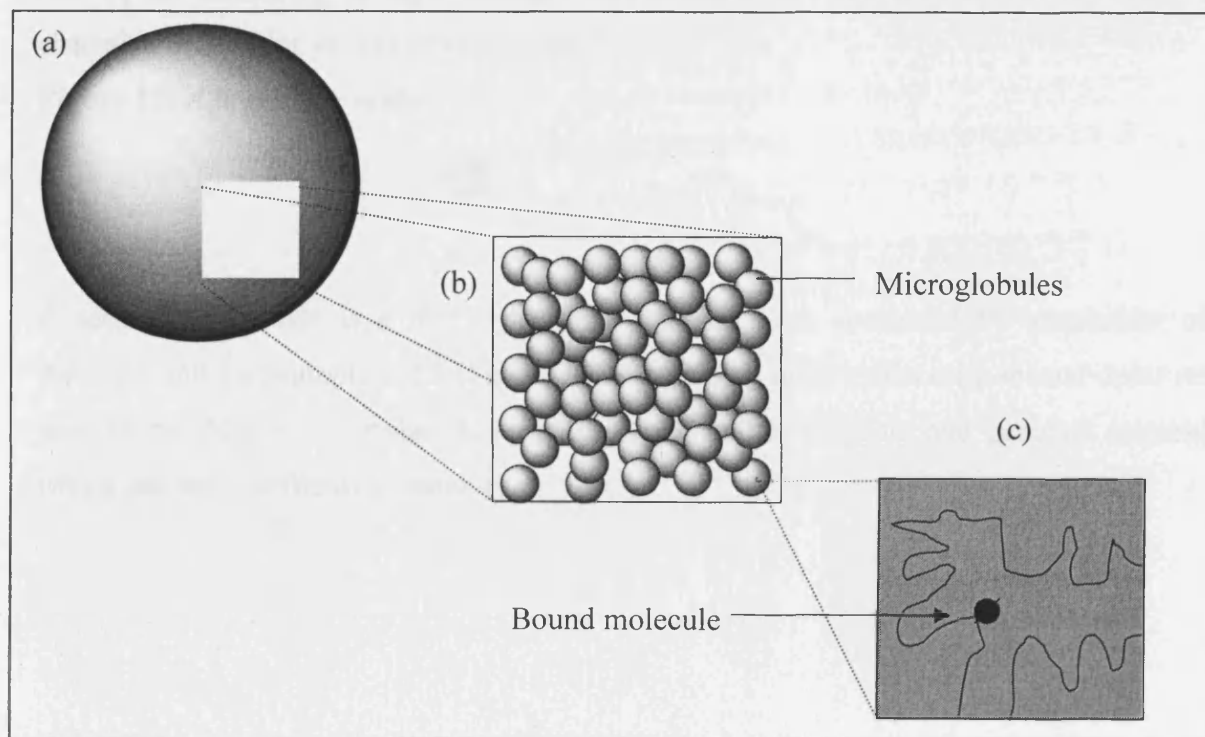
Non-porous silica has also seen some use as a support in chemical transformations.⁷³ Similar to the properties of porous silica; its non-porous counterpart encounters good selectivity, no swelling, and good mechanical stability.⁷⁴ This is particularly useful when in the case of a normal organic support, slow kinetics, swelling sensitivity and loss of mechanical stability can cause a problem in choosing a reagent. An example of the use of this type of inorganic support was reported by Varma *et al.* They used it to anchor manganese dioxide to perform oxidation of alcohols (Scheme 10). This was carried out under microwave conditions.²³

Scheme 10



Macroporous polystyrene resins have also been used as a support. These are styrene-divinyl benzene co-polymers that have an internal pore structure.³⁹ Usually these resins are prepared by carrying out polymerisation in the presence of a nonreactive diluent that phase separates during the polymerisation and defines the pore structure (See Figure 11 for example of pore structure). Reagents are transported through this pore structure rather than through spaces within a polymer gel.

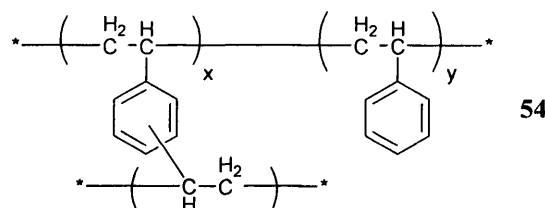
Figure 11: Schematic representation of the pore structure of a macroporous resin (a) ArgoPoreTM bead. (b) Microglobules (c) The internal pore structure.⁵⁵



1.3.2 Zero, first and second order resins

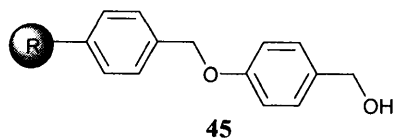
It is worth defining at this stage, the difference between a *zero*, *first* and *second* order resin. The foundation of all solid phase synthesis is the polymeric core. Polystyrene is the most common core resin, but other core matrices include polyacrylate, polyethylene glycol and polyacrylamide. The two most important factors to consider in solid phase organic synthesis are swelling and the bead size of the resin.⁷⁵ A core resin is not functionalised and does not contain an active unit. If we take an example using a polystyrene resin **54** (Figure 12), it has not had a substrate unit attached to the backbone, and consists of the two polymer chains crosslinked by divinyl benzene. The polystyrene resin can be functionalised to a first order resin by adding the appropriate linker such as a pyridine.

Figure 12 A zero order resin

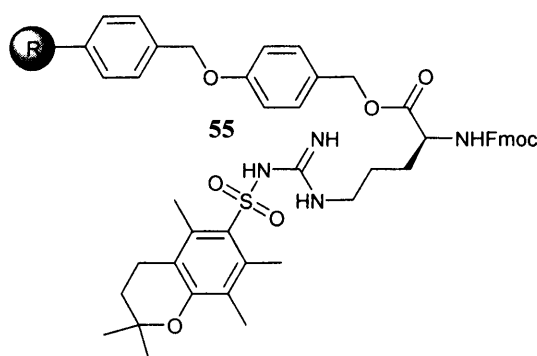


In a first order resin, a solid support contains a cleavable linker which is ready for introduction of a substrate. Many commercially available first order resins bear a common feature, that enables acid catalysed cleavage to liberate the final product from the solid support. An example of this is *Wang resin* **46** (depicted in Figure 6, p13).⁶⁰ The linker such as that in the Wang resin has been designed so that a stable carbocation can form on the resin side of the anchoring linkage. Several other resins have been also developed which are cleavable by a wider variety of conditions.⁵⁹

Figure 13: A first order resin



A second order resin is a first order resin that has been converted by attachment of a substrate unit an example is **55** (Figure 14). Remaining active sites on a second order resin need to be blocked otherwise they can react with other reagents and generate impurities which can prove difficult to remove.

Figure 14: A second order resin

1.4 Soluble supports

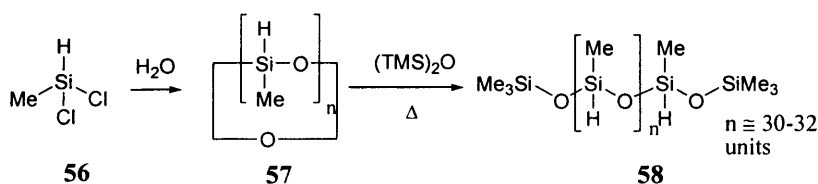
As well as insoluble polymer supports used in solid phase synthesis, there have also been reports of the use of soluble polymers for chemical synthesis. Due to the inherent problems associated with organic synthesis using a solid support, various research groups have replaced insoluble supports with soluble polymer supports, reverting the reaction conditions back to much like those found in classical organic synthesis.⁷⁶ Examples of these supports include non-crosslinked polystyrene and polyethylene glycol derivatives.⁷⁷

In recent years, soluble polymer supported reagents and catalysts have gained significant attention. Due to the associated problems of solid phase synthesis, mainly attachment and cleavage, parallel libraries are often generated in solution.⁷⁸ Whilst it may appear a soluble polymer will be difficult to separate, in practice the support is simply precipitated by addition of an *anti-solvent*. Although this is the simplest method of purification using soluble supports, other methods such as dialysis using a permeable membrane, centrifugation, gel permeation chromatography and adsorption chromatography have also been utilised to remove excess reagents and byproducts from the polymeric products.⁷⁹

1.5 Polymethylhydrosiloxane

This is the polymer to be studied in this PhD project, so will be considered briefly here. Now manufactured and used on a multi-ton scale, polymethylhydrosiloxane, (PMHS, **58**), was first synthesised over fifty years ago. In 1946, Sauer and co-workers hydrolysed⁸⁰ methylchlorosilane **56** to yield cyclic siloxanes **57** of between four and six repeat units, before equilibration with the ‘end-capping’ reagent hexamethyldisiloxane by heating at moderate temperatures (60-150 °C) (Scheme 11).

Scheme 11



The polymer, when not cross-linked, has found a wide application in the food, cosmetics and medicinal markets. It is valued for its lubricating properties and ability to lower surface tension. When branch points are introduced, the so-called ‘room temperature vulcanisation’ of PMHS results in a more structurally rigid material. The room temperature vulcanised products are renowned for their ability to repel water, finding application for the protection of leather, paper and fabric surfaces and in the protection of gypsum plaster boarding surfaces against water. The process, invoked by a reaction of PMHS with a silanol and catalysed by a metal salt such as dibutyldilauryl tin, evolves hydrogen gas as a by-product which, when harnessed, can be used to produce foam rubber products.⁸¹

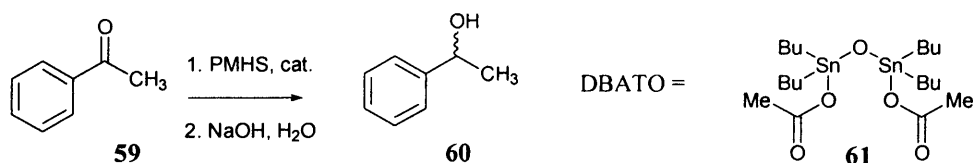
Silicones are considered inert and non-toxic. Indeed PMHS derived silicones have found use in the sausage skin industry. The silicones have also been used in the biomedical sciences, for example the Finney flexible rod prosthesis for patients suffering non-psychogenic impotence and in breast implant technology. Figure 15 shows the physical and chemical properties of PMHS.

In the area of organic synthesis, however, PMHS has yet to be fully exploited. Environmental legislation, public and corporate pressures to develop environmentally benign reagents have produced several applications of chemistry involving the use of this cheap and non-toxic compound. Figure 15 shows the physical and chemical properties of PMHS.

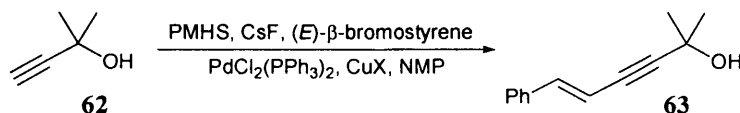
Figure 15: The physical and chemical properties of polymethylhydrosiloxane

Formula	Me ₃ SiO(MeHSiO) _{~35} SiMe ₃
Hydride equivalent weight	60 g mol ⁻¹
Density	1.0 g cm ⁻³
Viscosity	30 centiStokes
Appearance	Water clear, odourless
Solubility	Soluble in most organic solvents
Chemical reactivity	Inert to air and moisture

Previous work within the group has seen the utilisation of PMHS in the reduction of the carbonyl function in the presence of other moieties. For example, acetophenone (**59**) is reduced to the alcohol **60** using PMHS in the presence of a catalyst (Scheme 12). The catalyst used can be either TBAF,⁸² $\text{Ti}(\text{O}^i\text{Pr})_4$,⁸³ or DBATO^{81,84} (**61**).

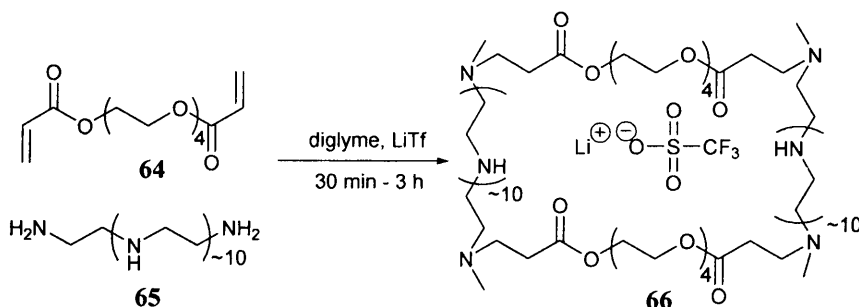
Scheme 12

The technique is not limited to ketones, but can be used to reduce esters and carboxylic acids when TBAF or Ti(OⁱPr)₄ is the catalyst. Other recent developments using PMHS has seen its use in cross-coupling reactions, in particular in the synthesis of natural products such as akalactone A (**63**).⁸⁵ The first coupling step in this process using alkyne **62** and bromostyrene is shown in Scheme 13.

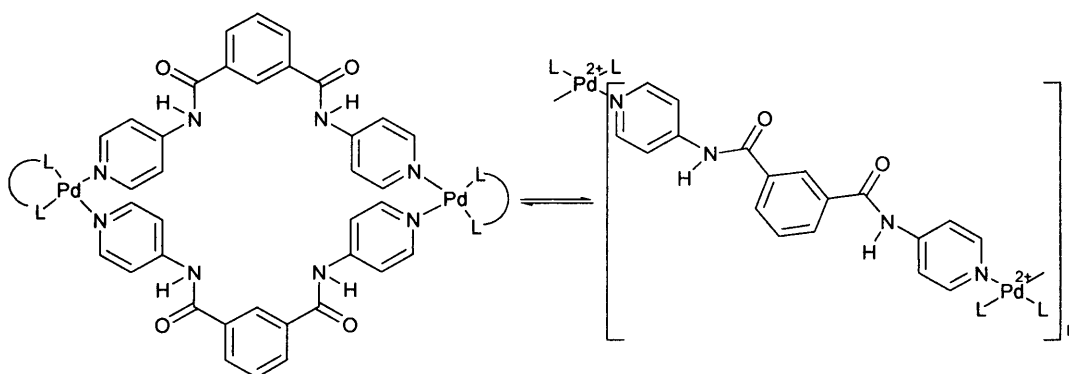
Scheme 13**1.6 Crosslinking of siloxanes and other resins**

A polymer in its non-crosslinked state is usually soluble in particular solvents, including polymethylhydrosiloxane. However, when the same polymer is turned into the crosslinked form, it becomes insoluble and thus its mechanical stability increases, thus making a more rigid backbone onto which other substituents can be grafted if need be.

A practical example is provided by crosslinked poly(ethylenimine) (**66**) prepared from tetraethyleneglycol diacrylate (**64**) and ethyleneimine **65** (Scheme 14). This is a stable solid suitable for use within electrochemical devices.⁸⁶

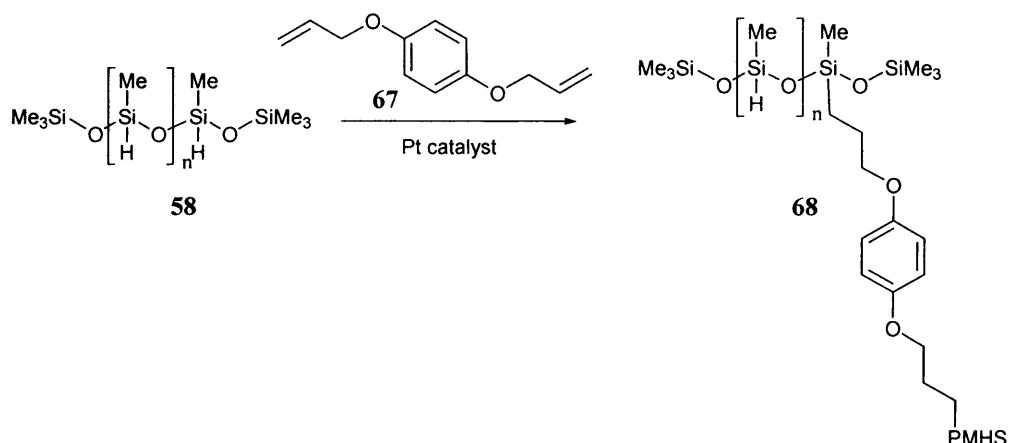
Scheme 14

In some cases a polymer can be crosslinked to give a more uniform structure, as reported by Puddephatt and co-workers who crosslinked a palladium(II) polymer to give a laminated sheet structure⁸⁷ (Scheme 15).

Scheme 15

Polystyrene, discussed in section 1.3.1, when uncrosslinked will dissolve in aprotic solvents such as toluene, dichloromethane and DMF. However, when it is used for organic synthesis it is crosslinked with divinylbenzene (DVB), giving it a mechanically stable gel-like consistency when in the presence of these same swelling solvents.⁸⁸ Usually crosslinking with 1% DVB provides a material which retains its shape, generally in a bead form, has good resistance to mechanical breakage and still swells in an appropriate solvent medium.

Siloxanes are normally crosslinked using titanates, for use within the coatings industry. In most cases in industrial applications, crosslinking is used as a way to improve physical properties of polymers.^{89,90} Siloxanes can be crosslinked by hydrosilylation reactions as demonstrated by Hogan and co-workers (Scheme 16)⁹¹. The polymer chains were crosslinked using a vinyl crosslinker **67** at different temperatures to give resins like **68**.

Scheme 16**1.7.1 Supported scavengers and reagents – past and present**

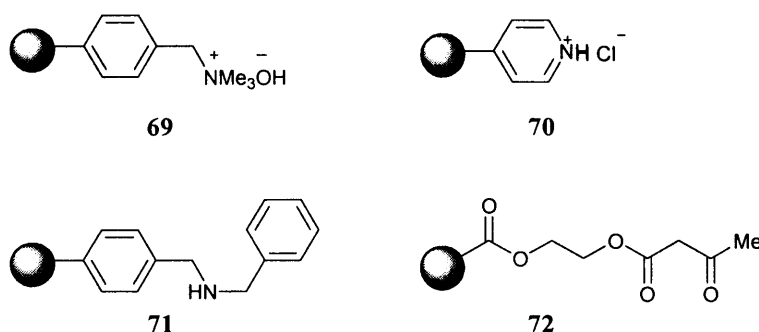
Polymeric reagents and scavengers have seen use in organic synthesis programmes from 1946, though later valuable contributions appeared in due course from Frechet,^{92,93} Cainelli,^{94,95} Camps,⁹⁶ Leznoff, Font, Hodge⁹⁷ and Sherrington³⁷ to mention a few. However, if anything this work was deemed too advanced since these reagents were

regarded by many to be either so expensive to disallow their use, too difficult to recycle or that reaction times were so slow with respect to solution phase, to be regarded useful. Due to these reasons some of these earlier contributions from the literature despite being cutting edge have often been poorly cited. Recently however, several new and improved solid supported reagents have been extensively developed, the number of which becoming commercially available is increasing at an incredible rate. This rise in popularity has come about due to the demand to generate large numbers of novel compounds using cleaner, more efficient means.

There are many reasons why solid supported reagents are so attractive in combinatorial chemistry programmes. The main advantages are that it is possible to use excess reagent to drive reactions to completion and, as work up is by simple filtration to remove products, the chemistry does not require extra steps in purification.⁹⁸ This filtration also results in isolation of the required solid supported species which is a crucial feature in cases where either the reagent acts as a catalyst, or where the used material can be regenerated and recycled.⁹⁹ Another attractive aspect is that normally toxic, noxious or hazardous reagents and their by-products, can be immobilised and therefore not released into solution thereby improving their general acceptability, utility and safety profile. Often more than one reagent can be used simultaneously and, due to anchoring of reagents on the support, even species normally incompatible in solution may be used together to achieve one-pot transformations that are not possible in homogeneous solution.¹⁰⁰ Furthermore, if the reactions proceed poorly or generate by-products and impurities, scavengers or catch and release techniques can be used to isolate pure products in a simple fashion without the need for conventional work up and purification procedures.¹⁰¹ The fact that only simple work up procedures are necessary, involving filtration and solvent removal or exchange, is a crucial feature for library generation as the chemistry should then be appropriately suited to automation using robotic devices.¹⁰²

Scavengers are functionalised resins, designed to react selectively with impurities present in the reaction mixture so that upon immobilisation they can be easily removed by filtration leaving clean products in solution. Two different classes of scavengers, those that are ionic (basic **69** and acidic **70** resins, normally referred to as ion exchange resins) and those which are covalent (nucleophilic **71** and electrophilic **72** reagents) (Figure 16).¹⁰³

Figure 16

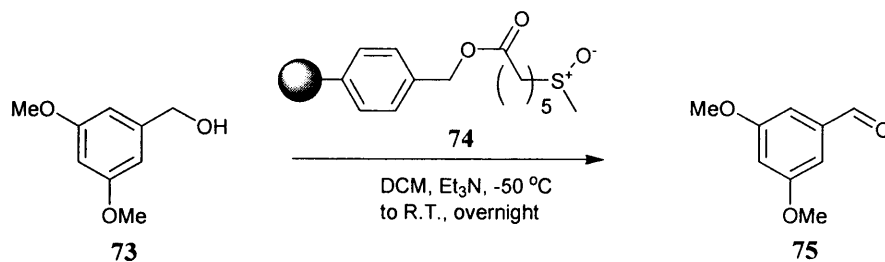


Most standard scavenging protocols are based on the concept of complementary reactivity.³⁸ In the simplest cases electrophilic and nucleophilic species are sequestered via an equal and oppositely functionalised polymer, likewise acids and bases can be removed via neutralisation with a polymeric acid or base. This method, commonly known as polymer-assisted purification, has been considerably expanded upon during the last few years with many highly desirable techniques now being available.^{104,105}

1.7.2 Polymer supported oxidation reagents

A common reaction used to oxidise alcohols to aldehydes and ketones is the Swern oxidation method.¹⁰⁶ An unpleasant feature of the process is the production of the major byproduct dimethyl sulfide, a toxic and putrid smelling gas. To overcome this, crosslinked chloromethyl polystyrene or *Merrifield* resin has been used to support 6-methanesulfinyl hexanoic acid to give the polymer-supported sulfoxide **74** (Scheme 17).¹⁰⁷ This is used as a substitute for DMSO in the oxidation procedure. Its use to oxidise the alcohol **73** to the aldehyde **75**, without over oxidation to the carboxylic acid, is shown in Scheme 17. The polymer-supported reagent has the advantage of not producing the unpleasant stench unlike its solution phase counterpart.

Scheme 17

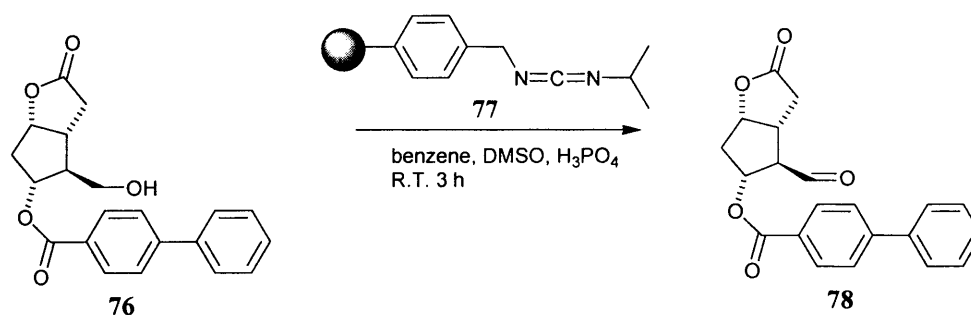


The polymer-supported sulfoxide allowed the oxidation reactions to be carried out under normal Swern oxidation conditions, thus showing the PS-sulfoxide to be a worthwhile DMSO substitute¹⁰⁸. A variety of alcohols have been used to demonstrate the utility of the

supported reagent, all with yields obtained above 90%. After oxidation, the sulphide byproduct, now polymer bound, could be easily separated from the product without the problems mentioned previously and was removed by simple filtration methods. The polymer-supported sulphide also had the beauty of being recycled and reused after oxidation with sodium periodate.

A procedure that has proven to be an extremely valuable technique when using acid sensitive compounds for oxidation is the related Moffatt oxidation¹⁰⁹. Under the classical conditions dicyclohexylcarbodiimide is used, leading to the corresponding urea being the major impurity and which can be difficult to remove from the product. Using water-soluble carbodiimides has partially overcome this problem, the isolation of water-soluble aldehydes or ketones can cause some difficulties.¹⁰⁸ With this in mind the polymer-supported version **77** (Scheme 18) offers a valuable solution.¹¹⁰

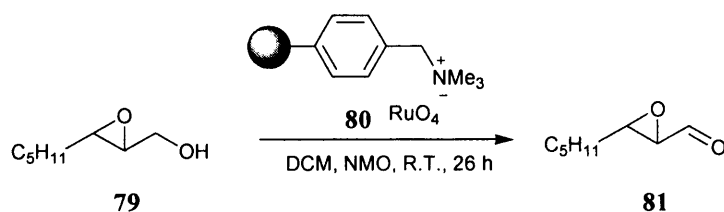
Scheme 18



Solvent combinations of choice are either benzene-DMSO mixtures or neat DMSO, with the latter requiring longer reaction times. An example is shown with the labile prostaglandin intermediate **76** which was readily converted to the aldehyde **78** in high yield (Scheme 18). The polymer bound urea could be transformed back to the carbodiimide **77** by dehydration of the urea using *p*-toluenesulfonyl chloride and triethylamine in DCM at reflux if so chosen.

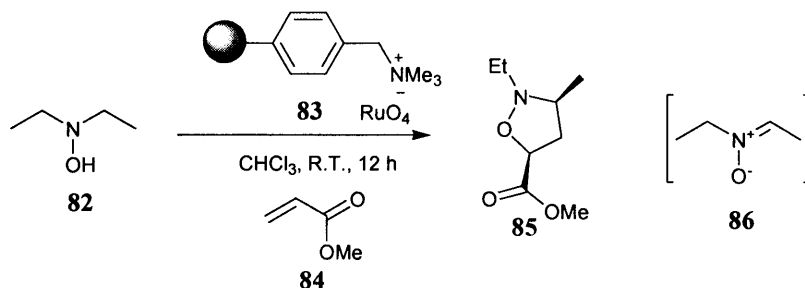
It is not necessarily the rule that because the oxidant is attached to a polymer that it needs to be used in large amounts, successful oxidations using PS-perruthenate reagents such as **80** (Scheme 19) have been carried out using either stoichiometric or catalytic amounts of the reagent.¹¹¹ The catalytic system has been shown to operate using an alcohol such as **79** in conjunction with a co-oxidant such as *N*-methylmorpholine *N*-oxide (NMO) obtaining the desired carbonyl compound **81** requiring little in terms of work up and purification (Scheme 19). Typically reactions were carried out in dichloromethane at room temperature using either trimethylamine *N*-oxide (TMO) which produces the volatile trimethylamine as the by-product, or *N*-methylmorpholine *N*-oxide (NMO).

Scheme 19



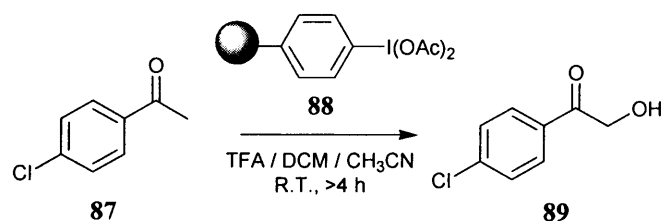
Oxygen has also been used as the co-oxidant to again provide the products free from impurities in order to extend the umbrella of 'clean technology'.¹⁰⁰ Reagent **83** has been used to generate nitrones by the oxidation of secondary hydroxylamines such as **82**. It is seen to provide, in the presence of a dipolarophile such as methyl acrylate **84**, the isoxazolidine **85** in high yield (91%) *via* a 1,3-dipolar cycloaddition of nitron **86** (Scheme 20).

Scheme 20

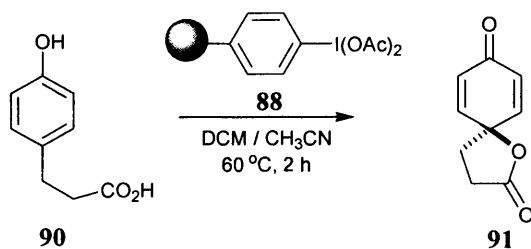


Polymer supported (diacetoxyiodo)benzene (PS-DIB) **88** is a versatile oxidising reagent and its synthesis was known for many years.¹¹² Its synthetic application has only recently been extended.¹¹³ The usefulness of the reagent is multi-faceted, acetophenones such as **87** can be α -hydroxylated using heat or excess PS-DIB, to give acyloins such as **89** (Scheme 21). A particularly interesting example of the use of **88** is an oxidative spirocyclisation reaction of the acid **90** to provide the spirodienone **91** (Scheme 22). Furthermore, the use of an excess of the PS-DIB **88** gave constantly high yields of the desired products, in contrast to the soluble material which can be capricious. The PS-DIB **88** consumed in reactions such as these shown was regenerated by oxidation with peracetic acid. The regenerated resin showed no loss in activity.

Scheme 21



Scheme 22



There are many ways to perform the dihydroxylation of olefin substrates. The *cis*-dihydroxylation of alkenes by osmium tetroxide to form *cis*-1,2-diols is one of the most reliable and commonly used synthetic transformations.⁹² However, the exposure hazards and toxicity associated with osmium tetroxide along with its high cost have led to the development of non-volatile tertiary amine–osmium tetroxide adducts **92** and **93** (Figure 17) which maintain the original reactivity of the reagent.

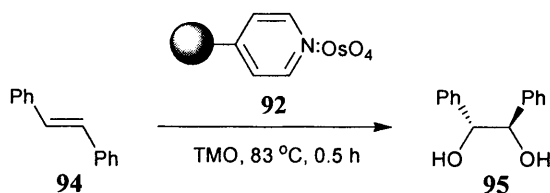
Figure 17



Later, catalytic systems were developed using catalytic amounts of the osmium tetroxide working in tandem with a stoichiometric amount of secondary oxidant in order to regenerate the tetroxide. The polymer bound reagents **92** and **93**¹¹⁴ require simple preparation starting from crosslinked poly-4-vinylpyridine or by using a resin bound 1,4-diazobicyclo[2.2.2]-octane (DABCO) equivalent. These resins are then treated with a solution of osmium tetroxide in cyclohexane to complex the tetroxide via the nucleophilic nitrogen function.

PS-Osmium tetroxide **92** (Scheme 23) has the advantage of an easy work up without the need to decompose residual osmium tetroxide. This decreases the exposure effects encountered with the original solution phase reaction and non-supported osmium. An example of the use of such a polymer-supported reagent is shown below. The dihydroxylation of stilbene (**94**) was carried out in *tert*-butyl alcohol with 0.2-1% of PS-osmium tetroxide **92** using hydrogen peroxide or trimethylamine *N*-oxide (TMO) as co-oxidant to give the diol **95** in high yield and purity (Scheme 23).

Scheme 23

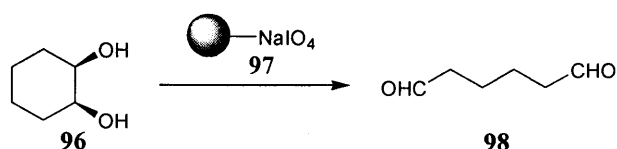


The reaction was high yielding and the best results with different substrates were obtained using either **92** or **93** (Figure 15) with TMO in *t*-butanol. It was reported that by iodometric testing no leeching of the osmium tetroxide into the product occurred. The reagent itself can be stored for weeks without any appreciable decline in reactivity.

Kobayashi has shown that polystyrene can be used to microencapsulate osmium tetroxide.¹¹⁵ The osmium tetroxide becomes physically enveloped by the polymer presumably on the basis of interactions between the π -electrons of the benzene rings of the polymer and a vacant orbital of osmium tetroxide. It is prepared by simply cooling a solution of polystyrene and osmium tetroxide from 40 °C to 0 °C, followed by washing to remove unencapsulated reagent. The effective use of PS-MC-osmium tetroxide was demonstrated by dihydroxylating a range of olefins using 5% of PS-MC-osmium tetroxide and *N*-morpholine *N*-oxide (NMO). In each case the product diol was obtained in high yield (74% or above) and satisfactorily without any detectable leeching of osmium tetroxide.

Another common reagent used is sodium periodate for the oxidative cleavage of vicinal diols such as **96** into dicarbonyl compounds such as **98** (Scheme 24). Its specificity and reactivity under mild, neutral conditions have made it a popular reagent amongst carbohydrate chemists. The reactions are usually performed in aqueous alcohols or THF, however the success of the reactions is limited by its insolubility in non-polar solvents.

Scheme 24

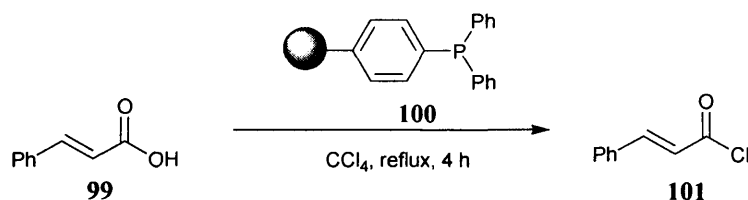


This in turn can pose problems for vicinal diols which are hydrophobic and thus have poor solubility in aqueous alcoholic media or for those product aldehydes which are hydrophilic and thus difficult to extract from water. To overcome these difficulties, silica gel has been used to support the sodium periodate reagent¹¹⁶ **97** (Scheme 24). The oxidation time is quite short and the reaction is high yielding.

There are many reactions in which triphenylphosphine is involved producing triphenylphosphine oxide as the byproduct. Although these reactions are straightforward to carry out the byproduct causes separation problems as it is not volatile or water soluble. So PS-triphenylphosphine however is not problematic since it is easily removed by filtration methods.^{117,118} PS-triphenylphosphine **100** and carbon tetrachloride have been used to

convert the *trans* cinnamic acid **99** to the corresponding acid chloride **101** (Scheme 25) and alcohols to the corresponding alkyl chlorides. The reactions give good yields under mild and neutral conditions with short reaction times under reflux.¹¹⁹

Scheme 25

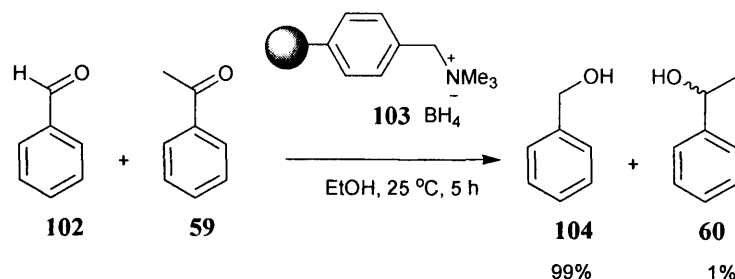


This reagent combination has also been used to prepare amides¹²⁰ from *N*-protected amino acids and amines. The three major amine protecting groups (CBz, Boc and Fmoc) are compatible with the conditions and the required amides were isolated in high yields.

1.7.3 Polymer supported reducing reagents

Hydride reducing agents are commonly used in order to reduce carbonyl functionalities to the corresponding alcohol. A mild reducing agent among metal hydrides is sodium borohydride. Amberlyst anion exchange resins of the quaternary ammonium type have been used to support borohydride anions to give what is now generally called polymer supported borohydride exchange resin (PS-BER) **101** (Scheme 26).¹²¹ It is prepared simply by stirring the Amberlyst resin (chloride form) with a solution of sodium borohydride. After filtering and washing with water to remove excess sodium borohydride, the resin is dried under vacuum to give the product **103** ready for use. In a series of competitive reductions, it was shown that the reduction of benzaldehyde **102** occurs faster than acetophenone **59** giving the corresponding benzyl alcohols **104** and **60**, presumably due to the higher reactivity of an aldehyde in comparison to a ketone (Scheme 26). Aromatic aldehydes such as **102** are reduced preferentially in the presence of aliphatic aldehydes.

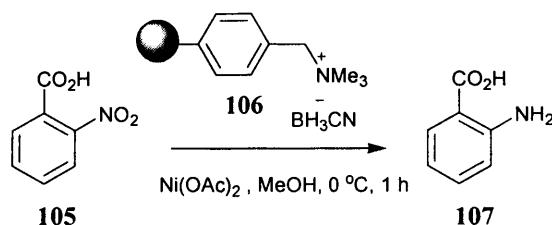
Scheme 26



In a similar vein, cyanoborohydride resin **106** is prepared in a similar way to the borohydride exchange resin **103**. PS-cyanoborohydride (**106**) has been used to mediate the reduction of the nitrobenzoic acid **105** to the aminobenzoic acid **107** at room temperature (Scheme 27).¹²² When compared with the parent cyanoborohydride, the reactions are slower, but they

proceed with high yields. The easy work up together with the retention of the cyanide ion on the resin makes PS-cyanoborohydride a safe and effective alternative to classical methodology.

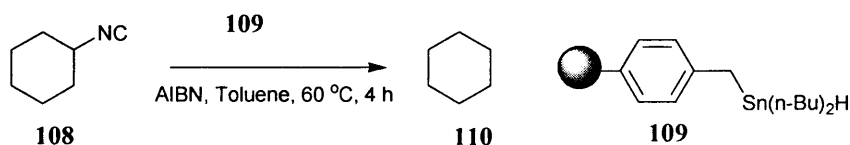
Scheme 27



It is known that the addition of transition metal salts to sodium borohydride enhances its reducing ability in comparison to the reducing agent alone. The same applies to the polymer supported reagent and nickel acetate. It has been shown that both aliphatic and aromatic nitro compounds can be reduced in short reaction times and in good yields. A wide range of substrate functionality is compatible with this reagent combination.

Tributyltin hydride is another commonly used versatile reducing agent, but the associated difficulties in separating this toxic species and related byproducts from the product has led to the development of a PS-tin hydride equivalent **109** (Scheme 28). The most recent preparation of this has been described by Nicolaou¹²³ using an adapted but previously reported hydrostannation protocol.¹²⁴ Numerous radical reactions have been mediated by these reagents¹²⁵ which have been developed and applied, typically in dry benzene or toluene at elevated temperatures. The example shown in Scheme 28 illustrates the conversion via the isocyanide **108** cyclohexane (**110**).

Scheme 28

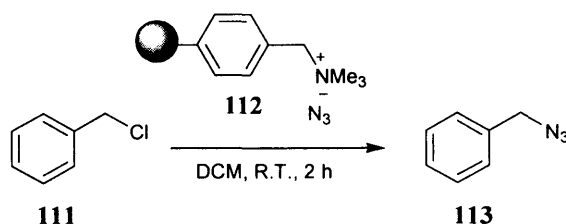


1.7.4 Polymer supported nucleophilic reagents

Alkyl azides prepared by way of nucleophilic substitution of a leaving group by an azide anion are well documented in the literature. Some of the problems associated with this reaction are due to the low solubility of inorganic azides in organic solvents. This has been overcome by using organic azides such as tetraalkylammonium azide; other methods use phase transfer conditions and in some cases Lewis acid catalysts. Usually heating of these thermally unstable compounds is required. An azide anion supported on Amberlite anion exchange resin has been used to substitute activated and non-activated alkyl halides at room

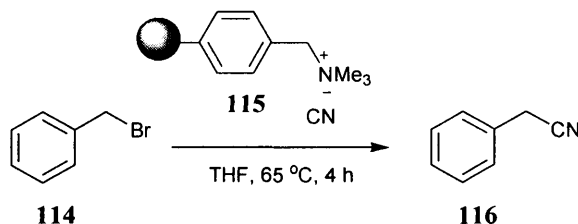
temperature. For example benzyl chloride (**111**) gives the azide **113** in quantitative yield (Scheme 29). The resin PS-azide **112** was prepared by mixing Amberlite ion exchange resin with an aqueous solution of sodium azide.¹²⁶

Scheme 29



The PS-cyanide **115** has been prepared from Amberlite ion exchange resin.¹²⁷ Many activated halides such as benzyl bromide (**114**) have been transformed into their corresponding nitriles in ethanol (Scheme 30).¹²⁸

Scheme 30



Amberlyst A-26 anion exchange resin has been converted from the hydroxide form **69** to the fluoride form **117** by treating with dilute aqueous hydrogen fluoride (Scheme 31).⁹⁴ Organic chlorides, bromides, iodides and methanesulfonates have been transformed into the corresponding fluoride by refluxing the mixture in hexane. Good yields were obtained starting from primary halides, whereas for the secondary halides an elimination pathway predominates giving the olefinic compounds. This can be suppressed by synthesising the appropriate sulfonate derivative as these are less prone to elimination.

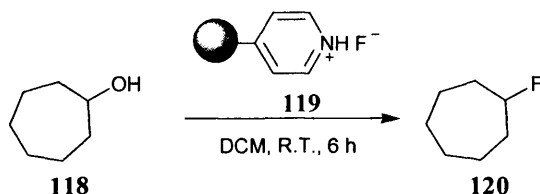
Scheme 31



Hydrogen fluoride is a hazardous reagent to work with at the best of times. One way to alter its handling hazards is to attach it to a polymer support. The preparation of poly-4-vinylpyridinium poly(hydrogen fluoride) (**119**) has been reported in the literature by Olah.¹²⁹ This is made from commercially available poly-4-vinylpyridine and anhydrous hydrogen fluoride. Brown coloured fumes of the polymer are seen when it is exposed to the air, and when dispersed in an organic solvent it provides an anhydrous source of hydrogen fluoride. This mixture has been used to convert a range of alcohols to the fluorides under mild

conditions and with good yields. In this way cycloheptanol (**118**) was converted to fluorocycloheptane (**120**) (Scheme 32).

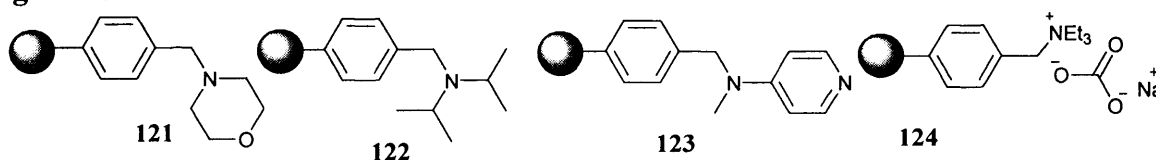
Scheme 32



1.7.5 Polymer-supported basic reagents

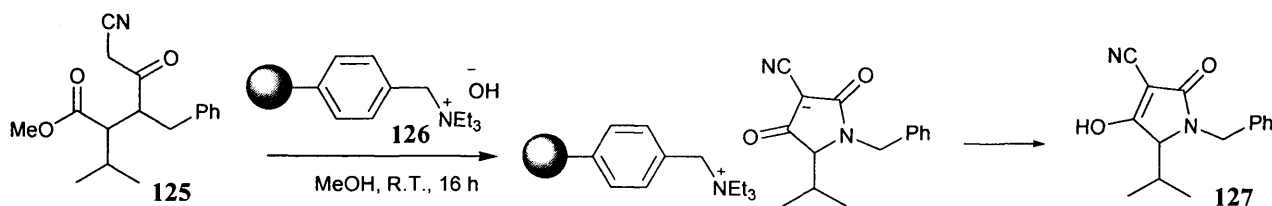
Commonly used bases are now available in polymer-supported forms such as *N*-methylmorpholine **121**, dimethylaminopyridine **122**, diisopropylethylamine **123**, carbonate **124** and hydroxide and can be substituted for the soluble type with little or no effect on the reaction kinetics (Figure 18).

Figure 18



Ganesan¹³⁰ has described a route in which he used the hydroxide form of Amberlyst A-26 resin **126** to mediate a Dieckmann cyclisation in the synthesis of a library of 2,4-pyrrolidinediones (tetramic acids). This is shown below in Scheme 33, the α -amino ester derivative **125** was treated with PS-hydroxide **126** in methanol at room temperature over 16h. Once complete only the successfully cyclised tetramic acid **127** remains bound to the solid support, other components are simply washed away.

Scheme 33



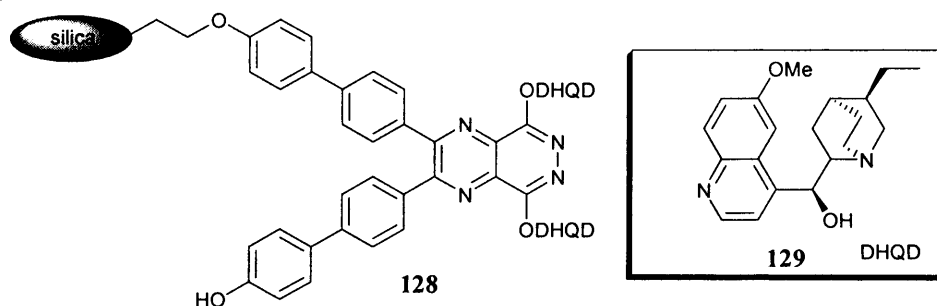
The product **127** was consequently released from the polymer support by acid treatment with TFA giving the tetramic acid in good yield and high purity.

1.7.6 Polymer-supported catalysts

The generation of hybrid catalysts which combine the attributes of homogeneous catalysts with the experimental ease of heterogeneous catalysts has lured many workers into this area of research. The promise of simple recovery and re-usability is usually hampered by the

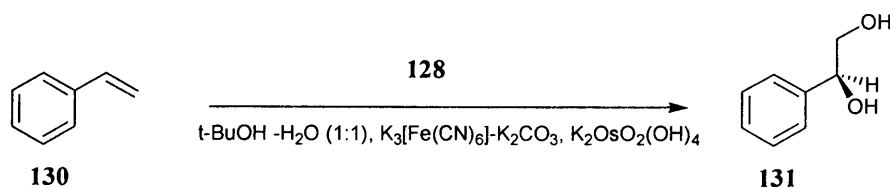
more difficult synthesis and characterisation of the support bound catalyst. The solid support also leads to a perturbation of the function of the catalyst.

Figure 19

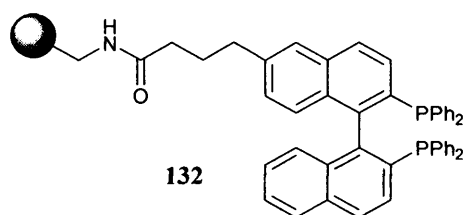


The catalytic system devised by Sharpless for the asymmetric dihydroxylation¹³¹ of olefins using the cinchona alkaloids was marked as a massive achievement. Unsurprisingly polymer supported versions have also been reported. In a quest to ease the recovery of the ligands after the reaction is complete, the use of PS-cinchona alkaloids has been studied. These suffer from the disadvantages of longer reaction times and lower enantioselectivity. This has led to the recent introduction of PEG-supported alkaloids which have similar reactivity and enantioselectivity to the original Sharpless system.¹⁰¹ Bolm and co-workers have reported asymmetric dihydroxylation with silica anchored alkaloids.¹³² A modified dihydroquinidine – diphenylpyrazinopyridazine [(DHQD)₂-DPP] based ligand was synthesised and attached to commercially available chloropropyl functionalised silica gel via an ether linkage to give solid supported catalyst **128** (Figure 19). Using the supported ligand **128**, styrene (**130**) was subjected to standard dihydroxylation conditions to give **131** in high yield and enantioselectivity (Scheme 34).

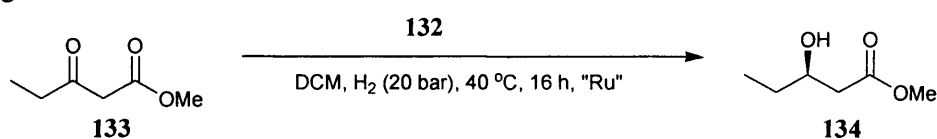
Scheme 34



The success of asymmetric hydrogenations using the *bis*(diphenylphosphino)-1,1'-binaphthyl (BINAP) ligand – transition metal complexes is measured by their widespread usage in both academic and industrial environments. The expense of the BINAP ligand and the associated problems of transition metals leaching into the products have led to the synthesis of PS-BINAP **132** (Figure 20).¹³³ Modifications were made to the BINAP ligand allowing it to be attached to the polymer via an amide linkage.

Figure 20

Using PS-BINAP **132** and DCM, hydrogen at 20 bar pressure at 40 °C for 16 hours with a ruthenium complex, the keto group of 3-oxopentanoic acid methyl ester **133** was reduced to give the β -hydroxy ester **134** in quantitative yield and high enantioselectivity (Scheme 35). The recovered catalyst was re-used and showed only a small loss in turnover.

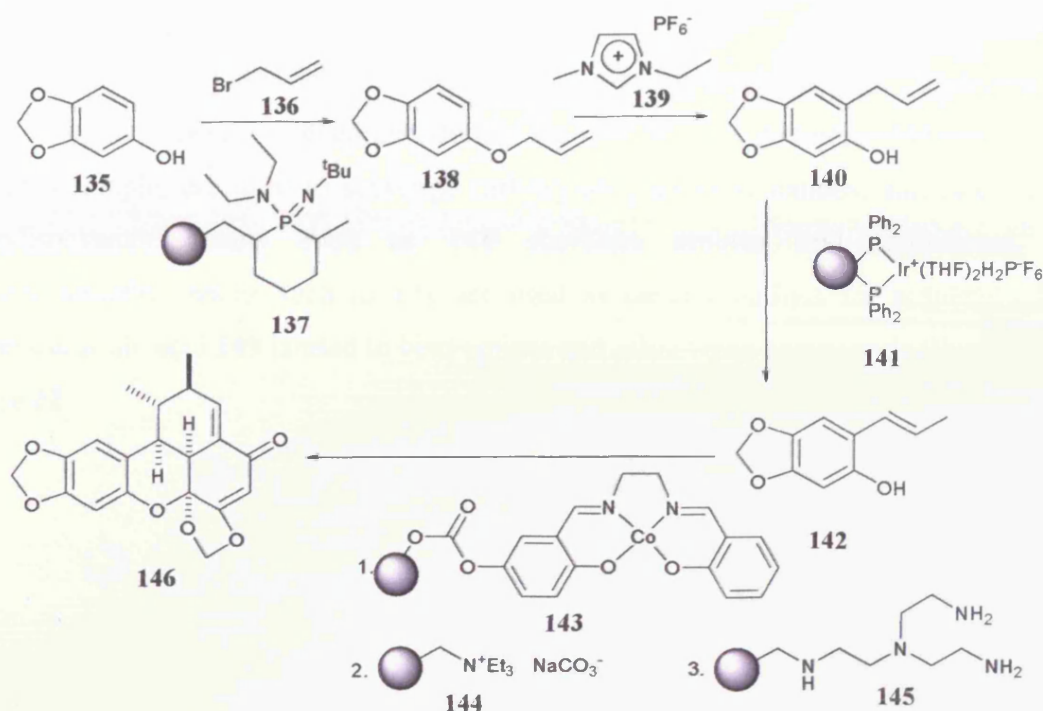
Scheme 35

1.8.1 Scavenger resins

In general one reagent is used in excess forcing a reaction to completion. This results in addition to the product some unused reagent remaining in solution. A resin is then added to selectively bind the excess reactant and allow purification of the product by simple filtration and evaporation¹³⁴. This concept was exploited by Ley and co-workers to great advantage in the synthesis of carpanone **146**, in which the scavenger resin **145** is a basic resin (Scheme 36).

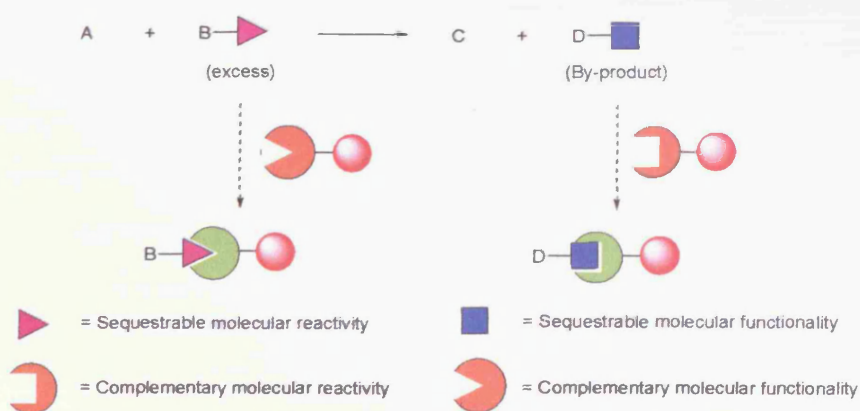
In effect, the substrate and scavenger resin used must have complementary reactivity in order to be effective. This is shown in the general scheme below. Starting with benzo-1,3-dioxol-5-ol (**135**), the 5-allyloxy-1,3-benzodioxole (**138**) was formed using allylbromide (**136**) in the presence of polymer-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (PS-BEMP) (**137**) as base. The benzodioxole **138** then undergoes Claisen rearrangement by heating in the imidazolidine **139** to give 6-allyl-1,3-benzodioxol-5-ol (**140**). In the presence of the supported iridium complex **141**, the benzodioxole **140** undergoes a bond shift to give (*E*)-6-propenylbenzo[1,3]dioxol-5-ol (**142**). Finally *via* the supported cobalt complex **143**, in the presence of supported sodium carbonate resin **144** and basic scavenger resin **145**, carpanone **146** is obtained in high yield and purity.

Scheme 36



Multiple scavenger resins can be used in a concerted fashion (even incompatible functional groups can be used because of their comparative isolation within the beads) so that a wide variety of compounds can be removed from the solutions. Similarly, because a variety of resins with different physical and chemical characteristics that remove the same impurity are available, the choice of resin can be optimized to the particular solution-phase system.

Figure 21: *Complementary reactivities of both scavenging and substrate groups enable effective scavenging to take place*

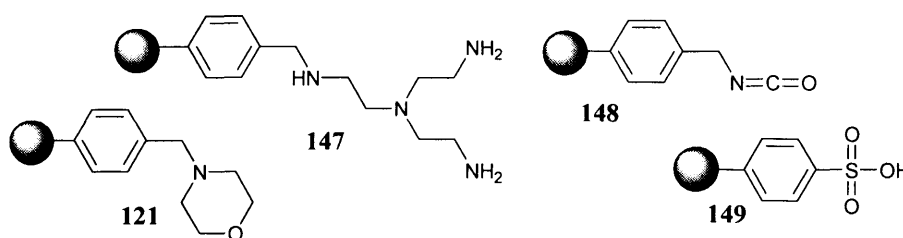


As shown in Figure 21, if one reagent is used in excess, then a scavenger with the appropriate functionality can be used to scavenge this excess, thus leaving the product in solution along with the by-product. A second scavenger can be employed to bind the

product. The by-product is removed by filtration and washing, with the pure product becoming available after cleaving from the support.

Some resins have been designed specifically for scavenging. Aminomethyl resins such as **147**, for example, are used to scavenge carboxylates, sulfonyl halides, and isocyanates.¹³⁵ Methylisocyanate resins such as **148** scavenge amines and hydrazines, while morpholinomethyl resins such as **121** are used as tertiary amines for scavenging acids. Benzenesulfonic acid **149** is used to bind amines and other basic compounds (Figure 22).

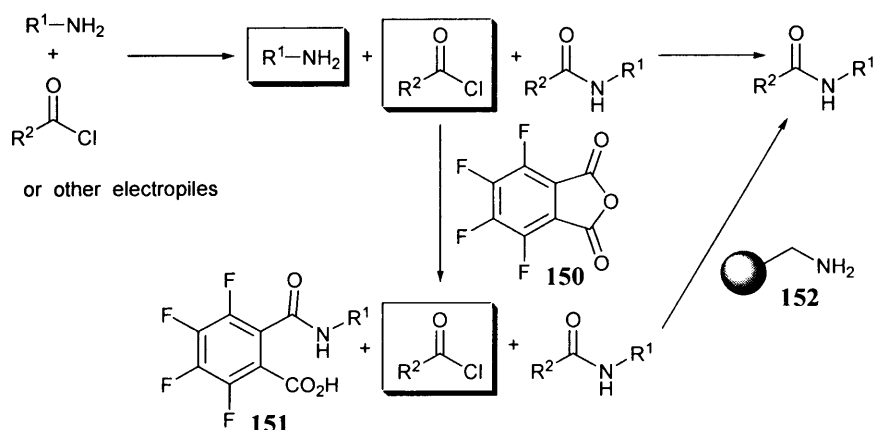
Figure 22



1.8.2 Activating reagents

Some starting materials such as anilines or alcohols react poorly within synthetic routes, hence the product mixtures will contain reactants difficult to remove with certain polymeric scavengers. If this can be activated by the addition of a highly reactive, bifunctional reagent to the product mixture, then this will proportionately transform the poorly reactive molecule into an activated intermediate which is easily trapped by a scavenger. Both electrophilic and nucleophilic reagents have been employed in this manner. An example of this strategy is shown in the following Scheme 38. An excess of amine is treated with the highly electrophilic tetrafluorophthalic anhydride **150**, this leads to an addition product **151**, which can then be removed by using a polymer-supported amine **152**.³⁸ This approach also enables any excess electrophiles, in this case unreacted acid chloride (or hydrolysed material) and tetrafluorophthalic anhydride **150** to be removed in parallel using an appropriate scavenger resin, thus generating a clean solution of the product.

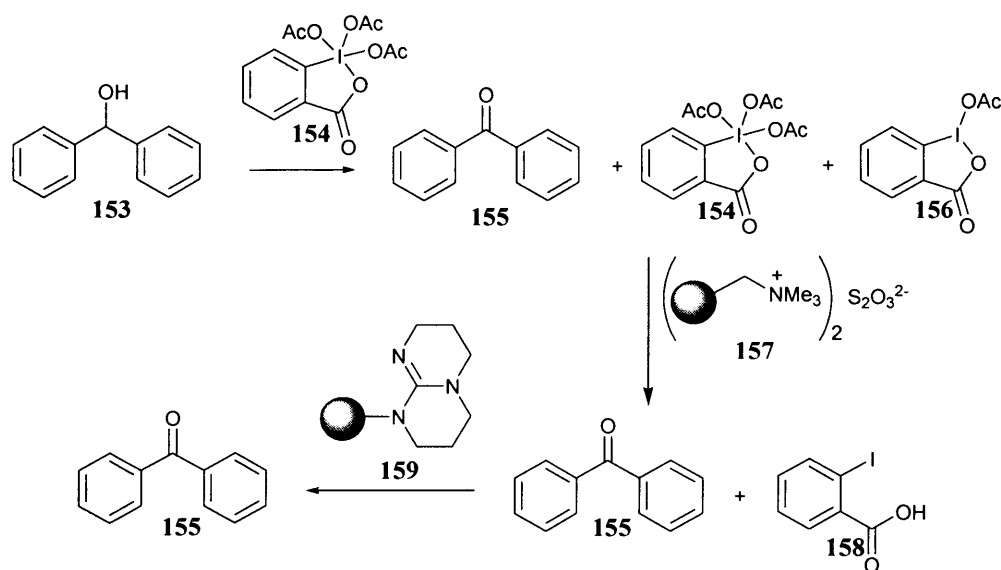
Scheme 38



1.8.3 Reagent priming

Tagged reagents have also found use in combinatorial synthesis. The interesting feature of these reagents is that they bear a functional group that does not affect their reactivity that is preserved in the reagent by-products and reacts with a complementary functionalised polymeric scavenger at the end of the reaction.³⁸ This is illustrated by the elaborate purification procedure devised for hypervalent iodine oxidation reactions by Parlow *et al.*¹³⁶ In fact, the Dess-Martin periodinane (**154**) contains an inherent masked carboxylic acid tag that is revealed at the end of the reaction. Therefore, purification can easily be achieved by treatment of the reaction mixture with a thiosulfate resin to destroy excess periodinane and a strong polymeric base to scavenge the carboxylic acid by-products. The use of these scavengers is shown in Scheme 39. Diphenylmethanol (**153**) in the presence of Dess-Martin periodinane **154** undergoes oxidation to benzophenone (**155**). Also present is some residual periodinane **154** and the by-product **156**. The mixture is treated with the thiosulfate resin **157** to reduce the periodinane to **158**. This leaves the product ketone **155** and another by-product **158** in solution which is removed by another scavenger, this time polymer supported base (PS-TBD) **159**. This leaves the final product ketone **155** in high purity necessitating minimal work-up.

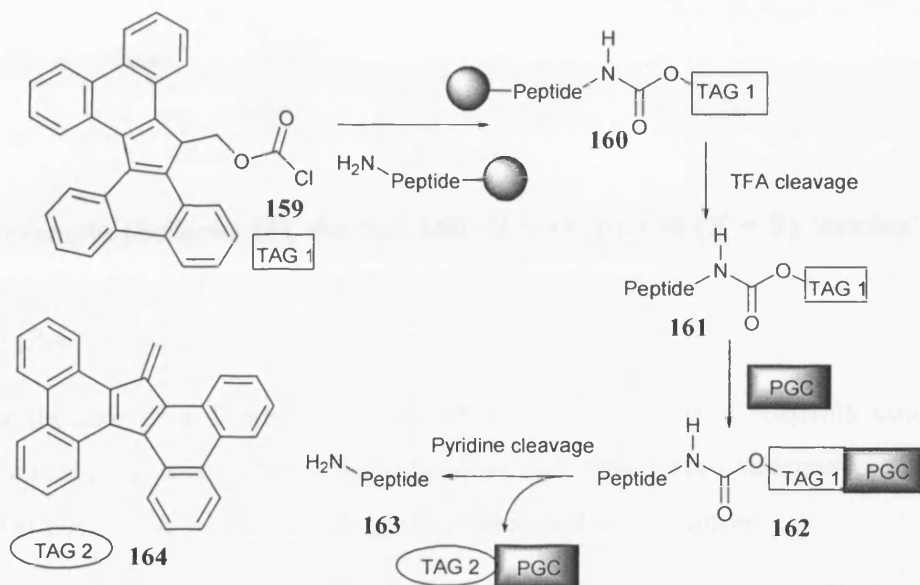
Scheme 39



1.8.4 Purification *via* adsorption

A technique related to reagent priming has been employed by Ramage and co-workers.¹³⁷ They have used a hydrophobic adsorption technique for the purifying synthetic polypeptides. A 'tag' is attached onto the *N*-terminus of a resin bound peptide and this is followed by cleavage from the resin to give species in solution along with a number of possible impurities. This may be due to either side reactions that occur during assembly and cleavage or due to incomplete coupling steps. For short sequences of less than 30 amino acids often the crude material which has been cleaved, may contain only a minor amount of impurities but nevertheless, one or more purification steps are required to obtain the peptide in pure form. When the peptides are treated with porous graphitised carbon (PGC), this absorbs the tag with high affinity, and now allows washing of the now immobilised material and hence, removal of the impurities. Subsequent base-catalysed removal of the 'tag' followed by elution provides a facile recovery process for the peptide. An example of this process is shown in Scheme 40. The acyl chloride TAG 1 **159** acylates the amino group of the peptide to give the resin-bound tagged peptide **160**. This is then cleaved from the support by TFA to leave the tagged peptide **161**. This peptide can be purified and then absorbed onto PGC to give the supported complex **162**. It is then cleaved from the tag to give the peptide **163**. After the cleavage treatment the polyaromatic material is transformed into TAG 2 **164** which remains on the PGC. The PGC can be regenerated by washing with hot 1,4-dioxane.

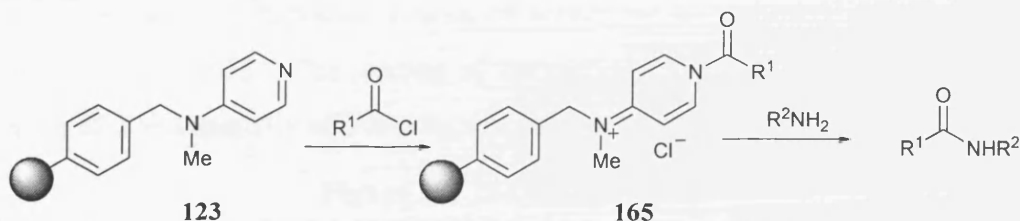
Scheme 40



1.8.5 Catch-and-release methods

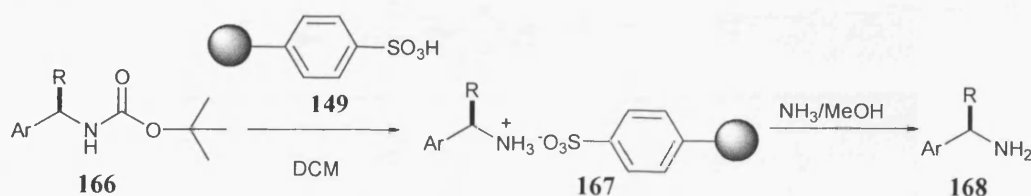
Another variation on selective binding is the immobilisation of the desired reaction product onto a solid support to form a stable intermediate that is thoroughly washed to remove soluble impurities. The intermediate is then subjected to a second transformation that ‘releases’ the product into solution. Examples of this are outlined below.

Scheme 41



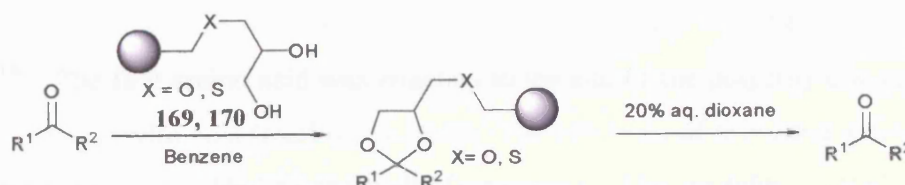
In Scheme 41 the DMAP resin **123** ‘catches’ an acyl chloride *via* nucleophilic attack to provide the intermediate **165**. Treatment of **165** with an amine releases the product amide.¹³⁸

Scheme 42



In the example above, the sulfonic acid resin **149** effects the deprotection of the Boc-protected amine **166** and catches the product amine as the supported salt **167**. The amine **168** is released by treatment with ammonia.³⁸

Scheme 43



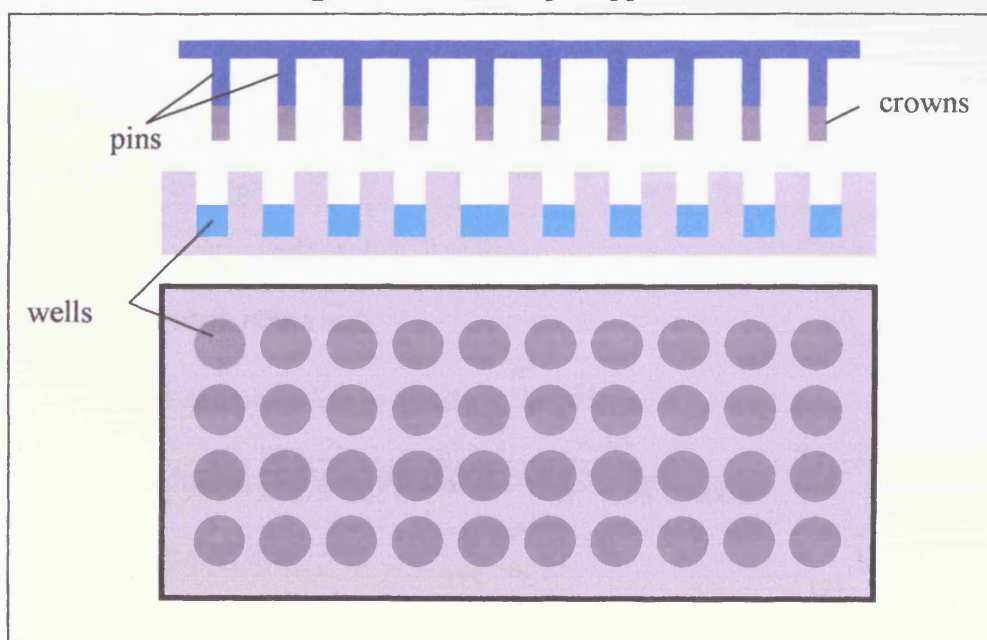
In a final example (Scheme 43), the diol **169** ($X = O$) or **170** ($X = S$) ‘catches’ the ketone allowing the formation of the acetal. This is then subsequently cleaved to allow release of the ketone after, for example, molecular manipulation.³⁸

Embracing the use of a limited selection of polymer-supported reagents combined with advanced scavenging protocols removes the slow and often time-consuming requirements of conventional purification using standard chromatographic techniques.

1.9.1 Parallel synthetic methods and SPOS

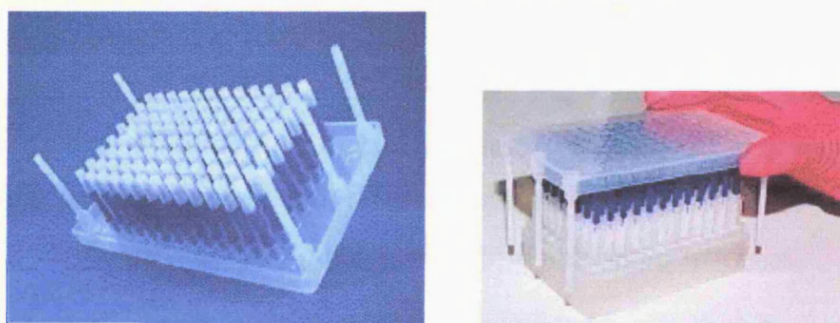
Polyolefin pins and polymer ‘teabags’¹⁰² are support methods based on macroscopic objects that can be physically handled and tracked. The pins are of modular design and are mounted with SynPhase™ crowns, which vary in size and loading.¹³⁹ These are also surface functionalised and do not require polymer swelling for substrate accessibility to reagents and wash solvents. Radiation grafting of a range of monomers has been carried out with polyethylene and polypropylene crowns, of which the aminomethyl polystyrene grafts are most suitable for SPOS. The loading of the largest crowns is in the order of 40 μ moles, indicative of a less spatially efficient format relative to polymer beads.

Figure 23: The multipin apparatus



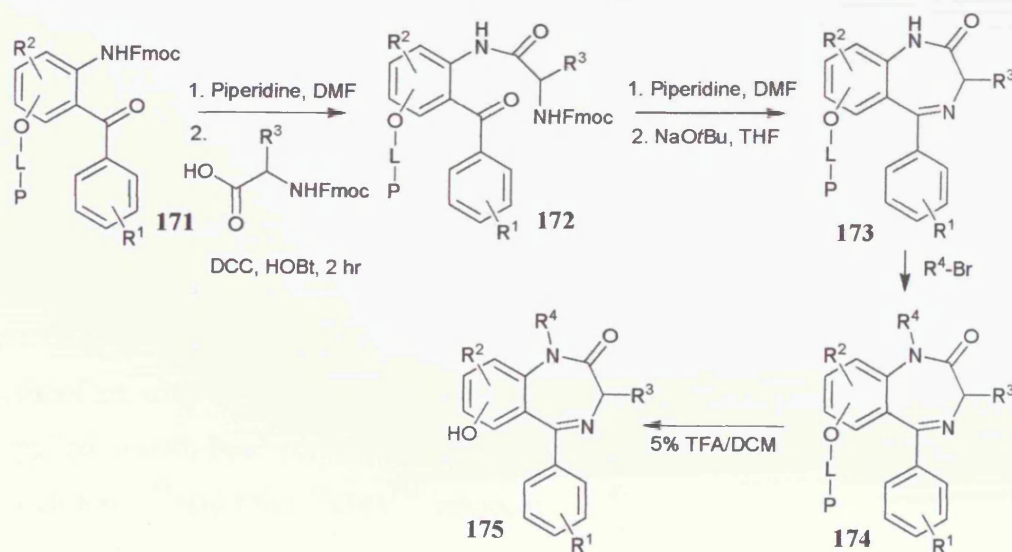
The multipin apparatus has a block of wells serving as reaction vessels (as shown in Figure 24) and a cover plate with mounted polyethylene rods fitting into the wells as shown in Figure 25¹⁴⁰. The first amino acid was attached to the end of the polyethylene rods or 'pins' grafted with polyacrylic acid (marked by blue). The solutions of protected amino acids and coupling reagents were added to the wells (turquoise). The peptides formed on the pins immersed into solutions. The sequence of peptides depended on the order of amino acids added to the wells. The peptides were screened after deprotection without cleaving them from the pins. With this method a marked difference is seen in comparison to other methods in that the number of products never exceeds the number of starting samples.

Figure 24: Using multipin apparatus



The multipin method is still used, and the multipin apparatus is a commercially available product. The multipin procedure was applied by Ellman and his colleagues in pioneering the preparation of organic libraries by parallel synthesis. Derivatives of 1,4-benzodiazepines were constructed from 2-aminobenzophenones, amino acids and alkylating agents (Scheme 44).

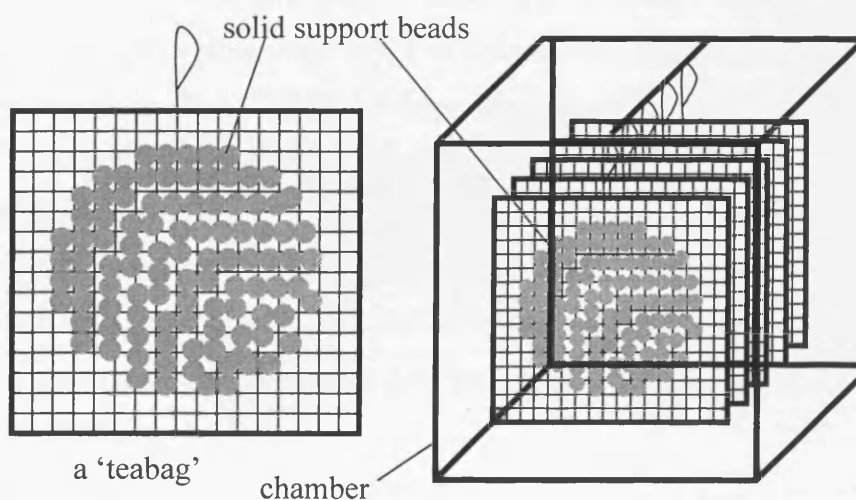
Scheme 44



The Fmoc protected 2-aminobenzophenones **171** were first attached to an acid labile linker (L) then through the linker to the pins (P). After removal of the protecting group it was coupled with a protected amino acid giving **172**. This was followed by the removal of the Fmoc protecting group and cyclisation to give **173**, then by alkylation of the ring nitrogen to introduce R^4 giving **174**. Finally the product **175** was cleaved from the support (Scheme 44).

The teabag method was developed by Houghten¹⁴¹ in 1985 for preparation of arrays of peptides (Figure 26). The beads of the solid support were enclosed in permeable plastic bags as shown below in Figure 26. These were then placed for coupling into a reaction vessel containing the solution of amino acid and the coupling reagent. All operations, including removal of protecting groups, couplings, washings and even cleavages were performed on solid supports enclosed in the bags. This procedure had a significant advantage in that all the bags that needed attachment of the same amino acid, such as alanine, were grouped together and placed in the same reaction vessel, and the coupling could be done in a single operation. The method is still used today by Houghten and his co-workers.

Figure 25: The teabag method developed by Houghten and colleagues to prepare peptides



A new development in polymeric supports is the radiofrequency (RF)-tagged microreactors, where the unique address associated with the tag is traced remotely by a reader.¹⁴² Groups of microreactors can be sorted and grouped at each step of a synthetic sequence, allowing the synthesis of an array of discrete compounds using conventional glassware. RF tagging has been applied to both bead containers and polystyrene-grafted polypropylene tubes, referred to as MicroKansTM and MicroTubesTM, respectively.¹⁴³

The Solid Phase Organic Trapping (SPOT) technique was introduced by Frank¹⁴⁴ and his group was also developed for preparation of peptide arrays. The synthesis is carried out on cellulose paper membranes derivatised to serve as anchors for the first amino acids of the sequences to be prepared. Small droplets of solutions of protected amino acids dissolved in low volatility solvents and coupling reagents are pipetted onto predefined positions of the membrane. The spots thus formed can be considered as reactors where the conversion reactions of the solid phase synthesis takes place. An array of as many as 2000 peptides can be made on an 8 × 12 cm paper sheet. The peptides can be screened on the paper after removing the protecting groups. The method was also used to make mixtures in the spots.

De Witt and co-workers also developed an apparatus for parallel synthesis¹⁴⁵. It was designed for the synthesis of small organic molecules. The solid support was placed into porous tubes immersed in vials containing solutions of reagents which diffused into the tubes. The temperature of the reaction mixtures could be controlled by heating or cooling the reaction block.

1.9.2 Automation

The parallel synthetic methods and reagents described previously opened the way for the parallel synthesis of considerably large arrays of compounds. Ellman and his colleagues, for example, prepared more than 10,000 1,4-benzodiazepine derivatives using the multipin apparatus^{102,146}. A new era and unprecedented flourishing of the field of combinatorial chemistry has begun, together with the appearance of the automatic synthesisers. As a consequence of automation, the parallel synthesis became the most extensively used method in combinatorial chemistry. Application of automatic machines have many advantages, unlike humans, they can work 24 hours a day, and unlike humans they make no errors are two distinct advantages.

1.10 The future

A dramatic increase in interest in using combinatorial techniques and automation has been reported within recent medicinal chemistry literature. This in turn shows a rise in the rate of drug candidate turnover. This interest has materialised due to the work of novel and pioneering peptide work of Geysen¹⁴⁷ and Houghten¹⁴¹. Due to the increased efficiency in preparing combinatorial libraries, this in turn has led to the rise in popularity of research methods using solid phase techniques, and these being applicable to low molecular weight, non-oligomeric, active molecules.

One major setback of parallel, solution phase synthetic methods is the sheer time and effort required to rapidly prepare and purify large numbers of organic molecules.^{148,149} Clearly polymer-supported reagents, catalysts and substrates make a significant impact upon the efficiency of parallel synthesis and will continue to do so.

2. RESULTS AND DISCUSSION

2.1 Aims and objectives

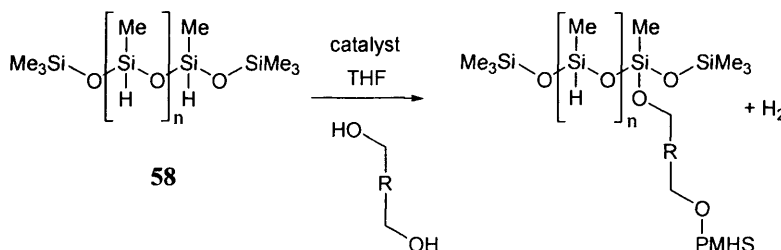
The main aims at the outset of the study are listed below:

- To synthesise both soluble and solid polysiloxane based polymers
- To synthesise scavenger agents/reagents based on these polymeric materials
- To test these scavengers in a variety of scavenging reactions

2.2.1 Crosslinking of PMHS

PMHS in its non-crosslinked form is a colourless, odourless, free flowing liquid. The initial objective of this research was to see if it was possible to crosslink the PMHS using a reagent containing a dialcohol function. This would require the use of an appropriate catalyst as outlined in Scheme 45.

Scheme 45



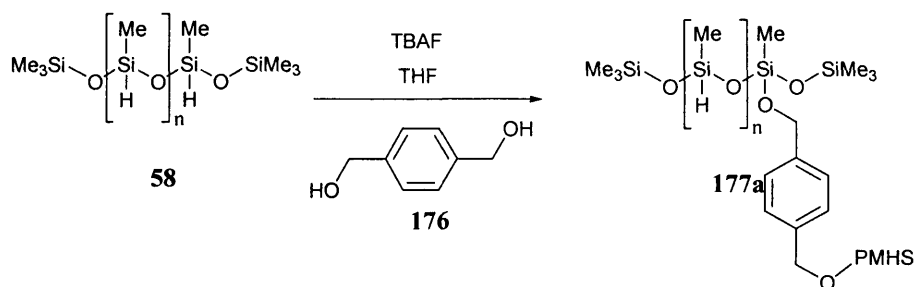
By crosslinking the PMHS chains, it was hoped that a stable solid would be formed. The catalysts first chosen were Wilkinson's catalyst; $[\text{RhCl}(\text{PPh}_3)_3]$ and TBAF. These were chosen as catalysts since they have been shown to promote the reaction of a silane and an alcohol.^{81,150} This reductive coupling is shown above. The reaction has the benefit of giving a quick visual indicator of success by the generation of hydrogen gas. For the resins produced, each resin is labelled as a, b or c and so on in addition to a conventional number. The structure of the polymeric product will clearly depend upon the catalysts and reaction conditions employed and therefore is labelled accordingly.

2.2.2 TBAF catalysis and crosslinking of PMHS

The first investigation was to test the crosslinking of PMHS (58) and 1,4-benzenedimethanol (170) in THF using TBAF as the catalyst (Scheme 46). 1,4-Benzenedimethanol (170) was used as the crosslinker because it was commercially available and the alcohol functions were

at positions 1 and 4 on the aromatic ring, therefore adequately ‘spacing’ the resin when crosslinked. This is based on the analogous crosslinker, 1,4-divinylbenzene, which is the archetypical crosslinker for polystyrene. This would hopefully give a solid resin or gel, however it was not known in what molar ratios the crosslinker should be used and whether it would produce a gel at all.

Scheme 46



This reaction, outlined in Scheme 46, was very exothermic and a lot of effervescence was seen when performing the reaction. On the first few attempts, using 1 and 2 mol% of 1,4-benzenedimethanol (176), a solid resin formed but dissolved in solution after a few hours (Figure 27). Finally, when the percentage of crosslinker was increased to 20 mol%, a stable resin **177a** was formed as a white solid in 95% yield after washing to constant weight using chloroform. The reaction was scaled up and the product resin **177a** was obtained as a white coloured, free flowing solid (20 g, 98%).

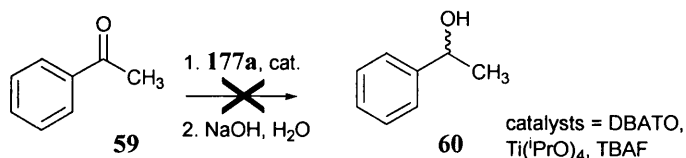
Figure 26

PMHS (mmol)	1,4-benzenedimethanol (mmol)	Equivalents of cross linker	Level of cross linking (%)	Stable resin
5	0.05	0.01	1	x
5	0.10	0.02	2	x
5	1.00	0.2	20	✓
20	4.00	0.2	20	✓

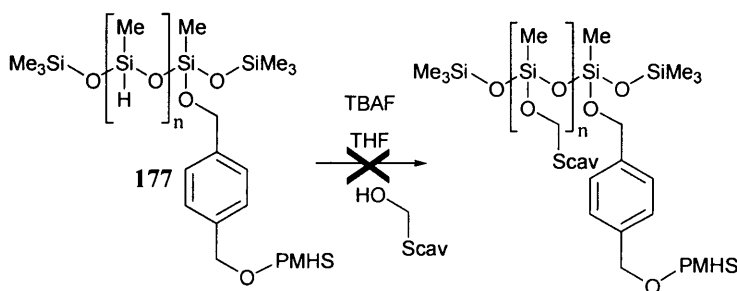
Although the reaction was successfully producing a resin, the percentage crosslinking was kept to a minimum so that the solid could be further functionalised through addition of other molecules containing a scavenger functional group. This is shown in Scheme 48, where *Scav* represents a scavenging molecule. Clearly, some Si-H bonds would be removed during the crosslinking process and the majority would remain for the resin to be further functionalised if possible, as shown in Scheme 48. Alternatively the crosslinked resin **54** could be used as a source of hydrogen to be used as a supported reducing agent. This is also shown below reducing acetophenone **59** to the alcohol **60** (Scheme 47). For monomeric

siloxanes this can be performed in the presence of a catalyst such as TBAF.^{81,82,83} However, in practice this process did not reduce acetophenone **59** to the corresponding alcohol **60**, possible due to inaccessibility of the Si-H functions within the polymer matrix. This means that the process Scheme 48 would not be possible in practice.

Scheme 47



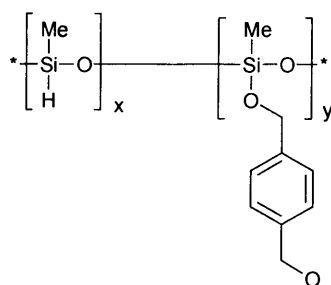
Scheme 48



The elemental composition of the resin **177a** after washing with chloroform (resulting in 5% total mass lost from the resin) was found to be (based on 100 units of crosslinked polymer) C, 26.3, H 5.68%, C₂₄₀H₄₈₀O₁₄₀Si₁₀₀ requires C, 34.1, H, 5.71%.

It is important to illustrate at this stage how the expected figures for the elemental analysis were calculated for the various polymers. The numbers were based on 100 units total of the polymer and the molar ratios of each linker used.

Figure 27



From Figure 27, the effective formula for the polymer is:

$$x [\text{OSiCH}_3] + y [\text{O}_3\text{SiC}_9\text{H}_{11}] = 100 \text{ units}$$

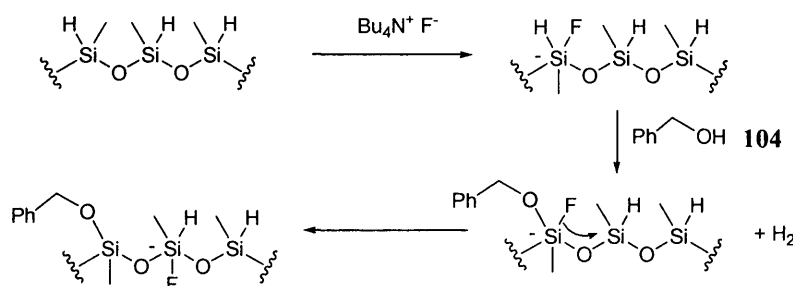
where x is percentage of free silane and y the percentage of crosslinker

If there is another linker present as well as the crosslinker then the formula is adjusted accordingly to account for this change in the structure of the polymer units.

PMHS in its uncrosslinked form [based on 30 repeat units of Me(H)SiO as well as a TMS and TMSO end groups] gives an expected elemental composition of C, 22.0, H, 7.07%. Therefore the carbon content of polymer **177a** has increased, although not to the expected value. This did not reveal a great deal about the structure of the resin. That the TBAF was removing more Si-H functions than was desired, was shown by IR spectroscopy. An IR spectrum of pure PMHS showed a strong absorption [ν_{max} (neat)/ cm^{-1} , 2170 (st)]. An IR spectrum of the crosslinked resin **177a** did not have an absorption in this region and therefore indicated the absence of Si-H groups. The IR spectrum provided conclusive evidence that the TBAF was destroying all of the Si-H of the polysiloxane, possibly due to the presence of water within the catalyst. Therefore, another catalyst was sought which did not destroy all of the Si-H bonds.

Initially, when beginning this project, the mechanism for the TBAF-catalysed silylation of an alcohol was not certain. The mechanism is thought to operate by a phenomenon known as *zipper* catalysis.⁸³ Similar to the mechanism proposed by Lawrence *et al.* for the reduction of acetophenone,⁸³ the fluoride moves down the polysiloxane chain as shown in Scheme 49 effectively zipping along the chain, producing hydrosiliconate ions as it goes. In the example below this is demonstrated with benzyl alcohol (**104**). The hydrosiliconate species are the ones that are thought to react with the alcohol to produce the new Si-O bond.

Scheme 49

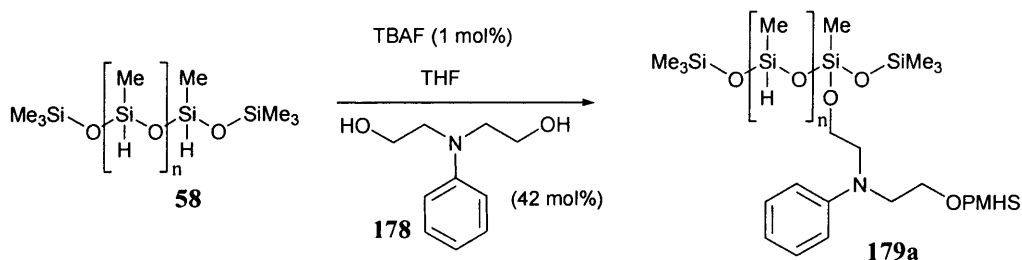


Since the resin **177a** no longer contained Si-H functionality necessary for addition of a scavenging molecule, we decided to attempt to include the scavenging molecule as part of the crosslinking agent. This was because of two things: firstly the TBAF was destroying all of the Si-H bonds and therefore not allowing further derivatisation of the resin and secondly by using the scavenging molecule as a crosslinker, a separate crosslinker would not be required. Different scavengers were exemplified by using different amine groups then these were used to remove benzyl bromide from a standard mixture as a test for their electrophile

scavenging ability. It was not known prior to attempting the syntheses which scavenger would perform well as a nucleophilic scavenger and which would behave poorly.

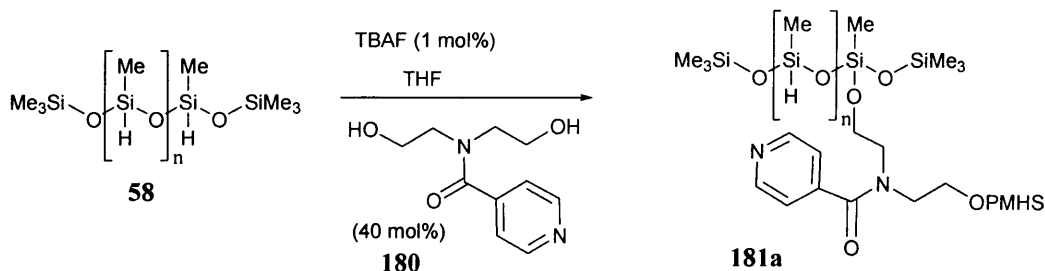
The first of these polymers to be prepared was the phenyldiethanolamine resin **179a**, the synthesis of which is shown in Scheme 50. The commercially available diol **178** was reacted with PMHS (**58**) using TBAF as catalyst. The diol was used only at 42 mol% (giving an 84 mol% equivalent of hydroxyl groups) since some silane was expected to react with traces of moisture.

Scheme 50



The phenyldiethanolamine linker **178**, was attached to PMHS **58** and then the solvent was removed under vacuum to give **179a** as a white solid. This was washed to constant weight (97% yield) and then submitted for elemental analysis. This indicated that the crosslinker had been incorporated into the resin (Found C, 30.9, H, 7.54, N, 1.80 C₅₂₀H₉₀₄N₄₂O₁₈₄Si₁₀₀ requires C, 46.3, H, 6.71, N, 4.37%), however, the level of incorporation of the scavenger molecule was low. The loading was 1.3 mmol/g. The expected loading was 3.1 mmol/g. It was possible that the crosslinker molecule was either not reactive enough or was too hindered for successful incorporation into the resin. Although being stable it was later found that this resin (**179a**) was ineffective as a nucleophilic scavenger for benzyl bromide (**114**), and hence it was not further developed. In terms of scavengers, anilines are not especially effective choices as the lone pair of the nitrogen required to attack electrophilic substrates, is delocalised into the phenyl ring.

Scheme 51

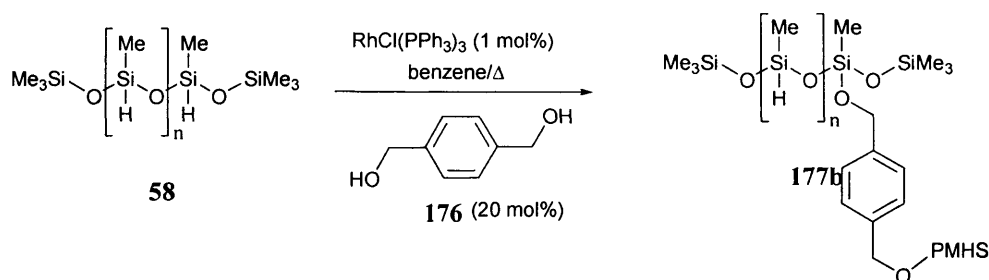


The same approach was used to make the isonicotinamide resin **181a** is shown in scheme 51. In the first instance, the isonicotinamide crosslinker **180** (used because it was readily available) was reacted with PMHS using TBAF as the catalyst. This was a straight forward

2.2.3 Wilkinson's catalyst and crosslinking of PMHS

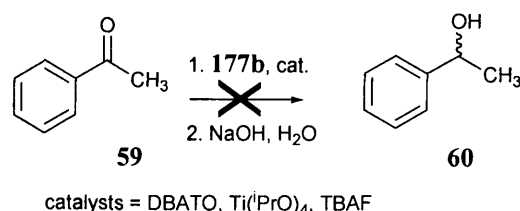
Wilkinson's catalyst was the next catalyst of choice. Through the work of Boudjouk *et al.*¹⁵⁰ it was known that the silylation of alcohols could take place in the presence of this catalyst. However, whether this reaction would produce the resins in the desired fashion was another matter. Boudjouk and co-workers used crown ether type molecules and hence although the reaction conditions were the same, the molecules to be used were different from those cited in the literature. It was hoped that a stable resin would be obtained containing the majority of Si-H bonds present, even after the crosslinking reaction. This was to allow further use of the resin as a supported reducing agent and if necessary to be further functionalised. With the use of Wilkinson's catalyst, completely anhydrous conditions had to be used. Crosslinked resin **177b** was obtained by using PMHS (**58**) and 1,4-benzenedimethanol (**176**) as shown below. The crosslinking reaction was performed in the presence of Wilkinson's catalyst (Scheme 53).

Scheme 53



Analysis of **177b** using IR spectroscopy revealed that not all of the Si-H functions had been destroyed and a peak at ν_{max} (nujol)/ cm^{-1} , 2168 (st) was observed. Thus it appeared that the polymer **177b** could be utilised as so desired as a supported reducing agent for example as in reaction scheme 54 below to reduce acetophenone **59** to the corresponding alcohol **60**. Elemental analysis of **177b** gave the following values: found C, 22.3, H, 6.88%, ($\text{C}_{260}\text{H}_{540}\text{O}_{140}\text{Si}_{100}$ requires C, 35.8, H, 6.21%). However, unlike the TBAF polymer **177a**, resin **177b** has available Si-H bonds according to the IR spectrum.

Scheme 54

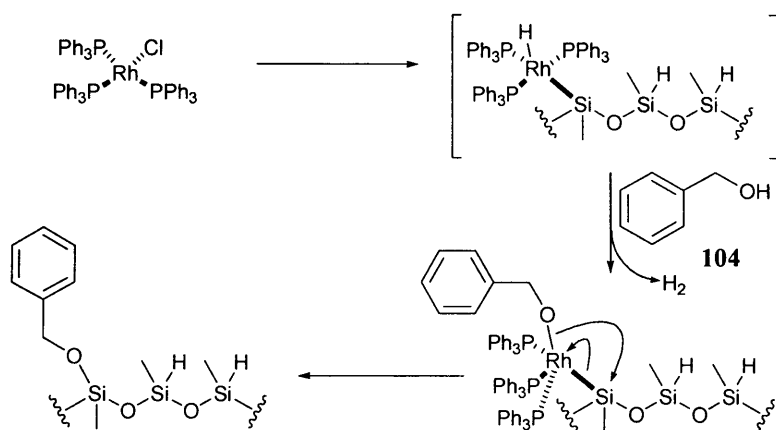


One problem with this reaction was that anhydrous benzene was hazardous. Another was that on consecutive attempts, a resin was not obtained, hence the reaction was also run in

anhydrous THF. Using THF as solvent improved the reproducibility of the reaction and it also produced a solid more reliably. However, in spite of the reaction in Scheme 53 successfully producing a resin, and this resin having Si-H bonds present, as seen *via* IR spectroscopy, these silane functions could not be successfully utilised in the reaction to reduce acetophenone (Scheme 54), when DBATO, $\text{Ti}(\text{iPrO})_4$ or TBAF were used as catalysts. The failure of these reactions can possibly be attributed to the hindered nature of the silane groups, buried within the polymer matrix, that perhaps are not accessible.

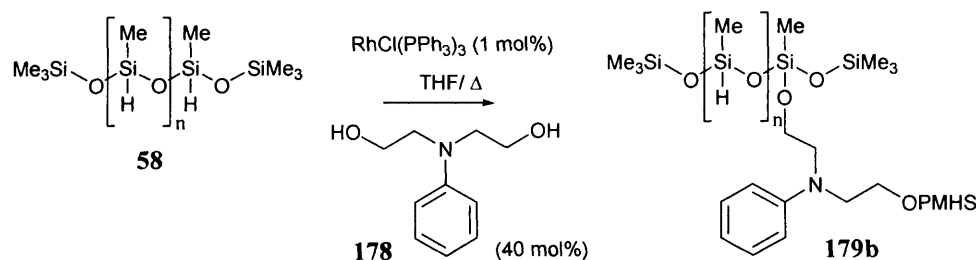
The reaction to form the resin is thought to proceed *via* the mechanism in Scheme 55 shown below. The first step is oxidative addition of the silane to Wilkinson's catalyst, followed by deprotonation of the benzyl alcohol (**104**). The intermediate then undergoes reductive elimination to give the new silyl ether.

Scheme 55



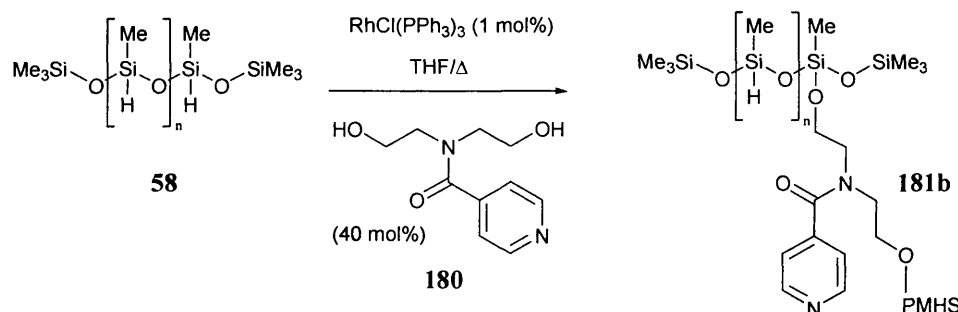
Similar to the synthesis of **179a**, the synthesis of another resin was attempted using a crosslinking agent containing a scavenger type molecule. This was performed using phenyldiethanolamine **178** as the crosslinker, PMHS **58** and Wilkinson's catalyst, and gave the phenyldiethanolamine resin **179b** (98% yield) as an orange solid (Scheme 56). Elemental analysis gave the following values: C, 32.1, H, 7.44, N, 1.77%, ($\text{C}_{520}\text{H}_{904}\text{N}_{42}\text{O}_{184}\text{Si}_{100}$ requires C, 46.3, H, 6.73, N, 4.37%). This gives a loading of 1.3 mmol/g. The nitrogen content was seen to be low. This indicates very little linker **178** is incorporated into the resin. The reasons for this may be the linker is too hindered sterically for the catalyst to facilitate its attachment or the diol is simply not reactive enough. The aniline may also be interfering with the Rh-catalysed cross-linking reaction itself.

Scheme 56



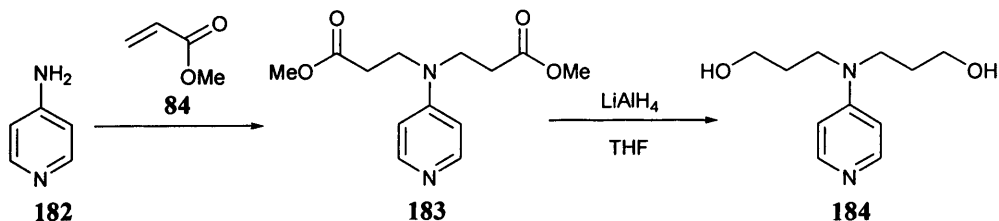
The crosslinker molecule, isonicotinamide **180** was used with Wilkinson's catalyst to give an isonicotinamide resin **181b** as shown in Scheme 57. The resin was washed to constant weight with the resin losing 6% mass after exposure to chloroform (giving 94% yield). The results from elemental analysis are C, 30.3, H, 7.12, N, 3.01% ($\text{C}_{460}\text{H}_{640}\text{N}_{80}\text{O}_{260}\text{Si}_{100}$ requires C, 38.8, H, 4.49, N, 7.87%). The loading was therefore 2.2 mmol/g. The expected loading was 3.1 mmol/g. The nitrogen composition of the resin was lower than expected possibly because it did not attach to the siloxane successfully. The resin **181b** was not a scavenger for benzyl bromide (like **181a**) and hence it was not developed further.

Scheme 57



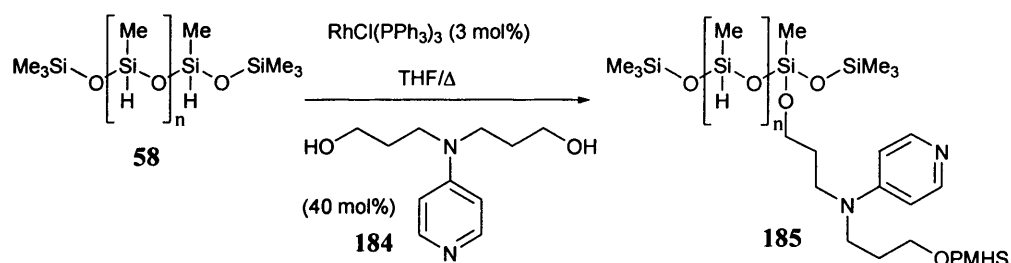
We then decided to attempt the synthesis of a scavenger having greater nucleophilic character. This could be achieved if DMAP could be incorporated into a resin. The DMAP crosslinker **184** was used for this reason and is shown in Scheme 58. The synthesis of the DMAP dialcohol species **184**, was fairly straightforward, since the 4-aminopyridine (**182**) and methyl acrylate **84** are commercially available. These were refluxed together to effect a double Michael addition to give the diester **183**, in 96% yield which needed no further purification. The diester **183** was then reduced using LiAlH_4 .¹⁵⁸ Following quenching of the reaction mixture and work up, the final pyridine propane-diol **184** was obtained in high yield (95%) and was sufficiently pure that purification was not necessary prior to attaching it to the PMHS **58**.

Scheme 58



The synthesis of the polymer **185**, uses the diol **184**. The components (**184** and PMHS) were refluxed in the presence of Wilkinson's catalyst with the anticipation that it would form supported DMAP resin **185**. Unfortunately the reaction (shown in scheme 59) formed a very thick mass that took a long time to dry and form a solid resin.

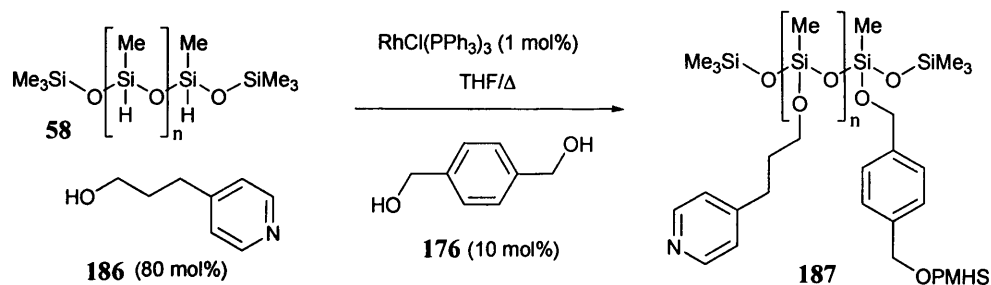
Scheme 59



Another problem was encountered during the washing phase of the resin **185**. When it was washed to constant weight, the resin lost large amounts of mass indicating instability and thus breakdown of the resin was likely to be inevitable during a scavenging reaction. Thus it was not used and another DMAP or pyridyl resin, with greater stability, was sought.

The synthesis of pyridine resin **187** was attempted using pyridine propanol **186** and the crosslinker **176**. It was not known whether this reaction would give a resin. It was performed essentially as a test reaction to check incorporation of pyridine into the resin. The reaction was catalysed by Wilkinson's catalyst and carried out under reflux conditions (Scheme 60).

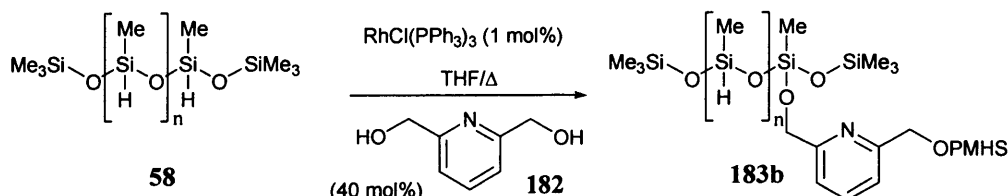
Scheme 60



The use of 4-pyridinepropanol **186** did not give a solid. On consecutive attempts, a solid was not obtained using $\text{RhCl}(\text{PPh}_3)_3$ as the catalyst, indicating the absence of a crosslinked resin. This is a problem using Wilkinson's catalyst. For this catalyst, if reagents were varied

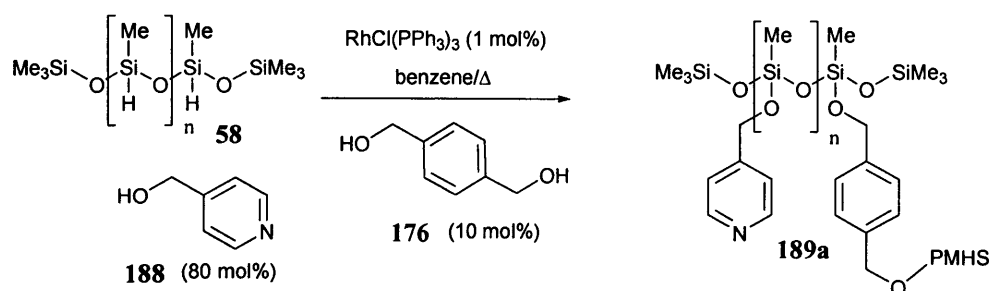
the reaction may not work successfully. Two possible explanations for this was the presence of the propyl chain on the pyridine molecule hindered its attachment to the PMHS, or that the pyridine was affecting the reactivity of the catalyst.

Scheme 61



Again the crosslinker was varied, this time using 2,6-pyridinedimethanol (**182**), hoping that this could be used as an effective scavenger as shown in Scheme 61. After work-up of the reaction mixture and drying under vacuum, the obtained solid (**183b**) was washed to constant weight using chloroform, resulting in a loss of 4% total mass of the resin (95% yield). The resin was submitted for microanalysis and this found C, 25.7, H, 6.54, N, 0.83% $\text{C}_{436}\text{H}_{568}\text{N}_{56}\text{O}_{212}\text{Si}_{100}$ (requires C, 41.0, H, 4.45, N, 6.14%). The loading was therefore 0.6 mmol/g. The expected loading was 4.38 mmol/g. The nitrogen-containing component had been incorporated into the resin, but the level was not as high as required. This could be due to **182** being a hindered molecule and was therefore not attached to the backbone resulting in a low nitrogen measurement. As it was not active towards benzyl bromide and hence was ineffective for use as a nucleophilic scavenger, this resin was not developed further and therefore was not tested subsequently. It was therefore decided to synthesise a pyridine resin where the nitrogen would be more “accessible” as a scavenger of substrates. This was achieved using commercially available 4-pyridinemethanol (**188**). The reaction was performed in benzene and catalysed by Wilkinson’s catalyst. The pyridine linker **188** was attached to PMHS **58** and the siloxane crosslinked by 1,4-benzenedimethanol (**176**) as shown in Scheme 62. An orange coloured solid (**189a**) was obtained.

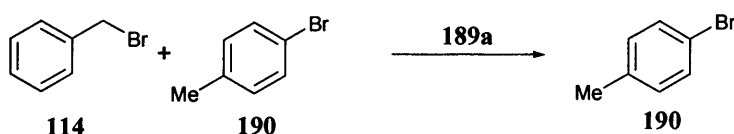
Scheme 62



After washing to constant weight using chloroform the resin **189a** was obtained as an orange coloured gel in 95% yield. Elemental analysis gave the following values: C, 31.9, H, 4.99, N, 3.69% ($\text{C}_{740}\text{H}_{940}\text{N}_{80}\text{O}_{300}\text{Si}_{100}$ requires C, 47.9, H, 5.07, N, 6.04%). This gave a loading of

2.6 mmol/g. The expected loading was 4.3 mmol/g. Nevertheless this was sufficient for further investigation. This resin was used in a scavenging reaction to scavenge for benzyl bromide (**114**). This was performed in the presence of a standard, in this case bromotoluene **190** as shown in scheme 63. The resin **189a** (0.5 g) (1.3 mmol) was used to remove the alkyl halide from 2 ml of the standard scavenging solution (1 mmol of benzyl bromide).

Scheme 63



However, despite working very successfully to scavenge for benzyl bromide (99% efficiency) it was difficult to reproduce the synthesis and so a more robust method was sought which would give a resin in every instance. The scavenging reaction is illustrated by the NMR spectra shown in Figures 28 and 29. The ^1H NMR spectrum of the standard mixture of benzyl bromide (**114**) and *p*-bromotoluene (**190**) is shown in Figure 28. The key signals used for analysis of the reaction are the benzyl methylene group at δ 4.6 and the tolyl methyl group at δ 2.4 ppm. After the scavenging process it can be seen, as illustrated in Figure 29 that the methylene peak of benzyl bromide (**114**) has disappeared indicating that it has been successfully removed by the scavenger **189a**, leaving the *p*-bromotoluene **190** in solution.

Figure 28: The ^1H NMR spectrum of the standard mixture of benzyl bromide (**114**) and *p*-bromotoluene (**190**)

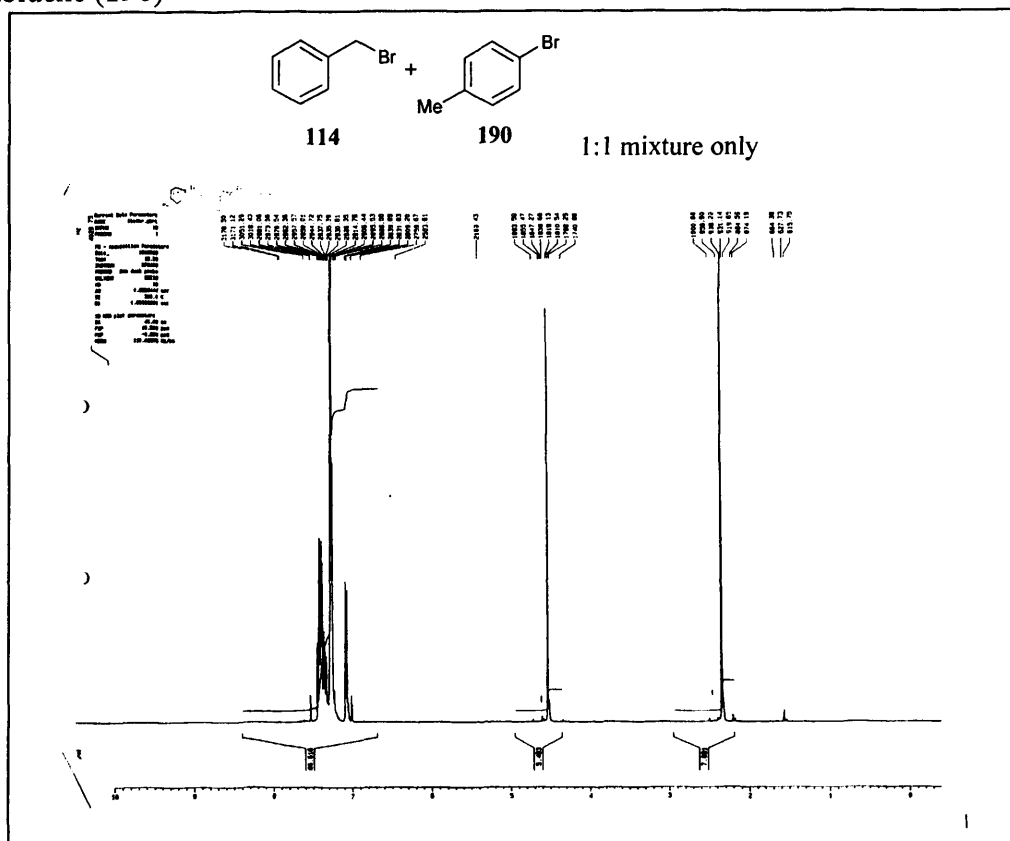
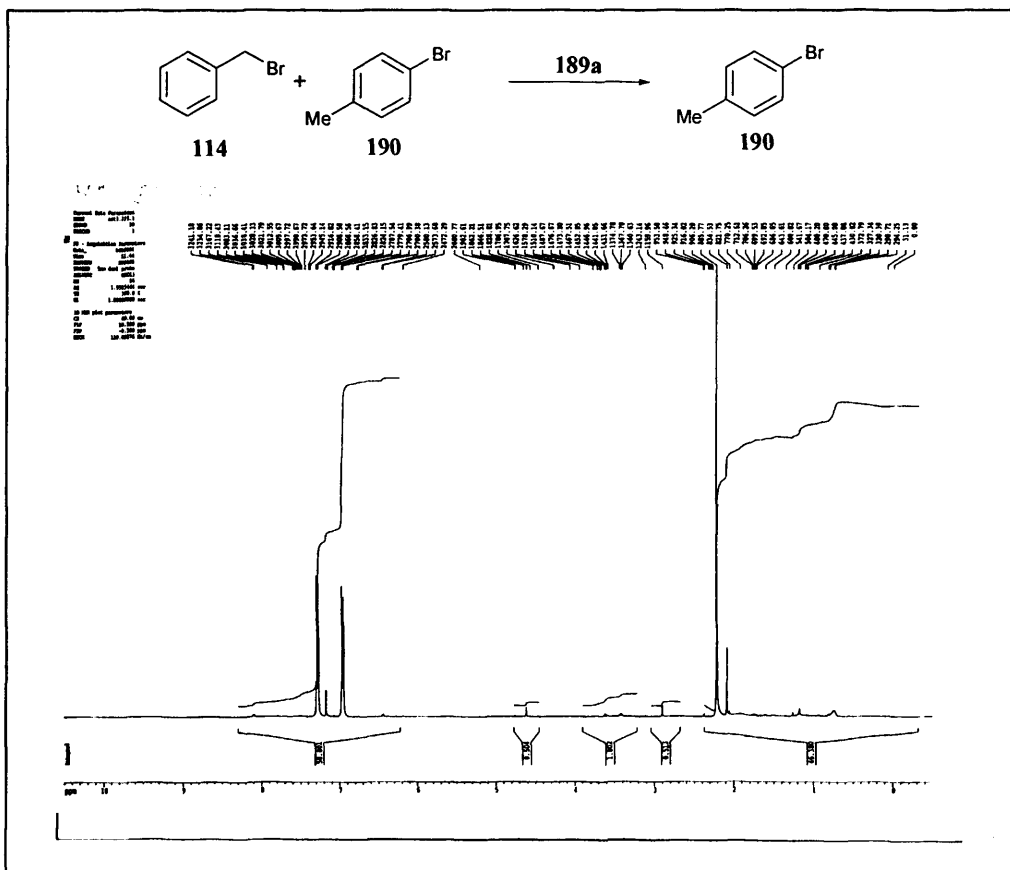


Figure 29: The ^1H NMR spectrum of the mixture after shaking with **189a**

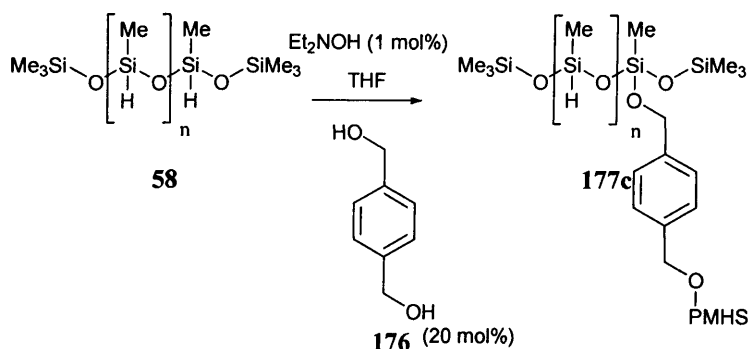


The Wilkinson's catalyst was proving expensive and not all the resulting resins were of a satisfactory standard. Scale up of the reaction would prove a problem and so a different catalyst was required for resin synthesis. These reactions were not scaled up due to the expense of the Wilkinson's catalyst (Aldrich £37 for 1 g) and so a different, cheaper catalyst was needed.

2.2.4 Hydroxylamine catalysis and crosslinking of PMHS

Another catalyst which was used for resin synthesis was Et_2NOH ¹⁵¹ which was not only easy to handle being a liquid, but was also cheap (Aldrich £10.10, 100 ml). Diethylhydroxylamine was shown by Bassindale *et. al.*¹⁵¹ to catalyse the coupling reaction of a silanol and a silane. It was therefore hoped it would catalyse the reaction between PMHS **58** and the crosslinker **176**. After addition of the diethylhydroxylamine catalyst (30 μl , 1 mol%) to the reaction mixture (PMHS **58** and THF), gas was seen to be evolved indicating that the reaction was a success (Scheme 64). The product was obtained as a white solid **177c** in 97% yield after washing to constant weight. The solid was similar in appearance to that obtained from the related TBAF-catalysed reaction. The IR spectrum also indicated that not all of the Si-H bonds had been removed during the crosslinking process by the presence of an identical peak to that seen in the spectrum of neat PMHS [ν_{max} (nujol)/ cm^{-1} , 2168 (st)].

Scheme 64

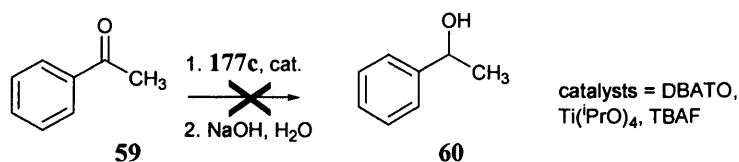


It is not known exactly how *N,N*-diethylhydroxylamine catalyses the reaction, only that, as well as being a very cheap catalyst and easily handled, the process was reproducible enabling scale up of the reaction without major pitfalls. The mechanism of action of this catalyst is thought to involve a phenomenon known as the α -effect as discussed later.¹⁵²

Although in theory the crosslinked PMHS resins could have been used as a supported reducing agent, in practice this was not the case. Possibly this was due to the difficulty in

accessing the available hydrogen within the polymer matrix. The reduction of acetophenone (**59**) was attempted using several catalysts, as shown in Scheme 65, but without success.

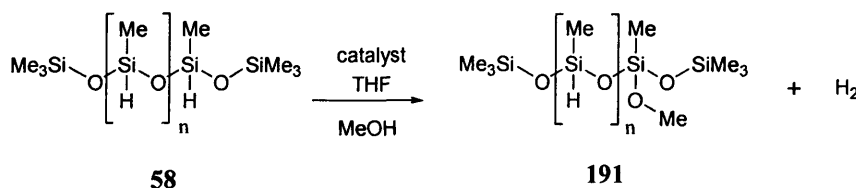
Scheme 65



2.2.5 Hydroxylamine catalysis and the α -effect

The hydroxylamine is thought to act as a nucleophilic catalyst. To test this idea a range of catalysts were studied. Some were expected to be good nucleophiles due to the action of the α -effect. This was investigated using gas emission with PMHS (**58**) and methanol as shown in Scheme 66 varying the catalyst to investigate the volume of gas emitted. This would produce the uncrosslinked siloxane **191** and hydrogen gas which could be measured using a manometer.

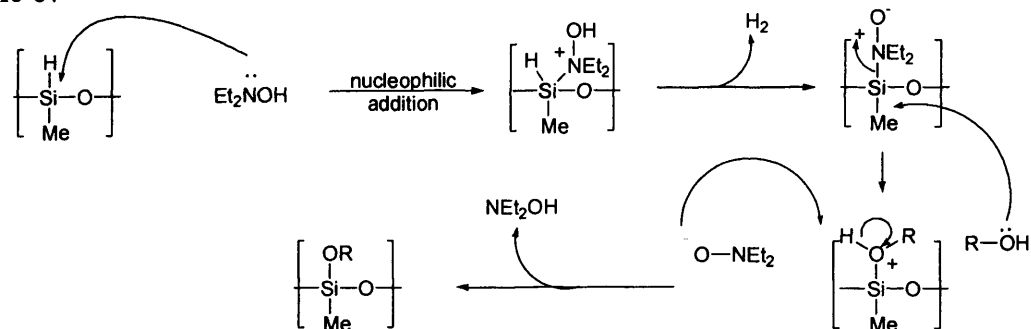
Scheme 66



The α -effect, in basic terms, is when the nucleophilicity of one lone pair is enhanced by the close proximity of another lone pair or 'X' substituent. If the orbital containing the electrons on the nucleophilic atom overlaps with the orbital of the lone pair of the X-substituent, then the energy of the HOMO is raised. In the case of diethylhydroxylamine, the nucleophilicity of the lone pair of the nitrogen group is enhanced significantly by the presence of the lone pairs of the oxygen next to it.

As can be seen in Scheme 67 below, the catalyst first attacks the PMHS *via* the lone pair of the nitrogen leading to addition of the nucleophile to the PMHS. This intermediate is then attacked by a molecule of the alcohol causing the hydroxylamine to be eliminated. The catalyst is regenerated in the last step by causing deprotonation and attaching the alcohol to the PMHS.

Scheme 67



The results of this investigation are shown below in the Figure 30. As can be seen from the different commercially available catalysts tested, in comparison to Et_2NOH (**82**), the catalyst that comes to close in terms of gas evolution is the *N*-Boc protected hydroxylamine **192**. The next closest is the piperidin-1-ol (**198**) which is not surprising as it is very similar in structure to hydroxylamine **82**. The hydroxylamine possessing a benzoyl moiety **197** leads to a small amount of gas evolution with respect to its Boc-protected counterpart due to the fact that the lone pair on the X-substituent (where $\text{X} = \text{O}$) is less activated because of the carbonyl function opposite. Slightly higher in gas evolution is hydrazide **199** although the X substituent is not as effective ($\text{X}=\text{N}$) due to it being flanked by a carbonyl group.

Figure 30: PMHS used was 8.33 mmol giving an expected volume of gas evolved to be 186 ml

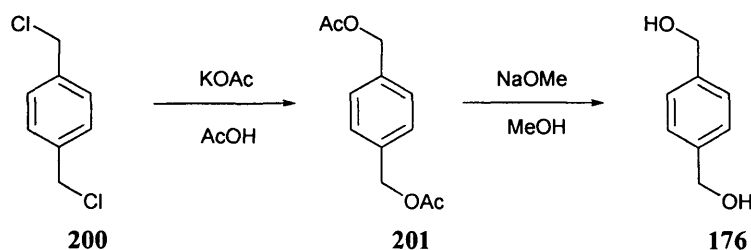
Catalyst	Volume of gas evolved (ml)
 192	160
 193	0
 82	190
 194	0
 195	0
 196	0
 197	35
 198	150
 199	80

Therefore, we can see that wherever there is a donating group present (the X-substituent), the volume of gas evolution increases and wherever the donating group is either removed or blocked from being able to donate by delocalisation effects, for example, the volume of gas evolved decreases. The hydrochloride salts **193**, **194**, **195** and **196** did not produce any gas. It was attempted to use these as their free bases, but they were too volatile to prepare.

2.2.6 Synthesis of 1,4-benzenedimethanol (**176**)

The crosslinking agent used, 1,4-benzenedimethanol (**176**) is a costly reagent from commercial sources (Aldrich £85 for 50 g). Hence it was decided to synthesise the crosslinker in house. We chose to synthesise the diol from the α,α' -dichloro-*p*-xylene (**200**) shown in scheme 68.⁹²

Scheme 68



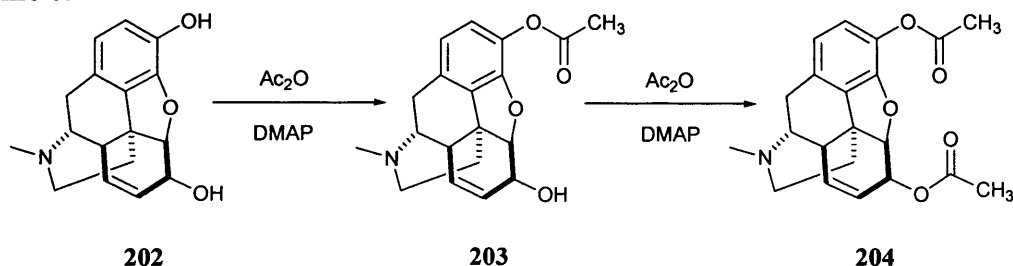
The ester **201** was formed from **200**, using potassium acetate. The intermediate ester was not isolated and hydrolysis of **201** gave 1,4-benzenedimethanol (**176**) in 93% yield as a white solid. This procedure was used because the starting material, the dichloride **200**, was purchased very cheaply (Aldrich £25 for 50 g) and the reaction could be scaled up with no problems.

2.3 DMAP and Pyridine resins

Polymers containing pyridine moieties have been widely studied in the preparation of polymer reagents and catalysts for general use in organic applications.^{11,17,30,38,39} Some of these have found commercial applications due to the availability of crosslinked poly(4-vinylpyridine) in various bead forms. Similarly, the emergence of commercial sources for the heterocyclic bead polymers such as poly(benzimidazole) suggests their application as simple heterogeneous hydrogenation catalysts or in other types of supported chemistry. Significant potential for a different kind of catalysis has recently drawn much attention to the possibilities of polymers containing 4-(dialkylamino)pyridine heterocycles as supported functional groups.¹⁵³

(Dimethylamino)pyridine (DMAP), is a material that has found numerous important applications since it became commercially available. It is an excellent catalyst for a variety of nucleophilic addition reactions, being most notably used in difficult acylations and silylations of tertiary and other hindered hydroxyls. DMAP is of particular interest to the research chemist and to the pharmaceutical and fine chemicals industry as its presence increases conversion yields while reducing side product formation in such otherwise slow reactions. This is the case shown below with conversion of morphine to heroin shown in Scheme 69. The reaction goes from morphine (**202**) through 3-acetylmorphine (**203**) to 3,6-diacetylmorphine (**204**) (heroin). The acetylation of the 3-hydroxy (phenolic) group of morphine which leads to formation of 3-monoacetylmorphine is a relatively fast process, while the second acetylation of the 6-hydroxy group which leads to heroin is a slower process.¹⁵⁴

Scheme 69



Current drawbacks to this soluble catalyst include its relatively high cost (Aldrich 25 g, £19.90) and the additional treatment that may be needed to remove it during product purification.

In contrast, a polymer bound catalyst possessing an activity comparable to DMAP would at once be easier to separate from reaction media and repurified for later recycling, which may favourably counterbalance the somewhat higher initial cost of such a material.¹⁵⁵

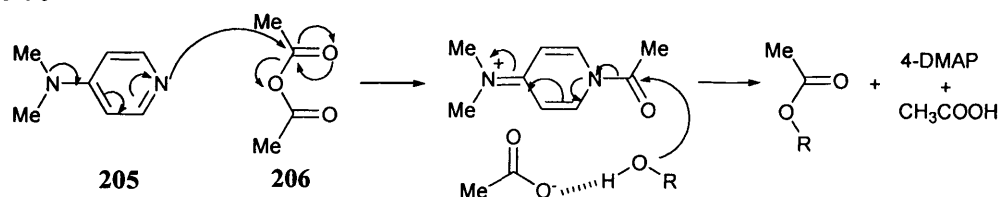
Heterocycles which contain an imine unit as part of their ring structure, in this case pyridine, do not utilise the nitrogen lone pair in their aromatic π -system and therefore it is available for donation to electrophiles, just as in any simpler amine. Pyridine and its simple derivatives are stable and relatively unreactive liquids, with strong penetrating odours that are unpleasant to some people. They are much used as solvents and bases, especially pyridine itself, in reactions such as *N*- and *O*-tosylation and -acylation. Pyridine and the picolines are completely miscible with water. Pyridine and its simple alkyl derivatives were for a long time produced by isolation from coal tar, in which they occur in quantity. In recent years this source has been displaced by synthetic processes: pyridine itself can be

produced on a commercial scale in 60-70% yields by the gas-phase high-temperature interaction of crotonaldehyde, formaldehyde, steam, air and ammonia over a silica-alumina catalyst.¹⁵⁶ A problem with pyridine is its toxicity.^{154,156} Exposure can render males infertile through long term use. A solid supported alternative is therefore attractive for elimination of long term health effects.

2.3.1 Synthesis of a DMAP resin

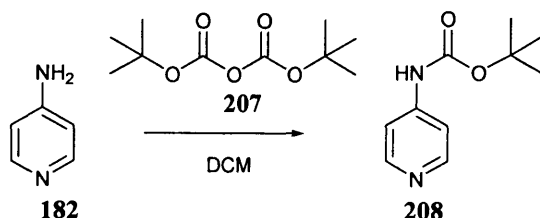
The effectiveness of DMAP (**205**) as a catalyst is due to the delocalisation of the NMe₂ lone pair. As shown in the example below in scheme 70, the presence of the second lone pair of the 4-position nitrogen influences the ring nitrogen. This is the reason why it is an effective scavenger whether or not attached to a solid support. The example below shows a ‘catch and release’ mechanism applicable to how DMAP functions as a scavenger. DMAP (**205**) attacks the acetic anhydride (**206**) resulting in the acylated DMAP intermediate. This is then attacked by an alcohol which causes cleavage of the acyl moiety from the DMAP forming the ester and acetic acid as a by-product. The DMAP is regenerated but has to be removed by chromatographic methods.

Scheme 70



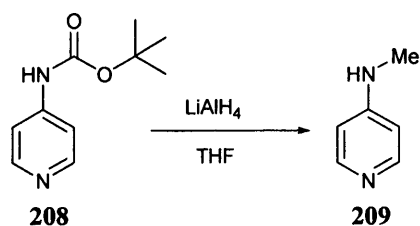
When the appropriate pathway was developed, the synthesis of a siloxane-bound DMAP was fairly straightforward, being produced using a linear 5 step synthetic pathway.^{157,158}

Scheme 71



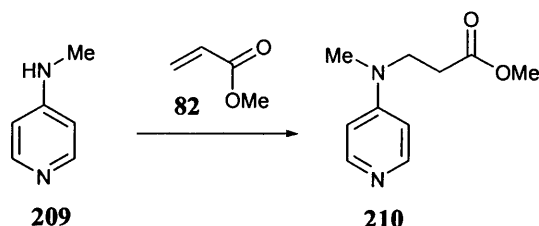
Initially, 4-aminopyridine (**182**) was Boc-protected using the anhydride **207** using the literature method developed by Spivey *et. al.* shown in Scheme 71.¹⁵⁹ This reaction was performed in DCM and gave the final product **208** as a white solid in 99% yield. The *tert*-butyl group of the Boc function was seen in the ¹H NMR spectrum as a large singlet (δ 1.50 ppm) integrating to the nine hydrogen atoms.

Scheme 72



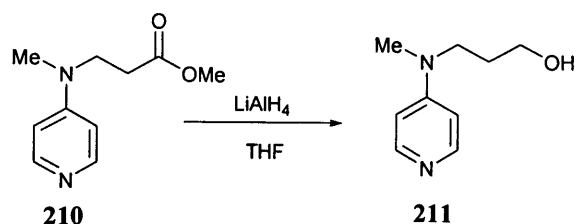
The Boc protected aminopyridine **208** was then reduced using LiAlH_4 to give the *N*-methylpyridine (**209**) as shown in Scheme 72. This is again a straightforward reaction though it was necessary to keep the reaction mixture cold during the addition of the LiAlH_4 as the reaction is highly exothermic and lead to a great deal of effervescence when the reducing agent was added too rapidly. After the addition, the reaction mixture was refluxed for 4 h, to enable complete reduction of the *Boc* group to a methyl moiety, work up of the reaction mixture gave the final product 4-*N*-methylaminopyridine (**209**) as a white solid in 98% yield. The transformation could clearly be seen in the ^1H NMR spectrum as a 3H singlet (δ 2.85 ppm) corresponding to the newly formed methyl group.

Scheme 73



Following the reduction step, *N*-methylaminopyridine (**209**) was used in an ester synthesis reaction using methyl acrylate (**82**) as the solvent which was therefore is present in excess during the reaction shown in Scheme 73.¹⁵⁸ The *N*-methylaminopyridine undergoes a Michael addition on heating to reflux. After removal of the excess methyl acrylate (**82**), under vacuum, aminoester **210** is obtained as an orange oil in 98% yield and did not require further purification before carrying it through to the next step. This could be seen in the ^1H NMR spectrum [δ 3.62 (2H, t, J = 6.3, CH_2), 3.60 (3H, s, OMe), 2.53 (2H, t, J = 6.3 Hz, CH_2O)] indicating the presence of the ester group.

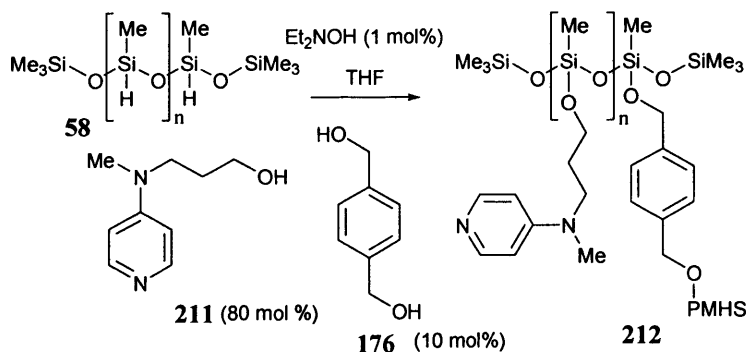
Scheme 74



Subsequently a reduction was performed on methyl 3-*N*-(methyl-4-aminopyridyl)propionate (**210**) using lithium aluminium hydride, with THF as solvent shown in scheme 74. This

presented a straight forward synthesis and work up, affording the final alcohol product **211** as an orange oil in 94% yield. The reduction was evident in the ^1H NMR spectrum [δ 1.83 (2H, quintet, $J = 7.1$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2$)]. The product did not require further purification before being used in the next step of the synthesis of the DMAP resin.

Scheme 75



The last step was to attach this alcohol **211** to the PMHS (**58**) and crosslinking it using 1,4-benzenedimethanol (**176**) as shown in Scheme 75. The reaction was catalysed using Et_2NOH and gave an orange coloured gel. The solvent was evaporated to give the polymer **212** which was washed to constant weight using chloroform in a filter syringe to give the final product in 95% yield. By elemental analysis it could be seen that the DMAP alcohol **211** had been incorporated into the resin **212**. Elemental analysis gave the following values: C, 54.7, H, 8.43, N, 10.9% ($\text{C}_{980}\text{H}_{1500}\text{N}_{160}\text{O}_{220}\text{Si}_{100}$ requires C, 53.9, H, 6.87, N, 10.3%). The experimental values are clearly close to 100% incorporation of the linker into the resin matrix. This gave a loading of 3.8 mmol/g. We now needed to see if it worked effectively as a scavenger.

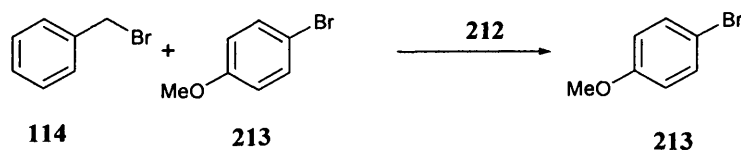
To function as an effective scavenger, the polymer must be stable to the reaction conditions. In other words, there is no point in taking a resin and attempting to scavenge from a *clean* mixture if more impurities are added from the resin. Secondly, but just as important, the resin itself has to be reactive towards the desired substrate.

The syntheses of the resins using diethylhydroxylamine proved to be reproducible. It was also a cheap starting material and hence scale up would not cause problems. The final DMAP resin **212** was also stable to washing stability testing. It was washed several times using chloroform until the resin weight became stable. It was then washed in a 'swell and shrink' wash sequence using THF, DCM and Et_2O in that order to flush out any impurities. These washings were dried and then weighed (5% mass lost w/w) and after the resin mass became constant it was carried through into scavenger testing.

2.3.2 Scavenger testing using DMAP resin 212

Primarily the resin was tested using a standard solution of benzyl bromide (**114**) and 4-bromoanisole (**212**). When successful this would lead to removal of the bromide **114** with the bromoanisole **213** remaining in solution (Scheme 76).

Scheme 76



The level of scavenging was measured in terms of percentage efficiency. Effectively this is a ratio of the level of substrate scavenged and a standard within the ¹H NMR spectra.

$$\text{Efficiency (\%)} = \left\{ 1 - \frac{(\text{Amount substrate remaining})}{(\text{Amount of standard})} \right\} \times 100$$

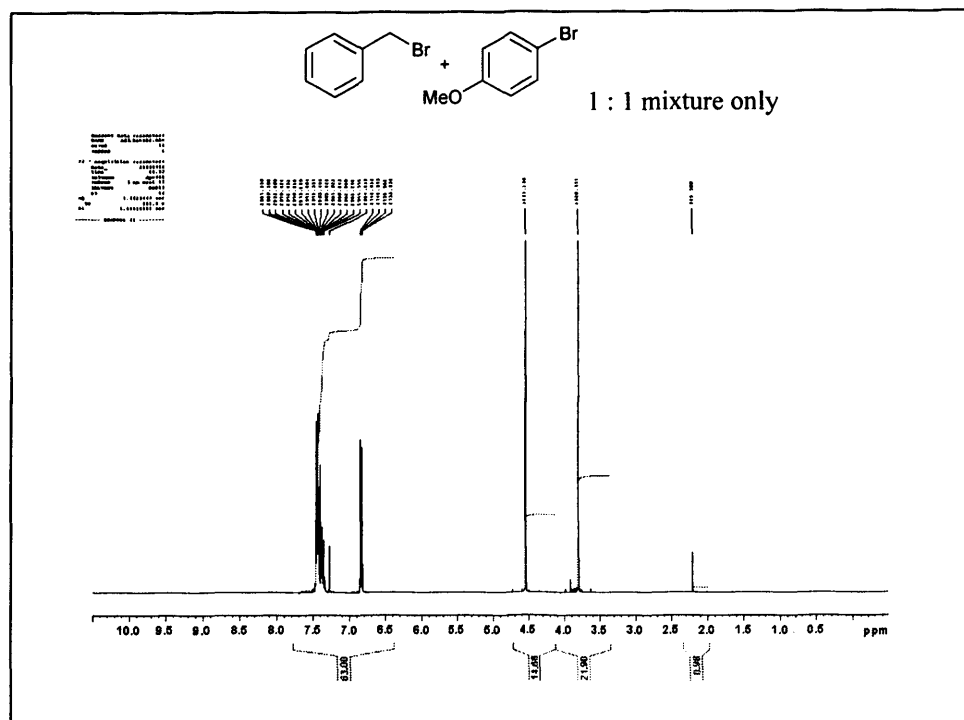
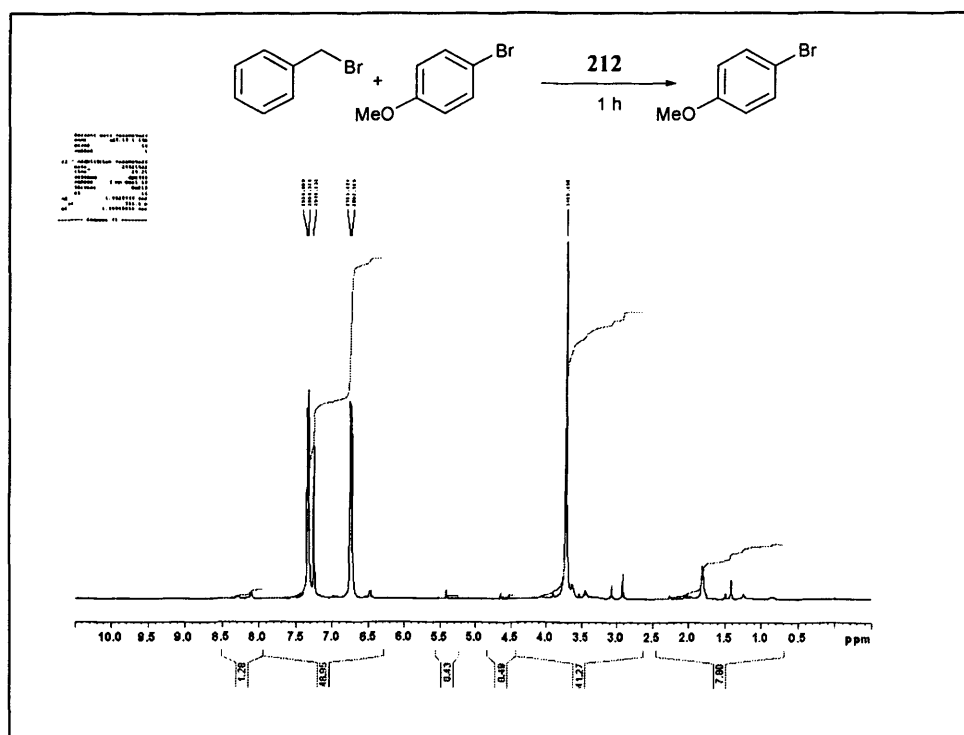
The effect of reaction time upon the scavenging experiments was investigated by carrying out a 'time-course' experiment. Small aliquots of a reaction mixture of resin **212** and the standard mixture of **114** and **213** were taken at different times and analysed by ¹H NMR. This was performed to check stability of the resin after various times. The results are shown in Figure 31.

Figure 31 The effects of time upon the scavenging of benzyl bromide by resin **212**

Time (h)	Efficiency (%)	DMAP present (%)
1	98	0
2	99	20
5	96	35
10	97	60
16	94	80
24	91	100

*Solvent used was THF; 0.5 g of resin **212** (1.9 mmol) was used in 2 ml standard scavenging solution (1 mmol of benzyl bromide)

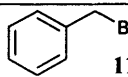
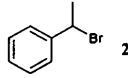
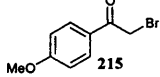

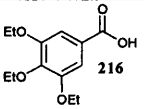
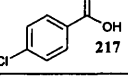
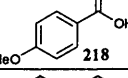
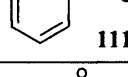
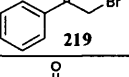
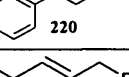
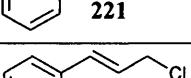
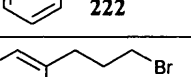
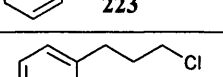
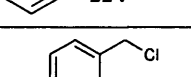
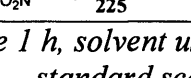
As an example of the scavenging efficiency of the DMAP resin **212**, the ¹H NMR spectra of the reaction mixtures both before (Figure 33) and after 1 hour (Figure 34) of scavenging are shown below.

Figure 32: The ^1H NMR spectrum of the mixture before addition of **212****Figure 33:** The ^1H NMR spectrum of the mixture after 1 hour shaking with **212**

As can be seen from Figure 31, the best time for the scavenger reaction is 1 hour. This is also illustrated in the ^1H NMR spectrum shown in Figure 33. Running the reaction longer than this results in 'leeching' of the linker in this case the DMAP linker **211**. The longer the

reaction is left running the greater the percentage of linker removed. With the shortest reaction time ascertained, we next attempted to scavenge different substrates (Figure 34).

Figure 34 Assessment of the polysiloxane **212** as a scavenger of different electrophiles

Substrate	Efficiency (%)	DMAP present (%)
 114	100	0
 214	50	100
 215	100	0
 102	0	0
 216	2	100
 217	30	100
 218	2	100
 111	100	0
 219	94	0
 220	88	0
 221	83	0
 222	75	0
 223	0	1
 224	30	15
 225	10	20

**Reaction time 1 h, solvent used was THF; 0.5 g of resin (1.9 mmol) was used in 2 ml standard scavenging solution (1 mmol of substrate)*

Starting with the best results, benzyl bromide (**114**), bromoacetophenones **215**, **219** and **220**, benzyl chloride (**111**), cinnamyl chloride (**222**) and bromide (**221**), are all scavenged successfully and are not complicated by any leeching of materials from the resin. As the

scavenging efficiencies are high for these substrates and the resin can therefore be used to scavenge these from solution without the risk of polymer breakdown.

As can be seen from Figure 35 that the chloride containing substrates tend to be scavenged less than their bromide counterparts. This is due to the bromide ion being a better leaving group than the chloride and hence is better at being taken from the mixture by the scavenger **212**. The halopropanes **223** and **224** are not effectively scavenged with **212**. This is probably due to their poorer electrophilic character, since they are not benzyl halides. One of our objectives has therefore been achieved. The resin **212** can be used to scavenge some electrophiles without breakdown of the resin. Below is shown a visual representation of the successful scavenging of benzyl chloride.

By comparison of the two spectra (Figures 35 and 36) it is clear that the benzyl chloride is completely removed from the standard solution. After the reaction the ^1H NMR spectrum (Figure 37) shows that the benzyl chloride has been removed and no DMAP linker has been released from the polymer.

Figure 35: The ^1H NMR spectrum of the benzyl chloride mixture before addition of **212**

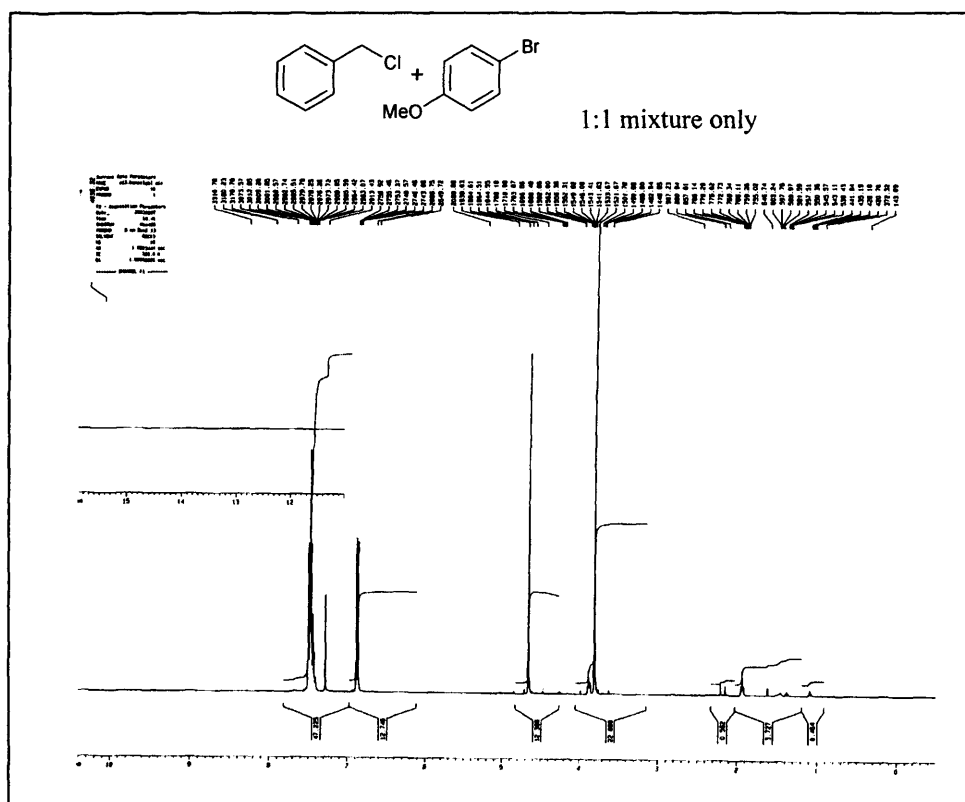
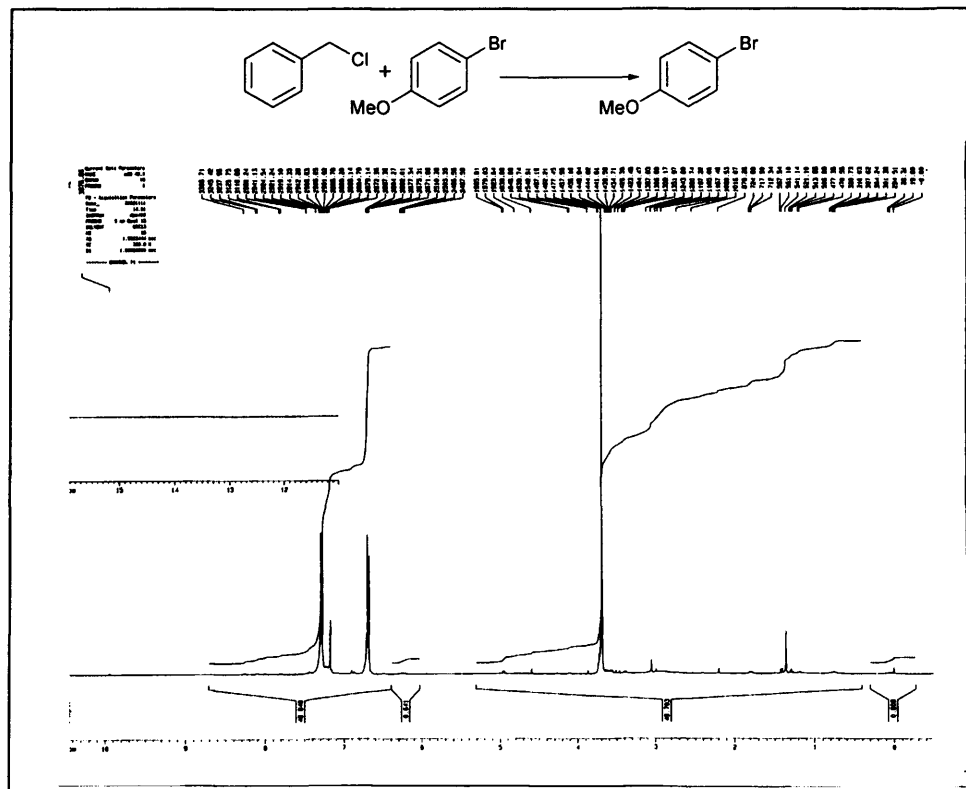


Figure 36: The ^1H NMR spectrum of the mixture after 1 hour shaking with **208**

It is clear that the resin **212** is not appropriate for scavenging carboxylic acids (see entries for carboxylic acids **216**, **217**, and **218**). The reason for these substrates being scavenged so poorly was that the acid led to protonation and subsequent removal of the DMAP alcohol **211**. Large amounts of this linker are seen in the ^1H NMR spectra of the scavenging reactions. This is illustrated below in Figures 38 and 39 for the attempted scavenge 3,4,5-triethoxycarboxylic acid. Evidently from the ^1H NMR spectra shown in Figure 39, the carboxylic acid remains and additional peaks are present. The resin **212** therefore cannot be used to scavenge for carboxylic acids.

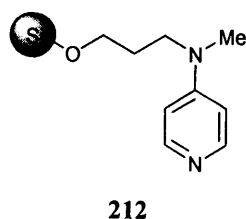
Figure 37

Figure 38: The ^1H NMR spectrum of the mixture of 3,4,5-triethoxybenzoic acid before addition of **212**

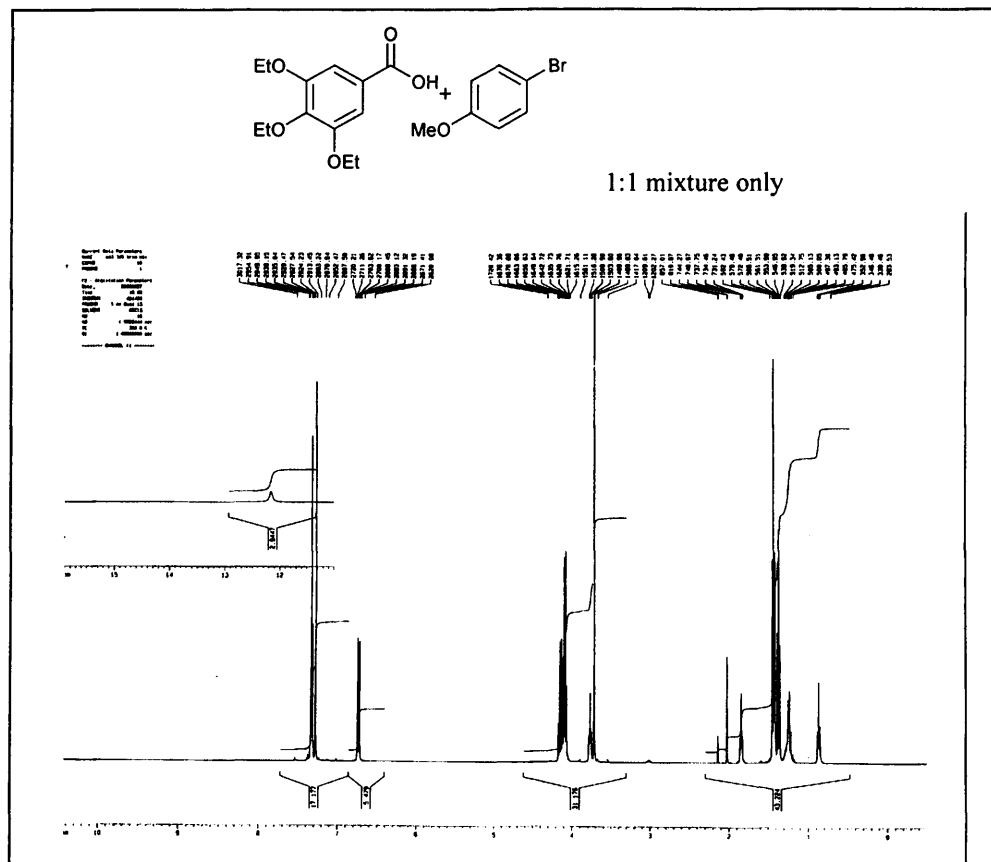
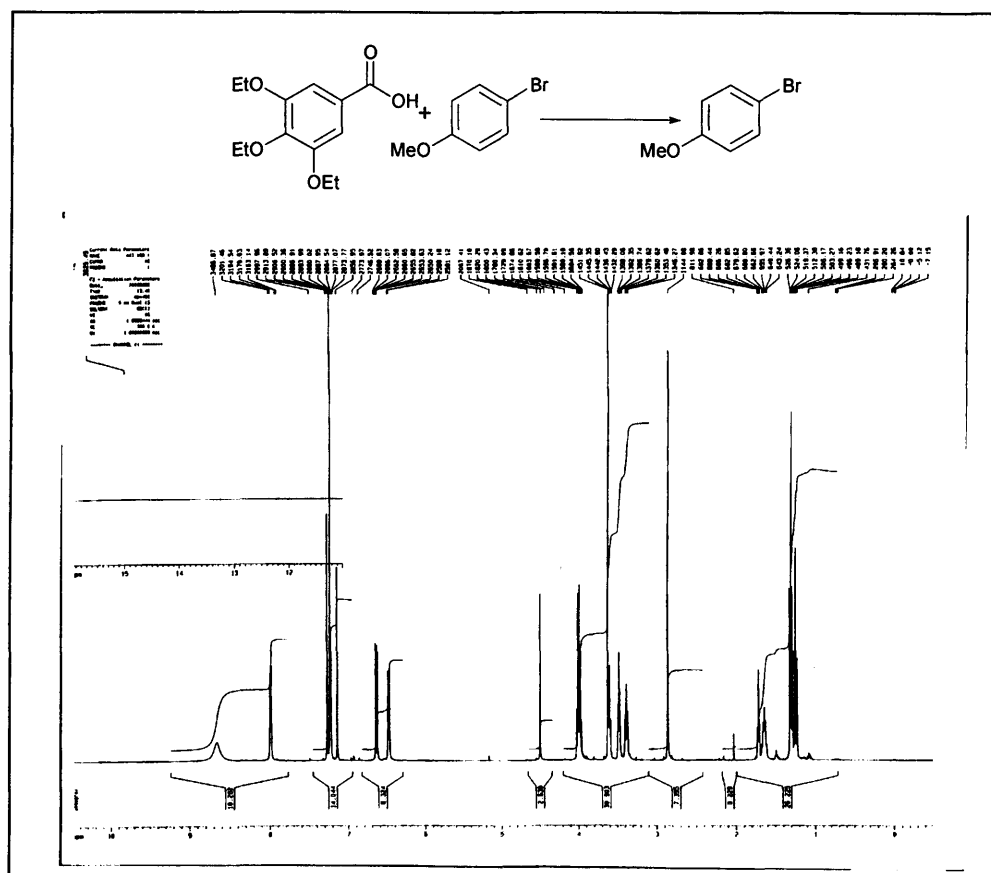
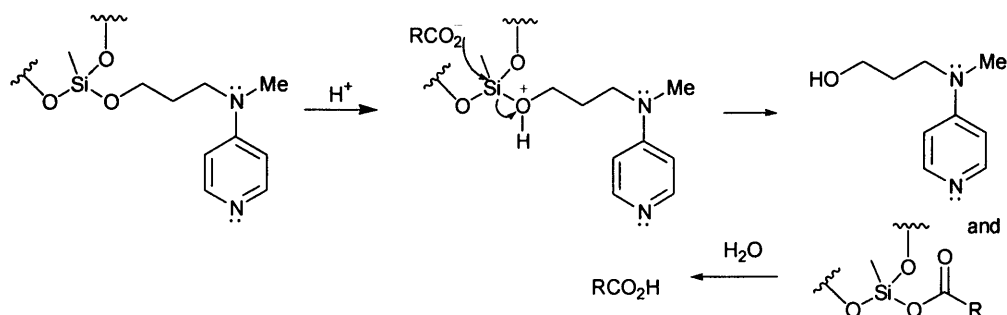


Figure 39: The ^1H NMR spectrum of the mixture 3,4,5-triethoxybenzoic acid after addition of **212**



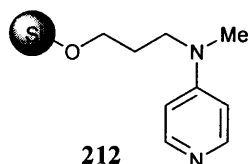
A possible mechanism to explain how the linker is lost from the resin is shown in Scheme 77. The acid may displace the alcohol by a process that first involves protonation of the propyloxy oxygen atom, followed by nucleophilic attack at the silicon atom by a nucleophile, possibly the carboxylate. The presence of small amounts of water may explain the subsequent hydrolysis of the silyl ester.

Scheme 77



The DMAP resin **212** (Figure 38) is ineffective at scavenging for aldehydes, this is due to the presence of a tertiary amine. Aldehydes are usually scavenged using a primary amine-type resin. The development of a polymer for scavenging aldehydes will be described later.

Figure 38

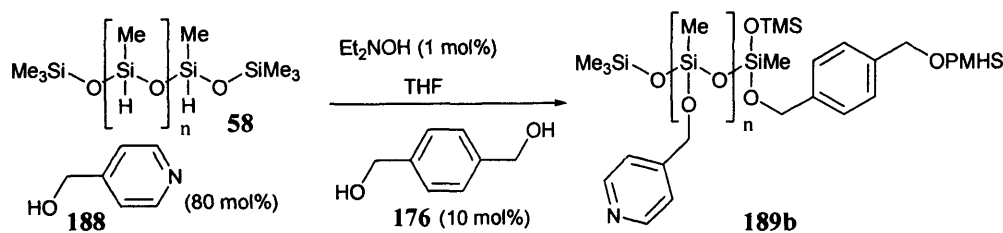


It is possible that the length of the alkyl chain of the DMAP resin causes it to be more of a labile molecule and is susceptible to attack under certain extreme reaction conditions such as acidic substrates. It is safe to say that the DMAP resin is not limited to scavenging benzyl bromide though what substrates to scavenge needs careful consideration.

2.3.3 Synthesis of pyridine resin **189b**

The catalyst Et_2NOH was used for the synthesis of the simple polymer **189b** containing a pyridine derived from 4-pyridinemethanol (**188**) which is commercially available. The pyridine moiety was attached in the same fashion as the DMAP linker and the resin was again crosslinked using the same reagent, 1,4-benzenedimethanol (**176**).¹⁵¹ After this the resin was worked up by removal of the solvent under vacuum and dried. After this it was washed to constant weight using chloroform resulting in 8% loss of total mass. This process is shown below in Scheme 78.

Scheme 78



The resin was afforded in 93% yield as a light yellow solid. After careful drying it was submitted for elemental analysis. This gave the following values: C, 31.9, H, 4.99, N, 3.69% ($\text{C}_{740}\text{H}_{940}\text{N}_{80}\text{O}_{300}\text{Si}_{100}$ requires C, 47.9, H, 5.07, N, 6.04%). This indicated that the pyridine-containing molecule had been incorporated into the resin structure. The nitrogen component was a little bit low (loading of 2.6 mmol/g). The expected loading was 4.3 mmol/g, hence this shows that the pyridinemethanol linker **188** was incorporated to a lesser degree than expected and hence gave a lower loading capacity.

2.3.4 Scavenger testing using pyridine resin **189b**

The resulting pyridine resin **189b** was stable to washing stability testing. This was done by washing the resin several times with chloroform until the mass was constant. It was washed to constant weight first of all using vacuum chamber apparatus to force solvent through the resin particles. This removed impurities and each washing was evaporated and the residue weighed until the mass of the resin became constant indicating stability. After this the resin was then used for scavenger testing (0.5 g of resin to 2 ml of standard solution or 1 mmol). Again the time course was performed to assess the minimum time required, and the integrity of the resin with respect to its exposure to the mixture (Figure 40).

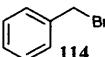
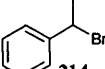
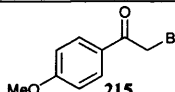

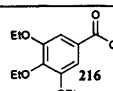
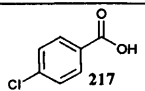
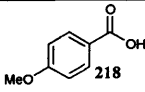
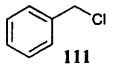
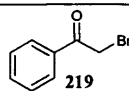
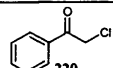
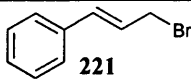
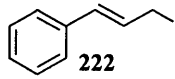
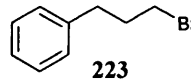
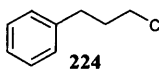
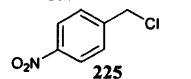
Figure 40 The effects of time upon the scavenging of benzyl bromide by resin **189b**

Time (h)	Efficiency (%)	Pyridinemethanol present (%)
1	97	2
2	95	10
5	95	30
10	96	50
16	94	78
24	95	100

*Solvent used was THF; 0.5 g of resin **189b** (1.3 mmol) was used in 2 ml standard scavenging solution (1 mmol of benzyl bromide)

Again it can be seen that the longer the resin is left in the mixture, the more the resin breaks down. This is indicated by greater amounts of the resin being present within the standard mixture. Hence, as was the case for the previous DMAP resin, the supported pyridine should be left in the reaction mixture for no longer than 1 hour.

Figure 41 Assessment of the polysiloxane **189b** as a scavenger of different electrophiles

Substrate	Efficiency (%)	Pyridinemethanol present (%)
 114	95	0
 214	20	10
 215	77	0
 102	0	0
 216	2	100
 217	10	100
 218	2	100
 111	63	0
 219	55	0
 220	40	0
 221	84	0
 222	10	0
 223	0	100
 224	0	50
 225	25	15

*Reaction time 1 h, solvent used was THF; 0.5 g of resin **189b** (1.3 mmol) was used in 2ml standard scavenging solution (1 mmol of substrate)

Again, as with the DMAP resin **212** shown in a previous section, the pyridine resin is also effective to other substrates as well as benzyl bromide. Its use is not limited to scavenging just one substrate. We can see from the table (Figure 41) that the resin is stable to certain halides. The scavenging efficiency has decreased slightly with respect to the DMAP resin **212**, this is due to the absence of the additional electron-donating group in the pyridine. It can still be seen that acetophenones **215**, **219**, **220** benzyl bromide **114**, benzyl chloride **111**, and cinnamyl bromide **221** and chloride **222** are the substrates that are successfully scavenged with no resin breakdown. It can be seen from the table (Figure 42) that bromopropane **223** and chloropropane **224** are not scavenged possibly due to the length of the carbon chain present or that it is not active enough to be scavenged by the nucleophilic pyridine scavenger.

The carboxylic acid substrates **216**, **217** and **218** cause resin breakdown possibly due to protonation of the pyridinemethanol linker and subsequent removal from the polysiloxane scaffold. Benzaldehyde (**102**) is not scavenged due to the tertiary amine present, which cannot form a stable imine. In terms of scavenging bromides and chlorides, the latter is not scavenged as efficiently due to the chloride being a less effective leaving group than bromide, hence rendering the molecule less electrophilic. Therefore, the cases with a direct comparison of the chloride and bromide versions of the same molecule as is the case with the cinnamyl analogues **221** and **222**, there is a marked difference in scavenging efficiencies.

Figure 42: The ^1H NMR spectrum of the benzyl chloride mixture before addition of **189b**

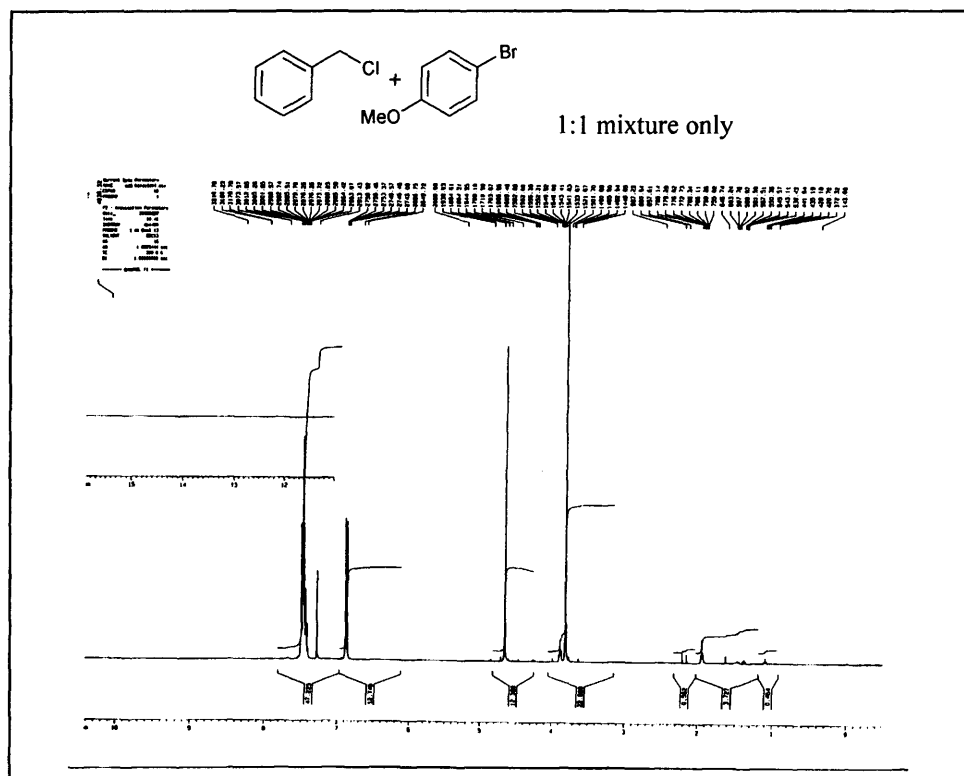
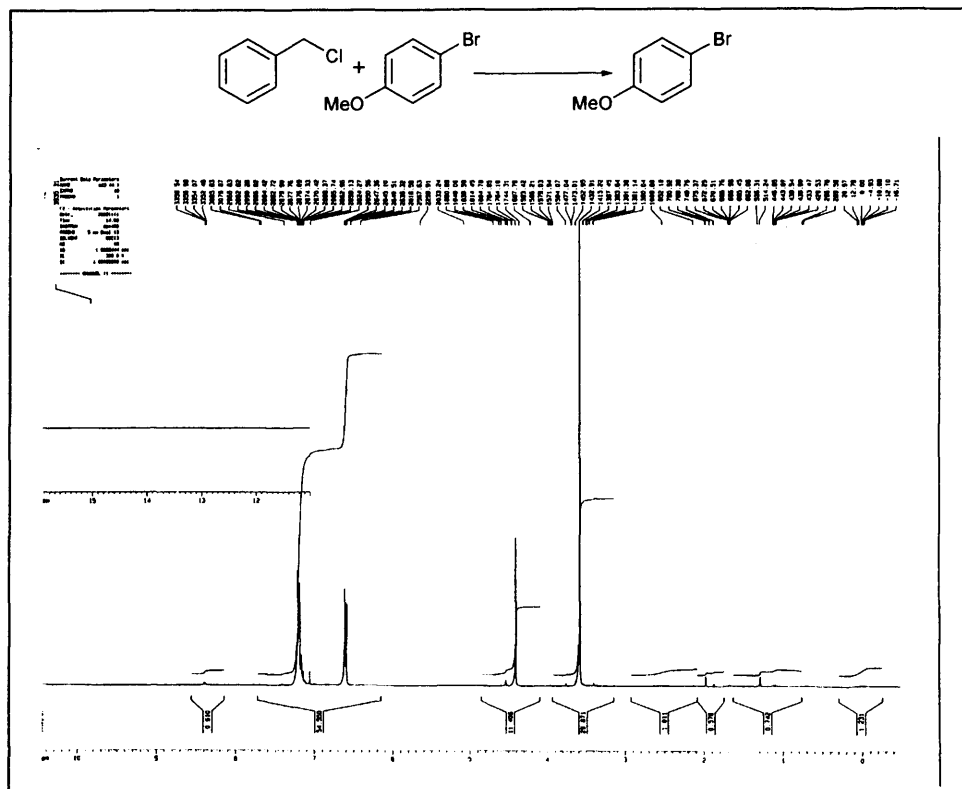


Figure 43: The ^1H NMR spectrum of the mixture after 1 hour shaking with **189b**

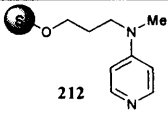
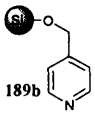
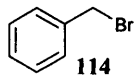
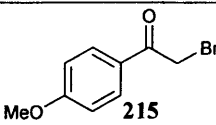
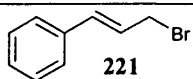
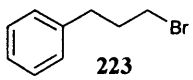
In Figure 42 and 43, it can be seen that benzyl chloride is not as effectively removed from the mixture by resin **189b**. It is also susceptible to attack by HBr or HCl, both of which are formed to a certain extent as by-products to the scavenging reaction. This enables the linker to be cleaved from the polymer backbone more easily due to protonation at the silyl ether bond. It is therefore best to utilise the pyridine resin with substrates where there is little chance of acidic conditions where the structure of the resin would be compromised. So it is not best suited to scavenging for carboxylic acids and their derivatives.

While it is clear that the pyridine resin **189b** is less reactive towards electrophiles than the DMAP resin **212**, it does have advantages. The synthesis of **189b** is easily achieved using reagents and catalysts that are all inexpensive and commercially available.

2.3.5 Comparisons of synthesised DMAP and pyridine to commercial resins

It was worthwhile to compare the DMAP and pyridine resins synthesised with those obtained commercially so the scavenging efficiencies could be measured with a type of 'market standard'. The two commercial resins used were polyvinyl pyridine (PVP) (loading 2.2 mmol/g) and polystyrene supported DMAP (2.6 mmol/g). Not all of the substrates shown in the tables previously were tested, only a select few to indicate a comparison.

Figure 44 Assessment of the PVP and polystyrene-supported DMAP as scavengers of different electrophiles and comparison against synthesised polymer resins

Substrate	Commercial (Aldrich) DMAP Efficiency (%)	 212	Commercial (Aldrich) PVP Efficiency (%)	 189b
Loading/Price per gram	2.6 mmol/£ 7.84	3.8 mmol/£ 1.80	2.2 mmol/£ 0.46	2.6 mmol/£ 1.80
Price per mmol	£ 3.01	£ 0.47	£ 0.21	£ 0.69
 114	100	100	100	95
 215	93	100	89	77
 221	84	83	85	84
 223	1	0	0	0

*Reaction time 1 h, solvent used was THF; 0.5 g of resin was used (1.1 mmol PVP, 1.3 mmol DMAP) in 2ml standard scavenging solution (1 mmol of substrate)

The scavenging properties of commercial DMAP and pyridine resins are similar. All four substrates are scavenged with near identical efficiencies. In the case of the bromoacetophenone substrate **215**, the commercial resins scavenged more efficiently than the synthesised resins **212** and **189b**. The reasons for this have already been discussed in a previous section. Although at this time the commercial resins are better in terms of stability, through more development work and testing, a competitive polysiloxane resin may be found.

2.3.6 Chemical and mechanical stabilities of DMAP and pyridine resins

In solution phase chemistry, mechanically stirring a reaction sometimes has no effect on the stability and effectiveness of reagents and substrates. However, this is not the case for supported reagents. If a reaction involving supported reagents is stirred too vigorously it can cause breakdown of the beads and this can mean the difference between a failed or a successful reaction.

The synthesised DMAP **212** and pyridine **189b** resins were tested in this way to check for mechanical stability. The test was done by placing the desired resin in THF and then stirring gently (in a 5 ml round bottomed flask with a magnetic stirrer) at first and then gradually

increasing the speed. Unfortunately even under gentle mechanical stirring the resins were broken apart resulting in various linkers being present in the solvent. Thus scavenging reactions with the siloxane resins, like 007's Martini, must be shaken and not stirred. This is common practice for reactions involving polymer-supported reagents or substrates.

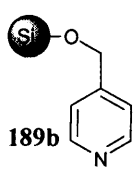
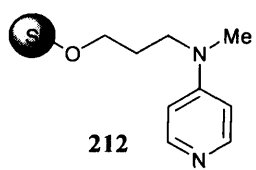
Figure 45 Stability of siloxanes **212** and **189b** towards various acids.

Acid	Result
Glacial acetic	100% linker present
Trifluoroacetic	100% linker present
1M Hydrochloric	100% linker present
5M Hydrochloric	Complete breakdown
Conc. Hydrochloric	Complete breakdown
1M Nitric	Complete breakdown
5M Nitric	Complete breakdown
Conc. Nitric	Resin forms black tar
1M Sulfuric	Complete breakdown
5M Sulfuric	Complete breakdown
Conc. Sulfuric	Black oil formed

As has been discussed previously we suspected that the siloxane resins were unstable towards acids. This was investigated further by assessing their stability towards a range of different acids, as shown in Figure 45. This was performed by placing 0.5 g of resin with 2 ml of acid in a filter syringe and shaking for 1 hour, after which time the liquid was removed and assessed by ^1H NMR in D_2O where possible. As can be seen, both resins were not resistant to the acids. The acetic acids resulting in linker removal, whereas the mineral acids resulted in complete destruction of the polymers, producing a black tar.

The effectiveness of a polymer-supported reagent often depends upon the swelling properties of the resin. Functional groups within a solvent-swollen resin will be more accessible for reaction than those in a non-swollen one. Practically it is important to know whether a solvent is going to give rise to expansion of the polymer, if only to contain it. Different solvents were used to investigate whether resins **212** and **189b** would swell or shrink. This was performed by placing 1ml of resin in a 10 ml measuring cylinder and adding enough solvent to fill the cylinder.

Figure 46 Assessment of swelling properties of **212** and **189b** in different solvents

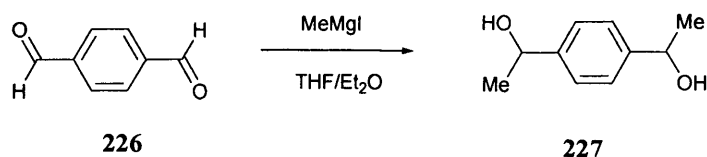
Solvent	 189b	 212
Water	No swelling	No swelling
Benzene	No swelling	No swelling
Diethyl Ether	Shrinking of resin (0.25 ml)	Shrinking of resin (0.32 ml)
Hexane	No swelling	No swelling
THF	Swelling of resin (0.10 ml)	Swelling of resin (0.10 ml)
DCM	Swelling of resin (0.20 ml)	Swelling of resin (0.20 ml)

As can be seen from Figure 46, with solvents such as water, benzene and hexane, there is no appreciable swelling or shrinkage observed on the resins. However when solvents such as diethyl ether is used the resin shrinks by 0.25 ml for the pyridine resin **189b** and 0.32 ml for the DMAP resin **212**. THF causes a 0.10 ml swelling, whereas DCM causes a slightly greater swelling of 0.20 ml possibly due to the fact that it is a chlorinated solvent.

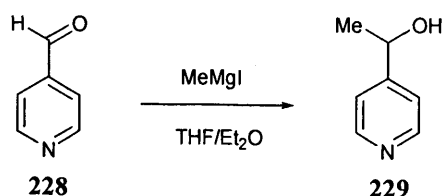
2.3.7 Protection of Si-O function

The scavenger tests indicated that in certain cases the Si-O bond was susceptible to attack from nucleophilic species produced as by-products of the scavenging reaction. Hence we decided to attempt to reduce lability the Si-O bond by sterically restricting access by using flanking alkyl groups.

Scheme 79



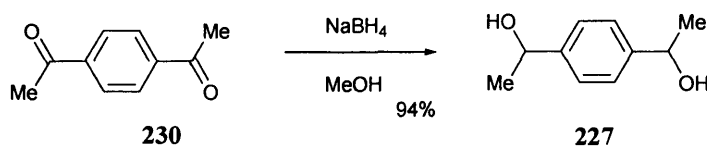
Scheme 80



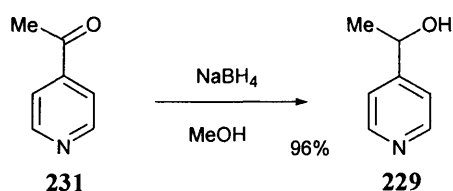
Initially, this was attempted by performing Grignard addition reactions on the aldehyde precursors of the alcohols **227** and **229** (both are commercially available) shown in scheme

79 and 80. However, these reactions proved problematic in that the final product was difficult to purify and so it was decided to proceed via the ketone precursor instead as shown below in Scheme 81 and 82. This constituted the reduction of ketones **230** and **231** to give the required alcohol products shown in schemes 81 and 82. These product alcohols **227** and **229** were obtained in high purity and yield, 94% and 96% respectively and hence were not purified before proceeding to the next step.

Scheme 81

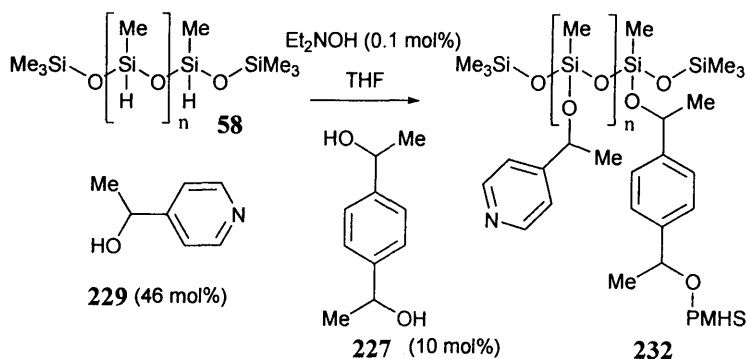


Scheme 82



These linkers were then taken and attached in the usual way to PMHS (**58**) using Et₂NOH as the catalyst as shown below in Scheme 83. The resin **232** thus obtained was washed to constant weight in a filter syringe using chloroform and lost 5% of the total resin mass. The resin was afforded in 96% yield. This was submitted for elemental composition analysis [found C, 40.9, H, 7.02, N, 4.78% C₄₃₂H₇₃₃N₄₆O₁₉₄Si₁₀₀ requires C, 41.6, H, 5.88, N, 5.17%]. The loading was therefore 3.4 mmol/g. The expected loading was 3.7 mmol/g, which is close to the actual figure.

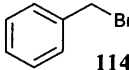
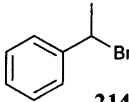
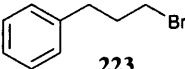
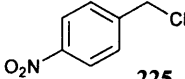
Scheme 83



The presence of the methyl group was expected to protect the silyl ether bond from attack by nucleophiles and in effect shield it by causing hindrance. It was anticipated that it would still function as a scavenger similar to the pyridine resin previously synthesised. The problem with this resin was not in its stability; the presence of the protecting alkyl group, was clearly making the resin more stable. However, the nucleophilicity of the resin

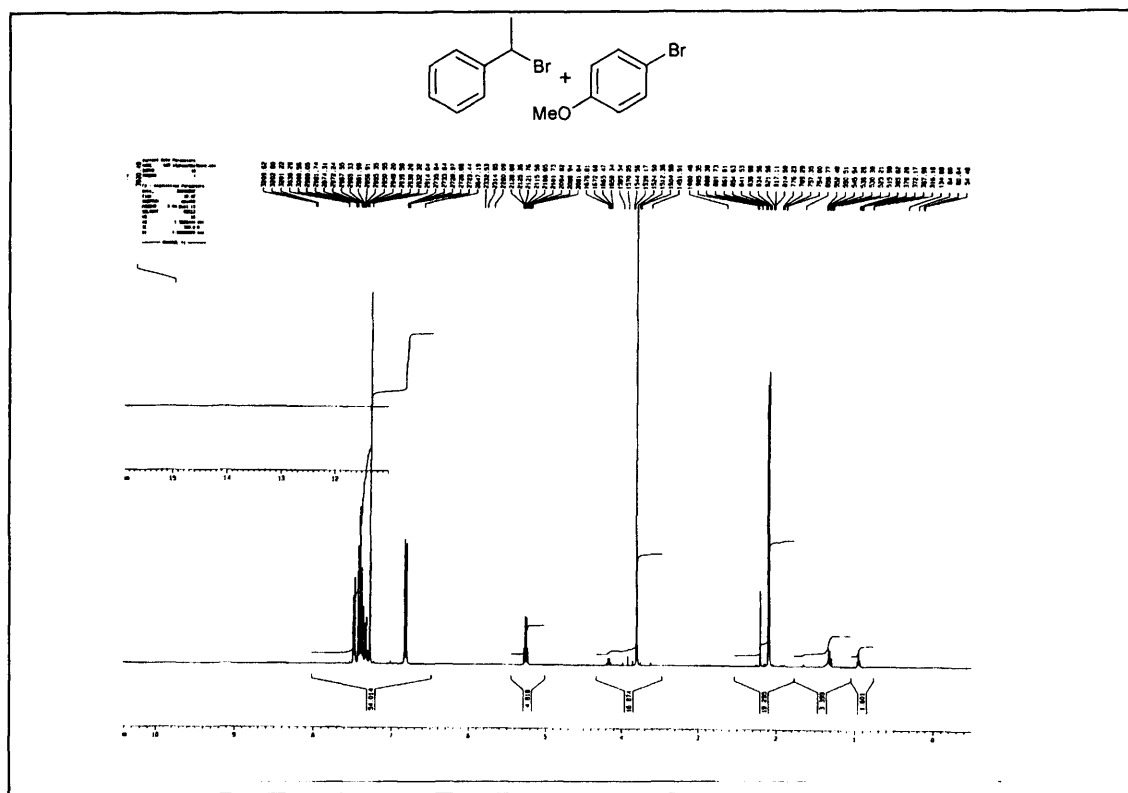
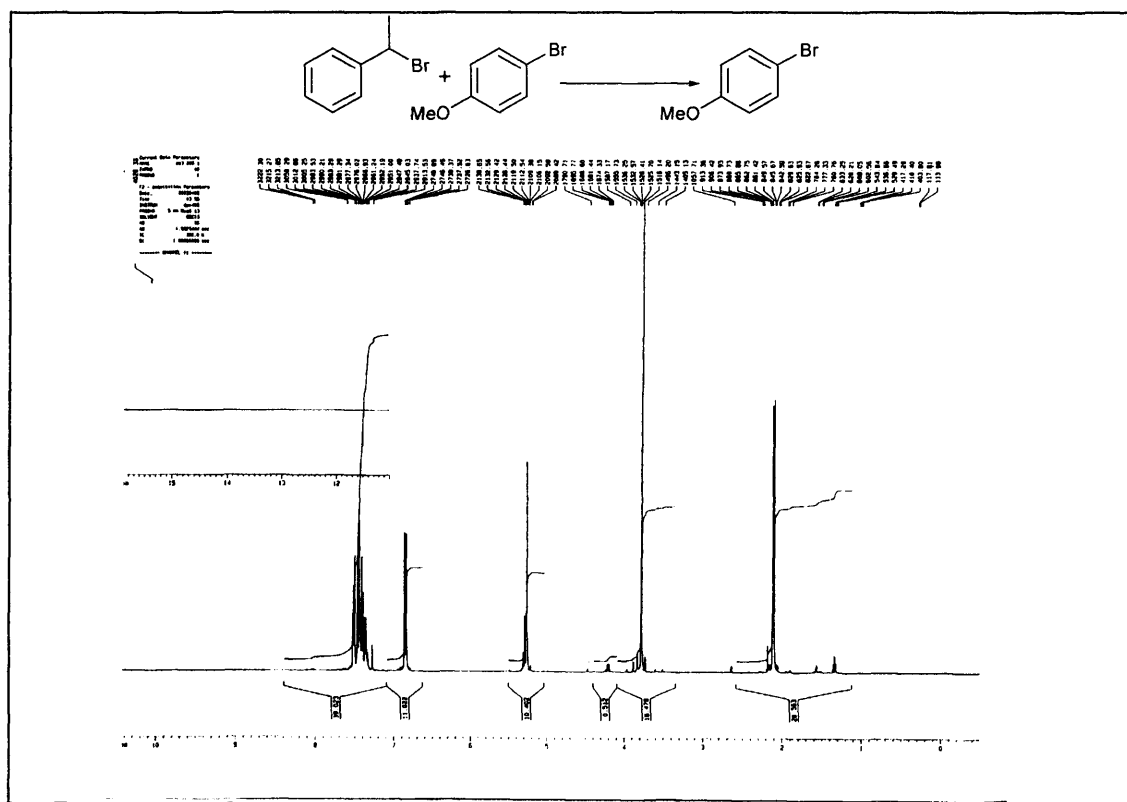
decreased dramatically, thus reducing its effectiveness as a scavenger. The resin was not therefore carried forward into further testing using varied substrates. It is not clear why the methyl groups should make the resin less nucleophilic.

Figure 47 Scavenging of alkyl halides with 232

Substrate	Efficiency (%)	Linker present (%)
 114	52	0
 214	0	0
 223	0	0
 225	0	0

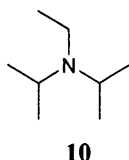
**Reaction time 1 h, solvent used was THF; 0.5 g of resin(1.7 mmol) was used in 2ml standard scavenging solution (1 mmol of substrate)*

Both the stability and lack of reactivity of the resin can be seen by inspection of the ^1H NMR spectra in Figures 48 and 49. Here can be seen that the presence of the methyl group shielding the Si-O bond protects it from attack. The before and after spectra are nearly identical. The lack of scavenging ability may be linked to a more hindered polymer matrix that now has to accommodate the additional methyl group both on the scavenging moiety and crosslinker.

Figure 48: The ^1H NMR spectrum of the standard mixture before addition of **232****Figure 49:** The ^1H NMR spectrum of the mixture after a shake for 1 h addition of **232**

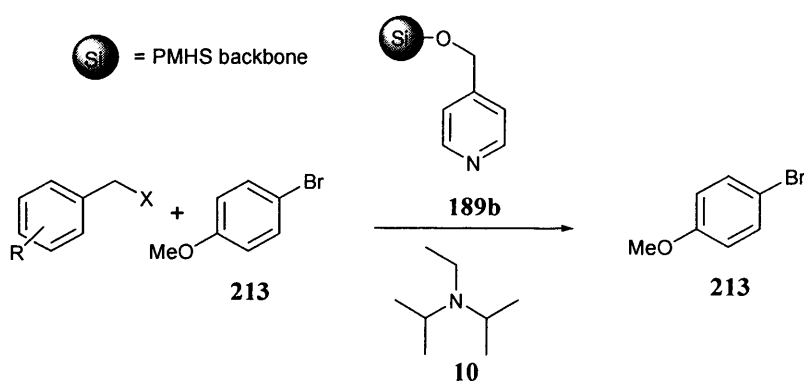
The production of HBr or HCl and this attacking the siloxane backbone may have been responsible for the presence of the respective linkers within the mixtures. To remedy this we decided to use Hunig's base, diisopropylethylamine (**10**) (Figure 50). This was added to the standard mixture and was present while some scavenging reactions were performed. The poorer results from Figure 42 were used to exhibit this point, where the linker was being removed in very high concentrations. The problem was that the linker was being removed even in low concentrations of Hunig's base by cleavage of the pyridine from its attachment point on the PMHS. The possible theory of how the linker is removed has been discussed with the example using DMAP **212**.

Figure 50



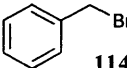
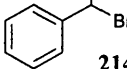
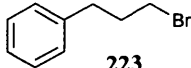
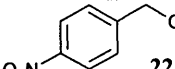
However, very little improvement was seen and in some cases, the level of scavenging was seen to be reduced (Figure 53). It was not known why the presence of Hunig's base **10** had a detrimental effect on the scavenging efficiency. The scavenging efficiency for benzyl bromide (**114**) previously was 98%, however in the presence of Hunig's base **10** (75 mol%) it decreases to 87%. The efficiency for bromoethyl benzene **214** decreases 5% from previous, but on a positive note, the amount of linker present decreases by half. A general reaction scheme is shown in scheme 84.

Scheme 84



The result with the bromopropane substrate **219** was 100% linker present, indicating major breakdown of the resin. In the presence of Hunig's base this has been dramatically reduced, it has not improved the scavenging efficiency but the resin is not breaking down in the presence of this substrate. Finally, with the nitrobenzyl chloride **225** a drop is seen in the scavenging efficiency of 5%, but the linker present has also dropped by half (Figure 52).

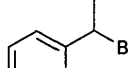
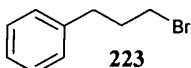
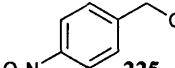
Figure 51: Effects of Hunig's base upon scavenging of electrophiles with **189b**.

Substrate	Efficiency (%)	Pyridinemethanol present (%)
 114	87	0
 214	15	5
 223	0	1
 225	20	8

**Reaction time 1 h, solvent used was THF; 0.5 g of resin (1.3 mmol) was used in 2ml standard scavenging solution (1 mmol of substrate)*

The presence of the base acts as a buffer and decreases the removal of the linker (pyridinemethanol). We also attempted to remove any moisture present in the reaction mixture by adding ground 4Å molecular sieves as the presence of even the smallest amount of water might affect the scavenging by producing acid (*via* hydrolysis of the alkyl halide) thus causing breakdown of the resin. As can be seen from Figure 53, the previous substrates that cause resin break down were used to test this hypothesis. It was gratifying to see that here was a decrease in the amount of linker being removed due to the presence of the molecular sieves.

Figure 52: Effects of molecular sieves upon the scavenging ability of siloxane **189b**

Substrate	Efficiency (%)	Linker present (%)
 214	15	0
 223	0	1
 225	5	0

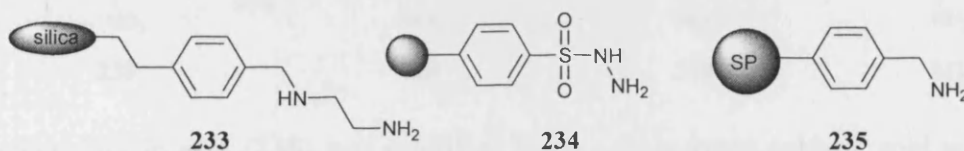
**Reaction time 1 h, solvent used was THF; 0.5 g of resin (1.3 mmol) was used in 2 ml standard scavenging solution (1 mmol of substrate)*

2.4 Hydrazine resin

Although pyridine resins have been produced to scavenge for substrates such as benzyl bromide and similar active compounds, these were not effective in removing aldehydes from a standard mixture. Hence it was thought that a resin containing a primary amine linker would fulfil this role and it would be possible to scavenge for aldehydes.

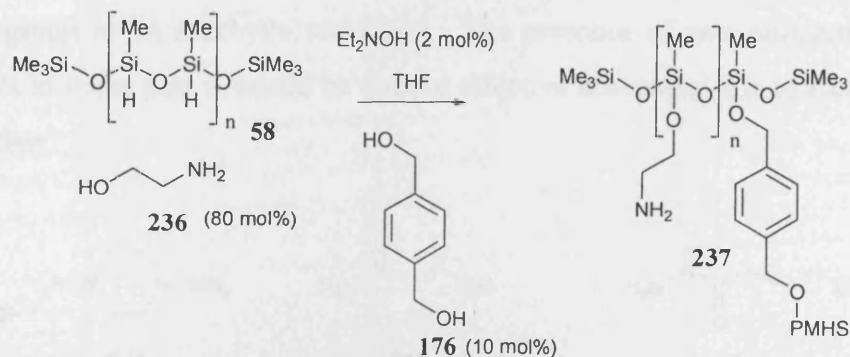
Flynn, Kaldor¹⁰³, Hodges⁶¹ and others have described the use of polymer-supported amines to scavenge for aldehydes and other electrophiles. Resins that fulfil this role are shown below in Figure 53. Resin **233** is a supported ethylenediamine, **234** is a supported hydrazide while **235** is a supported amine. All three are commercially available.

Figure 53



Initially there were many ideas put forward to achieve the goal of developing a siloxane-based aldehyde scavenger. The linker had to possess two functional groups: an amine moiety at one end in order to scavenge for the aldehyde substrates, and a hydroxyl at the other so that it could be attached to the polysiloxane support. The simple aminoalcohol, 2-aminoethanol (**236**) fulfilled this role. It was to be attached to PMHS (**58**) as shown in scheme 85, using 1,4-benzenedimethanol (**176**) as the crosslinker in the presence of a hydroxylamine catalyst.

Scheme 85

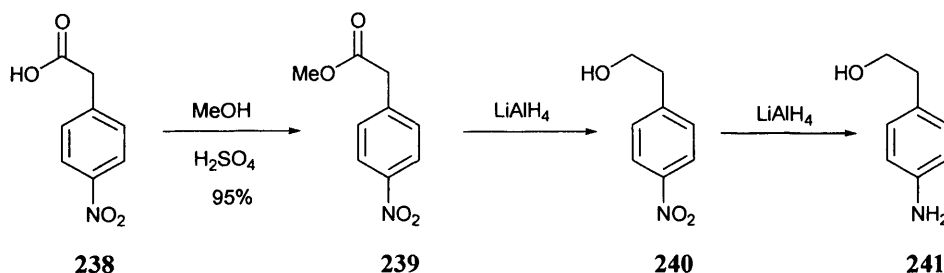


This gave a white solid **237** in 97% yield which was washed to constant weight and dried. This was then submitted for elemental analysis [found C 30.6, H 5.42, N 10.9% C₂₆₀H₅₄₀N₈₀O₁₄₀Si₁₀₀ requires C, 31.7, H, 5.50, N, 11.4%]. The loading was 3.5 mmol/g. The expected loading 3.7 mmol/g. Unfortunately, resin **237** proved to be ineffective in

scavenging benzaldehyde from a standard solution. This was possibly due to the scavenging linker being too inaccessible and being too close to the main polymer matrix. So a more effective resin was sought.

A linker containing an aromatic ring was thought useful, but its synthesis proved problematic. The scavenging amine function should be available because of the extended carbon chain, keeping it further from the resin backbone. The intended synthetic route of one target aminoalcohol is shown in Scheme 86.

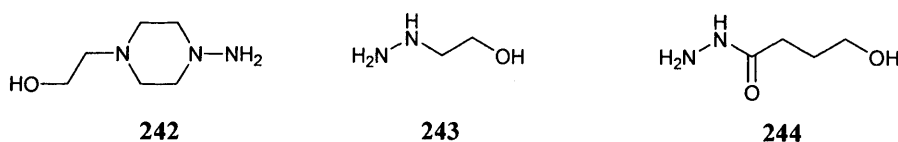
Scheme 86



p-Nitrophenylacetic acid (**238**) was esterified using concentrated sulfuric acid in methanol. The mixture was refluxed for 2 hours and then the excess methanol was removed under vacuum. The residue was dissolved in diethyl ether and washed with NaHCO₃. After this the aqueous layer was extracted with further Et₂O. After removing the solvent a white solid thought to be ester **239** was obtained in 98% yield. This was carried through to the next step without purification. This was a reduction using LiAlH₄. Although the transformation looks straightforward, in practice the steps using LiAlH₄ to reduce the molecule produced a mixture of products that proved difficult to separate using column chromatography.

Instead of making an amine-containing siloxane polymer we decide to make one containing a hydrazine group as an aldehyde scavenger. The presence of two nitrogen atoms of the hydrazine would mean that it would be a more effective scavenger due to electron donation and the α -effect.

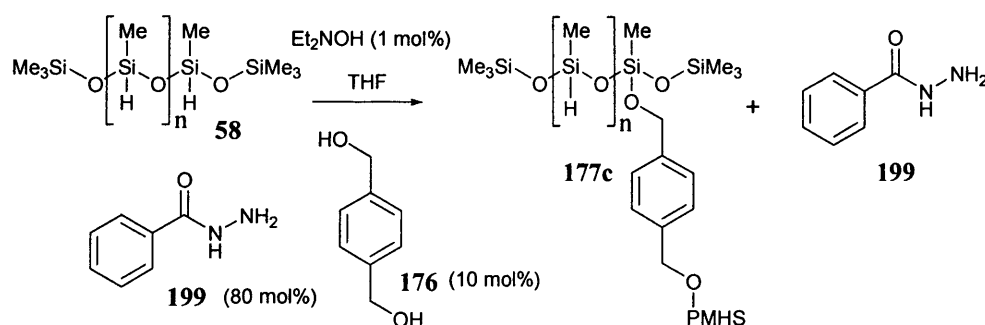
Figure 54



There was a choice of three different hydrazine resins for synthesis that also contain a hydroxyl group (shown in Figure 54). The hydrazines **242** and **243** proved too expensive and were instantly ruled out as the cost of synthesis would be too high. Hence hydrazine linker **244** was a more viable option for synthesis and resin production.

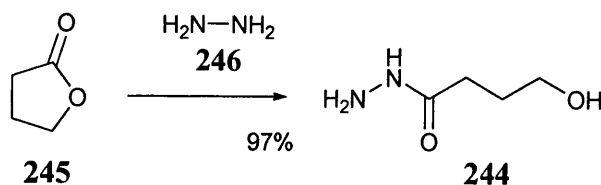
Before the use of a hydrazine alcohol linker was attempted it was necessary to check whether the linker would attach in the usual fashion via the alcohol moiety. At this stage we were not sure whether the NH would act in the same way as the OH group and therefore complicate the process. Therefore, a gas evolution test was performed using benzoic hydrazide, PMHS (**58**) and 1,4-benzenedimethanol as shown in Scheme 87. If the hydrazide **199** did not react, only 60 ml of gas would be evolved. If the hydrazide were to react the total estimated gas evolved would be 560 ml. However, in the reaction shown in Scheme 87, only 80 ml was evolved indicating that the hydrazide was not incorporated into the polymer matrix.

Scheme 87

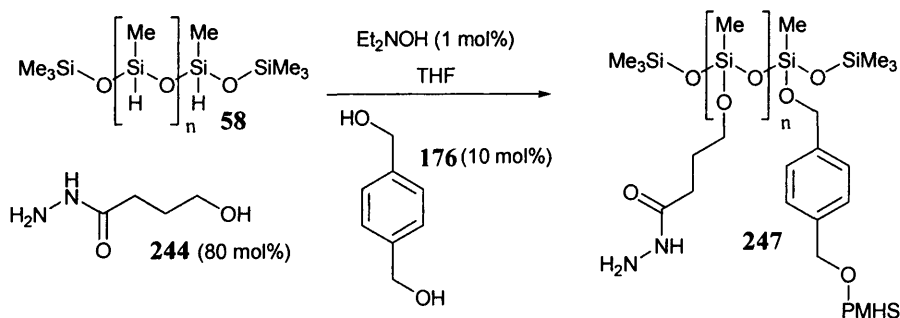


The reaction scheme for the synthesis of **244** is shown in Scheme 88. Even though the hydrazide **244** is commercially available, but very expensive, it was prepared quite simply, as shown in Scheme 88 using the literature method of Wallace and co-workers.¹⁶⁰ Heating the γ -butyrolactone (**245**) and hydrazine monohydrate (**246**) together caused a simple ring-opening reaction and gave the final product 4-hydroxybutyric acid hydrazide (**244**) in 97% yield. This was not purified before being used in the next step.

Scheme 88



Scheme 89

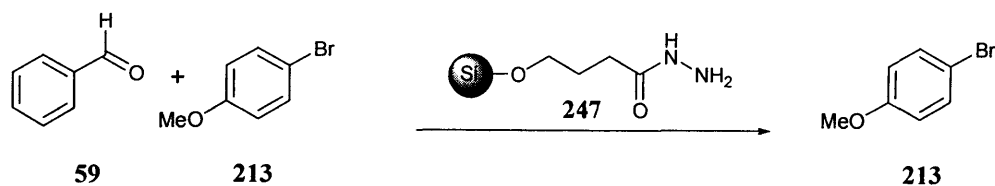


The hydrazine linker **244** was then attached to the PMHS (**58**) in the usual way using Et_2NOH as a catalyst and 1,4-benzenedimethanol (**176**) as crosslinker as shown in Scheme 89. The resin **247** was afforded as a white solid in 97% yield after washing to constant weight with chloroform. It was then submitted for elemental analysis which indicated successful incorporation of the hydrazine linker **244**. This was washed to constant weight using chloroform. Elemental composition was found to be C, 33.4, H, 6.97, N, 12.4% ($\text{C}_{580}\text{H}_{1100}\text{N}_{160}\text{O}_{300}\text{Si}_{100}$ requires C, 38.9, H, 6.15, N, 12.5%). This gives a loading of 4.5 mmol/g, close to the expected value.

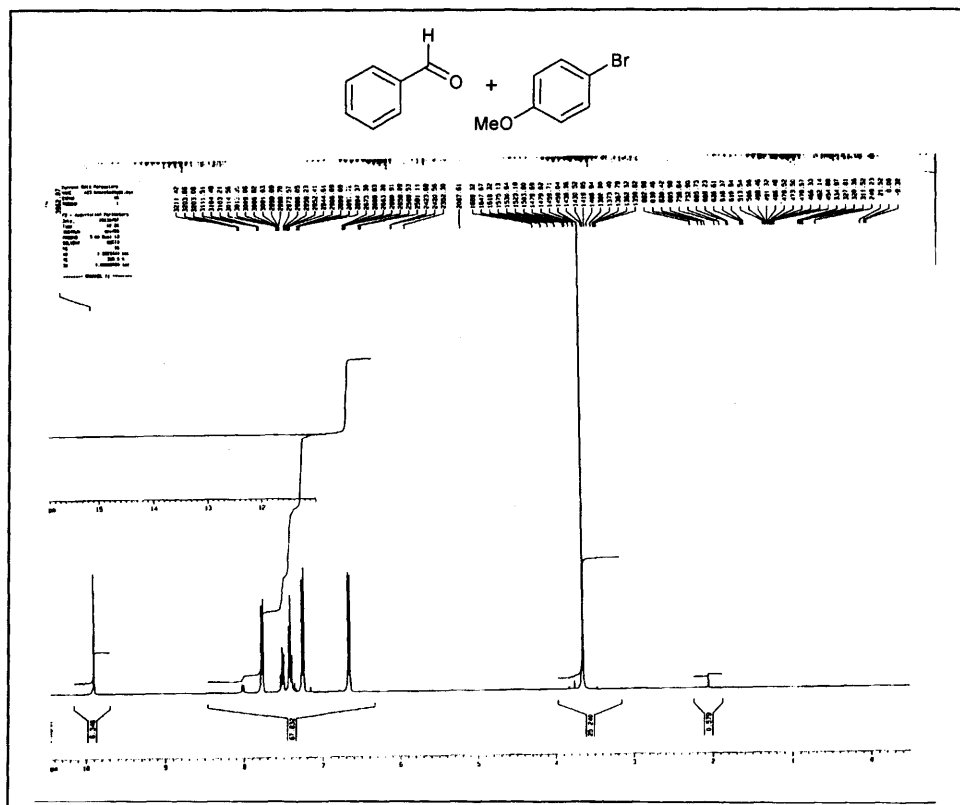
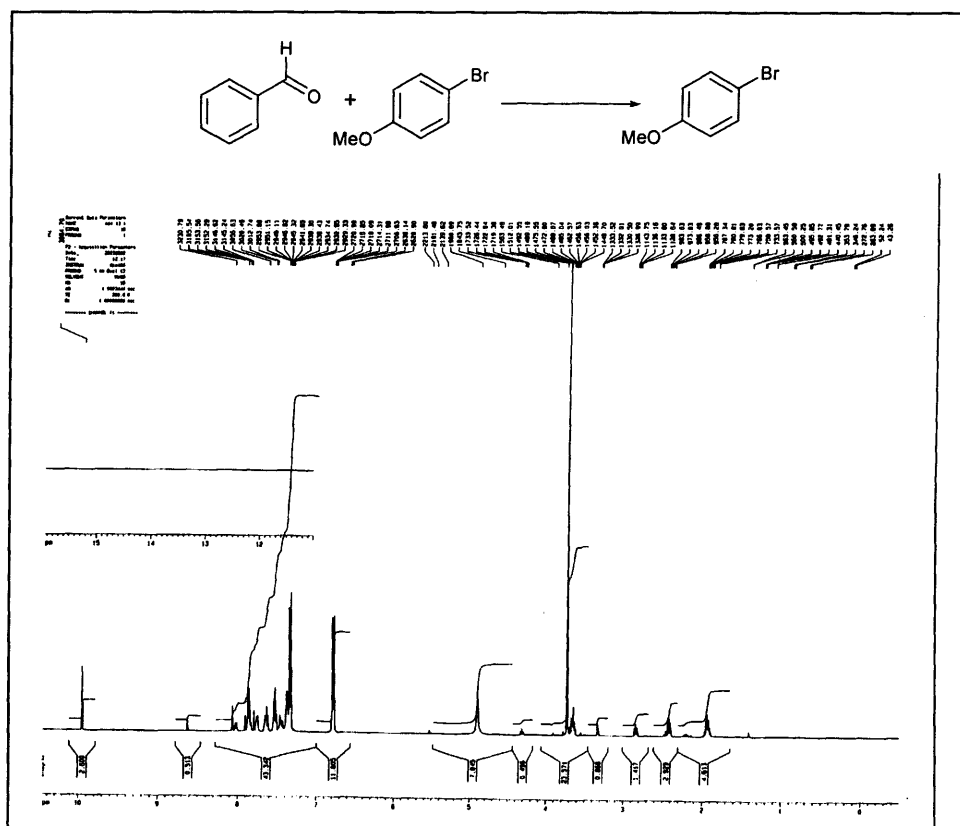
2.4.1 Scavenging for aldehydes

A standard mixture was used for the scavenger testing with the hydrazine resin **247** (0.5 g, 2.3 mmol). This consisted of benzaldehyde (**59**), and the standard **213** in THF (2 ml, 1mmol) as shown in scheme 90. We hoped that the aldehyde **59** would be removed by the hydrazine resin **247** to leave the bromoanisole **213** in solution.

Scheme 90



The scavenging reaction was attempted using **247** and the standard mixture. The efficiency was 60%, but a problem had arisen in that the hydrazine linker **244** was leeching out of the resin. An addition of 4Å molecular sieves to the reaction, the efficiency had increased to 82%. The leeching had decreased but not to a satisfactory level. Here the effect can be seen of the hydrazide linker molecule **244** leeching from the resin used to scavenge benzaldehyde.

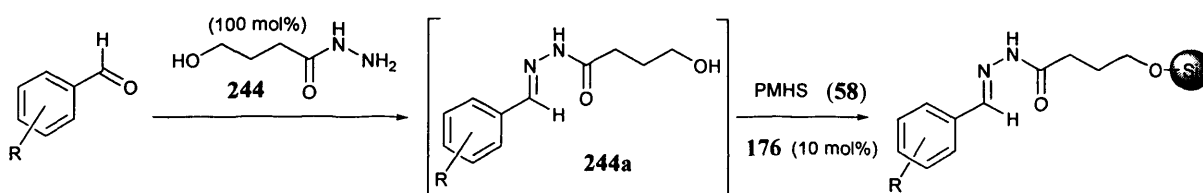
Figure 55: The ^1H NMR spectrum of the standard mixture before addition of **247****Figure 56:** The ^1H NMR spectrum of the mixture after a shake for 1 h addition of **247**

The standard mixture is seen in Figure 55. After the reaction we can see peaks present around 3-4 ppm indicating leaching of the hydrazine linker **244** into the mixture (Figure 56). Another approach was considered at this stage.

2.4.2 Solution phase methods for aldehyde scavenging

Since the instability of the polymer was causing problems, we decided to see whether we could avoid using an isolated resin. In this process, rather than using the resin to scavenge for the aldehyde substrate, the aldehyde is first reacted with the hydrazide linker in solution, and the intermediate hydrazone **244a** is then scavenged from solution as before.

Scheme 91



The standard benzaldehyde mixture and the hydrazine **244** were shaken together in order to allow formation of the imine intermediate **244a**. After 1 hour, PMHS (**58**) and benzenedimethanol **176** were added and the mixture shaken for 1 hour until a gel formed. This solid is removed by filtration in a filter syringe under vacuum. Only the bromoanisole standard is left in solution. Rather than scavenging for an aldehyde, effectively it primes the substrate so that it can bound to the resin using a crosslinker and the catalyst as shown in the above Scheme 91. The aldehyde forms a stable hydrazone intermediate and thus the hydroxyl of the intermediate is exposed allowing its removal from the mixture *via* formation of a resin bound imine. It was hoped that the efficiency of the scavenging reaction would be increased, as the aldehyde is removed while the hydrazide is still in solution. The efficiency using benzaldehyde, as measured by inclusion of *p*-bromoanisole (**213**), was 96% (see Figure 61). The ¹H NMR spectra of the mixture before and after the *in situ* polymerisation are shown below in Figures 57 and 58. These clearly show that the process is a much cleaner method resulting in no leaching of the linker from the PMHS.

Figure 57: The ^1H NMR spectrum of the mixture prior to *in situ* polymerisation with PMHS and hydrazide **244**

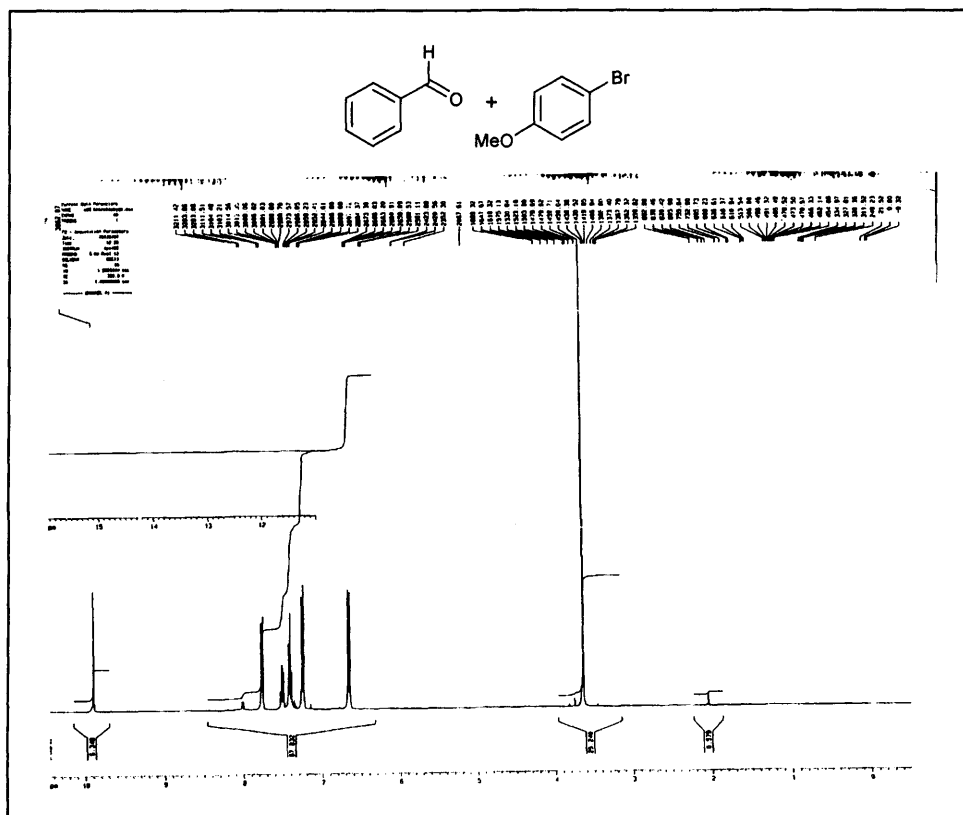


Figure 58: The ^1H NMR spectrum after *in situ* polymerisation with **244**

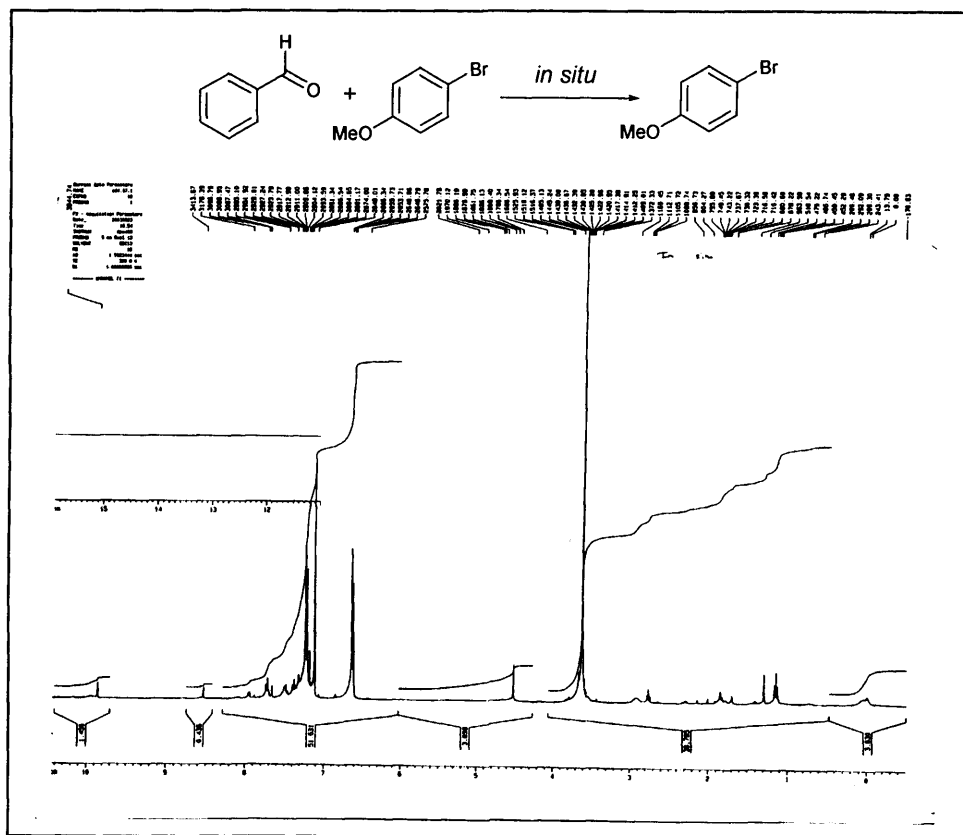
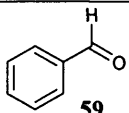
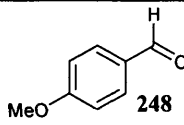
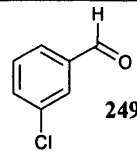
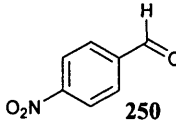


Figure 59: Scavenging of benzaldehydes using *in situ* polymerisation

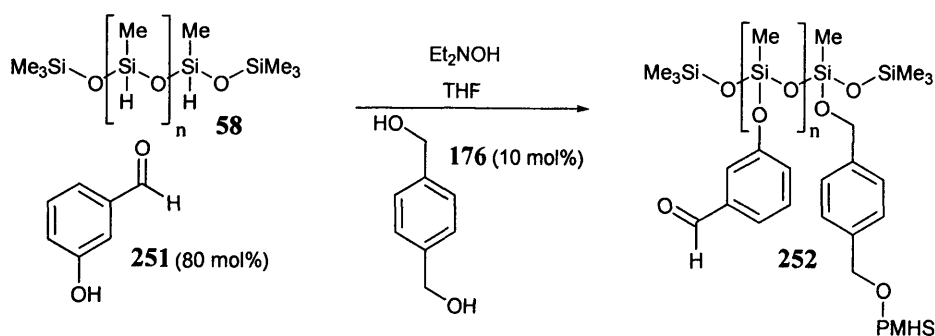
Substrate	Efficiency (%)
 59	96
 248	55
 249	87
 250	80

*Reaction time 1 h, solvent used was THF; 1 g of PMHS (16 mmol) was used in 2 ml standard scavenging solution (1 mmol of substrate)

The results of scavenging reactions of various other aldehyde substrates are shown in Figure 59. Benzaldehyde itself is scavenged with the highest efficiency. Comparing aldehydes **248** and **250**, the presence of the electron-withdrawing group results in an increase in the scavenging efficiency due to the carbonyl becoming more reactive to nucleophiles. The presence of the electron-donating group in aldehyde **248** results in a significant decrease of the scavenger efficiency. The scavenger efficiency using aldehyde **249** was slightly higher than that of **250** possibly due to sigma electron-withdrawing effects.

2.5.1 Aldehyde resin

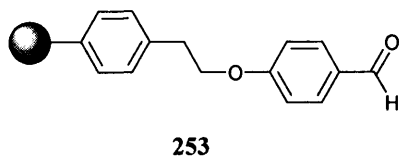
Scheme 92



A resin was required that could scavenge amines. In order for this to be possible, the easiest choice was a resin containing an aldehyde as the scavenging linker. There are few resins

that are used to scavenge amines. An aldehyde *Wang*-type resin **253**^{41,56,59,122} used for scavenging primary amines in the presence of secondary amines is shown in Figure 60.

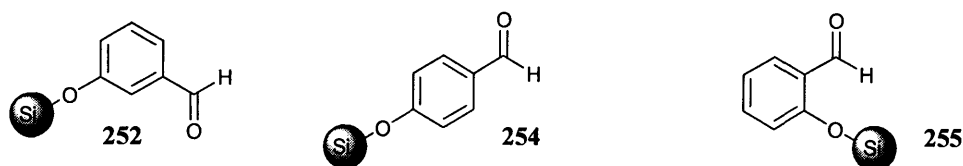
Figure 60



The scavenging group used was 3-hydroxybenzaldehyde (**251**), this was linked to the siloxane backbone using 1,4-benzenedimethanol as crosslinker as shown in scheme 92. This process was catalysed by Et₂NOH as before. The reaction was successful and produced a solid. This solid **252** was dried under vacuum and then washed to constant weight using chloroform, in a filter syringe. A total of 4% mass was lost during this resin washing process. The resin **252** was obtained as a light orange gel in 94% yield. On analysing the resin firstly using IR it was seen that the carbonyl function was still intact as the C=O stretch could be seen at 1696 cm⁻¹. [Found C, 54.4, H, 5.97%, C₇₃₀H₈₁₂O₂₇₆Si₁₀₀ requires C, 52.2, H, 4.83%] The loading is therefore 3.6 mmol/g. The theoretical loading was very close to this amount (3.7 mmol/g).

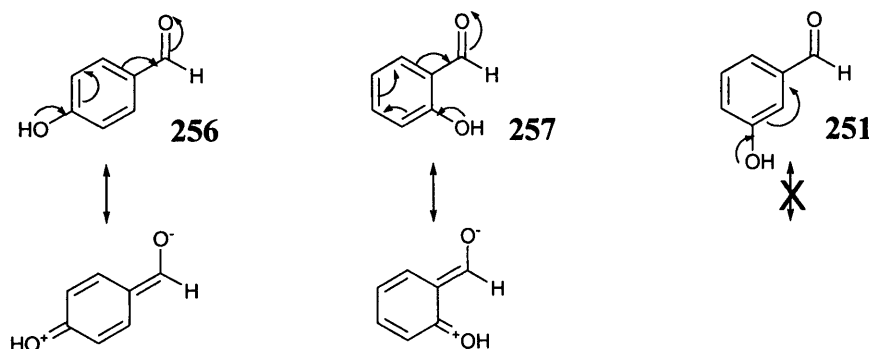
Two other benzaldehydes polymers were prepared (**254** and **255**) and all three were to be tested to see which resin would be the most effective at scavenging for amines. Three different analogues of hydroxybenzaldehyde were used with the hydroxyl functions being in the 2, 3 and 4 positions.

Figure 61



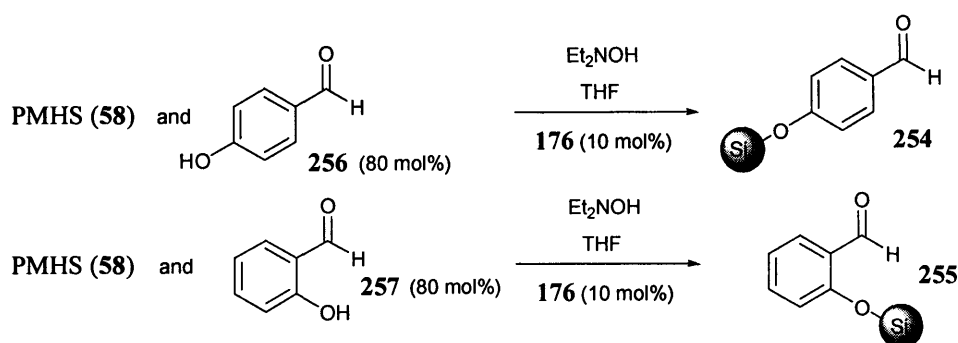
The initial thinking was that the siloxane **252** would be the most effective scavenger due to the positioning of the hydroxyl moiety. As can be seen from in Scheme 93, in the benzaldehydes **256** and **257**, delocalisation of the OH oxygen lone pair is possible. However, with the same group in the 3 position, delocalisation of the lone pair is not possible. It was expected that where electron-donation is possible the carbonyl would be less reactive towards nucleophiles. Therefore the resin **252** derived from the 3-hydroxybenzaldehyde (**251**) should be a more reactive and effective scavenging linker for amines.

Scheme 93



As can be seen from scheme 93, for the benzaldehydes with the hydroxyl function in the 2 and 4-positions, delocalisation is possible, however, with the hydroxyl group in the 3 position delocalisation of the lone pair is not possible, therefore making the 3-hydroxybenzaldehyde a more effective scavenging linker for amines.

Scheme 94



The siloxane polymers incorporating **256** and **257** were prepared as shown in Scheme 94. Siloxane **254** was obtained from the benzaldehyde **256** as a light yellow gel in 95% yield (ν_{\max} 1665 cm^{-1}) [Found C, 52.7, H, 6.08, $\text{C}_{730}\text{H}_{812}\text{O}_{276}\text{Si}_{100}$ requires C, 52.2, H, 4.83%] (loading is 3.5 mmol/g). Siloxane **255** derived from *ortho*-hydroxybenzaldehyde (**257**) was obtained as a light brown gel in 95% yield (ν_{\max} 1664 cm^{-1}) [Found C, 52.5, H, 5.99%, $\text{C}_{730}\text{H}_{812}\text{O}_{276}\text{Si}_{100}$ requires C, 52.2, H, 4.83%] (loading is 3.5 mmol/g).

2.5.2 Scavenging for amines

As outlined above, it was expected that the resins **254** and **255** (derived from 2- and 4-hydroxybenzaldehydes) were going to be less effective than the resin **252** in removing benzylamine from a standard mixture as shown below in Scheme 95. Each resin (0.5 g) was used to scavenge benzylamine (1 mmol) from 2 ml of standard solution.

Scheme 95

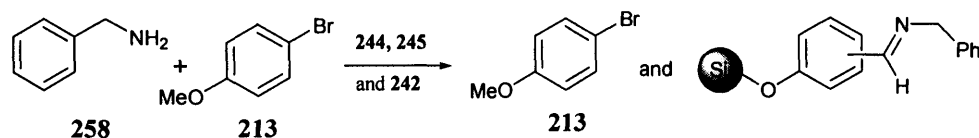


Figure 62: Benzylamine scavenging with benzaldehydes siloxanes 254, 255 and 252

RESIN	EFFICIENCY (%)
<p>254</p>	62
<p>255</p>	55
<p>252</p>	96

*Reaction time overnight, solvent used was THF; 0.5 g of resin was used in 2ml standard scavenging solution (1 mmol of substrate)

Inspection of Figure 63 reveals that this expectation is borne out. The polymer **252**, incorporating 3-hydroxybenzaldehyde, is significantly better than the two other resins. There was some resin decomposition in all three reaction mixtures. The 3-hydroxybenzaldehyde resin **252** was used for the time course experiments to ascertain the best time to run the scavenging reaction. The results are shown below in Figure 63.

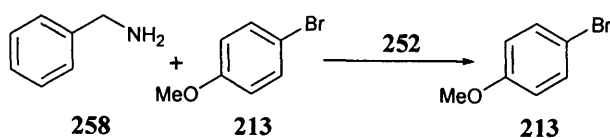


Figure 63: Benzylamine scavenging of **252** with time

Time (h)	Efficiency (%)	Hydroxybenzaldehyde present (%)
1	97	1
2	95	3
5	96	21
10	97	35
16	90	75
24	87	100

*Solvent used was THF; 0.5 g of resin was used in 2 ml standard scavenging solution (1 mmol of substrate)

The optimum time for running the scavenger reaction appears to be about 1 hour due the labile nature of the benzaldehyde linker **251**. If the resin is allowed to react for longer periods of time then it begins to break down in solution. This is illustrated by the ^1H NMR spectra shown in Figures 64 and 65.

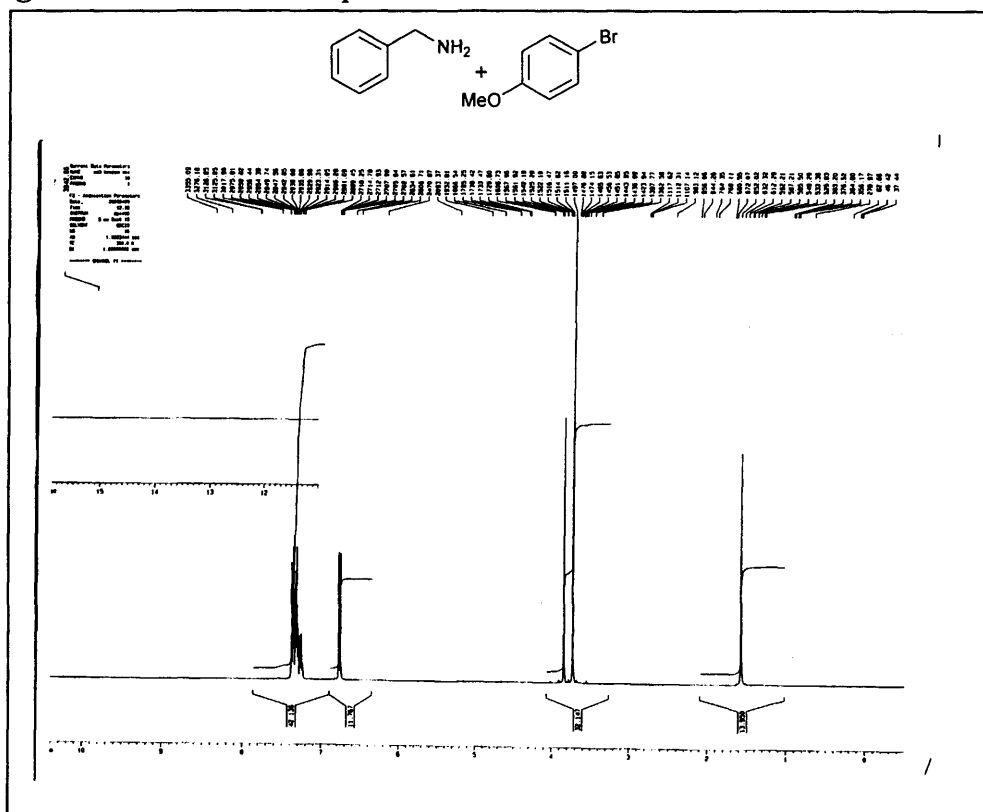
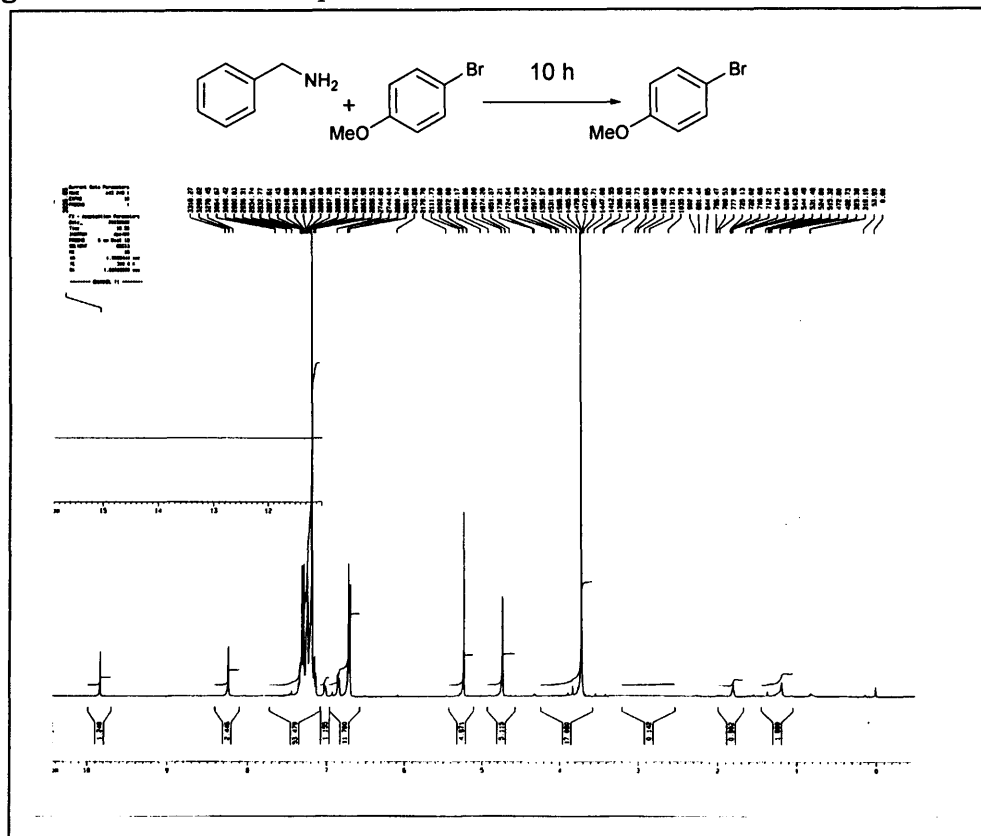



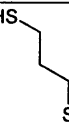
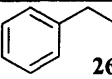
Figure 64: The ^1H NMR spectrum of the standard mixture before addition of **252**

Figure 65: The ^1H NMR spectrum of the mixture after a shake for 10 h with **252****Figure 66:** Effect of different nucleophiles with resin **252**

Substrate	Efficiency (%)	Linker present (%)
 259	5	2
 260	90	4
 261	84	1
 262	0	0
 263	0	2

*Reaction time 1 h, solvent used was THF; 0.5 g of resin **252** was used in 2ml standard scavenging solution (1 mmol of substrate)

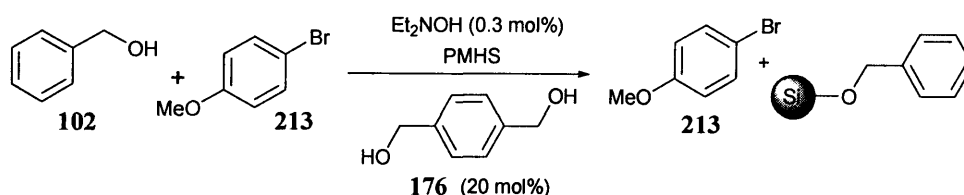
A selection of other amines were tested to see if they too could be scavenged with the aldehyde resin. A scavenging time of 1 hour was used. It can be seen from Figure 69 that

the levels of scavenging vary with the structure of the amine. Changing the substrate from the primary amine benzylamine (**262**) to piperidine (**260**) causes a small change in the scavenging efficiency. This is significant because the reaction between the aldehyde and the secondary amine produces a transient iminium species. This is also observed with the scavenging of pyrrolidine (**261**). However this clearly must be sufficiently stable on the resin for the amine to be removed successfully. Aniline (**259**) is only poorly scavenged, due to its reduced nucleophilicity associated with the delocalisation of the lone pair of the nitrogen into the aromatic ring. Using a longer chain amine such as the propylamine substrate **263** shows none scavenged possibly due to the imine formed may not be as stable as that from benzylamine. We can also see from the Table that the resin is only able to scavenge for amine substrates, as the thiol substrate **262** is not scavenged from solution.

2.6 PMHS and alcohol scavenging – *in situ* polymerisation

Scavengers used to remove alcohols are not found easily in the literature. Flynn and co-workers have reported the use ROMP gel oligomeric acid chlorides to remove alcohols from solution.¹⁶¹ Ladlow *et. al.* have reported the use of small and large diameter bromopolystyrene beads in scavenging alcohols by way of supporting a silane on polystyrene.¹⁶² Both of these methods cited in the literature are high yielding, but require several steps in order to synthesise and then use the scavenger. We therefore attempted to scavenge alcohols from solution as shown in Scheme 96 using the *in situ* polymerisation developed earlier.

Scheme 96



As the best time for this reaction was not known at the outset, a time course was performed, the results of which are shown in Figure 68.

Figure 67

Time (h)	Efficiency (%)
1	100
2	100

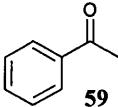
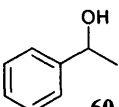
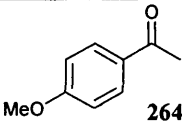
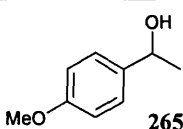
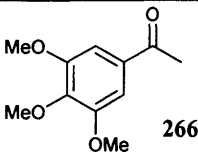
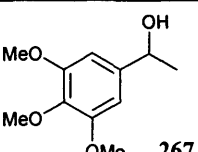
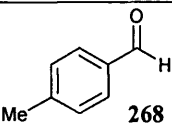
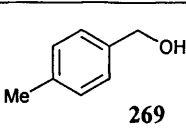
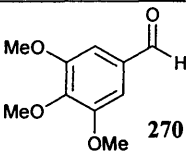
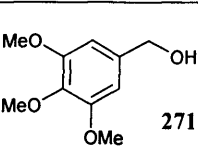
*Solvent used was THF; 0.5 g of PMHS was used in 2ml standard scavenging solution (1 mmol of substrate)



The reaction was complete in 1 h and so it was decided that this was the optimum time scale for the rest of the *in situ* scavenging reactions to be completed. It was not necessary to leave the reactions for longer periods of time.

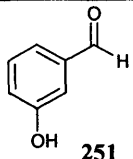
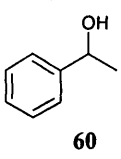
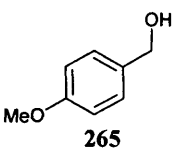
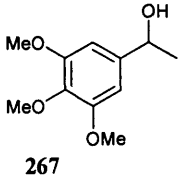
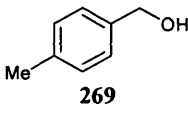
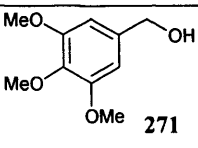
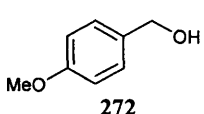
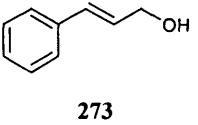
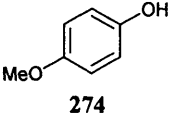
Some of the alcohols shown in Figure 68, needed to be prepared from the corresponding aldehyde or ketone. This was simply a matter of reduction using sodium borohydride. All reactions were high yielding and the products did not require further purification before performing the scavenging reactions.

Figure 68: Synthesis of substrates for the *in situ* polymerisation alcohol scavenge

Aldehyde or ketone used	Yield (%)	Alcohol formed
 59	99	 60
 264	98	 265
 266	99	 267
 268	97	 269
 270	99	 271

Each of the alcohols shown in the Table above were used to produce a standard 1:1 mixture along with a standard and these were used to perform scavenger reactions. It can be seen from Figure 69 that regardless of whether the alcohol is a first or secondary substrate, they are all scavenged equally and successfully removed from solution.

Figure 69: Scavenging different alcohols from solution *in situ*

Substrate	Efficiency (%)	Substrate	Efficiency (%)
 251	100	 60	100
 265	100	 267	100
 269	100	 271	100
 272	100	 273	100
 274	100		

*Reaction time 1 h, solvent used was THF; 0.5 g of PMHS was used in 2ml standard scavenging solution (1 mmol of substrate)

As before the best way to illustrate the efficiency of the scavenging process is by inspection of ^1H NMR spectra. The spectra for the scavenge of *p*-methylbenzyl alcohol is shown in Figures 70 and 71. We can see on comparison of the ^1H NMR spectrum of the 1:1 mixture of the alcohol with bromoanisole with the mixture after the reaction, the alcohol is 100% scavenged from the mixture by the PMHS in the presence of the hydroxylamine catalyst. As can be seen from the results above (Figure 69), the system of *in situ* polymerisation works for a variety of alcohol species. Even phenols are scavenged, something that could possibly not have worked due to the delocalisation of the lone pairs on the oxygen. The result of scavenging alcohol 272 is shown in Figure 72 and 73. The alcohol is successfully scavenged from the standard mixture with 100% scavenging efficiency. Little siloxane material remains in solution after the polymerisation process.

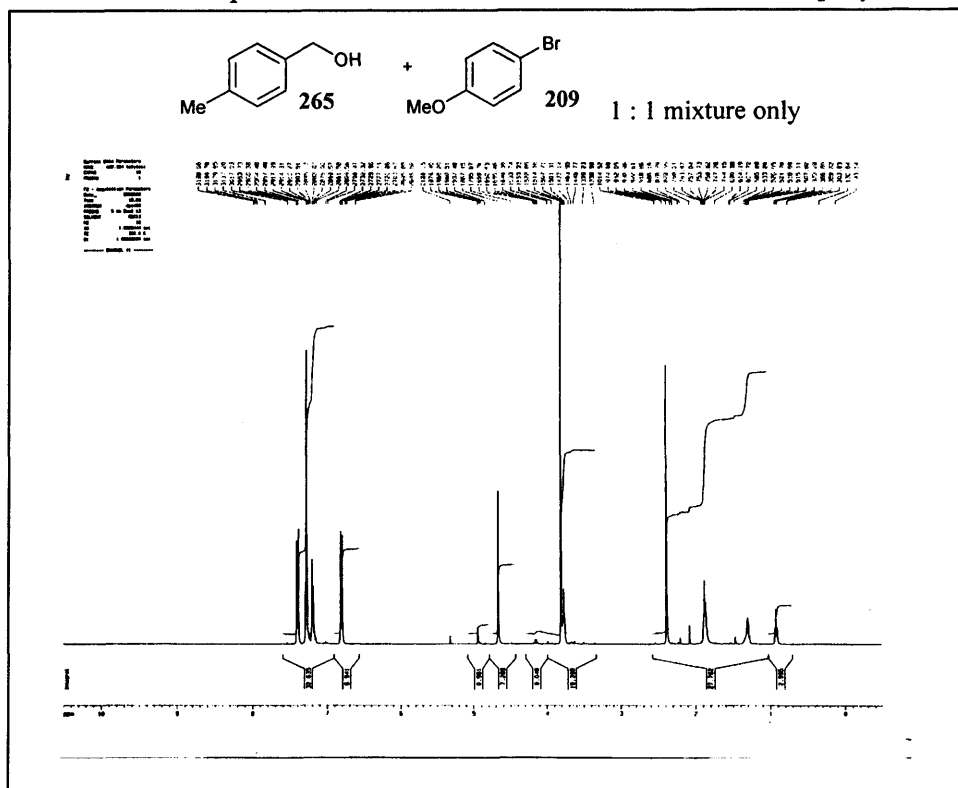
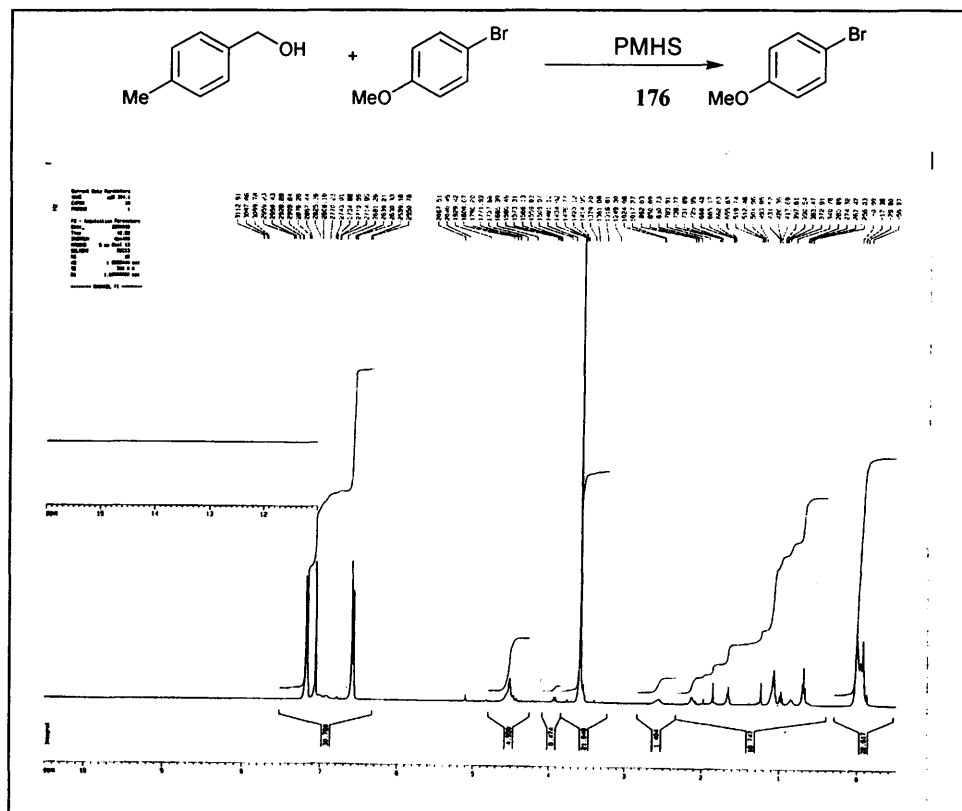
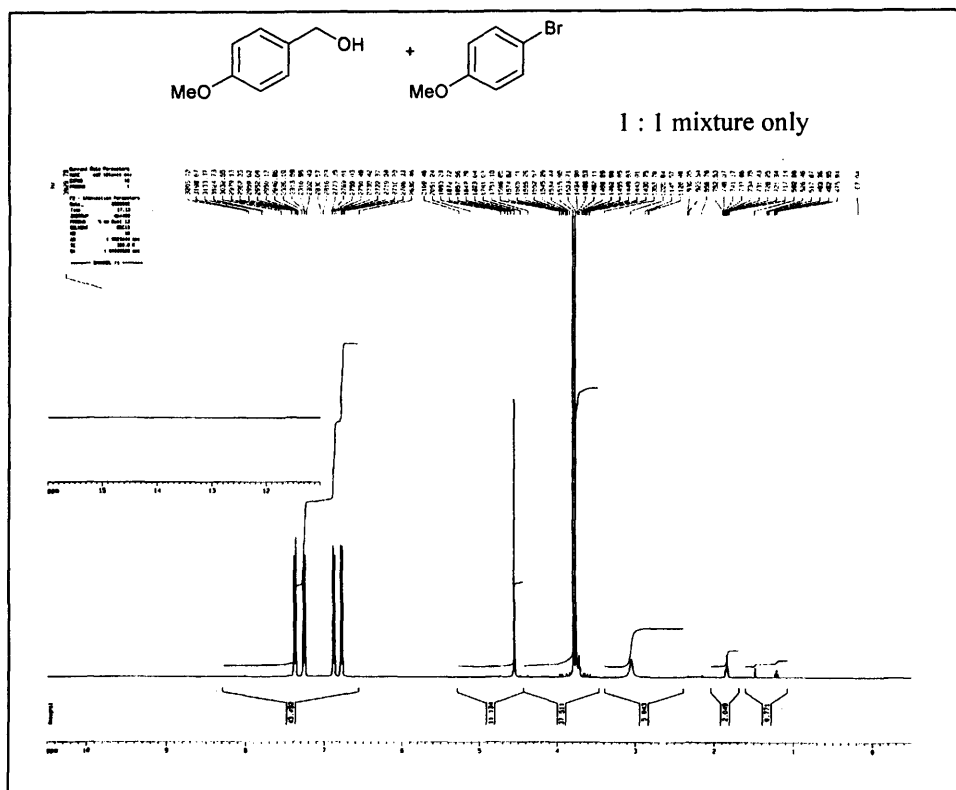
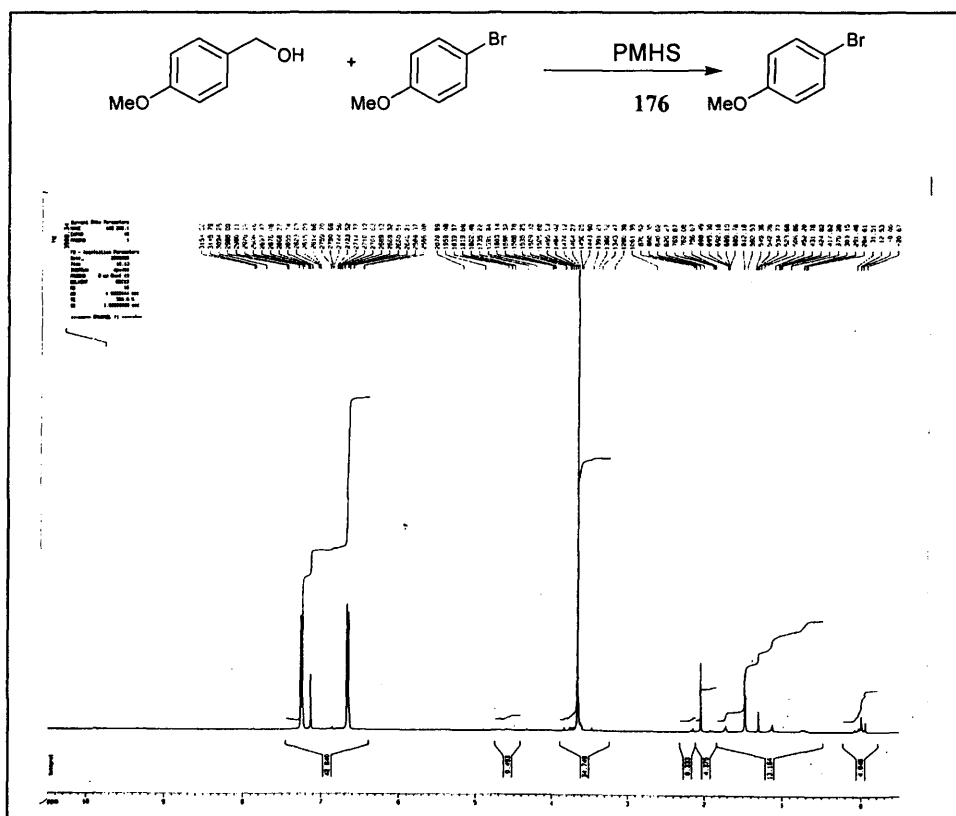
Figure 70: The ^1H NMR spectrum of the mixture of **269** and **213** before polymerisation**Figure 71:** The ^1H NMR spectrum of the mixture of **265** and **209** after polymerisation

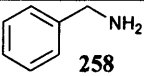
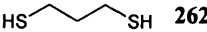
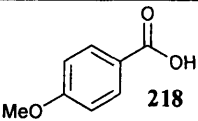
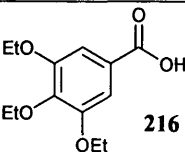
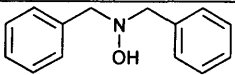
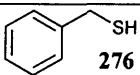
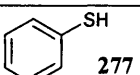
Figure 72: The ^1H NMR spectrum of the mixture of **272** and **213** before polymerisation**Figure 73:** The ^1H NMR spectrum of the mixture of **272** and **213** after polymerisation

2.6.1 Scavenging for different functional groups

The *in situ* polymerisation reaction clearly works well for scavenging alcohols from solution. We next decided to study the functional group selectivity of this technique. A variety of substrates possessing NH, OH and SH functionality were tested varying from acids to thiols. The results are shown in Figure 75.

As can be seen from Figure 74, the reactions show that the *in situ* scavenging reaction works only with a molecule possessing a hydroxyl functionality (i.e. the hydroxylamine **275** and carboxylic acids such as **216**, **218**). These three substrates are scavenged but not as well as alcohols. We have already observed that carboxylic acids are problematic with other siloxane polymers. The two carboxylic acids may also reduce the effectiveness of hydroxylamine as a catalyst as they may simply react and form a salt. All the other molecules having NH (**258**) and SH groups (**262**, **276** and **277**) are not scavenged. The process shows remarkable selectivity. This will therefore allow the possible selective scavenge of an alcohol in the presence of an amine. The selective reaction of alcohols with silanes must be related to the greater strength of the silicon-oxygen bond.

Figure 74: *In situ* polymerisation scavenging of other functional groups.

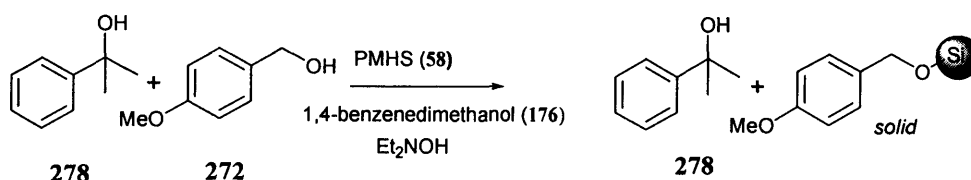
Substrate	Efficiency (%)
 258	0
 262	0
 218	75
 216	50
 274	60
 276	0
 277	0

*Reaction time 1 h, solvent used was THF; 0.5 g of PMHS was used in 2ml standard scavenging solution (1 mmol of substrate)

2.6.2 Scavenging from a 3 component mixture

The potential selectivity of the *in situ* polymerisation reaction was demonstrated further by the scavenge of a primary alcohol in the presence of a tertiary one. We have already shown that primary and secondary alcohols are readily scavenged by the *in situ* polymerisation process. The reaction was therefore conducted using a mixture of the primary alcohol **272** and the tertiary alcohol **278** as is shown in Scheme 96. [0.5 g (8.3 mmol) of PMHS was used in 2 ml (1 mmol) of standard solution].

Scheme 97



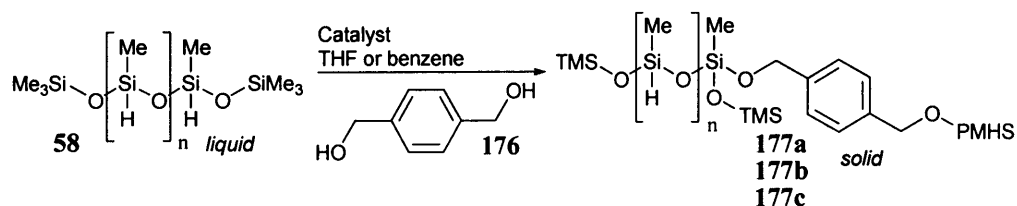
This reaction was selective in that the primary alcohol could be scavenged in the presence of the tertiary, the latter being left in solution with the standard. Hence, the reaction was successful with an efficiency of 99% with respect to primary alcohol scavenged.

2.6.3 Summary, Conclusions and Limitations

There are many successes that have arisen from this study. The main goal of synthesising supported scavengers was achieved. This is a new project in the research group, with no prior work from colleagues here at Cardiff. The results in this study have just started to scratch the surface of what we hope will be a much bigger story. Some of the successes are summarised below.

Beginning with the crosslinked resins **177a**, **177b** and **177c**. These were synthesised using three different catalysts, TBAF, Wilkinson's and Et_2NOH . The intention was to utilise the resins formed to reduce acetophenone. However after attempting this reduction with crosslinked PMHS **58** in the presence of DBATO, $\text{Ti}(\text{iPrO})_4$ and TBAF, no reaction was observed. Nevertheless the synthesis of the solid polymers was a significant advance, as they constituted the first examples in our group when we had intentionally effected the state-change of PMHS from liquid to solid.

Scheme 98



Without covering results already discussed, the hydroxylamine catalyst Et_2NOH proved to be the most successful catalyst for resin synthesis. It was also both a cheap and easily handled catalyst. DMAP resin **212** and pyridine resin **189b** (Figure 75) were synthesised using this catalyst.

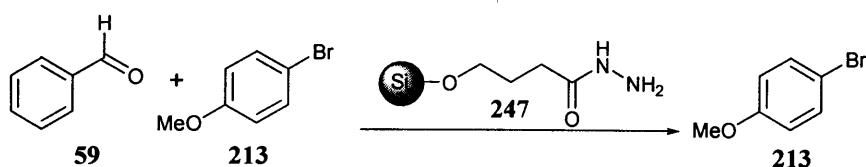
Figure 75



There are limitations with these resins. This arises from the labile nature of the Si-O bond between the linker and the PMHS backbone. When the resins are left for long periods of time within a reaction mixture or standard solution, it causes leeching of the DMAP or pyridine linker from the resin. This is more pronounced when the reaction is performed in non-anhydrous solvents. Therefore, to avoid this effect, a minimum reaction time was established of 1 hour and this time was applied to all scavenging reactions. The resins are not resilient to acidic and basic conditions and hence attempting to scavenge carboxylic acids causes breakdown of the resins. The DMAP and pyridine resins can however, be used to scavenge benzyl halides and cinnamyl halides without causing removal of the DMAP and pyridine linkers.

Another scavenger resin synthesised using Et_2NOH was hydrazine resin **247**. This was used to scavenge aldehydes. However, leeching of the linker was observed. This led to the development of the *in situ* crosslinking process. The process was performed to scavenge aldehydes, by inclusion of the hydroxyhydrazine **244** and benzenedimethanol **176** followed by *in situ* polymerisation (Scheme 99).

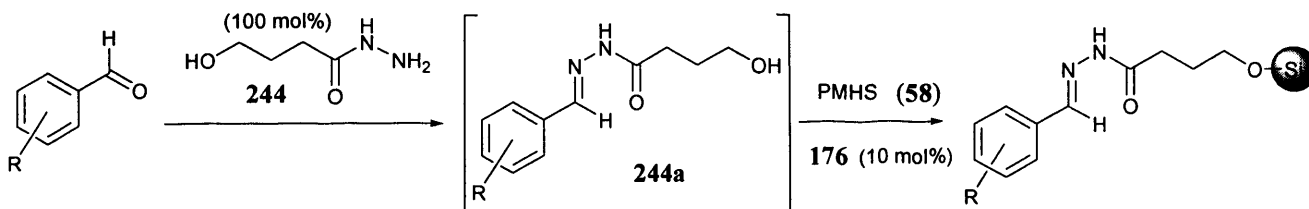
Scheme 99



In this technique the aldehyde scavenging reaction was performed in solution and then *in situ* polymerisation, effectively the PMHS was used to remove the 'alcohol' intermediate from

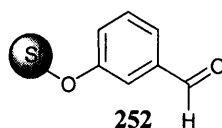
solution. This was a much more successful technique than the supported reagent method. This technique is probably so successful because the Si-O bond to the linker is formed only when it is required and is only exposed to reaction conditions, reagents etc. for a short period of time.

Scheme 100



An aldehyde was attached to the PMHS backbone to be used as a scavenger for amines. Resin **252** was attached using Et_2NOH as the catalyst. After testing with a variety of substrates, the resin was seen to be more selective for primary amines than secondary amines.

Figure 76

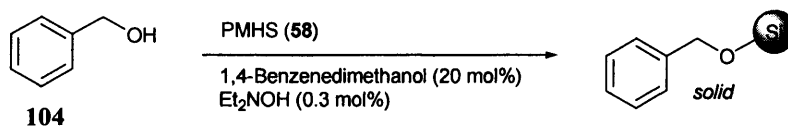


However, aniline and propylamine were poorly scavenged due to their poor nucleophilicities, the former due to delocalisation effects and the latter due to steric effects. Reaction times were kept to 1 hour to prevent the linker from being removed from its attachment on the PMHS backbone.

The stability of the commercial resins is greater in the presence of all substrates, whereas the synthesised resins had the problem of linker leeching, this would be remedied by more development work using these PMHS supported resins. For the moment, the scavenging of benzyl bromides and cinnamyl halides caused no problems to the synthesised resins.

Following on from the previously mentioned *in situ* polymerisation. A variety of alcohols and carboxylic acids were scavenged from standard solutions using the technique. Any molecule possessing a hydroxyl function could be scavenged successfully from solution (Scheme 100). Tertiary alcohols could not be scavenged due to steric effects.

Scheme 101



The work discussed here is by no means complete. The proof-of-principle exemplified with a number of scavenging processes should be applicable to a variety of other scavenging processes. Many more developments in this new and exciting area of polymer supported reagents are envisioned.

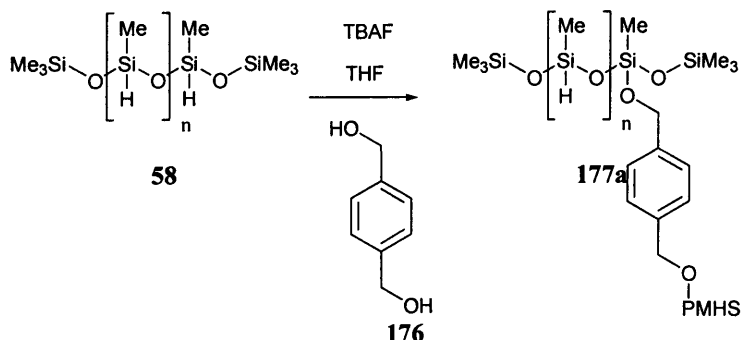
3. EXPERIMENTAL

General

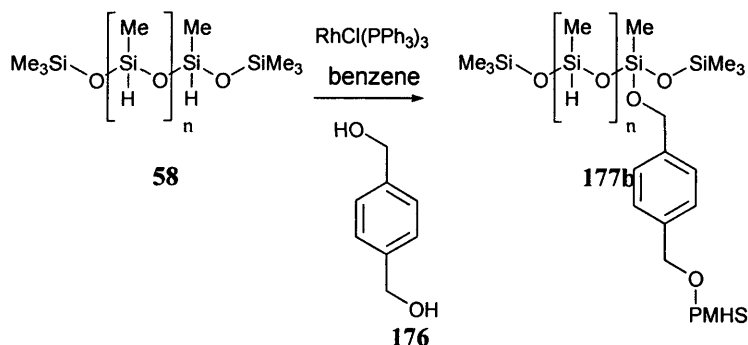
All ^1H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker DPX-400 spectrometer, with ^{13}C spectra being recorded at 100MHz. The following abbreviations were used; s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet etc; all coupling constants are measured in Hertz (Hz). The abbreviations δ_{H} and δ_{C} denote ^1H and ^{13}C NMR, respectively, taken at 300K. Chemical shifts abbreviations (δ_{H} and δ_{C}) are reported in parts per million (ppm) from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 (CHCl_3) ppm for ^1H NMR and 77.30 (CHCl_3), centre line, for ^{13}C NMR. Unless stated, deuteriochloroform was used as a solvent for NMR measurements.

Mass spectra were obtained using a Fisons VG platform II spectrometer. High resolution mass spectra were obtained by the EPSRC mass spectrometry service, Swansea. Melting points were determined on a Kofler Hot Stage Micro Melting Point Apparatus and are uncorrected. Infrared spectra were recorded in the range $4000\text{-}600\text{cm}^{-1}$ using a Perkin-Elmer 1600 series spectrophotometer as thin films, or as Nujol mulls on sodium chloride plates. Thin Layer Chromatography (TLC) was performed on Merck 5554 60F silica gel coated aluminium plates and detection was effected with a solution of potassium permanganate, followed by heating the plates or by using a UV lamp. Purification of compounds was achieved by medium pressure chromatography using Merck 9385 60 silica gel.

All reactions using air / moisture sensitive reagents were performed in oven-dried or flame-dried apparatus, under a nitrogen atmosphere. Anhydrous ethyl acetate was obtained by pre-drying with dried magnesium sulfate and then fresh distillation from calcium hydride and anhydrous diethyl ether was obtained by distillation from sodium benzophenone ketyl. Dry tetrahydrofuran was obtained through fresh distillation from sodium wire and dry dichloromethane was obtained by distillation from calcium hydride. Anhydrous benzene and toluene were obtained by allowing each to stand over sodium wire for 24 hours prior to use.

Cross-linked PMHS **177a**

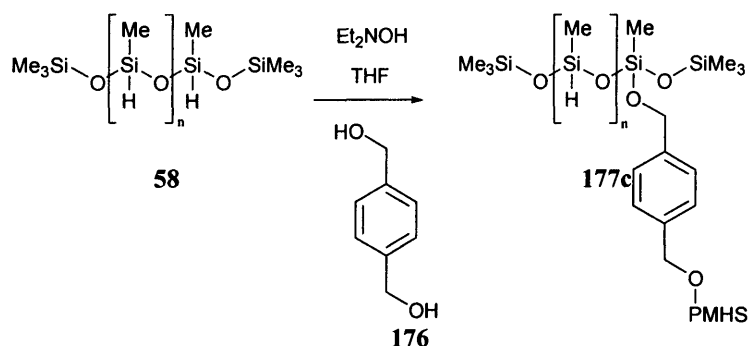
(PMHS) (**58**) (0.3 g, 5 mmol) was weighed into a 10 ml vial. 1,4-Benzenedimethanol (**176**) (13.8 mg, 0.10 mmol) was dissolved in a portion of THF (2.5 ml) and placed in the vial along the other reactants. TBAF (13.1 mg, 0.05 mmol) was then dissolved in another portion of THF (2.5 ml) and this was added via syringe to the stirring mixture. It was left stirring overnight and a white solid **177a** was formed. The solvent was removed *in vacuo* and the solid became very fine powder. This was taken, placed into a filter syringe and washed to constant weight by washing several times with chloroform. The final product was a white, free flowing solid (0.297 g, 95%) ν_{max} (neat on lens plate)/ cm^{-1} , 2985 (br, st), 1665 (st), 1585 (st), 1511 (st), 1449 (st); (based on 100 polymer units) Found C, 26.3, H 5.68%, $\text{C}_{260}\text{H}_{540}\text{O}_{140}\text{Si}_{100}$ requires C, 35.8, H, 6.21%.

Cross-linked PMHS **177b**

Following the method used by Boudjouk *et al*¹⁵⁰ a 5ml one necked round bottomed flask was equipped with condenser and nitrogen balloon, was placed 1,4-benzenedimethanol (**176**) (0.138 g, 1 mmol), PMHS (**58**) (0.3 g, 5 mmol), benzene (2.5 ml) and $\text{RhCl}(\text{PPh}_3)_3$ (46.2 mg, 0.05 mmol). The mixture was refluxed overnight. The red colour of the catalyst disappeared within 15 minutes of stirring and the mixture became yellow and homogenous. As the reaction proceeded, the yellow colour turned to dark orange and returned to red when the reaction was complete (typically 20 h). During the course of the reaction a gas evolved (probably H_2). The solvent was removed *in vacuo* to leave an orange coloured resin **177b**.

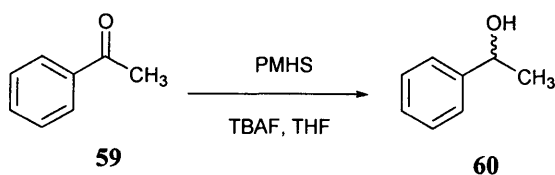
The resin was washed with chloroform several times until the resin weight became constant (0.408 g, 98%). ν_{\max} (neat on lens plate)/ cm^{-1} , 3162 (br, st), 2174 (st), 1665 (st), 1585 (st), 1511 (st), 1449 (st); (based on 100 polymer units) Found C, 22.3, H, 6.88, $\text{C}_{260}\text{H}_{540}\text{O}_{140}\text{Si}_{100}$ requires C, 35.8, H, 6.21%.

Cross-linked PMHS 177c



Following the method of Gentle *et al.*¹⁵¹ a 100 ml one necked round bottomed flask was equipped with condenser and nitrogen balloon, was placed 1,4-benzenedimethanol (**176**) (1.38 g, 10 mmol), PMHS (**58**) (3 g, 50 mmol), and THF (50 ml). Et_2NOH (50 μl , 0.5 mmol) was injected into the mixture after all the substituents had dissolved. As the reaction proceeded a gas evolved (probably H_2), the mixture was left stirring overnight. The solvent was removed *in vacuo* to leave a light orange coloured resin **177c**. The resin was washed several times with chloroform until the weight of the resin stabilised (4.02 g, 97%). ν_{\max} (neat on lens plate)/ cm^{-1} , 3162 (br, st), 2168 (st) 1665 (st), 1585 (st), 1511 (st), 1449 (st); Found C, 20.3, H, 7.12, $\text{C}_{260}\text{H}_{540}\text{O}_{140}\text{Si}_{100}$ requires C, 35.8, H, 6.21%.

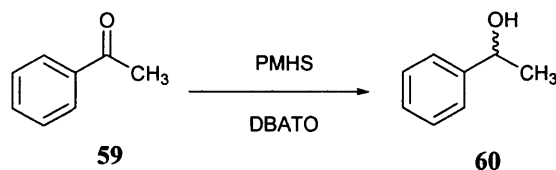
Reduction of acetophenone using PMHS and TBAF



The method of Drew, Lawrence *et al.*⁸³ was used. To a stirred mixture of acetophenone (**59**) (120 mg, 1 mmol) and TBAF (5.223 mg, 0.02 mmol) in anhydrous THF (2ml) was added polymethylhydrosiloxane (90 mg, 1.5 mmol). The mixture was stirred at room temperature until the reaction was complete (by t.l.c.). Sodium hydroxide (5 ml of a 3 N solution) was added dropwise. After stirring vigorously overnight the solution was extracted with diethyl ether (3 \times 15 ml). The combined organic extracts were washed with water, dried over MgSO_4 , filtered and evaporated *in vacuo*. The final product **60** was a pale yellow oil (118

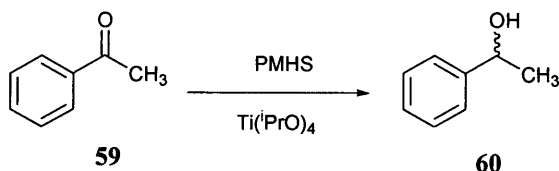
mg, 97%). ν_{\max} (neat on NaCl plates)/ cm^{-1} , 3462 (br, st), 2879 (md), 1500 (st), 1462 (md), 1070 (st), δ_{H} (400 MHz; CDCl_3), 7.24 (5H, m, aromatic), 4.85 (1H, q, $J=6.4$ Hz), 2.67 (1H, s, OH), 1.47 (3H, d, $J=6.4$ Hz).

Reduction of acetophenone using PMHS and DBATO



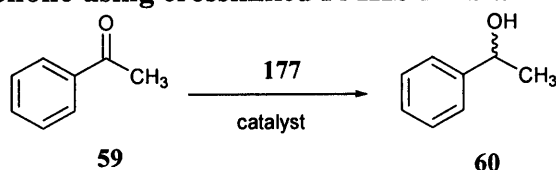
This was carried out following a method developed by Lawrence *et al.*³¹ To a solution of acetophenone (120 mg, 1 mmol) was added DBATO (73.4 mg, 0.2 mmol) in dry ethanol. PMHS (90 mg, 1.5 mmol) was added and the reaction was stirred at room temperature until it was complete (by t.l.c.). The product was purified by column chromatography (CHCl_3) to give the final product as a yellow oil (119 mg, 99%). ν_{\max} (neat on NaCl plates)/ cm^{-1} , 3465 (br, st), 2881 (md), 1498 (st), 1461 (md), 1065 (st), δ_{H} (400 MHz; CDCl_3), 7.24 (5H, m, aromatic), 4.85 (1H, q, $J=6.4$ Hz), 2.67 (1H, s, OH), 1.47 (3H, d, $J=6.4$ Hz).

Reduction of acetophenone using PMHS and $\text{Ti}(\text{iPrO})_4$



The method of Breeden and Lawrence was used.⁸² PMHS (90 mg, 1.5 mmol) was placed in a 25 ml round bottomed flask along with acetophenone (**59**) (120 mg, 1 mmol), $\text{Ti}(\text{iPrO})_4$ (284 mg, 1 mmol) and THF (2ml). The mixture was refluxed overnight and then allowed to cool. 1 M NaOH (15 ml) was added. This was allowed to stir for 1 h. The organic layer was extracted with diethyl ether (3×20 ml). The combined organic extracts were dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The product was obtained as a light yellow oil (117 mg, 96%). ν_{\max} (neat on NaCl plates)/ cm^{-1} , 3460 (br, st), 2885 (md), 1510 (st), 1464 (md), 1073 (st), δ_{H} (400 MHz; CDCl_3), 7.24 (5H, m, aromatic), 4.85 (1H, q, $J=6.4$ Hz), 2.67 (1H, s, OH), 1.47 (3H, d, $J=6.4$ Hz).

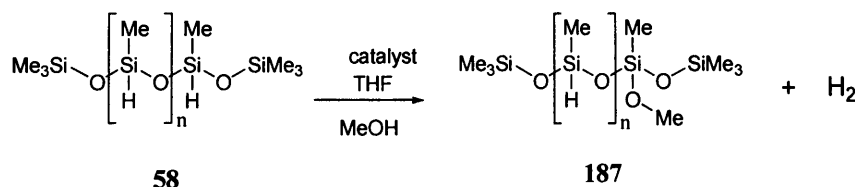
Reduction of acetophenone using crosslinked PMHS 177b and 177c



catalysts = DBATO, TBAF, $\text{Ti}(\text{iPrO})_4$

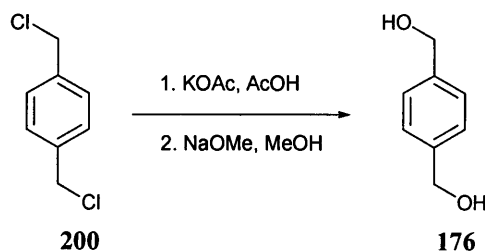
Using the above procedures, and substituting crosslinked PMHS in each procedure, the reactions were carried out but were unsuccessful.

Test of catalysts to establish mechanism: General procedure

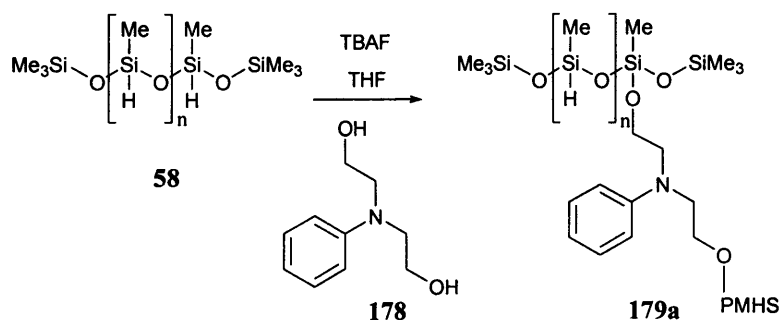


PMHS (**58**) (0.5 g, 8.33 mmol) was placed in a 10 ml round bottomed flask which was connected to a manometer to measure the volume of gas evolved. To this was added MeOH (2.5 ml) and THF (2.5 ml). The catalyst (0.5 mmol) was then added and the mixture was left stirring and the volume of gas was left to collect. (Refer to results and discussion section).

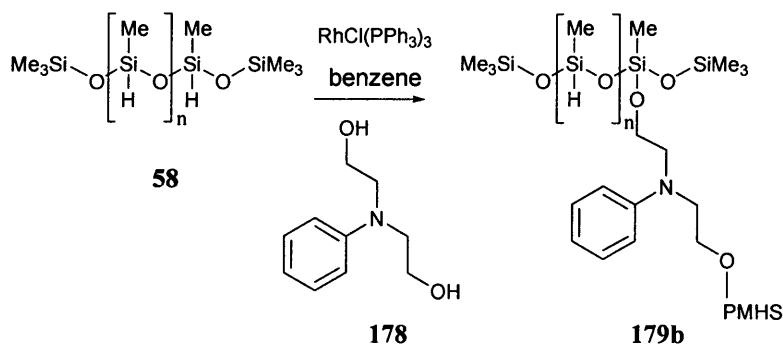
1,4-Benzenedimethanol (**176**)⁹²



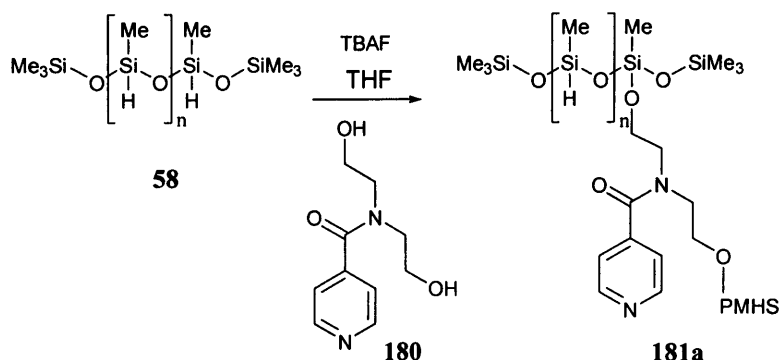
α,α' -Dichloro-*p*-xylene (**200**) (25 g, 144 mmol) was dissolved in acetic acid (100 ml) in a 250 ml round bottomed flask equipped with a condenser. KOAc (25 g, 255 mmol) was added and the reaction was refluxed overnight. The acetic acid was evaporated under vacuum and then MeOH (50 ml) was added followed by NaOMe (30 ml), the mixture was then heated for 10 minutes and 1M HCl was added dropwise until the pH of the mixture was approximately 2. The methanol was removed *in vacuo* and water (200 ml) was added and the mixture was cooled to give the final product as a white powder **176** (18.5 g, 93%). δ_{H} (400 MHz; CDCl_3), 4.99 (4H, aromatic, s), 4.59 (4H, s).

Diethanolamine resin **179a**

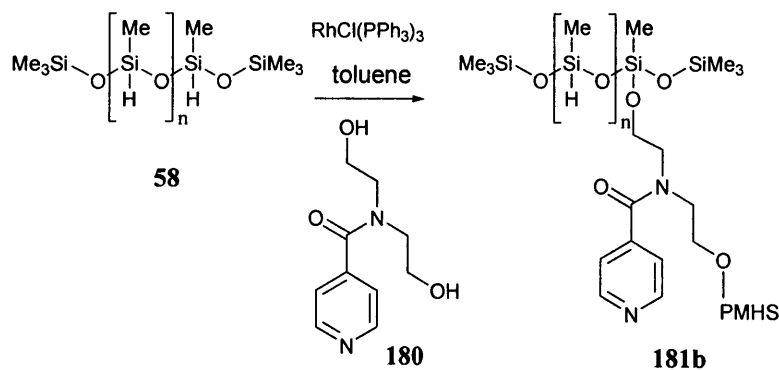
PMHS (**58**) (0.3 g, 5 mmol), *N*-phenyldiethanolamine (**178**) (0.386 g, 2.1 mmol) and THF (5ml) were placed in a round bottomed flask equipped with magnetic stirrer and condenser. TBAF (13.1 mg, 0.05mmol) was dissolved in some THF (5 ml) and this was added dropwise to the stirring mixture. This resulted in rapid formation of a white solid **179a**. The solvent was removed *in vacuo* to leave a white powder like polymer. This was washed using chloroform to constant weight (0.672 g, 97%). (based on 100 polymer units) Found C, 30.9, H, 7.54, N, 1.80% $C_{520}H_{904}N_{42}O_{184}Si_{100}$ requires C, 46.5, H, 6.73, N, 4.37%. The loading was 1.3 mmol/g.

Diethanolamine resin **179b**

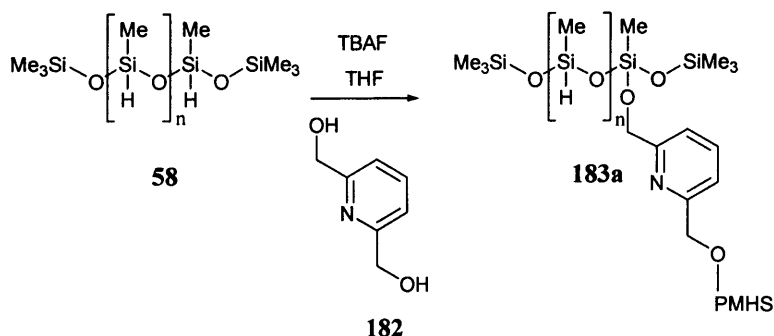
Following the same procedure as used for **179a**. PMHS (**58**) (0.3 g, 5 mmol), *N*-phenyldiethanolamine (**178**) (0.386 g, 2.1 mmol), $RhCl(PPh_3)_3$ (46.2 mg, 0.05mmol) and THF (5ml) were combined. The solvent was removed *in vacuo* to leave an orange coloured resin **179b**. This was washed using chloroform to constant weight (0.675 g, 98%). (based on 100 polymer units) Found C, 32.1, H, 7.44, N, 1.77 $C_{520}H_{904}N_{42}O_{184}Si_{100}$ requires C, 46.5, H, 6.73, N, 4.37%. The loading was 1.3 mmol/g.

Isonicatinamide resin 181a

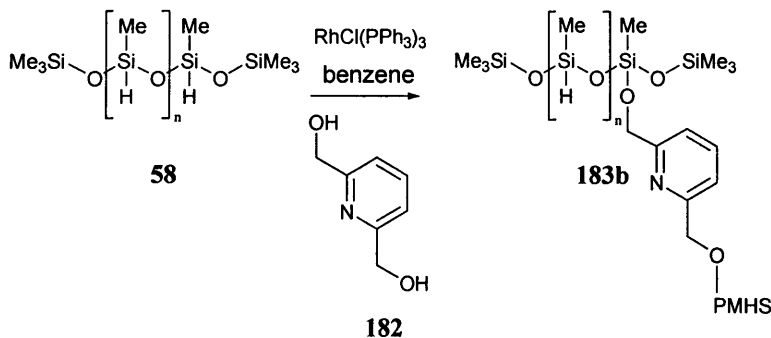
A 10 ml round bottomed flask equipped with magnetic stirrer and condenser and nitrogen inlet had PMHS (**58**) (0.3 g, 5 mmol), *N,N*-bis(2-hydroxyethyl)isonicatinamide (**180**) (0.410 g, 2 mmol) and THF (5ml) were placed in it. TBAF (13.1 mg, 0.05 mmol) was dissolved in some THF (5 ml) and this was added dropwise to the stirring mixture. This resulted in rapid formation of a white solid **181a**. The solvent was removed *in vacuo* to leave a white powder like polymer. This was washed using chloroform to constant weight (0.676 g, 95%). (based on 100 polymer units) Found C, 31.6, H, 7.55, N, 3.13% $C_{460}H_{640}N_{80}O_{260}Si_{100}$ requires C, 38.8, H, 4.49, N, 7.87%. The loading was calculated as 1.1 mmol/g.

Isonicatinamide resin 181b

This reaction was carried out following the same procedure as that for **181a**. PMHS (**58**) (0.3 g, 5 mmol), *N,N*-bis(2-hydroxyethyl)isonicatinamide (**180**) (0.410 g, 2 mmol) and THF (5ml), $RhCl(PPh_3)_3$ (46.2 mg, 0.05 mmol) were combined. The solvent was removed *in vacuo* to leave an orange coloured resin **181b**. This was washed using chloroform to constant weight (0.669 g, 94%). (based on 100 polymer units) Found C, 30.3, H, 7.12, N, 3.01 $C_{460}H_{640}N_{80}O_{260}Si_{100}$ requires C, 38.8, H, 4.49, N, 7.87%. The loading was calculated to be 1.1 mmol/g.

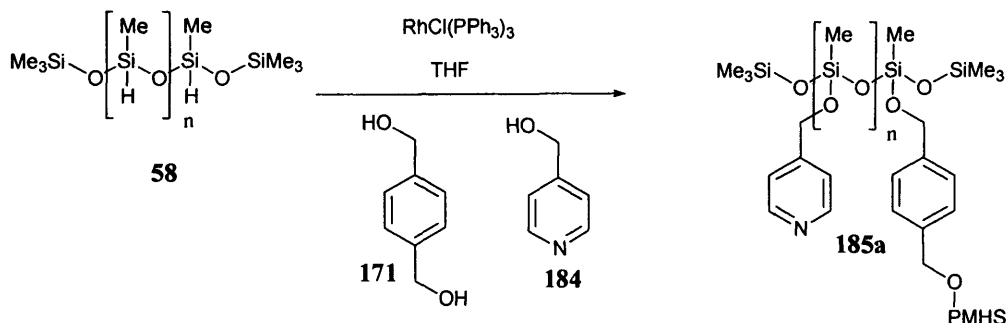
Pyridine resin **183a**

A 10 ml round bottomed flask equipped with magnetic stirrer and condenser was charged with 2,6-pyridinedimethanol (**182**) (0.278 g, 2 mmol), PMHS (**58**) (0.3 g, 5 mmol), and THF (5ml). TBAF (13.1 mg, 0.05mmol) was dissolved in some THF (5 ml) and this was added dropwise to the stirring mixture. This resulted in rapid formation of a white solid **183a**. The solvent was removed *in vacuo* to leave a white powder like polymer. This was washed using chloroform to constant weight (0.658 g, 96%). (based on 100 units) Found C, 24.8, H, 7.28, N, 0.81% $\text{C}_{436}\text{H}_{568}\text{N}_{56}\text{O}_{12}\text{Si}_{100}$ requires C, 41.0, H, 4.45, N, 6.14%. The loading was calculated to be 0.6 mmol/g.

Pyridine resin **183b**

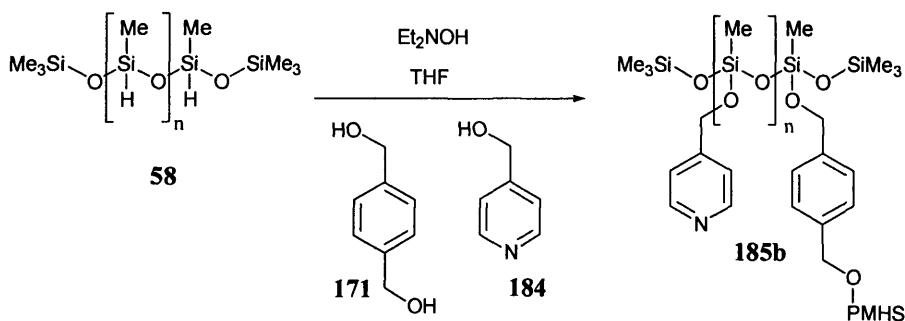
Following the procedure for **183a**, the reagents were combined using an identical procedure. 2,6-pyridinedimethanol (**182**) (0.278 g, 2 mmol), PMHS (**58**) (0.3 g, 5 mmol), $\text{RhCl}(\text{PPh}_3)_3$ (46.2 mg, 0.05mmol) and THF (5ml) gave an orange coloured resin **183b**. This was washed using chloroform to constant weight (0.652 g, 95%). (based on 100 polymer units) Found C, 25.7, H, 6.54, N, 0.83 $\text{C}_{436}\text{H}_{568}\text{N}_{56}\text{O}_{212}\text{Si}_{100}$ requires C, 41.0, H, 4.45, N, 6.14%. The loading was calculated to be 0.7 mmol/g.

Pyridine resin 189a



The reagents were combined using the procedure for **183a**. 1,4-benzenedimethanol (**171**) (0.208 g, 1.5 mmol), PMHS (**58**) (0.9 g, 15 mmol), 4-pyridinedimethanol (**184**) (0.139 g, 12 mmol), $\text{RhCl(PPh}_3)_3$ (46.2 mg, 0.05 mmol), and THF (5 ml) gave an orange coloured resin **185a**. This was washed using chloroform to constant weight (1.19 g, 95%). (based on 100 units) Found C, 48.1, H, 7.03, N, 5.54% $\text{C}_{740}\text{H}_{940}\text{N}_{80}\text{O}_{300}\text{Si}_{100}$ requires C, 47.9, H, 5.07, N, 6.04%. The loading was calculated to be 4.0 mmol/g.

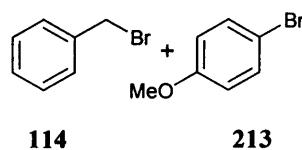
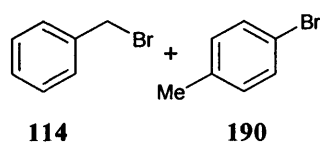
Pyridine resin 189b



PMHS (**58**) (9 g, 150 mmol), 4-pyridinedimethanol (**184**) (13.9 g, 120 mmol), 1,4-benzenedimethanol (**172**) (2.08 g, 15 mmol) and THF (250 ml) were placed in a round bottomed flask equipped with magnetic stirrer and condenser. Et_2NOH (300 μl , 0.5 mmol) was placed with the reagents and the mixture was stirred overnight. During the course of the reaction, effervescence was seen and a gas evolved (probably H_2). The solvent was removed *in vacuo* to leave a light orange coloured resin. The pyridine resin **185b** was taken, washed firstly using chloroform several times using a filter syringe and vacuum chamber to force the solvent through using suction. After each set of washes the solvent was removed *in vacuo* to check if the resin mass became constant. When this was complete a second wash cycle using a 'swell/shrink' process using DCM, Et_2O and THF in that order to flush out remaining impurities from the resin (23.42 g, 93%). (based on 100 polymer units) Found C, 31.9, H,

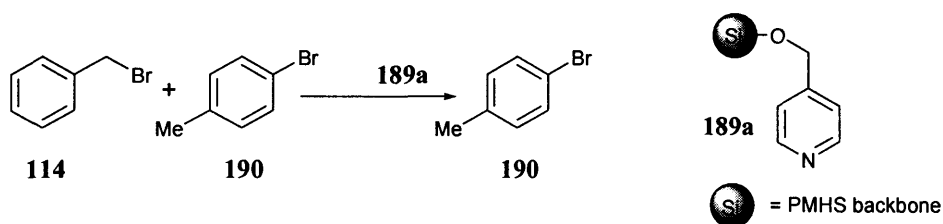
4.99, N, 3.69% $C_{740}H_{940}N_{80}O_{300}Si_{100}$ requires C, 47.9, H, 5.07, N, 6.04%. The loading was calculated to be 2.6 mmol/g.

Preparation of standard solution of benzyl bromide and other substrates



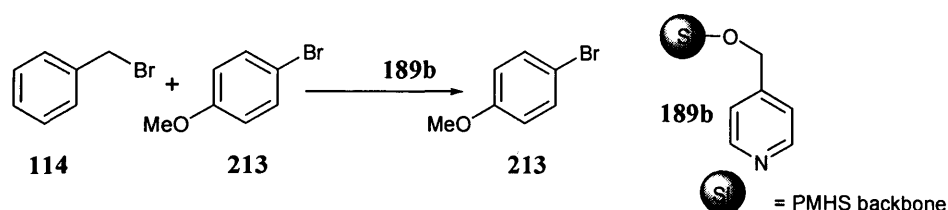
The standard mixture was prepared by placing benzyl bromide (8.5 g, 0.05 mol) and bromotoluene (8.5 g, 0.05 mol) into solvent ($CHCl_3$ or THF) (100 ml). The mixture was shaken and then allowed to settle for 5 minutes before use. This procedure was repeated and used with other substrates used in later scavenger reactions; it was also altered using bromoanisole as the standard. Each standard mixture was checked by 1H NMR before use.

Scavenging for benzyl bromide using pyridine resin 189a



The pyridine resin (**189a**) was taken, washed firstly using chloroform several times using a filter syringe and dried carefully under vacuum. Then a standard mixture of benzyl bromide (**114**) and 4-bromotoluene (**190**) in THF (1 ml, 0.5 mmol) was taken and placed with the resin (0.5 g, 1.9 mmol). The mixture was shaken for 1 h and then the solution was filtered and the solvent removed *in vacuo*. The residue was taken up in $CDCl_3$ and an NMR spectrum was obtained.

Time course experiment using pyridine resin 189b



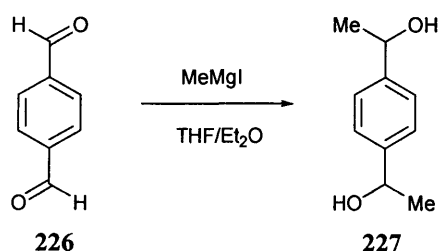
Pyridine resin **189b** (0.5 g, 1.3 mmol) was placed into a filter syringe and to this was added a standard mixture of benzyl bromide (**114**) and 4-bromoanisole (**213**) in THF (1 ml, 0.5 mmol). The mixture was shaken for the times shown in the table 5 (refer to Results and

Discussion chapter). After the designated time, the filtrate was removed and the solvent was removed *in vacuo*. The residue was taken up in CDCl_3 and an ^1H NMR was obtained.

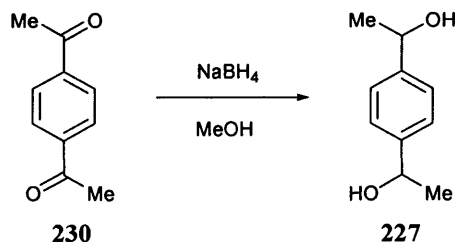
Scavenger testing using pyridine resin 189b: General procedure

A small amount of the pyridine resin (**189b**) (1.3 mmol) was placed into a filter syringe and to this was added a standard mixture of different substrates shown in the table 6 (Refer to Results and discussion section) and 4-bromoanisole (**213**) in THF (2 ml, 1 mmol). The mixture was shaken for 1 h. After this time, the filtrate was removed and the solvent was removed *in vacuo*. The residue was taken up in CDCl_3 and an ^1H NMR was obtained. The results are shown in table 5 (Refer to Results and discussion section).

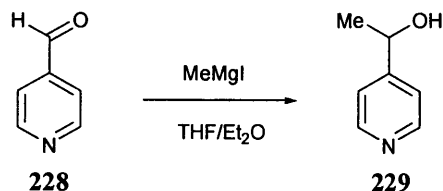
Attempted synthesis of 1,4-bis-(1-hydroxyethyl)benzene (**227**)¹⁶³



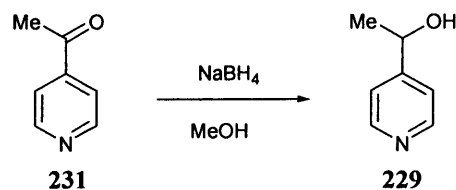
MeI (10.5 g, 75 mmol) was dissolved in anhydrous Et_2O (100 ml) and added dropwise to magnesium turnings (1.8 g, 75 mmol) in Et_2O (100 ml) in a 500 ml round bottomed flask equipped with a nitrogen balloon. A small portion was added initially to initiate the reaction. After the addition was complete, the mixture was allowed to stir for 10 minutes until all the magnesium had been used. Terephthalaldehyde (**226**) (10 g, 75 mmol) was dissolved in THF (100 ml) was added dropwise but at such a rate so as to prevent precipitation of the Grignard reagent formed. The reaction was left stirring overnight and was quenched using NH_4Cl . The product was extracted using EtOAc (3×100 ml). The organic extracts were combined and dried over anhydrous MgSO_4 , filtered and the solvent removed *in vacuo*. The ^1H NMR showed much impurities and it was not feasible to purify this compound hence another route was used.

1,4-Bis-(1-hydroxyethyl)benzene (227)^{163,173}

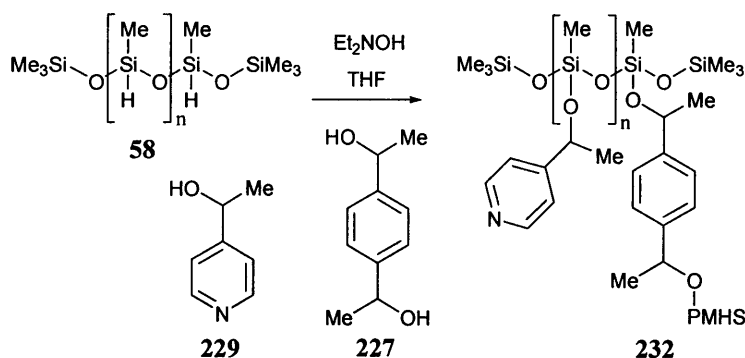
1,4-Diacetylbenzene (**230**) (10 g, 61 mmol) was placed in a 500 ml round bottomed flask along with MeOH (200 ml). NaBH₄ (9.33 g, 247 mmol) was added slowly to control the level of effervescence, after the addition was complete, the mixture was left stirring overnight. The reaction was quenched using NH₄Cl. The product was extracted using EtOAc (3 × 100 ml). The organic extracts were combined and dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo*. The product was a white solid **227** (9.54 g, 94%) m.p. 114 °C (lit. m.p. 115 °C). δ_{H} (400 MHz; CDCl₃), 7.49 (4H, aromatic, s), 4.55 (2H, q, J = 6.5 Hz, CH), 1.27 (6H, d, J = 6.5 Hz, Me).

Attempted synthesis of 1-pyridin-4-ylethanol (229)

MeI (13.11 g, 94 mmol) was dissolved in anhydrous Et₂O (100 ml) and added dropwise to magnesium turnings (2.2 g, 94 mmol) in Et₂O (200 ml) in a 500 ml round bottomed flask equipped with a nitrogen balloon. A small portion was added initially to initiate the reaction. After the addition was complete, the mixture was allowed to stir for 10 minutes until all the magnesium had been used. Pyridine-4-carboxaldehyde (**228**) (10 g, 94 mmol) was dissolved in THF (75 ml) was added dropwise but at such a rate so as to prevent precipitation of the Grignard reagent formed. The reaction was left stirring overnight and was quenched using NH₄Cl. The product was extracted using EtOAc (3 × 100 ml). The organic extracts were combined and dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo*. The NMR spectrum showed that the reaction was not clean and impurities were present, but it was not purified instead another route was used.

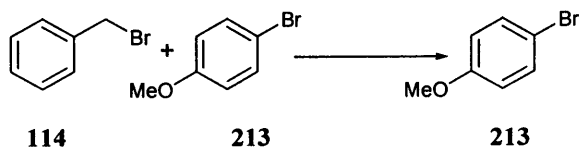
1-Pyridin-4-ylethanol (229) ^{164,170}

4-acetylpyridine (**231**) (10 g, 83 mmol) was placed in a 500 ml round bottomed flask along with MeOH (200 ml). NaBH₄ (9.4 g, 267 mmol) was added slowly to control the level of effervescence, after the addition was complete, the mixture was left stirring overnight. The reaction was quenched using NH₄Cl. The product was extracted using EtOAc (3 × 100 ml). The organic extracts were combined and dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo*. The product was a white solid **229** (9.85 g, 96%). m.p. 62 °C (lit. m.p. 63°C) δ_{H} (400 MHz; CDCl₃), 8.46 (2H, d, *J* = 6.5 Hz, H2 and H6), 7.55 (2H, d, *J* = 6.5 Hz, H3 and H5), 4.88 (1H, q, *J* = 6.6 Hz, CHMe) 1.49 (3H, d, *J* = 6.6 Hz, Me).

1-Pyridin-4-ylethanol resin (232)

PMHS (**58**) (7.0 g, 177 mmol), 1-pyridin-4-ylethanol (**229**) (10 g, 82 mmol) and 1,4-bis-(1-hydroxyethyl)-benzene (**227**) (1.73 g, 1.17 mmol) were placed in a 250 ml round bottomed flask along with anhydrous THF (150 ml) and the substituents were stirred until they were homogenous. Et₂NOH (200 μ l, 0.2 mmol) was added and effervescence was seen, the gas given off being probably H₂. The mixture was stirred overnight and then the solvent was removed *in vacuo* to give a light yellow coloured resin **232**. This was washed using chloroform to constant weight (17.94 g, 96%). (based on 100 polymer units) Found C, 40.9, H, 7.02, N, 4.78 C₄₃₂H₇₃₃N₄₆O₁₉₄Si₁₀₀ requires C, 41.6, H, 5.88, N, 5.17%. The loading was calculated to be 3.4 mmol/g.

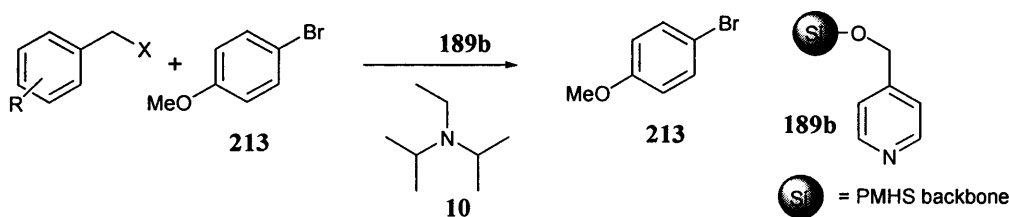
Scavenger testing using methyl pyridine resin 232 : General procedure



The resin batch **232** was taken and washed to constant weight using chloroform. A small amount of the pyridine resin (0.5 g, 1.7 mmol) was placed into a filter syringe and to this was added a standard mixture of different substrates shown in the table (Refer to Results and Discussion section) and 4-bromoanisole (**213**) in THF (2 ml, 1 mmol). The mixture was shaken for 1 h. After this time, the filtrate was removed and the solvent was removed *in vacuo*. The residue was taken up in CDCl_3 and an ^1H NMR was obtained. The results are shown in table 7 (Results and discussion section).

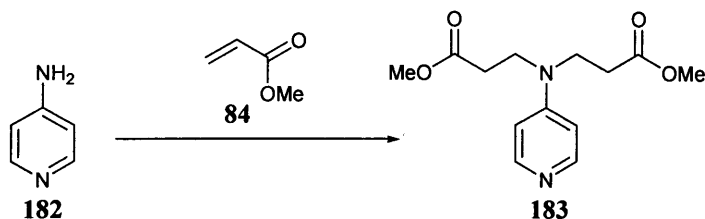
Scavenger testing using methyl pyridine resin 189b in the presence of Hunig's base 10:

General procedure



Pyridine resin (**189b**) (0.5 g, 1.3 mmol) was placed in a filter syringe and to this was added a standard mixture of substrates shown in the table (Refer to Results and discussion section) and 4-bromoanisole (**213**) in THF (2 ml, 1 mmol). To this was added Hunig's base **10** (129 mg, 1mmol). The mixture was shaken for 1 h. After this time, the filtrate was removed and the solvent was removed *in vacuo*. The residue was taken up in CDCl_3 and an ^1H NMR was obtained. The results are shown in table 8 (Refer to Results and discussion section).

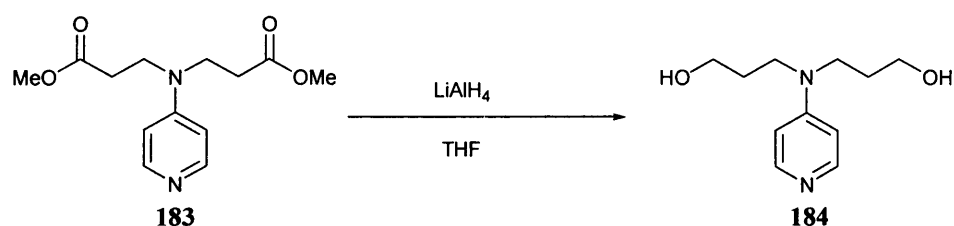
4-*N,N*-Di(2-methoxycarbonyl)ethylpyridine (**183**)¹⁵⁸



4-Aminopyridine (**182**) (9 g, 83 mmol) was placed in a 250 ml round bottomed flask along with methyl acrylate (**84**) (83 ml). The mixture was refluxed overnight. Initially the it was a heterogeneous mixture with the pyridine being present as a white solid but on heating to

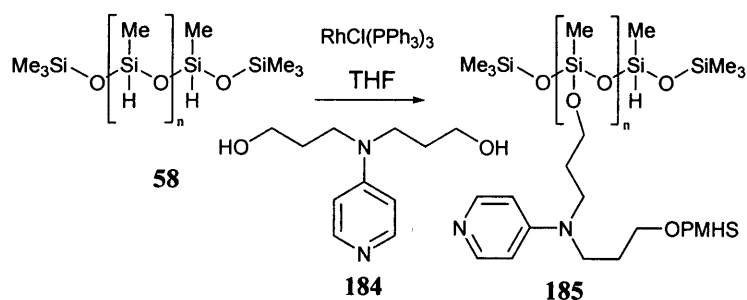
reflux, this dissolved into the methyl acrylate forming a yellow coloured solution. The excess methyl acrylate was removed *in vacuo* and methanol (2×100 ml) was added and evaporated *in vacuo* to give an orange coloured oil **183** (21.34 g, 96%). ν_{max} (neat on NaCl plates)/ cm^{-1} , 2852 (br, st), 1665 (st), 1735 (st), 1596 (st), 1513 (st), 1375 (st), 1197 (br, st); δ_{H} (400 MHz; CDCl_3), 7.97 (2H, d, $J = 6.2$ Hz, H2 and H6), 6.04 (2H, d, $J = 6.2$ Hz, H3 and H5), 3.29 (4H, t, $J = 7.2$ Hz), 3.12 (6H, s), 2.13 (4H, t, $J = 7.2$ Hz).

4-*N,N*-Di(3-hydroxypropyl)pyridine (**184**)¹⁶⁵



To 4-*N,N*-di(2-methoxycarbonyl)ethylpyridine (**183**) (15 g, 77.3 mmol) was added LiAlH_4 (11.83 g, 312 mmol) in THF (150 ml) at 0°C . The LiAlH_4 was added over 40 minutes at such a rate that the temperature was maintained at approximately 0°C . After the addition was complete, the mixture was left stirring overnight. The mixture was quenched using slow addition of sodium sulfate decahydrate. The solid was filtered and washed with ethyl acetate (3×100 ml). The filtrate was taken and the solvent was removed *in vacuo* to give an orange oil (15.52 g, 95%). δ_{H} (400 MHz; CDCl_3), 8.05 (2H, d, $J = 6.9$ Hz, H2 and H6), 6.63 (2H, d, $J = 6.9$ Hz, H3 and H5), 3.68 (4H, t, $J = 7.4$ Hz, CH_2N), 3.42 (4H, t, $J = 7.4$ Hz, CH_2O), 1.85 (4H, quintet, $J = 7.4$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2$).

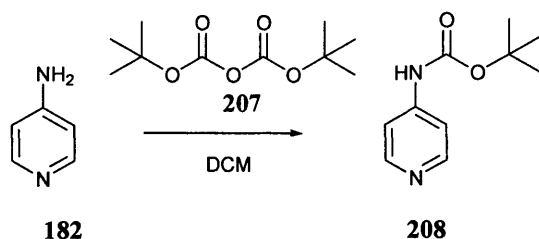
DMAP resin (**185**)



PMHS (**58**) (0.9 g, 15 mmol), DMAP dialcohol **180** (0.139 g, 12 mmol), and THF (5ml) were placed in a round bottomed flask equipped with magnetic stirrer and condenser. $\text{RhCl(PPh}_3)_3$ (46.2 mg, 0.5 mmol) was placed with the reagents and the mixture was refluxed

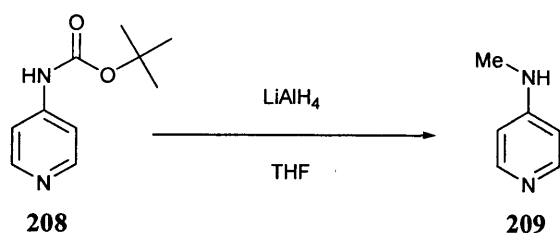
overnight. The red colour of the catalyst disappeared within 15 minutes of stirring and the mixture became yellow and homogenous. As the reaction proceeded, the yellow colour turned to dark orange and returned to red when the reaction was complete (typically 20 h). During the course of the reaction a gas evolved (probably H₂). The solvent was removed *in vacuo* to leave an orange coloured resin. During washing of the resin to test stability, more and more weight was lost from the resin indicating it was not stable.

(*tert*-Butoxy)-*N*-(4-pyridyl)carboxamide (208**)**¹⁵⁹



A solution of Boc₂O (**207**) (21.8 g, 0.10 mol) in DCM (100 ml, not anhydrous) was added over 20 minutes to a stirred suspension of 4-aminopyridine (**182**) (9.4 g, 0.10 mol) in DCM (200 ml). The resulting pale yellow solution was stirred at room temperature for 25 minutes and acidified with 1 M HCl (115 ml, 0.12 mol). The phases were separated, and the aqueous layer was washed with DCM. The aqueous layer was mixed with a fresh portion of DCM (200 ml) and was treated with solid K₂CO₃ (10.55 g, 0.08 mol). The phases were separated and the extraction was completed with additional portions of DCM (2 × 100 ml). The combined organic extracts were dried over anhydrous MgSO₄, evaporated *in vacuo* to give the product as a white solid **208** (19.36 g, 99%). δ_H (400 MHz; CDCl₃), 8.45 (2H, d, *J* = 5.3 Hz, H2 and H6), 7.43 (2H, d, *J* = 5.3 Hz, H3 and H5), 1.50 (9H, s).

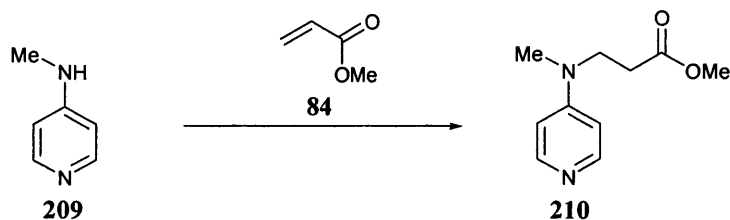
(*N*-methyl)-4-aminopyridine (209**)**¹⁵⁹



To a solution of (*tert*-butoxy)-*N*-(4-pyridyl)carboxamide (**208**) (17.78 g, 91.6 mmol) was added LiAlH₄ (13.96 g, 370 mmol) in THF (250 ml) at 0 °C. The LiAlH₄ was added over 40 minutes at such a rate that the temperature was maintained at approximately 0 °C. After the addition was complete, the mixture was gradually heated and refluxed for 4 h. The mixture

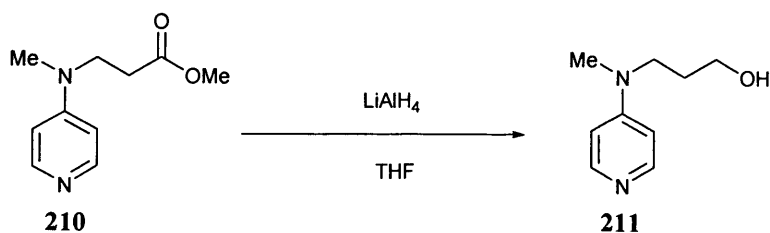
was quenched using slow addition of sodium sulfate decahydrate. The solid was filtered and washed with ethyl acetate (3×100 ml). The filtrate was taken and the solvent was removed *in vacuo* to give a white solid **209** (9.71 g, 98%). δ_{H} (400 MHz; CDCl_3), 8.20 (2H, d, $J = 6.3$ Hz, H2 and H6), 6.43 (2H, d, $J = 6.3$ Hz, H3 and H5), 2.85 (3H, d, $J = 5.0$ Hz, Me).

Methyl-3-*N*-(methyl-4-aminopyridyl)propionate (**210**)¹⁵⁸



(*N*-methyl)aminopyridine (**209**) (9 g, 83 mmol) was placed in a 250 ml round bottomed flask along with methyl acrylate (**84**) (83 ml). The mixture was refluxed for 20 h. Initially the it was a heterogeneous mixture with the pyridine being present as a white solid but on heating to reflux, this dissolved into the methyl acrylate forming a yellow coloured solution. The excess methyl acrylate was removed *in vacuo* and methanol (2×100 ml) was added and evaporated *in vacuo* to give an orange coloured oil **210** (15.82 g, 98%). ν_{max} (neat on NaCl plates)/ cm^{-1} , 2930 (br, st), 1665 (st), 1606 (st), 1524 (st), 1393 (st), 1062 (st), 997 (st); δ_{H} (400 MHz; CDCl_3), 8.15 (2H, d, $J = 5.6$ Hz, H2 and H6), 6.43 (2H, d, $J = 5.6$ Hz, H3 and H5), 3.62 (2H, t, $J = 6.3$, CH₂), 3.60 (3H, s, OMe), 2.92 (3H, s, NMe), 2.53 (2H, t, $J = 6.3$ Hz, CH₂O).

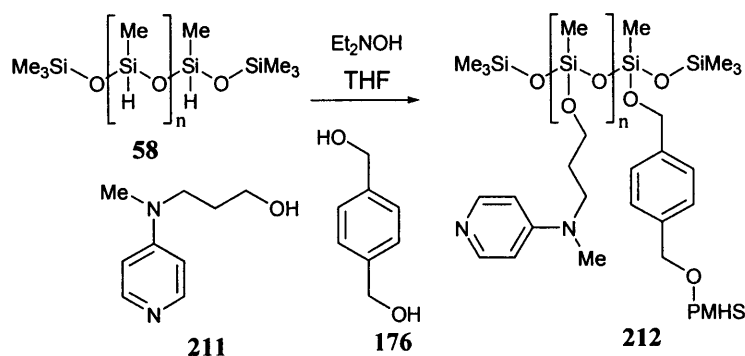
3-(*N*-methyl-4-aminopyridyl)propan-1-ol (**211**)¹⁵⁸



To methyl-3-*N*-(methyl-4-aminopyridyl)propionate (**210**) (15 g, 77.3 mmol) was added LiAlH₄ (11.83 g, 312 mmol) in THF (150 ml) at 0 °C. The LiAlH₄ was added over 40 minutes at such a rate that the temperature was maintained at approximately 0 °C. After the addition was complete, the mixture was left stirring overnight. The mixture was quenched using slow addition of sodium sulfate decahydrate. The solid was filtered and washed with ethyl acetate (3×100 ml). The filtrate was taken and the solvent was removed *in vacuo* to give an orange oil (12.09 g, 94%). δ_{H} (400 MHz; CDCl_3), 8.07 (2H, d, $J = 6.6$ Hz, H2 and

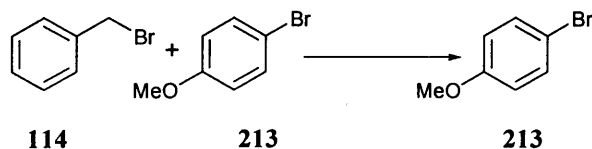
H6), 6.50 (2H, d, J = 6.6 Hz, H3 and H5), 3.67 (2H, t, J = 7.1 Hz, CH₂O), 3.35 (2H, t, J = 7.1 Hz, CH₂N), 2.17 (3H, s, Me), 1.83 (2H, quintet, J = 7.1 Hz, CH₂CH₂CH₂).

DMAP resin **212**¹⁵¹



PMHS (**58**) (4.5 g, 75 mmol), DMAP alcohol **211** (6.95 g, 60 mmol), 1,4-benzenedimethanol (**176**) (1.54 g, 7.5 mmol) and THF (5ml) were placed in a round bottomed flask equipped with magnetic stirrer and condenser. Et₂NOH (300 μ l, 0.3 mmol) was placed with the reagents and the mixture was stirred overnight. During the course of the reaction a gas evolved (probably H₂). The solvent was removed *in vacuo* to leave an orange coloured resin. The DMAP resin (**212**) was taken, washed firstly using chloroform several times using a vacuum chamber to force the solvent through using suction. After each set of washes the solvent was removed *in vacuo* to check if the resin mass became constant. When this was complete a second wash cycle using a 'swell/shrink' process using DCM-Et₂O-THF (DCM swelled the resin, ether shrunk the resin, then THF caused it to swell again) in that combination to flush out remaining impurities from the resin and then carefully dried (12.39 g, 95%). (based on 100 units) Found C, 54.7, H, 8.43, N, 10.9 C₉₈₀H₁₅₀₀N₁₆₀O₂₂₀Si₁₀₀ requires C, 53.9, H, 6.87, N, 10.3. The loading was calculated to be 3.9 mmol/g.

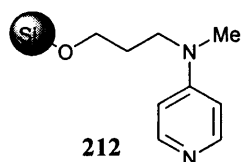
Time course scavenger testing using DMAP resin **212**: General procedure



The resin was carefully dried under vacuum. After this was done, a small amount of the DMAP resin **212** (0.5 g, 1.9 mmol) was placed into a filter syringe and to this was added a standard mixture of benzyl bromide (**114**) and 4-bromoanisole (**213**) in THF (2 ml, 1 mmol). The mixture was shaken for the times shown in table 3 (Refer to Results and Discussion

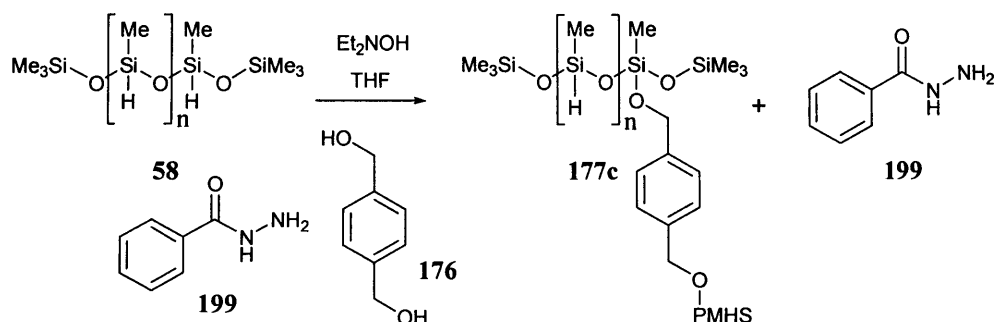
section). After the designated time, the filtrate was removed and the solvent was removed *in vacuo*. The residue was taken up in CDCl_3 and a ^1H NMR spectrum was obtained.

Scavenger testing using DMAP resin **212**: General procedure



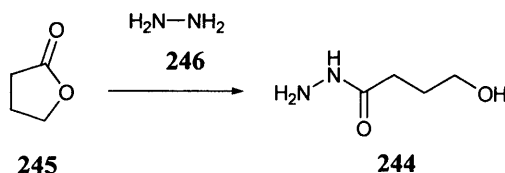
After this was done, a small amount of the DMAP resin (**212**) (0.5 g, 1.9 mmol) was placed into a filter syringe and to this was added a standard mixture of different substrates shown in the table below and 4-bromoanisole (**213**) in THF (2 ml, 1 mmol). The mixture was shaken for 1 h. After this time, the filtrate was removed and the solvent was removed *in vacuo*. The residue was taken up in CDCl_3 and an ^1H NMR was obtained. The results are shown in the table 4 (Refer to results and discussion section).

Test of gas evolution with a hydrazide¹⁵¹



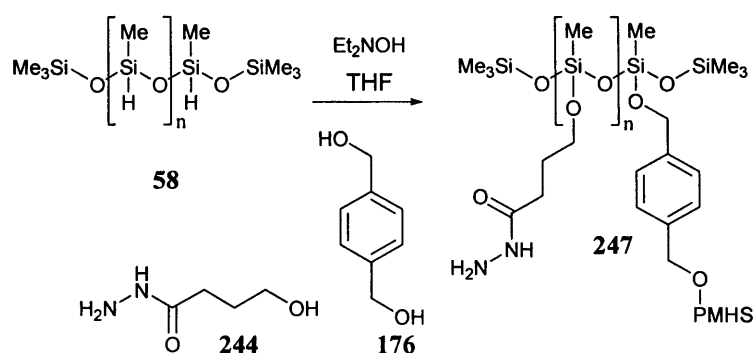
PMHS (**58**) (1.5 g, 25 mmol) was placed in a 100 ml round bottomed flask which had been connected to a manometer to measure the volume of gas evolved. To this was added 1,4-benzenedimethanol (**176**) (500 mg, 3.5 mmol), benzoic hydrazide (**199**) (2.9 g, 21.5 mmol) and THF (50 ml). Et_2NOH (200 μl , 0.5 mmol) was then added and the mixture was left stirring and the volume of gas was left to collect. The total estimated gas to be evolved was 560 ml. After the reaction was complete (24 h) 80 ml was evolved

Synthesis of (4-hydroxybutanoyl)hydrazine (**244**)¹⁶⁶



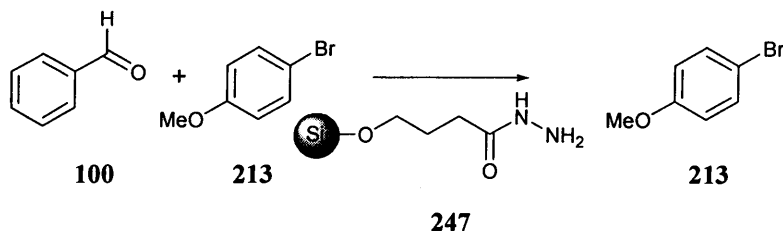
Hydrazine monohydrate (**246**) (11.0 g, 0.22 mol) was added slowly to γ -butyrolactone (**245**) (17.2 g, 0.20 mol) due to the fact that it is an exothermic reaction. After the addition was complete, the mixture was heated at 100 °C overnight. The crude product was cooled to room temperature, further cooled using an ice bath and was recrystallised from hot EtOH to give the alcohol **244** as a white solid (20.67 g, 97%); m.p. 92-93 °C (lit.¹⁶⁶ m.p. 91-92 °C); δ_{H} (400 MHz; CDCl_3), 4.97 (3H, s, H_2NNH), 3.63 (2H, t, J = 6.4 Hz, CH_2O), 2.15 (2H, t, J = 6.4 Hz, CH_2O), 1.87 (2H, quintet, J = 6.4 Hz, $\text{CH}_2\text{CH}_2\text{CH}_2$).

Synthesis of hydrazine resin (**247**)¹⁵¹



Following the procedure for resin **185b**, PMHS (**58**) (7.7 g, 128 mmol), hydrazide **244** (12 g, 102 mmol), 1,4-benzenedimethanol (**176**) (1.8 g, 12.8 mmol), Et_2NOH (200 μl , 0.2 mmol) and THF (250 ml) were combined to give a white coloured resin **247**. The crude resin was taken and washed several times with chloroform using vacuum chamber equipment to force it through the solid. Each washing was taken, the solvent evaporated and then the residue, if any, was weighed to see if the resin mass became constant (20.82 g, 97%). Found C, 33.4, H, 6.97, N, 12.4% $\text{C}_{580}\text{H}_{1100}\text{N}_{160}\text{O}_{300}\text{Si}_{100}$ requires C, 38.9, H, 6.15, N, 12.5%.

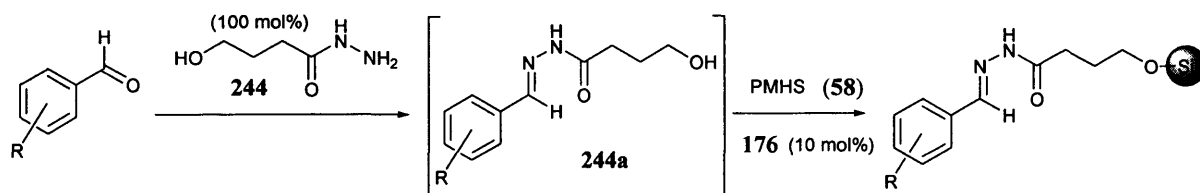
Scavenging for aldehydes



A standard mixture of benzaldehyde (**100**) and bromoanisole (**213**) in THF (2 ml, 1 mmol) was placed with a small amount of resin **247** (0.5 g, 2.2 mmol) and the mixture was shaken for 1 h and then filtered. The filtrate had the solvent removed *in vacuo* and the residue was

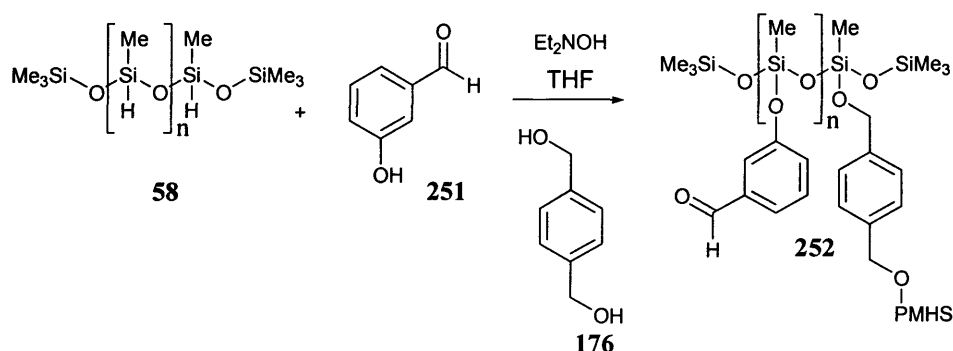
taken up in CHCl_3 and a ^1H NMR was obtained of the mixture. The efficiency was 90% but 5% of the hydrazine linker **244** was leeching out.

Solution phase methods for aldehyde scavenging



The hydrazide **244** (354 mg, 3 mmol) was placed in a filter syringe together with 1:1 aldehyde/*p*-bromoanisole in THF (2 ml, 1 mmol) and the mixture was shaken for 1 h on a vortex shaker. PMHS (**58**) (0.5 g, 8.3 mmol) was then added together with 1,4-benzenedimethanol (**176**) (114 mg, 0.83 mmol) and the mixture was shaken for 1 h or until a gel forms. The solid was washed with CHCl_3 (3×5 ml). The solvent was removed *in vacuo* and the residue was taken up in CDCl_3 and a ^1H NMR spectrum was obtained. The results of different aldehydes are shown in table 9 (Refer to Results and discussion section).

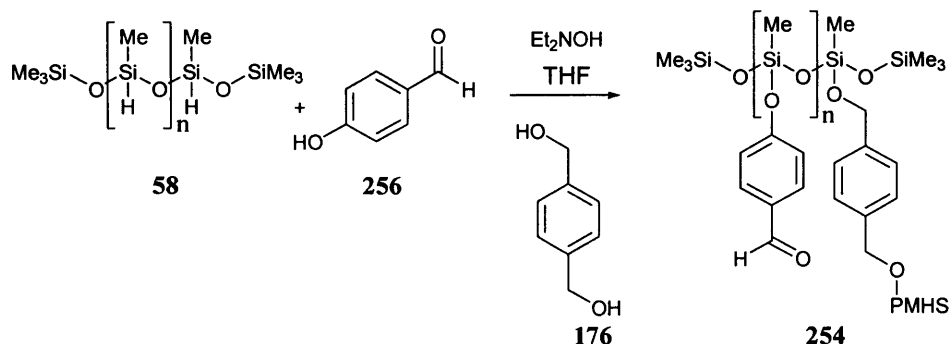
Benzaldehyde resins **252**, **254** and **255**¹⁵¹



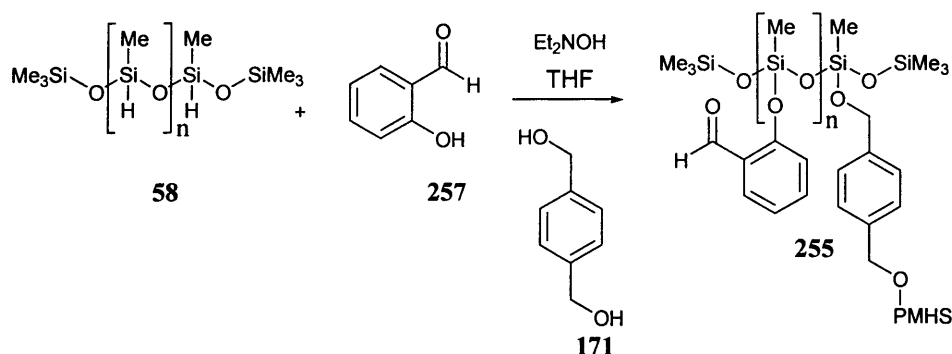
PMHS (**58**) (9 g, 150 mmol), 3-hydroxybenzaldehyde **251** (14.65 g, 120 mmol), 1,4-benzenedimethanol (**176**) (2.07 g, 15 mmol) and THF (250 ml) were placed in a round bottomed flask equipped with a nitrogen balloon. The mixture was stirred until all the substituents had dissolved and then Et_2NOH (200 μl , 0.2 mmol) was added, a gas was seen to be given off, probably H_2 . The mixture was left to stir overnight and then the solvent was removed *in vacuo* to give a white coloured resin **252**. The crude resin was taken and washed several times with chloroform using vacuum chamber equipment to force it through the solid. Each washing was taken, the solvent evaporated and then the residue, if any, was weighed to see if the resin mass became constant (24.35 g, 94%). ν_{max} (neat on NaCl)/ cm^{-1} ,

3202 (br), 1696 (st), 1667 (st), 1580 (st), 1490 (st), 1279 (st); (based on 100 polymer units)

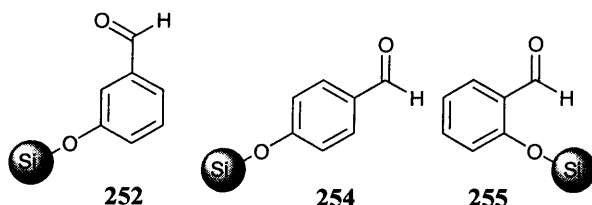
Found C, 54.4, H, 5.97%, $C_{730}H_{812}O_{276}Si_{100}$ requires C, 52.2, H, 4.83.



This procedure was repeated using the benzaldehyde linkers **256** to give resin **254** (24.55 g, 95%). ν_{\max} (neat on NaCl)/ cm^{-1} , 3162 (br, st), 1665 (st), 1585 (st), 1511 (st), 1449 (st); Found C, 52.7, H, 6.08, $C_{730}H_{812}O_{276}Si_{100}$ requires C, 52.2, H, 4.83% and **257** to give resin **255** (24.47 g, 95%). ν_{\max} (neat on NaCl)/ cm^{-1} , 1664 (st), 1270 (st), 1004 (st); Found C, 52.5, H, 5.99%, $C_{730}H_{812}O_{276}Si_{100}$ requires C, 52.2, H, 4.83%.



Scavenger testing using benzaldehyde resins (**252**, **254**, **255**): General procedure



Aldehyde scavenger resin (0.5 g, 1.8 mmol) was placed in a filter syringe along with 1:1 benzylamine/*p*-bromoanisole (2 ml, 1 mmol) in THF. The mixture was shaken for 1 h and then filtered. The resin was washed using CHCl_3 (3×5 ml). The filtrate was removed and evaporated under vacuum. The residue was taken up in CDCl_3 and a ^1H NMR was obtained. The results of the three resins are shown in table 10 (Refer to Results and Discussion section).

Time course experiment using benzaldehyde resin 252: General procedure

Aldehyde scavenger resin (0.5 g, 1.8 mmol) was placed in a filter syringe along with 1:1 benzylamine/*p*-bromoanisole (2 ml, 1 mmol) in THF. The mixture was shaken for the times shown and then filtered. The resin was washed using CHCl₃ (3 × 5 ml). The filtrate was removed and evaporated under vacuum. The residue was taken up in CDCl₃ and a ¹H NMR was obtained. The results of the three resins are shown in table 11 (Refer to Results and discussion section).

Scavenger testing using benzaldehyde resin and different substrates (252): General procedure

Aldehyde scavenger resin (0.5 g, 1.8 mmol) was placed in a filter syringe along with 1:1 substrate/*p*-bromoanisole (2 ml, 1 mmol) in THF. The mixture was shaken for 1 h and then filtered. The resin was washed using CHCl₃ (3 × 5 ml). The filtrate was removed and evaporated under vacuum. The residue was taken up in CDCl₃ and a ¹H NMR was obtained. The results of the three resins are shown in table 12 (Refer to Results and discussion section).

PMHS and alcohol scavenging – *in situ* polymerisation: General procedure

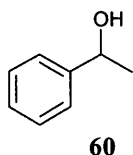
PMHS (**58**) (0.5 g, 8.3 mmol) was placed in a filter syringe along with 1:1 benzyl alcohol/*p*-bromoanisole (2ml, 1mmol) and 1,4-benzenedimethanol (**176**) (100 mg, 1.67 mmol). The mixture was shaken until all the reactants had dissolved and then Et₂NOH (30 µl, 0.03 mmol) was added and the mixture was shaken for 1 h until a white coloured gel formed. This was washed with CHCl₃ (3 × 5 ml). The filtrate had the solvent removed *in vacuo*. The residue was taken up in CDCl₃ and a ¹H NMR was obtained. The results are shown in table 13 (Refer to Results and Discussion section).

Synthesis of benzyl alcohols: General procedure¹⁶⁷

Aldehyde or ketone (40 mmol) was placed in a 150 ml round bottomed flask along with methanol (50 ml). The aldehyde was allowed to dissolve and then NaBH₄ (4 g, 106 mmol)

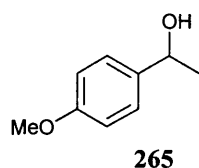
was added at such a rate so as not to cause too much effervescence to occur. The addition was over a period of 30 minutes. The mixture was stirred under a nitrogen atmosphere for 4 h and then quenched with 10% HCl (15 ml) and the mixture was left stirring for a further 30 minutes to allow complete quenching of the reaction mixture. The organic product was extracted using EtOAc (3 × 100 ml) and the organic extracts were combined and dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo*.

1-Phenylethan-1-ol



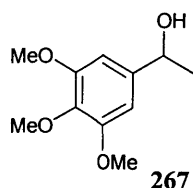
The alcohol **60** was obtained from the reduction of acetophenone as an oil (4.93 g, 99%). δ_{H} (400 MHz; CDCl₃), 7.24 (5H, m, Ph), 4.85 (1H, q, J = 6.4 Hz), 2.67 (1H, s, OH), 1.47 (3H, d, J = 6.4 Hz).

1-(4-methoxy)phenylethanol¹⁶⁸

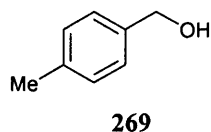


The alcohol **265** was obtained from the reduction of 4-methoxyacetophenone (4.92 g, 98%). δ_{H} (400 MHz; CDCl₃), 7.23 (2H, d, J = 6.6 Hz, H2 and H6), 6.64 (2H, d, J = 6.6 Hz, H3 and H5), 4.87 (1H, q, J = 6.4 Hz), 3.87 (3H, s, OMe), 1.48 (3H, d, J = 6.4 Hz).

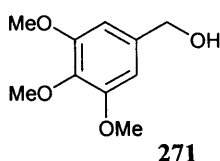
(3,4,5-Trimethoxy)phenylethanol¹⁶⁹



This alcohol **267** was prepared by reduction of 3,4,5-trimethoxyacetophenone (4.91 g, 99%). δ_{H} (400 MHz; CDCl₃), 6.62 (2H, s, H2 and H6), 4.87 (2H, q, J = 6.4 Hz), 3.87 (6H, s, 2 × OMe), 3.85 (3H, s, OMe), 1.47 (3H, d, J = 6.4 Hz, Me).

(4-Methyl) benzyl alcohol^{170,171}

The alcohol **269** was obtained from the reduction of *p*-tolualdehyde as an oil (4.89 g, 97%). δ_{H} (400 MHz; CDCl_3), 7.41 (2H, d, $J = 7.7$ Hz, H2 and H6), 7.39 (2H, d, $J = 7.7$ Hz, H3 and H5) 4.85 (3H, s, Me), 2.56 (2H, s, CH_2O).

3,4,5-Trimethoxybenzyl alcohol^{172,173}

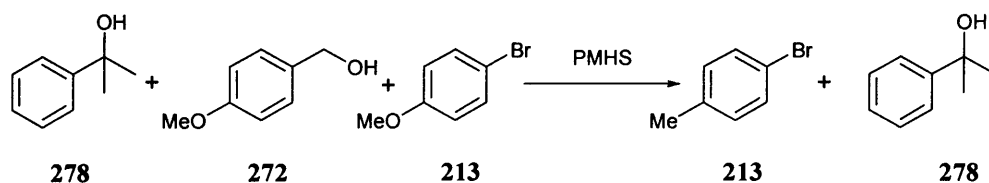
The alcohol **271** was obtained from the reduction of 3,4,5-trimethoxybenzaldehyde (4.95 g, 99%). δ_{H} (400 MHz; CDCl_3), 6.52 (2H, s, H2 and H6), 3.87 (9H, s, $\text{MeO} \times 3$), 3.85 (2H, s).

Scavenging for different benzyl alcohols: General procedure

PMHS (**58**) (0.5 g, 8.3 mmol) was placed in a filter syringe along with 1:1 substrate/*p*-bromoanisole (2 ml, 1mmol) and 1,4-benzenedimethanol (**176**) (100 mg, 1.67 mmol). The mixture was shaken until all the reactants had dissolved and then Et_2NOH (30 μl , 0.03 mmol) was added and the mixture was shaken for 1 h until a white coloured gel formed. This was washed with CHCl_3 (3 \times 5 ml). The filtrate had the solvent removed *in vacuo*. The residue was taken up in CDCl_3 and a ^1H NMR was obtained. The results are shown in table 15 (Refer to Results and discussion section).

Scavenging for different functional groups: General procedure

PMHS (**58**) (0.5 g, 8.3 mmol) was placed in a filter syringe along with 1:1 substrate/*p*-bromoanisole (2 ml, 1mmol) and 1,4-benzenedimethanol (**176**) (100 mg, 1.67 mmol). The mixture was shaken until all the reactants had dissolved and then Et_2NOH (30 μl , 0.03 mmol) was added and the mixture was shaken for 1 h until a white coloured gel formed. This was washed with CHCl_3 (3 \times 5 ml). The filtrate had the solvent removed *in vacuo*. The residue was taken up in CDCl_3 and a ^1H NMR was obtained. The results are shown in table 16 (Refer to Results and Discussion section).

Scavenging from a 3 component mixture

PMHS (**58**) (0.5 g, 8.3 mmol) was placed in a filter syringe along with 1:1 substrate/*p*-bromoanisole (2 ml, 1 mmol) and 1,4-benzenedimethanol (**176**) (100 mg, 1.67 mmol). The mixture was shaken until all the reactants had dissolved and then Et₂NOH (30 μl, 0.03 mmol) was added and the mixture was shaken for 1 h until a white coloured gel formed. This was washed with CHCl₃ (3 × 5 ml). The filtrate had the solvent removed *in vacuo*. The residue was taken up in CDCl₃ and a ¹H NMR was obtained. The alcohol was cleaved from the support using 5M NaOH (2 ml).

References

- 1 Deratani, A.; Darling, G. D.; Horak, D.; Frechet, J. M. J. *Macromolecules*, **1987**, *20*, 767-772.
- 2 Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3293-3295.
- 3 Brown, R. *Contemp. Org. Synth.*, **1997**, *4*, 216-221.
- 4 Chinchilla, R.; Dodsworth, D. J.; Nájera, C.; Soriano, M. J. *Tetrahedron Lett.*, **2000**, *41*, 2463-2466.
- 5 Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron Lett.*, **1996**, *37*, 4527-4554.
- 6 Xiao, X. Y.; Nova, M. P. *Combinatorial Chemistry Synthesis and Application*, Edited by Wilson S.R.; Czarnik A. W. New York: Wiley and Sons Inc. **1997**, 135-152.
- 7 Caldarelli, M.; Baxendale, I. R.; Ley, S.V. *Green Chemistry*, **2000**, *2*, 43-45.
- 8 <http://www.avogadro.co.uk/organic/azodyes/azodyes.htm>
- 9 Mason, S. J.; Balasubramanian, S. *Org. Lett.*, **2002**, *4*, 4261-4264
- 10 Merrifield, R. B. *J Am. Chem. Soc.*, **1963**, *85*, 2149.
- 11 Parlow, J. J.; Vasquez, M. L.; Flynn, D. L. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 2391-2394.
- 12 Zander, N.; Frank, R. *Tetrahedron Lett.*, **2001**, *42*, 7783-7785.
- 13 Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett.*, **1997**, *38*, 7959-7963.
- 14 Parlow, J. J.; Starkey, G. W.; Flynn, D. L. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 2385-2387.
- 15 Hutchinson, P. C.; Heightman, T. D.; Procter, D. J. *J. Org. Chem.*, **2004**, *69*, 790-801.
- 16 Eames, J.; Watkinson, M. *Eur. J. Org. Chem.* **2001**, 1213-1224.
- 17 Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis*, **2000**, *8*, 1035-1042.
- 18 Mitra, S. S.; Sreekumar, K. *Polymer*, **1997**, *38*, 1363-1366.
- 19 Akelah, A.; Sherrington, D. C.; *Chem. Rev.*, **1981**, *81*, 557-561.
- 20 Akelah, A.; Sherrington, D. C.; *Polymer*, **1983**, *23*, 1369-1375.
- 21 Bing, Y. *Acc. Chem. Res.*, **1998**, *31*, 621-626.
- 22 Habermann, J.; Ley, S. V.; Smits, R. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2421-2427.
- 23 Varma, R. S. *Tetrahedron*, **2002**, *58*, 1235-1255.
- 24 Choma, J.; Kloske, M.; Jaroniec, M. *J. Coll. Int. Sci.*, **2003**, *266*, 168-174.

-
- 25 Egner, B. J.; Bradley, M. *Drug Discovery Today*, **1997**, 2, 102-105
- 26 Kurusu, Y. *Chin. J. Polym. Sci.*, **1999**, 17, 1-7.
- 27 Parlow, J. J. *Tetrahedron Lett.* **1995**, 36, 1395-1396.
- 28 Baxendale, I. R.; Lee, A. L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 1850-1857
- 29 Letsinger, R. L.; Kornet, M. J. *J. Am. Chem. Soc.*, **1963**, 85, 3045.
- 30 Kim, K.; Wang, B. *Chem. Commun.*, **2001**, 2268-2269.
- 31 Qian, H.; Shao, L.; Huang, X. *Synlett.*, **2001**, 1571-1572.
- 32 Jal, P. K.; Patel, S.; Mishra, B. K. *Talanta*, **2004**, 62, 1004-1028.
- 33 Varma, R. S.; Saini, R. K.; Dahiya, R. *Tetrahedron Lett.*, **1997**, 38, 7823-7824.
- 34 Crich, D.; Neelamkavil, S. *J. Am. Chem. Soc.*, **2001**, 30, 7449-7450.
- 35 Chen, W.; Xu, L.; Xiao, J-X. *Chem. Commun.*, **2000**, 10, 839-840.
- 36 Liu, G.; Fan, Y.; Carlson, J. R.; Zhao, Z-G.; Lam, K. S. *J. Comb. Chem.*, **2000**, 2, 467-474.
- 37 Ahn J. H.; Sherrington, D. C. *Macromolecules*, **1996**, 29, 4164-4168.
- 38 Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3814-4195.
- 39 Takemoto, T.; Yasuda, K.; Ley, S. V. *Synlett.*, **2001**, 10, 1555-1556.
- 40 Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1907-1910.
- 41 Ley, S. V.; Baxendale, I. R.; Brusotti, G.; Caldarelli, M.; Massi, A.; Nesi, M. *II Farmaco*, **2002**, 57, 321-330.
- 42 Corradini, R.; Sforza, S.; Dossena, A.; Palla, G.; Rocchi, R.; Filira, F.; Nistri, F.; Marchelli, R. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2690-2696.
- 43 Malenfant, P. R. L.; Frechet, J. M. J. *Chem. Commun.*, **1998**, 2657-2658.
- 44 Albright, R. L. *Reactive Funct. Polym.* **1986**, 4, 155-174.
- 45 Zalipsky, S.; Chang, J. L.; Albericio, F.; Barany G., *Reactive Funct. Polym.* **1994**, 22, 243-258.
- 46 Ley, S. V.; Massi, A. *J. Comb. Chem.*, **2000**, 2, 104-107.
- 47 Hruby, V. J.; Upson, D. A.; Agarwal, N. S. *J. Org. Chem.*, **1977**, 42, 3552-3556
- 48 Fromont, C.; Bradley, M., *Chem. Commun.*, **2000**, 283-284
- 49 Pei, Y.; Houghten, R. A.; Kiely, J. S. *Tetrahedron Lett.*, **1997**, 38, 3349-3352
- 50 Grotli, M.; Gotfredsen, C. H.; Rademann, J.; Buchardt, J.; Clark, A. J.; Duus, J. O.; Meldal, M. *J. Comb. Chem.*, **2000**, 2, 108-119.

-
- 51 McCairn, M. C.; Tonge, S. R.; Sutherland, A. J. *J. Org. Chem.*, **2002**, 67, 4847-4855.
- 52 Maeji, N. J.; Valerio, R. M.; Bray A. M.; Campbell, R. A.; Geysen H. M. *Reactive Funct. Polym.* **1994**, 22, 203-212.
- 53 Mergler, M.; Tanner, R.; Gosteli, J.; Grogg, P. *Tetrahedron Lett.* **1988**, 29, 4005-4008.
- 54 Nielsen, J.; Lyngso, L. O. *Tetrahedron Lett.* **1996**, 37, 8439-8442.
- 55 Hodges, J. C. *Synlett.*, **1999**, 152-158.
- 56 Blankemeyer-Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.* **1990**, 31, 1701-1704.
- 57 Berkessel, A.; Gasch, N.; Glaubitz, K.; Koch, C. *Org. Lett.*, **2001**, 3, 3839-3842.
- 58 Wang, Y.; Wilson, S. R. *Tetrahedron Lett.*, **1997**, 38, 4021-4025.
- 59 Angot, S.; Ayres, N.; Bon, S. A. F.; Haddleton, D. M. *Macromolecules*, **2001**, 34, 768-774.
- 60 Wang, S. *J. Am. Chem. Soc.*, **1973**, 95, 1328-1333.
- 61 Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.*, **1997**, 119, 4882-4886.
- 62 Rink, H. *Tetrahedron Lett.*, **1987**, 28, 3787-3790.
- 63 Albericio, F.; Kneib-Cordonier, N.; Biancalana, S. L.; Masada, R. I.; Huson, D.; Barany, G. *J. Org. Chem.*, **1990**, 55, 3730-3743.
- 64 Congreve, M. S.; Ladlow, M.; Marshall, P.; Parr, N.; Scicinski, J. J.; Sheppard, T.; Vickerstaffe, E.; Carr, R. A. E. *Org. Lett.*, **2001**, 3, 507-510.
- 65 Graven, A.; Meldal, M. *J. Am. Chem. Soc.*, **2001**, 3, 3198-3203.
- 66 Adachi, K.; Achimuthu, A. K.; Chujo, Y. *Macromolecules*, **2004**, (ASAP article <http://pubs.acs.org/cgi-bgi/asap.cgi/mamobx/asap/pdf/ma0400618.pdf>)
- 67 Djakovitch, L.; Koehler, K. *J. Am. Chem. Soc.*, **2001**, 123, 5990-5999.
- 68 Blanco, B.; Mehdi, A.; Moreno-Manas, M.; Pleixats, R.; Reye, C. *Tetrahedron Lett.*, **2004**, 45, 8789-8791.
- 69 Miller, J. M.; Wails, D.; Hartman, J. S.; Schebesh, K.; Belelie, J. L. *Can. J. Chem.*, **1998**, 76, 382-388.
- 70 Grim, R. E. *Applied Clay Mineralogy*; McGraw Hill: London **1962**
- 71 Theng, B. K. G. *The Chemistry of Clay-Organic reactions*; Wiley: New York **1974**.
- 72 Breiting, H-G. *Tetrahedron Lett.*, **2004**, 5, 6127-6131.
- 73 Xi, F.; Wu, J. *Journal of Chromatography A*, **2004**, 1057, 41-47.
- 74 Cassagnau, P.; Melis, F. *Polymer*, **2003**, 44, 6607-6615.
- 75 *Advanced Chemtech Handbook of Combinatorial & Solid Phase Organic Chemistry – A Guide to Principles, Products and Protocols*, Edited by Bennett, W. D.; Christensen, J. W.; Hamaker, L. K.; Peterson, M. L.; Rhodes, M. R.; Saneii, H. H., **1998**.

-
- 76 Enholm, E. J.; Gallagher, M. E. *Org. Lett.*, **2001**, 3, 3397-3399.
- 77 Enholm, E. J.; Gallagher, M. E.; Jiang, S.; Batson, W. A. *Org. Lett.*, **2000**, 3, 3355-3357.
- 78 Enholm, E. J.; Cottone, J. S. *Org. Lett.*, **2001**, 3, 3959-3962.
- 79 Wentworth, A. D.; Wentworth, P.; Mansoor, U. F.; Janda, K. D. *Org. Lett.*, **2000**, 2, 477-480.
- 80 Sauer, R. O.; Scheiber, W. J.; Brewer, D. S. *J. Am. Chem. Soc.*, **1946**, 68, 962.
- 81 Bushell, S. M. Rapid Carbonyl Reduction and alkylation using environmentally friendly siloxanes, PhD, UMIST, Manchester, **2000**.
- 82 Breeden, S. W.; Lawrence, N. J. *Synlett.*, **1994**, 833-835.
- 83 Drew, M. D.; Lawrence, N. J.; Fontaine, D.; Sehkri, L.; Bowles, S. A.; Watson, W. *Synlett.* **1997**, 989-991.
- 84 Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 3381-3391.
- 85 Brocchini, S. *Adv. Drug Deliv. Rev.*, **2001**, 53, 123-130.
- 86 Erickson, M. J.; Frech, R.; Glatzhofer, D. T. *Polymer*, **2004**, 45, 3389-3397.
- 87 Qin, Z.; Jennings, M. C.; Puddephatt, R. J. *Chem. Commun.* **2002**, 354-355.
- 88 Le Bideau, F.; Coradin, T.; Gourier, D.; Henique, J.; Samuel, E. *Chem. Commun.*, **2001**, 1408-1409.
- 89 Rana, S.; White, P.; Bradley, M. *J. Comb. Chem.*, **2001**, 3, 9-15.
- 90 Garin, S.; Lecamp, L.; Youssef, B.; Bunel, C. *Eur. Polym. J.*, **1999**, 35, 473-482.
- 91 Hogan, P. M.; Tajbakhsh, A. R.; Terentjev, E. M. *Physical Review E*, **2002**, 65, 041720, 1-5
- 92 Deratani, A.; Darling, G. D.; Horak, D.; Frechet, J. M. J. *Macromolecules*, **1987**, 20, 767-772.
- 93 Farrall, M. J.; Frechet, J. M. J. *J. Org. Chem.*, **1976**, 41, 3877-3882.
- 94 Cainelli, G.; Manescalchi, F. *Synthesis*, **1976**, 472-478.
- 95 Cainelli, G.; Manescalchi, F. *Synthesis*, **1975**, 723-728.
- 96 Montheard, J. P.; Chatzopoulos M.; Camps, M. *J. Macromol.Sci. Rev. Macromol. Chem. Phys.*, **1988**, C28, 503-509.
- 97 Hodge, P.; Richardson, G. *J. Chem. Soc., Chem. Commun.*, **1975**, 622-627.
- 98 Ley, S. V.; Mynett, D. M.; Koot, W. J. *Synlett.*, **1995**, 1017-1022.
- 99 Parlow, J. J.; Flynn, D. L. *Tetrahedron*, **1998**, 54, 4013-4017.
- 100 Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1-3.

-
- 101 Han, H.; Janda, K. D. *J. Am. Chem. Soc.*, **1996**, *118*, 7632-7637.
- 102 Bunin, B. A.; Plunkett, M. J.; Ellman, J. A.; *In Combinatorial Peptide and Nonpeptide Libraries*, Edited by G. Jung, VCH, Weinheim, **1996**, 405.
- 103 Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J., *Tetrahedron Lett.* **1996**, *37*, 7193-7196.
- 104 Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett.*, **1997**, *38*, 7959-7963.
- 105 Parlow, J. J.; Weidner, J. J.; Flynn, D. L. *Tetrahedron Lett.*, **1999**, *40*, 239-245.
- 106 Ashok, S.; Omura, K.; Swern, D. J. *J. Org. Chem.*, **1976**, *41*, 7856-7859.
- 107 Liu, Y.; Vederas, J. C. *J. Org. Chem.*, **1996**, *61*, 7856-7859.
- 108 Bhalay, G.; Dunstan, A.; Glen, A. *Synlett.*, **2000**, 1846-1859.
- 109 Moffat, J. *J. Org. Chem.*, **1971**, *36*, 1909-1915.
- 110 Weinshenker, N. M.; Shen, C-M *Tetrahedron Lett.*, **1972**, 3281-3285.
- 111 Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1907-1910.
- 112 Nogami, G.; Togo, H.; Yokoyama, M. *Synlett.*, **1998**, 534-537.
- 113 Finch, H.; Ley, S. V.; Thomas, A. W. *J. Chem. Soc. Perkin Trans. 1*, **1999**, 669-672.
- 114 Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *Synthesis*, **1989**, 45-49.
- 115 Endo, M.; Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1998**, *63*, 6094-6098.
- 116 Shing, T. K. M.; Zhng, Y-L. *J. Org. Chem.*, **1997**, *62*, 2622-2625.
- 117 Gibson, R. H.; Kroll, L. C. *J. Am. Chem. Soc.*, **1971**, *73*, 3062-3064.
- 118 Hughes, I. *Tetrahedron Lett.* **1996**, *37*, 7596-7959.
- 119 Hodge, P.; Richardson, G. J., *J. Chem. Soc. Chem. Commun.* **1975**, 622-624.
- 120 Brinkman, H. R.; Landi, Jr., J. J. *Synthesis*, **1992**, 1093-1095.
- 121 Bailey, F. C.; Gibson, H. W. *J. Chem. Soc., Chem. Commun.* **1977**, 815-818.
- 122 Hutchins, R. O.; Natale, N. R.; Taffer, I. M. *J. Chem. Soc., Chem. Commun.* **1978**, 1088-1092.
- 123 Murphy, F.; Nicolaou, K. C.; Pastor, Pastor, J.; Winssinger, N. *Angew, Chem. Int. Ed.*, **1998**, *37*, 2534-2539.
- 124 Gerigk, U.; Gerlach, M.; Neumann, W. P.; Vieler, R.; Weintritt, V. *Synthesis*, **1990**, 448-452
- 125 Gerlach, M.; Jordens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.*, **1991**, *56*, 5971-5975.
- 126 Hassner, A.; Stern, M. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 478-484.
- 127 Castells, J.; Dunach, E. *Chem. Lett.* **1984**, 1859-1862.

-
- 128 Gordon, M.; DePamphilis, M. L.; Griffin, C. E. *J. Org. Chem.*, **1963**, *28*, 698-710.
- 129 Li, X-Y.; Olah, G. A. *Synlett.*, **1990**, 267-273.
- 130 Ganesan, A.; Kulkarni, B. A. *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2454-2561.
- 131 Kolb, H. C.; Sharpless, K. B.; VanNieuwenhze, M. S. *Chem Rev.* **1994**, *94*, 2483-2485.
- 132 Bolm, C.; Gerlack, A.; Maischak, A. *Chem. Commun.*, **1997**, 741-743.
- 133 Ashton, M. R.; Baxter, A. D.; Bayston, D.; Fraser, J. L.; Moses, E.; Polywka, M. E. C. *J. Org. Chem.*, **1998**, *63*, 3137-3141.
- 134 Shapiro, R. H. *Org. React.*, **1979**, *23*, 405-409.
- 135 Chen, J. S.; Dixon, B. R.; Dumas, J.; Britelli, D. *Tetrahedron Lett.*, **1999**, *40*, 9195-9198.
- 136 Parlow, J. J.; Case, B. L.; South M. S. *Tetrahedron*, **1999**, *55*, 6785-6790.
- 137 Brown, A. R.; Irving, S. L.; Ramage, R.; Raphy, G. *Tetrahedron*, **1995**, *51*, 11815-11830.
- 138 Shai, Y.; Jacobson, K. A.; Patchornik, A. *J. Am. Chem. Soc.*, **1985**, *107*, 4249-4252.
- 139 Krchnak, V.; Dalton, C. *Modern Drug Discovery*, **2002**, 23-28
- 140 <http://www.mimotopes.com/combichem/array.html>
- 141 Houghten, R. A. *Proc. Natl. Acad. Sci. USA*, **1985**, *82*, 5131-5135.
- 142 Atrash, B.; Bradley, M.; Kobylecki, R.; Cowell, D.; Reader, J. *Angew. Chem. Int. Ed.*, **2001**, *40*, 938-941.
- 143 Smith, J. M.; Gard, J.; Cummings, W.; Kanizsai, A.; Krchňák, V. *J. Comb. Chem.*, **1999**, *1*, 368 -370.
- 144 Blankenmeyer-Menge, B.; Nimitz, B.; Frank, R. *Tetrahedron*, **1990**, *31*, 1701-1704
- 145 De Witt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 6909-6914.
- 146 Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Methods in Enzymology*, **1996**, *267*, 448-465.
- 147 Geysen, H. M.; Meloen, R. H.; Barteling, S. J. *Proc. Natl. Acad. Sci. USA*, **1984**, *81*, 3998-4002.
- 148 Cornelis, A.; Laszlo, P. *Synthesis*, **1980**, 849-854.
- 149 Ashton, M. R.; Baxter, A. D.; Bayston, D.; Fraser, J. L.; Moses, E.; Polywka, M. E. C. *J. Org. Chem.*, **1998**, *63*, 3137-3145.
- 150 Chauhan, B. P. S.; Boudjouk, P. *Tetrahedron Lett.*, **1999**, *40*, 4123-4126.
- 151 Bassindale, A. R.; Gentle, T. E. *J. Organomet. Chem.*, **1996**, *521*, 391-393.
- 152 Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, **1990**, 77-79.

-
- 153 McComas, W.; Chen, L.; Kim, K. *Tetrahedron Lett.*, **2000**, 41, 35-38.
- 154 Klemenc, S. *Forensic Sci. Int.*, **2002**, 129, 194-199.
- 155 Mowry, A.; Renoll, T.; Huber, K. *J. Am. Chem. Soc.*, **1946**, 68, 1105-1107.
- 156 Joule, J. A.; Mills, K. *Heterocyclic Chemistry – Fourth Edition*, **2000**, 124-126.
- 157 Greenidge, P. A.; Merette, S. A. M.; Beck, R.; Dodson, G.; Goodwin, C. A.; Scully, M. F.; Spencer, J.; Weiser, J.; Deadman, J. J. *J. Med. Chem.*, **2003**, 46, 1293-1305.
- 158 Delaney, E. J.; Wood, L. E.; Klotz, I. M. *J. Am. Chem. Soc.*, **1982**, 104, 799-807.
- 159 Spivey, A. C.; Fekhnner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.*, **1999**, 9430-9443.
- 160 Wallace, J. S.; Baldwin, B. W.; Morrow, C. J. *J. Org. Chem.*, **1992**, 57, 5231-5239.
- 161 Moore, J. D.; Byrne, R. J.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *Org. Lett.*, **2003**, 23, 4241-4244.
- 162 Thomas, G. L.; Ladlow, M.; Spring, D. R., *Org. Biomol. Chem.*, **2004**, 12, 1679-1681.
- 163 Mowry, D. T.; Renoll, M.; Huber, W. F. *J. Am. Chem. Soc.*, **1946**, 68, 1105-1109.
- 164 Takahashi, K. *Chem. Pharm. Bull.*, **1960**, 8, 1106-1109
- 165 Pfenninger, A. *Synthesis*, **1986**, 89-92.
- 166 Libermann, D.; Denis, J.-C.; *Bull. Soc. Chim. Fr.* **1961**, 1952-1954.
- 167 Masuyama, A.; Tsuchiya, K.; Okahara, M. *Bull. Chem. Soc. Jpn.* **1985**, 58, 2858-2859.
- 168 Keus, D.; Kaminski, M.; Warkentin, J. *J. Org. Chem.*, **1984**, 49, 343-347.
- 169 Miyamoto, H.; Yasaka, S.; Takaoka, R.; Tanaka, K.; Toda, F. *Enantiomer*, **2001**, 6, 51-56.
- 170 Venkateswarlu, S.; Raju, M. S. S.; Subbaraju, G. V. *Biosci. Biotechnol. Biochem.* **2002**, 66, 2236-2238.
- 171 Allan, G. R.; Carnell, A. J. *J. Org. Chem.*, **2001**, 66, 6495-6497.
- 172 Lisowski, V.; Enguehard, C.; Lancelot, J.-C.; Caignard, D.-H.; Lambel, S.; Leonce, S.; Pierre, A.; Atassi, G.; Renard, P.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, 11, 2205-2208.
- 173 Maya, A. B. S.; Rey, B.; Clairac, R. P. L.; Caballero, E.; Barasoain, I.; Andreu, J. M.; Medarde, M. *Bioorg. Med. Chem. Lett.* **2000**, 10, 2549-2552.

