The development of PolyHIPE monoliths for use as supports in organic synthesis

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Abstract

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Jane F. Brown, Ph.D. Thesis, October 2003

As part of the ongoing research efforts to discover alternative support materials to polymer beads for use in polymer-supported synthesis, particularly under flow-through, this project involved the synthesis of PolyHIPE (High Internal Phase Emulsion) polymer monoliths. PolyHIPEs containing high loadings of chloromethyl groups were efficiently prepared by the direct copolymerisation of 4-vinylbenzyl chloride and divinylbenzene monomers. As revealed by characterisation of the materials obtained, the VBC monomer hydrolysed to an extent during the polymerisation, replacing a small amount of the chloromethyl functionalities with hydroxymethyl groups.

Functionalisation of the PolyHIPEs, in batch and flow-through reactions, produced supports with aminomethyl and hydroxymethyl linkers attached. Conversions were often higher as a result of the flow-through modifications. Capacities were increased further with the introduction of trisaminomethyl and trishydroxymethyl linkers, which showed potential as supports for polymer assisted solution phase (PASP) synthesis and solid phase organic synthesis (SPOS), respectively.

Chloromethyl PolyHIPE was shown to be an excellent support for batch and flow-through Suzuki cross-coupling reactions. A remarkably high yield of pure biaryl product was obtained using PolyHIPE in cubic form and an electron-rich boronic acid. In comparison to polymer beads, PolyHIPE was found to be a much more efficient support in both batch and continuous flow modes. PolyHIPE converted a greater amount of chloromethyl groups into biaryl product under identical reaction conditions. Under flow, the channelling effect observed with the beads was completely eliminated with PolyHIPE monoliths. The utility of hydroxymethyl-functionalised PolyHIPEs (Wang and tris-OH) in Suzuki coupling reactions was investigated and both showed promise as supports in this application.

Acknowledgements

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Last but not least, I would like to take this opportunity to thank my mum, dad and brother for their encouragement, their words of wisdom and overall, for helping me to achieve my goals. Finally, words cannot describe how grateful I am to Craig for his help and support, especially in recent months. You're simply the best!

Memorandum

The work reported in this thesis has been carried out at the Department of Chemistry, University of Durham, between October 2000 and September 2003. This work has not been submitted for any other degree either in Durham or elsewhere and is the original work of the author except where acknowledged by means of appropriate reference.

Statement of Copyright

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Contents

Abbreviations

BET	Brunauer, Emmett and Teller
BNAH	1-benzyl-1,4-dihydronicotinamide
CEC	capillary electrochromatography
CLEAR	cross-linked ethoxylate acrylate resin
DCC	N,N'-dicyclohexylcarbodiimide
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMA	N,N'-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane, glyme
DMF	N,N'-dimethylformamide
DVB	divinylbenzene
EDCI	N-ethyl-N'-[3-dimethylamino)propyl]carbodiimide hydrochloride
EI	electron ionisation
Fmoc	9-fluorenylmethyloxycarbonyl
FTIR	Fourier transform infrared
GC-MS	gas chromatography-mass spectroscopy
HIPE	high internal phase emulsion
HLB	hydrophilic-lypophilic balance
HMBA	4-hydroxymethylbenzoic acid
HMP	4-hydroxymethyl phenol
HMPA	4-hydroxymethylphenoxyacetic acid
HMPB	4-hydroxymethyl-3-methoxyphenoxybutyric acid
HMTA	hexamethylenetetramine
HOBT	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure & Applied Chemistry
LC-MS	liquid chromatography-mass spectroscopy
LPOS	liquid phase organic synthesis
MS	mass spectroscopy

MSNT	1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole
NMI	N-methylimidazole
NMR	nuclear magnetic resonance
PASP	polymer-assisted solution phase
PEG	poly(ethylene glycol)
PEGA	polyacrylamide cross-linked with PEG
POEPOP	polyoxyethylene-polyoxypropylene
POEPS	polyoxyethylene-polystyrene
RAM	Rink amide linker, (2,4-dimethoxyphenyl)(4-alkoxyphenyl)-methylamine
ROMP	ring opening metathesis polymerisation
SEM	scanning electron microscopy
SPOS	solid phase organic synthesis
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMDS	1,1,3,3-tetramethyldisilazane
VBC	4-vinylbenzyl chloride

Chapter 1

Introduction

1.1 Overview

This year marks the 40th anniversary of the first reported organic synthesis on a polymer support. Yet, despite its lengthy existence, rapid growth in this research area has only occurred since the emergence of combinatorial chemistry and parallel synthesis in the late 80's. With increasing demands for new, biologically active compounds, synthetic chemists are required to accelerate greatly their rate of production of chemical entities. Current methods in organic synthesis enable the construction of target molecules of almost any complexity, yet there still exists a need to develop new, strategically important processes which are ecologically sound and more efficient. While the development of both synthetic and analytical technologies in supported chemistry has occurred at an increasing rate, it is surprising that few new polymeric supports specifically designed for organic synthesis have been reported.[1] This introductory chapter begins with a general description of the types of supports employed in polymer-supported synthesis. The focus will then turn to the topic of

solid phase organic synthesis, which will include an investigation into examples of solid phase Suzuki cross-coupling reactions in the literature. A review of the developments in solid phase supports will follow, with an emphasis on alternative forms, particularly monolithic materials. In the final section, PolyHIPE technology will be described, together with recent examples of the use of PolyHIPE in solid phase synthesis and catalysis.

1.2 Polymer-Supported Synthesis

Polymer-supported synthesis refers to syntheses in which the starting reagents and intermediates are bound to either *insoluble* (solid phase) or *soluble* (liquid phase) polymeric materials, known as supports. These allow for the facile separation of products and intermediates from residual starting material and solvent, and must be mechanically stable as well as chemically inert under the reaction conditions employed. They are also required to contain a high loading of reactive groups (> 1.5 mmol g^{-1} polymer), which can be conveniently functionalised so that synthetic intermediates can be covalently bound to them via appropriate linker molecules. Perhaps most importantly, support materials must exhibit sufficient permeability and swelling capacity to enable reagents to diffuse into the matrix to access internally bound reactive sites. For environmental and economical reasons, polymeric supports should also allow mmol-scale synthesis and complete recycling after cleavage of the product.

1.2.1 Soluble Polymeric Supports

Soluble polymers and copolymers are, in principle, ideal candidates as reaction supports. In many cases they behave like reactants in homogeneous reactions, exhibiting high reactivity in solution and overcoming the problem of 'restricted active site access' common to insoluble polymers. The recovery and separation of such polymers can be readily achieved by addition of a suitable precipitant or by micro- or ultra-filtration. Unlike reactions performed on insoluble supports, reactions on soluble polymers can be monitored successfully by high-resolution solution phase ^{1}H and ^{13}C NMR spectroscopy. However, the main problems associated with soluble supports are that they tend to be highly hygroscopic and have low loading capacities (~0.2 mmol g^{-1}). The filtration and precipitation techniques used to recover soluble polymers are considered expensive and

inconvenient, and often, large amounts of solvent are needed to precipitate them quantitatively.

Currently, the most commonly used soluble polymer in liquid phase organic synthesis (LPOS) is poly(ethylene glycol) (PEG). Its high chemical stability, good reactivity, and broad solubility profile make it an excellent candidate as a soluble polymer. Furthermore, it is easily precipitated and recovered in nonpolar solvents such as diethyl ether. Bayer and Mutter[2] first studied PEG as a support in 1971. Janda and co-workers[3] later demonstrated that PEG could be used as a support to synthesise the first combinatorial peptide library. This was followed by the development of PEG-supported ligands for use in organic synthesis and more recently, bifunctional PEGs containing benzyl ether dendrons (*Figure 1.1*) have been prepared in an attempt to increase the capacity of this type of support. With a loading of 0.8 mmol g^{-1}, these soluble polymers have been shown to be excellent supports in organic synthesis.[4]

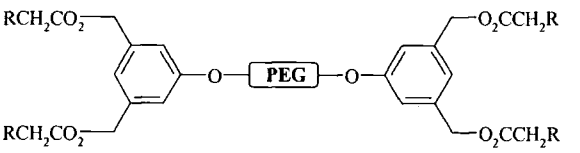
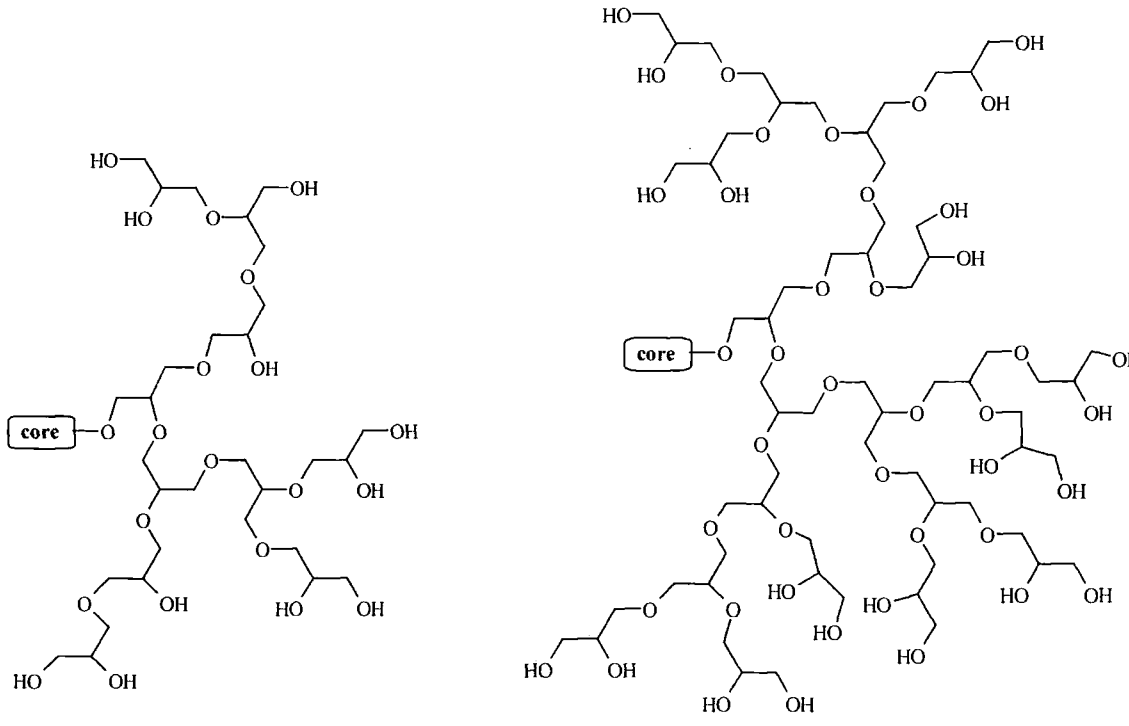


Figure 1.1 Bifunctional PEG-containing benzyl ether dendrons

Linear polymers bearing functional groups on every monomer unit, such as polyvinylalcohol and polyacrylamide, have also found application as high loading soluble supports in organic synthesis.[5] Oligonucleotides have previously been synthesised using both polymers, however, the general use of these supports is limited due to poor solubility and reduced chemical stability. Recently, Frey and Haag[6] reported a significant advancement in the development of soluble polymers for supporting organic reactions. They described the controlled synthesis of well-defined hyperbranched polyglycerol supports with loading capacities of 4.1 mmol g^{-1}. The linear glycerol units were further converted into terminal 1,2-diols, producing perfectly branched structures known as 'pseudo dendrimers', with diol loadings of 7.1 mmol g^{-1} (*Figure 1.2*). In an attempt to increase the scope of possible reactions on the polyglycerol support, the conversion of the pendant hydroxyl groups into other linker functionalities was also successfully demonstrated.



Hyperbranched polyglycerol
4.1 mmol diol g^{-1}

Pseudo-dendritic polyglycerol
7.1 mmol diol g^{-1}

Figure 1.2 Hyperbranched polyglycerol and pseudo dendrimer supports

1.2.2 Insoluble Polymeric Supports

Insoluble polymers and copolymers are by far the most commonly employed supports in organic synthesis, giving rise to the term solid phase organic synthesis (SPOS). These materials are easily separated by standard laboratory techniques and tend to have higher loading capacities and greater stability than soluble supports. Insoluble supports can also be recycled after cleavage and are considered to be more attractive for high-throughput synthesis and automation. However, insoluble supports, like their soluble counterparts, have limitations. In particular, problems often arise purely as a result of the heterogeneous nature of the reactions and inaccessibility of functional groups. Also, the task of modifying and optimising solution phase chemistry to the solid phase remains laborious and time-consuming, and regular monitoring of reactions is often difficult.

SPOS is reported to be an attractive alternative to classical solution phase synthesis as excess reagents can be used to drive reactions rapidly to completion resulting in greater yield, and work-up is simplified because the supported species are easily purified by filtration and washing. For this reason, the technology is

considered to be clean and hence more environmentally friendly.[7] Merrifield took the first step towards introducing solid supports to organic synthesis in 1963.[8] His primary focus was on the synthesis of peptides using cross-linked beads as supports, a technology which earned him the Nobel Prize for chemistry.

Functional supports can be prepared either by polymerisation or copolymerisation of monomers bearing the desired functionality, or by chemical modification of preformed polymers. The latter is the most frequently employed approach, and in this respect, the insoluble polymer of choice for organic chemists has tended to be the one originally introduced by Merrifield, divinylbenzene (DVB)-cross-linked polystyrene copolymer (*Figure 1.3*).

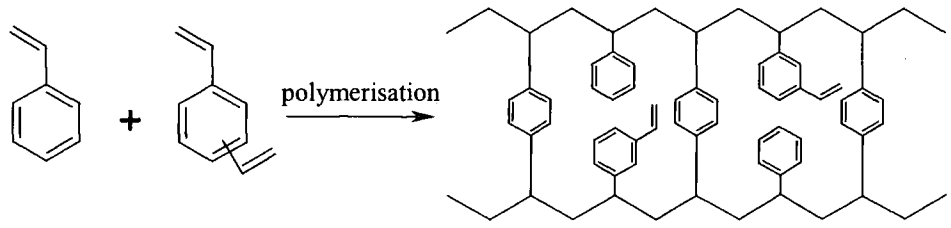


Figure 1.3 Synthesis of poly(styrene-divinylbenzene) copolymer

This resin can be further characterised according to its swelling behaviour as gel-type or macroporous. Gel-type resins are produced by suspension polymerisation in the form of hard, transparent beads. Typically, they contain 1-2% divinylbenzene cross-linker and have internal surface areas as low as 10 $m^2 g^{-1}$. This, coupled with the fact that 99% of the functional groups are hidden inside the beads, means that gel-type resins must swell in 'good' solvents (those with solubility parameters similar to that of the polymer) in order to provide access to their reactive sites. Furthermore, gel-type beads are only useful if the matrix is able to resist osmotic shock *i.e.* the process of swelling and de-swelling in both good and bad solvents, without mechanical damage. It could be argued that flowing reagent solution through bead-filled columns under pressure would solve the problem of reactive site inaccessibility, however, the beads become soft and compressible when highly swollen, which limits their use in flow-through applications.

The macroporous varieties are produced in a similar way. They are usually highly cross-linked (> 10%) and have internal surface areas as high as 1000 $m^2 g^{-1}$.

Unlike gel-type beads, they do not need to swell to allow access to their interior because they possess a permanent porous structure. This is due to the presence of a porogen in the comonomer mixture, which causes phase separation of the polymer matrix (*Figure 1.4*). Their large internal surface areas allow easy access to reactive sites and hence, rapid functionalisation in a variety of solvents. Furthermore, their resistance against osmotic shock is far greater than that of gel-type beads.

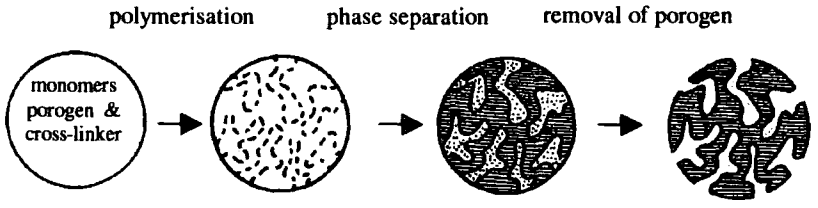


Figure 1.4 Schematic of the effect of porogen in macroporous resin[9]

Unfortunately, the main shortcomings of these materials are that they have a tendency to react at the surface and are often difficult to handle due to high electrostatic potential. As with gel-type resins, it could be argued that flowing reagent solution through bead-packed columns under pressure would force reactions to take place inside the beads as well as on the surface. However, a channelling effect is observed whereby the solution prefers to flow around the beads and into the interstitial voids, rather than through them (*Figure 1.5*).

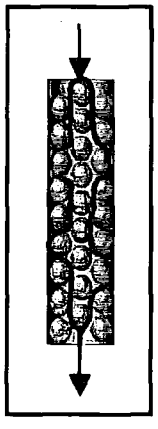


Figure 1.5 Schematic of channelling effect

1.3 Solid Phase Organic Synthesis

1.3.1 Solid Phase Linkers

Linkers are often used in SPOS to bind covalently the molecules to be synthesised onto the polymeric support (*Figure 1.6*). Their main purpose is to allow the easy attachment of starting materials, and also to enable selective and often milder cleavage at the end of the synthesis. Ideally, cleavage should occur under conditions that do not degrade the target molecule or result in excessive contamination of the product. Therefore, the choice of linker largely determines the conditions under which the product is released and the reaction conditions suitable for the synthesis.

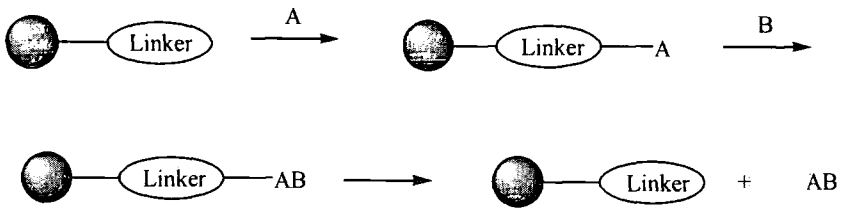


Figure 1.6 Principle of solid phase organic synthesis

Various linkers have been developed for use in solid phase peptide and organic synthesis. The structures of some of the most commonly used varieties are shown in *Figure 1.7*.

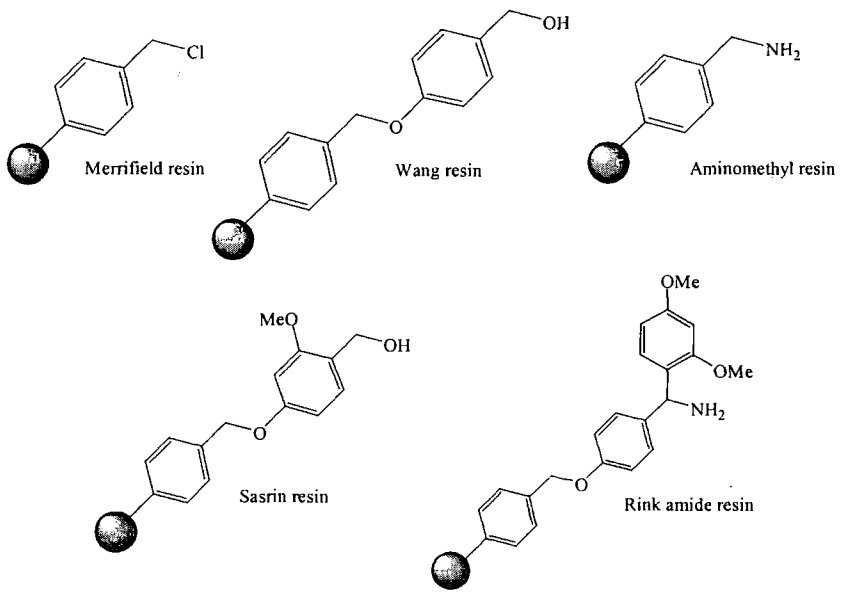


Figure 1.7 Structures of the most commonly used linkers

Merrifield resin has tended to be the most popular type of support for the synthesis of peptides. Carboxylic acid attachment is achieved by heating the resin in DMF with the appropriate carboxylic acid cesium salt in the presence of potassium iodide.[10] Transesterification with methoxide in the final cleavage step results in methyl ester products (*Figure 1.8*).

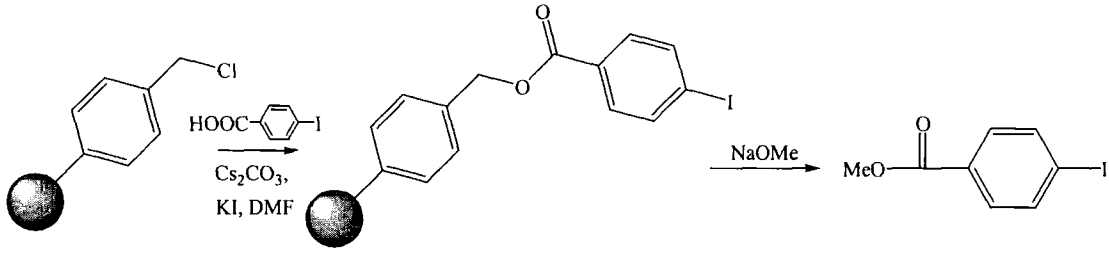


Figure 1.8 Synthesis of methyl ester on Merrifield resin

Phenols and phenolic derivatives can be coupled onto Merrifield resin via cesium salts or by reaction with potassium carbonate in the presence of sodium iodide (*Figure 1.9*).[11]

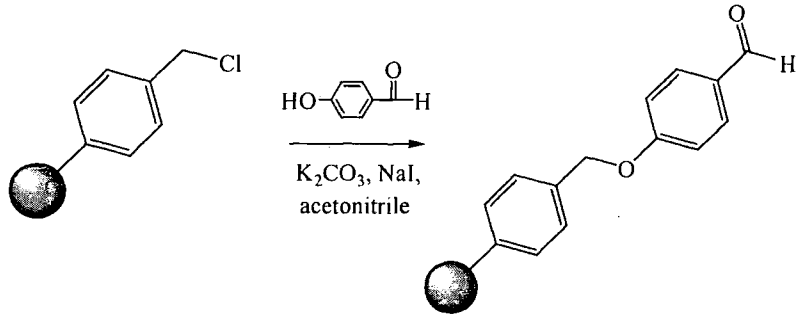


Figure 1.9 Attachment of phenol to Merrifield resin

One of the most widely used linkers in organic synthesis is the Wang linker. Wang-type resins are the standard supports for the solid phase immobilisation of acids and phenols for SPOS. Carboxylic acid attachment can be achieved either by standard protocol with EDCI/HOBT, by DMAP catalysed esterification or in the case of aromatic and hindered carboxylic acids, by MSNT/NMI activation (*Figure 1.10*). Esters of the Wang linker are readily hydrolysed by treatment with TFA in DCM or with Lewis acids such as Et_2AlCl.

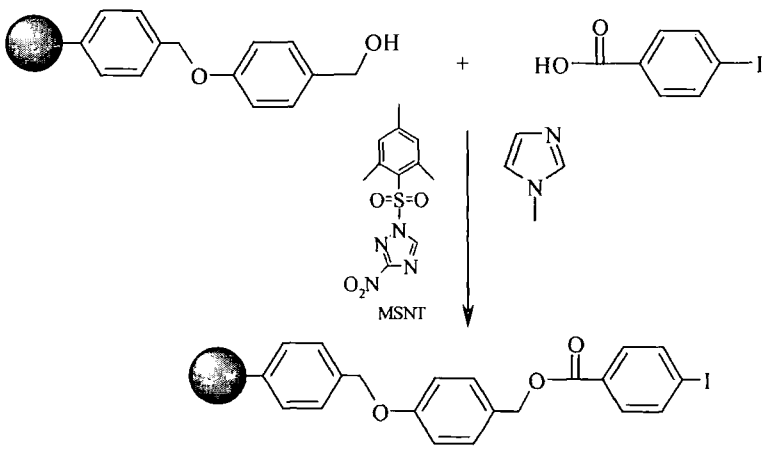


Figure 1.10 Synthesis of Wang-immobilised carboxylic acid

Aminomethylated resins tend to be utilised as base resins for the attachment of various carboxylic acid-containing linkers, one example being the immobilisation of HMPA linker as shown in *Figure 1.11*. In this particular resin, the linker part of the molecule is attached to the support by means of a spacer. For SPOS applications, it has been suggested[12] that flexible spacers assist with the diffusion of reagents to the immobilised reactive sites by increasing their distance from the support. Aminomethylated resins are also useful scavengers for electrophiles including acid chlorides, sulfonyl chlorides and isocyanates (section 1.4.1).

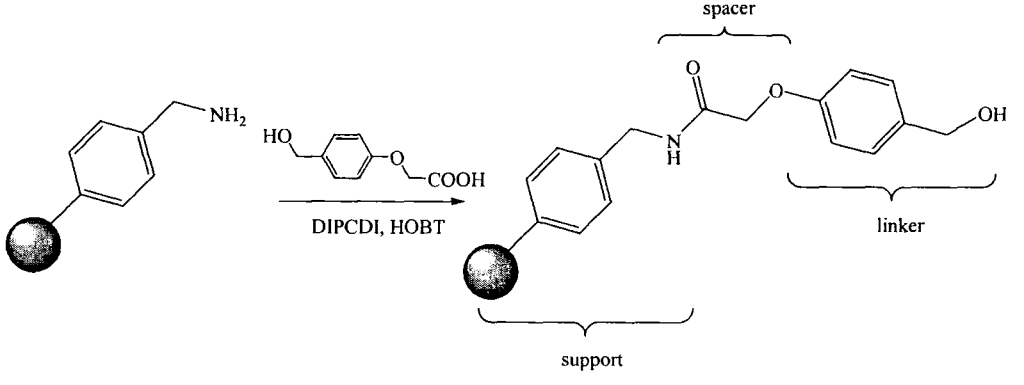


Figure 1.11 Coupling of HMPA linker onto aminomethyl resin

A vast array of popular organic reactions such as Diels-Alder, Wittig and Michael additions have been optimised and successfully performed utilising resins of the type described above, and several comprehensive reviews are recommended to the reader on this subject.[13] One particular reaction, which is reported to adapt well to the solid phase is the Suzuki cross-coupling reaction. This synthesis has been widely

studied and is significant because the biaryl compounds produced are important subunits present in many biologically active compounds, as well as being valuable mesogenic units in the liquid crystalline industry.

1.3.2 Solid Phase Suzuki Cross-Coupling Reactions

In the Suzuki coupling, an aryl- or heteroarylboronic acid or ester is coupled with an arene bearing a good leaving group in the presence of a palladium(0) catalyst and a base. Syntheses involving both polymer-bound boronic acids and aryl halides have been extensively reported, however the latter method tends to be the most popular and is generally preferred. It has been suggested that this is due to fewer boronic acid derivatives being commercially available than functionalised aryl halides. For the purposes of this report, only examples of this latter type have been chosen for review.

In 1994, Friesen and Frenette[14] were the first to demonstrate that the Suzuki cross-coupling reaction could be performed on a solid support. Synthesis began by reacting Merrifield beads (1% DVB, 1.2 mmol $-CH_2Cl$ groups g^{-1}) with bromo or iodobenzoic acid to yield the polymer-bound aryl halides. Initially, the effect of various palladium catalysts on the coupling reaction of the aryl iodide with 4-methoxyphenyl boronic acid was investigated utilising standard Suzuki conditions (3-5 mol % catalyst, DME, 2M $Na_2CO_3(aq)$, reflux overnight). Cleavage with NaOMe afforded the biaryl ester products as shown in *Figure 1.12*. With the exception of $[Pd_2(C_3H_5)Cl_2]$, all of the catalysts tested were reported to be equally effective in the coupling reaction (yields > 95%, purities > 90%). Subsequent studies focussed on coupling a wide range of substituted aryl boronic acids (electron-rich to electron-deficient) onto polymer-bound aryl bromides (*ortho-*, *meta-*, *para-* and poly-substituted) employing one catalyst, $Pd(PPh_3)_4$. As expected, the aryl bromides were found to be less reactive than the aryl iodides, as reflected in the lower yields obtained.

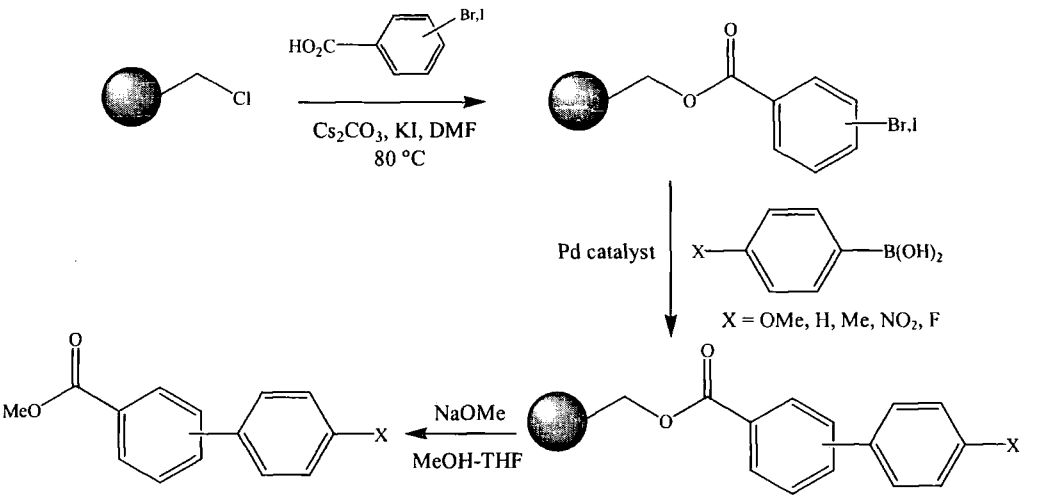


Figure 1.12 Synthesis of biaryls via Suzuki coupling of aryl boronic acids with Merrifield-bound aryl halides

In the same year, Ellman and Backes[15] employed aminomethylated polystyrene beads (2% DVB) in the Suzuki coupling reaction of an acylsulfonamide, utilising Kenner's "Safety-Catch" linker. Standard conditions were employed and good conversions were reported for a range of arylboronic acids (electron-poor to electron-rich, as well as *ortho*-substituted). High yields of both carboxylic acid and amide products were obtained upon nucleophilic cleavage from the support (*Figure 1.13*).

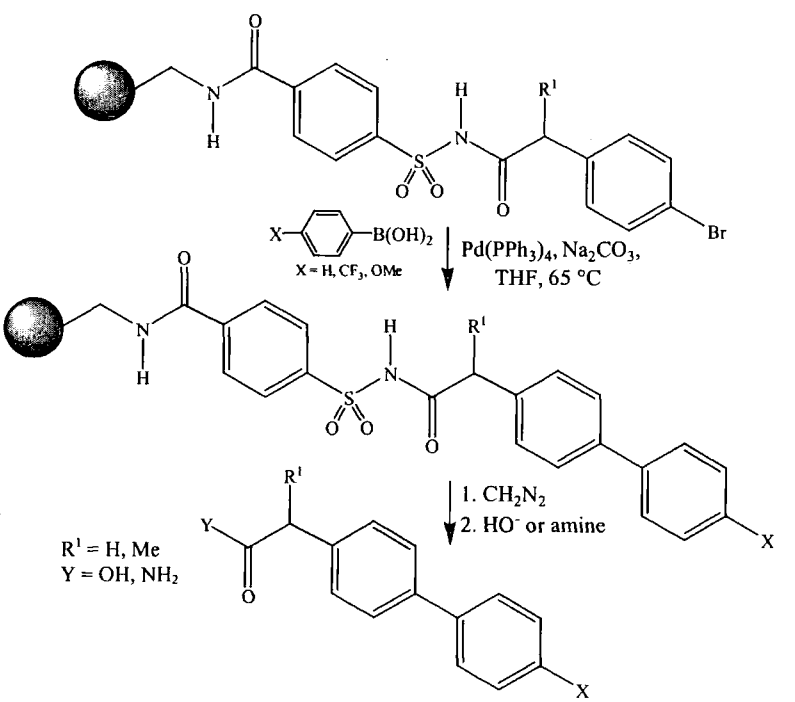


Figure 1.13 Use of aminomethylated resin in the Suzuki coupling of an acylsulfonamide

Several years later, with the aim of identifying a common set of conditions for the solid phase Suzuki coupling of a wide range of substrates, Guiles and co-workers[16] performed Suzuki reactions on commercially available SASRIN and Wang beads (0.89 mmol -CH_2OH groups g^{-1}). The resins were coupled with an iodobenzoic acid using EDCI/HOBT reagents, and various catalysts were tested for use in the Suzuki coupling of phenylboronic acid at room temperature. Pd(0) varieties were discovered to be most effective, whereas Pd(II) and Ni(II) catalysts were ineffective. The majority of the couplings were complete in 18 hours, however, *o*-iodobenzoate was found to be slower than its *meta-* or *para-* counterparts due to steric effects, and the bromo-substituted benzoates were reported to be completely unreactive under the conditions employed. Cleavage with dilute trifluoroacetic acid produced the acid products in varying yield and purity (*Figure 1.14*). Similar conditions were then used to couple successfully a variety of boronic acids (aryl, alkyl, alkenyl and heteroaromatic) and in each case, the optimal palladium catalyst was found to depend upon the boron reagent selected.

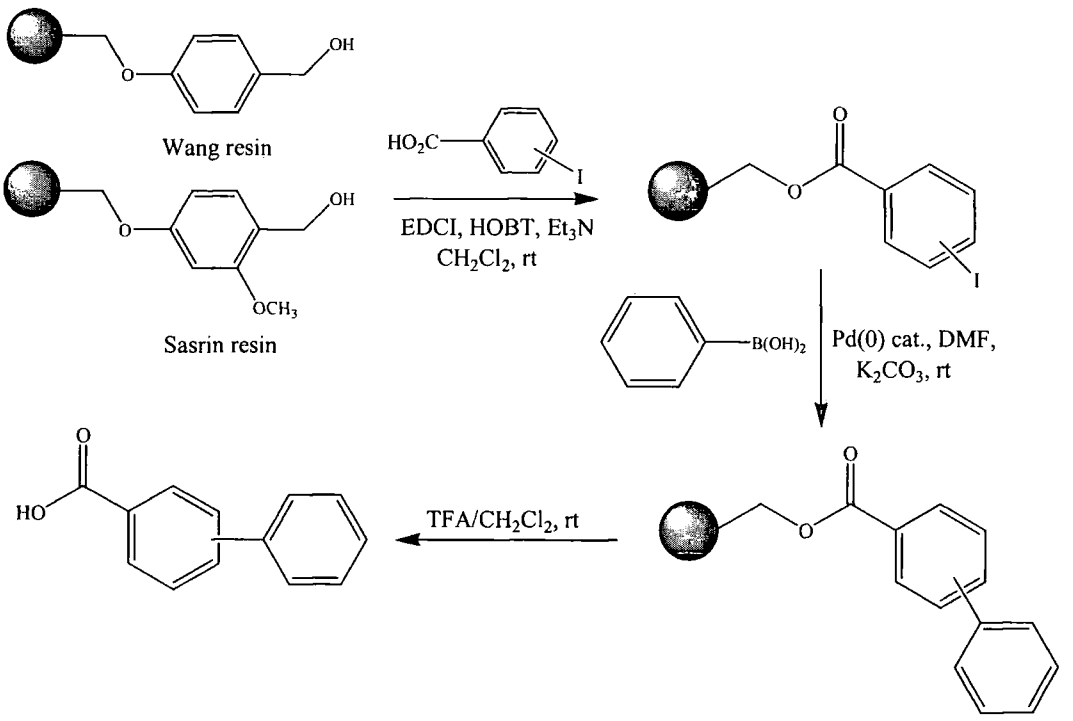


Figure 1.14 Synthesis of biaryl carboxylic acids via the Suzuki coupling of phenylboronic acid with Sasrin and Wang-bound aryl iodide

In order to obtain greater diversification of small molecule libraries and to increase the number of molecular species generated, Han *et al.*[17] also utilised Wang resin in the solid phase Suzuki reaction. They developed a method for attaching haloarylsilane linkers onto commercially available Wang beads and demonstrated the successful coupling of a variety of boronic acids. Initial couplings were carried out using both standard aqueous conditions [2M Na_2CO_3, DME] and anhydrous conditions [1:1 Et_3N/DMF]. As comparable results were obtained in each case, subsequent couplings were performed using only the anhydrous route. The highest yields of *ipso*-substituted biaryl products were obtained upon cleavage with electrophilic species such as ICl and Br_2/Pyr, whereas poorer yields were reported with CF_3COOH (*Figure 1.15*).

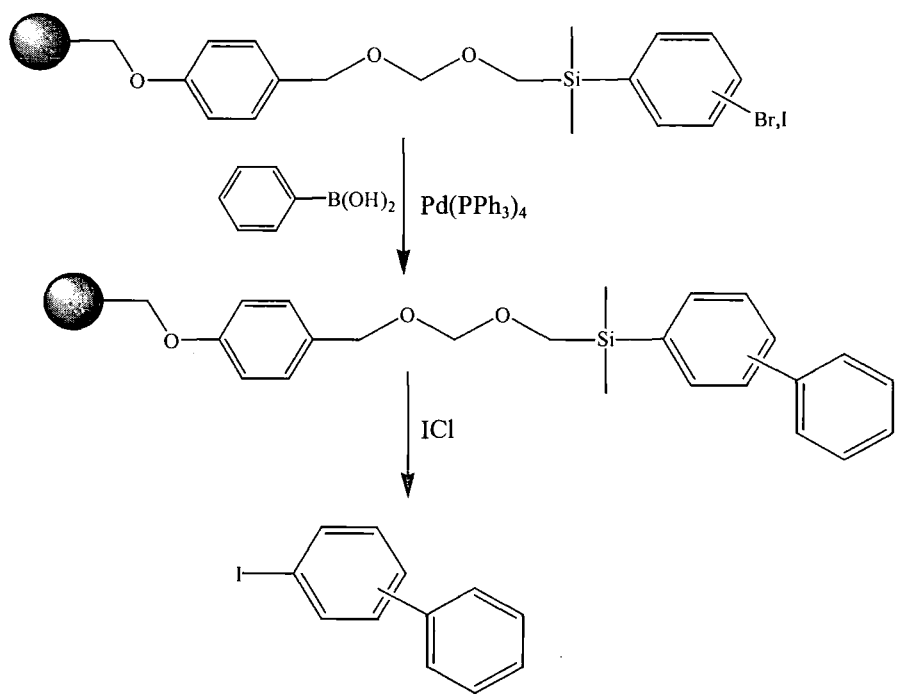


Figure 1.15 Use of Wang-bound haloarylsilane linkers in the coupling of phenylboronic acid

While many groups focused on the use of elaborate linker molecules for solid phase Suzuki reactions, Larhed and co-workers[18] were the first to report microwave-assisted Suzuki couplings on Rink amide (RAM) TentaGel resins (0.23 mmol $-NH_2$ groups g^{-1}). In an attempt to deliver products in high yield and in very short reaction times, they demonstrated that an irradiation effect of 45 W resulted in greater than

99% conversion of the starting material in just 3.8 minutes, with minimal degradation of the support. The coupling of phenyl boronic acid onto the iodine bound intermediate followed by cleavage with TFA yielded 98% product, together with a small amount of PEG (*Figure 1.16*). A 97% yield was obtained via the bromine coupling. A further seven boronic acids were tested in the study, with each acid producing similar yields to the phenyl boronic acid.

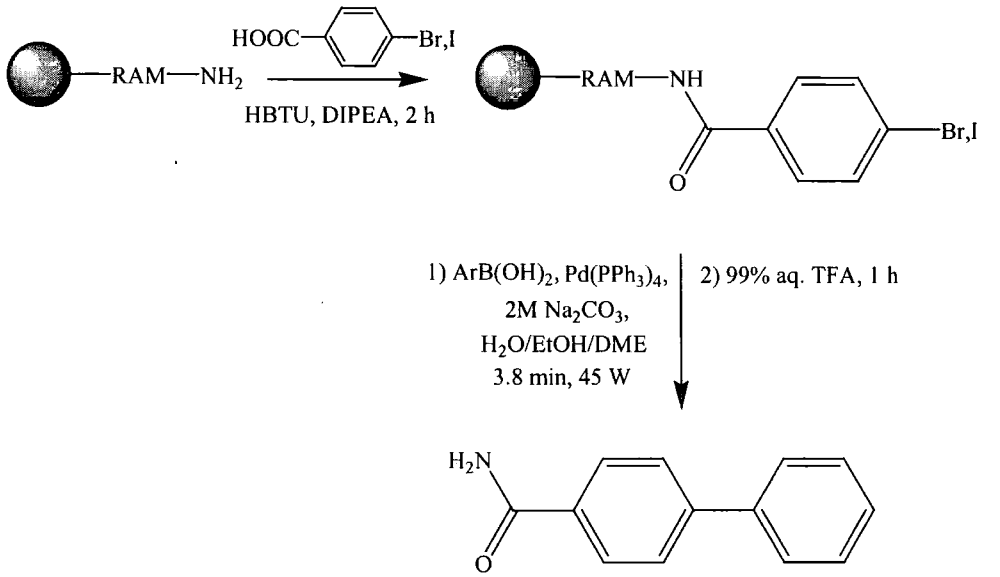


Figure 1.16 Synthesis of amido biaryls via microwave-assisted Suzuki coupling

Several years later, in similar studies to those carried out by Ellman and co-workers on acylsulfonamide linkers, Baxter *et al.*[19] demonstrated the utility of arylsulfonate ester linkers in the Suzuki coupling reaction. 4-Bromophenethyl alcohol was immobilised onto the polystyrene based linker to yield the sulfonate ester, followed by the coupling of 4-methylphenyl boronic acid. The product was cleaved by reaction with neat diethylamine, producing the biaryl amine in 23% yield and 90% purity (*Figure 1.17*).

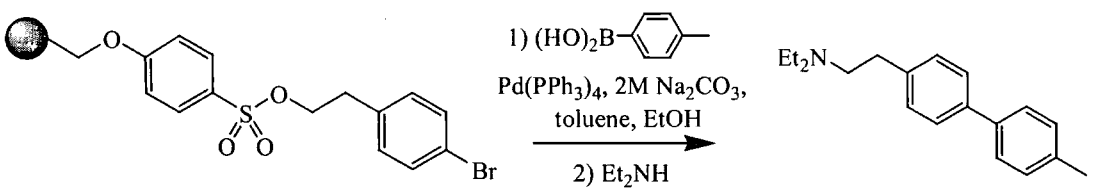


Figure 1.17 Synthesis of biaryl amines utilising arylsulfonate ester linkers in the Suzuki cross-coupling of 4-methylphenyl boronic acid

At the same time, Chamoin and co-workers[20] reported the synthesis of biaryl and heterobiaryl aldehydes utilising the Leznoff acetal linker in the Suzuki reaction. Commercial Merrifield resin (1 mmol $-CH_2Cl$ groups g^{-1}) was functionalised via the sodium alkoxide of solketal, and hydrolysis of the acetonide enabled 2-, 3-, and 4-bromobenzaldehydes to be attached. The polymer-supported bromides were coupled with various boronic acids, and the aldehyde products were obtained by cleavage of the acetal with 3M HCl/dioxane (*Figure 1.18*). Yields of 45% - 95% were isolated after column chromatography.

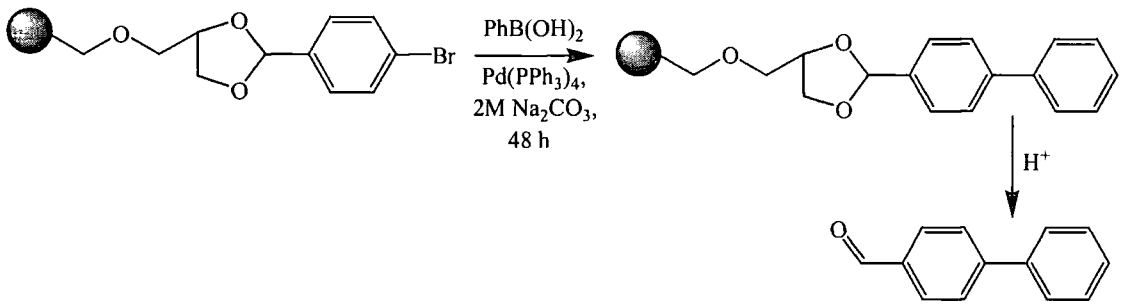


Figure 1.18 Suzuki synthesis of biaryl aldehydes using the Leznoff acetal linker

In a shift away from linker development towards novel resin supports for Suzuki cross-coupling, Bradley and Fromont[21] recently described a practical approach to the synthesis of high-loading resin beads employing triple branching symmetrical dendrimers. Synthesis began by preparing the trifunctional dendrimer monomers, which were then used to derivatise aminomethyl beads loaded with polyamine scaffolds. Generation 1 dendrimers (8000 beads g^{-1}) were reported to have capacities of 116 nmol g^{-1}. The pendant methyl ester groups of the trifunctional dendrimer moieties were displaced by propane-1,3-diamine, resulting in free amino functionalities, which were then used to attach HMPB linker. This allowed 4-iodobenzoic acid to be linked onto the dendrimer supports. The Suzuki coupling of 4-methylbenzene boronic acid was then performed under standard conditions and cleavage of the biaryl from a single resin bead produced satisfactory HPLC and ^1H NMR data (*Figure 1.19*). It was noted however that the beads were susceptible to shattering as a result of solvent shock, thereby limiting their overall utility.

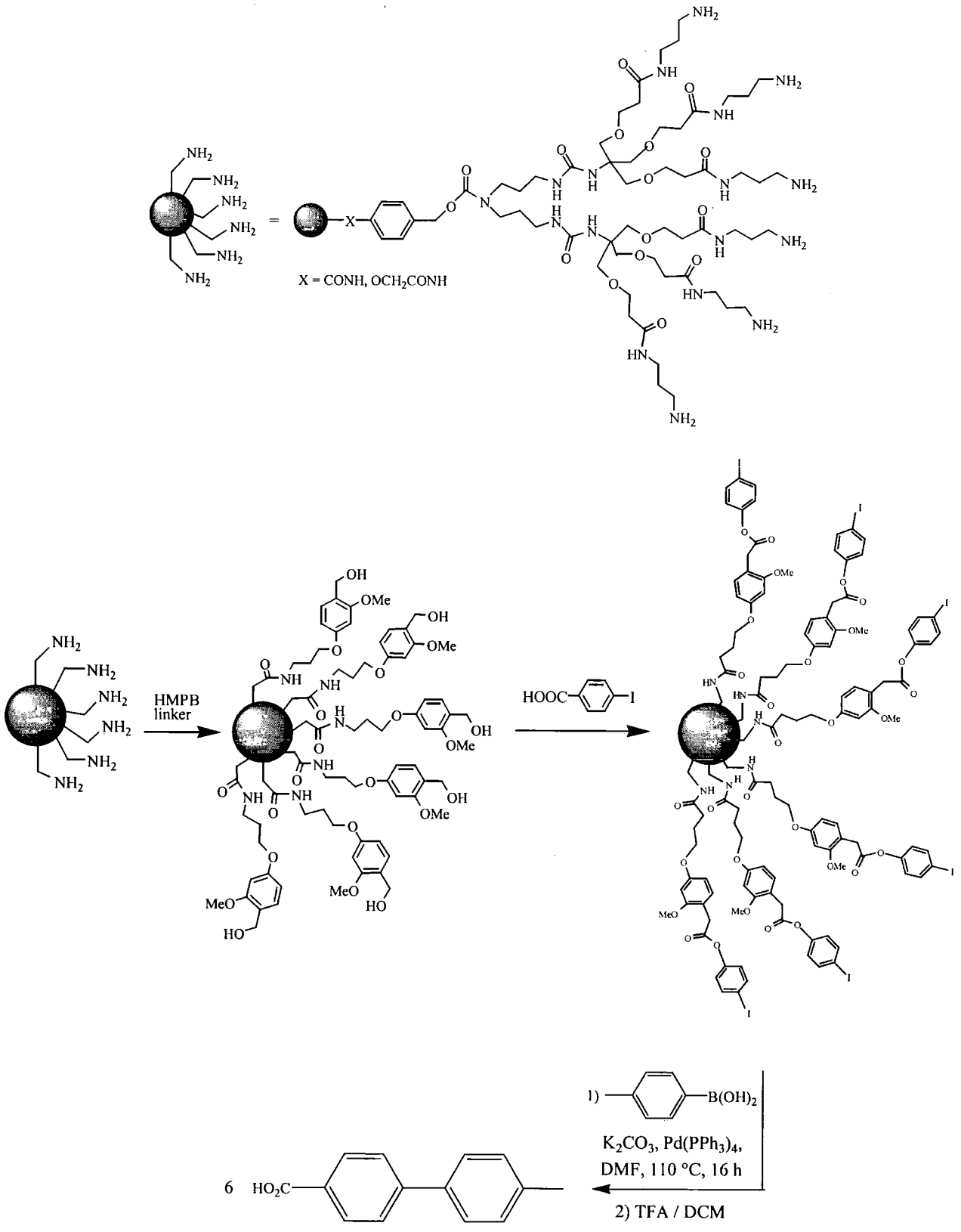


Figure 1.19 Use of high-loading dendrimer beads in the Suzuki coupling reaction

In the quest to find an alternative support to polymer beads, Sherrington and co-workers[22] tested the utility of VBC-based polymer discs in the solid phase Suzuki reaction. Attachment of 5-bromosalicylic acid methyl ester to a disc containing PEG cross-linker and 50% chloromethyl groups was reported to occur with good conversion. Suzuki coupling on the disc and subsequent cleavage resulted in an overall 10.5% conversion to product (*Figure 1.20*). Although the conversion was poor, the monolithic form and convenient size of the disc-shaped support was considered to be ideal for automated mechanical handling.

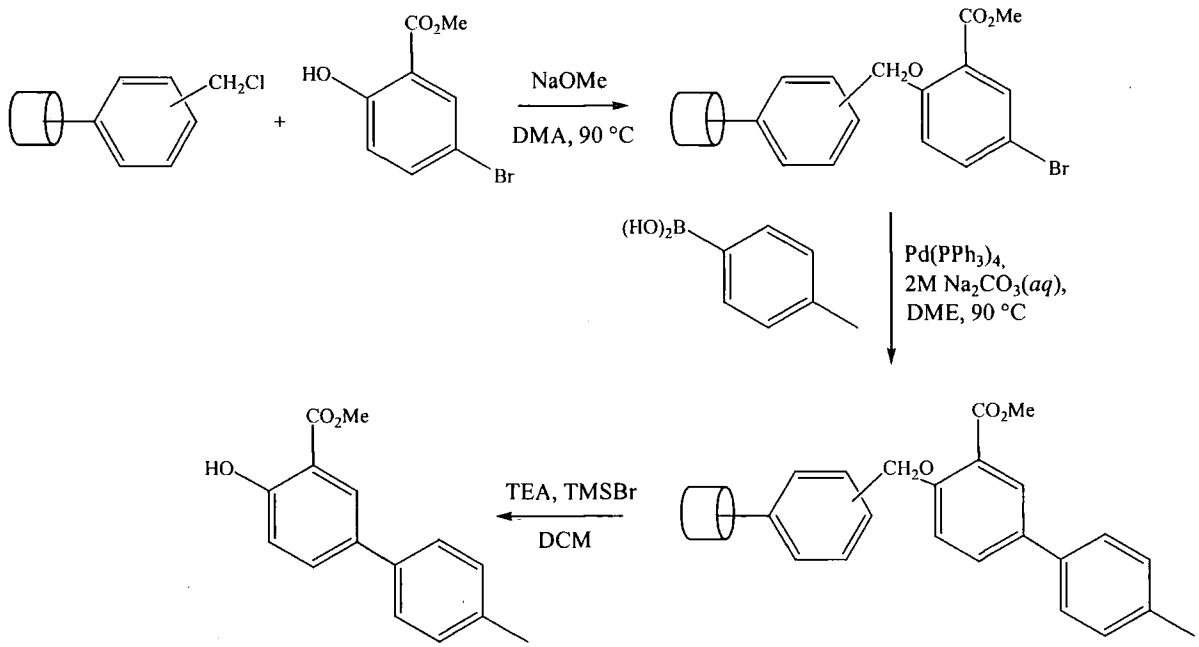


Figure 1.20 Use of VBC-based polymer discs in the solid phase Suzuki coupling reaction

Similarly, Darlak *et al.*[23] evaluated the suitability of CLEAR as a support in the Suzuki reaction. Based on cross-linked ethoxylate acrylate, this resin possesses a highly branched, highly cross-linked ethylene glycol matrix and exhibits excellent swelling properties in a variety of solvents. *Para*-iodobenzoyl chloride was loaded onto the resin via HMPA linker, followed by the Suzuki coupling of phenyl boronic acid. Acidolytic cleavage resulted in crude 4-phenyl benzoic acid with excellent yield (94%) and high purity (75%).

More recently, Lutz and Bleicher[24] developed a general method for the triflation of phenols on Multipin supports, followed by Suzuki cross-coupling with

aryl boronic acids. Multipin technology, involving fixed polymer crowns in a 96-well plate format, is classed as an alternative approach to bead-type polymer supports. Crowns, named after their shape, are rigid unreactive base polymers onto which mobile surface polymers are grafted. Crown-shaped pinheads (Multipin; 2-4 mm diameter) have loadings of 1.2 - 2.2 μmol per crown. Synthesis began with the immobilisation of FmocPheOH onto Rink-MA/DMA polyethylene grafted crowns, followed by the coupling of 3-, or 4-hydroxybenzoic acid. Triflation was achieved by treatment with a solution of $PhNTf_2$ and DIPEA. In the Suzuki coupling stage, the addition of KBr and a large excess of aryl boronic acid, was reported to be essential for complete conversion of the triflated intermediate (*Figure 1.21*). Crude products were obtained in reasonable to high purity (69-94%) using a variety of boronic acids.

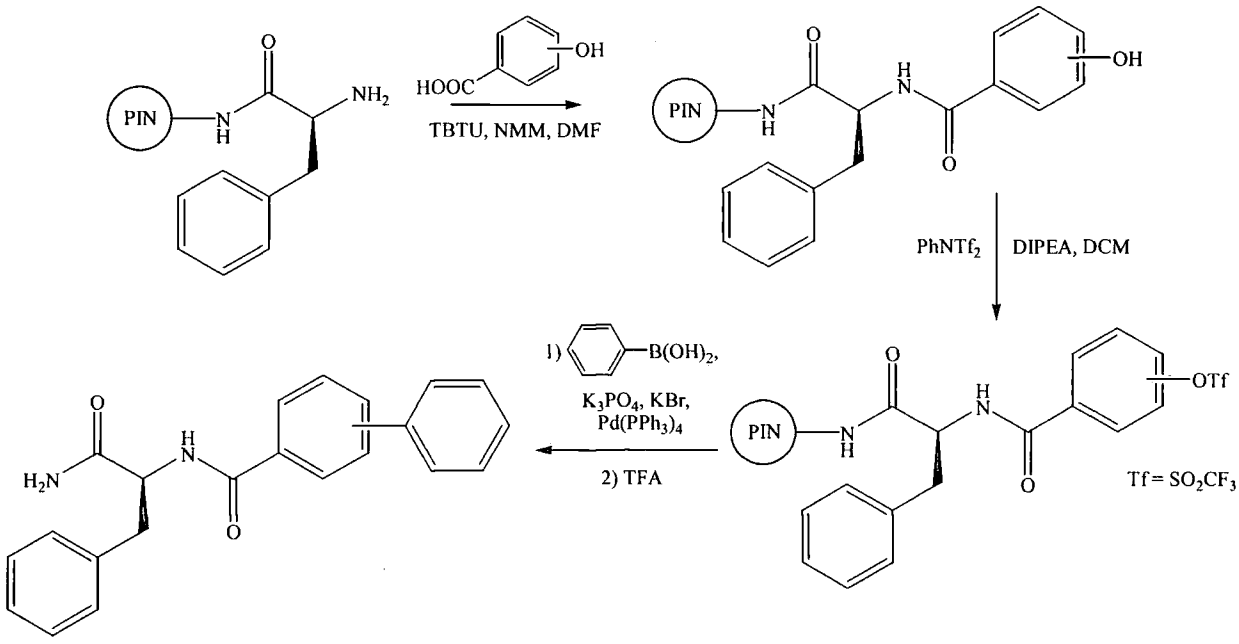


Figure 1.21 Triflation of phenols on Multipin supports and subsequent Suzuki coupling with phenylboronic acid

There has certainly been much interest in SPOS in recent years. The process of attaching a substrate onto a support, reacting it with an excess of reagents and isolating the desired molecule by cleavage and filtration, has formed the basis of combinatorial chemistry and has been utilised in a variety of synthesis programmes. Yet, despite the widespread use of SPOS, there are several problems associated with its practice such as: limited techniques for the proper monitoring of reactions;

contaminated products; overall slow reaction times; and the time consuming optimisation of solution phase chemistry onto a support. These problems do not exist with reactions in solution, in fact, many believe that the advantages of solution phase synthesis far outweigh those of its solid phase counterpart. Therefore, in order to combine the advantages of both techniques, polymer-assisted solution phase (PASP) synthesis was developed.

1.4 Polymer-Assisted Solution Phase Synthesis

In PASP synthesis, reagents or catalysts are attached to a polymer support and used to carry out chemical transformations in solution. This technique utilises all of the benefits of SPOS and since it is carried out in solution, reaction monitoring can be readily achieved by conventional methods and minimal optimisation is required. Furthermore, solid-supported agents specifically designed to scavenge by-products can be used to purify reaction products present in solution. As a result of the PASP approach, the popularity of polymer-supported reagents, catalysts and scavengers has increased and long synthetic sequences have now become possible. For the purposes of this study, only polymer-supported scavengers will be discussed.

1.4.1 Solid Phase Scavengers

Solid-supported scavengers were introduced into organic synthesis programmes to quench selectively or sequester by-products of reactions, or to remove excess starting reagents. Reactive scavenger resins act to entrain impurities, either covalently or ionically, upon completion of solution phase reactions. More than one resin can be employed concurrently to remove multiple reagents and by-products, thus significantly easing reaction work-up. Kaldor *et al.*[25] developed a series of polymer-supported nucleophiles and electrophiles for the selective removal of a variety of unwanted species (*Figure 1.22*).

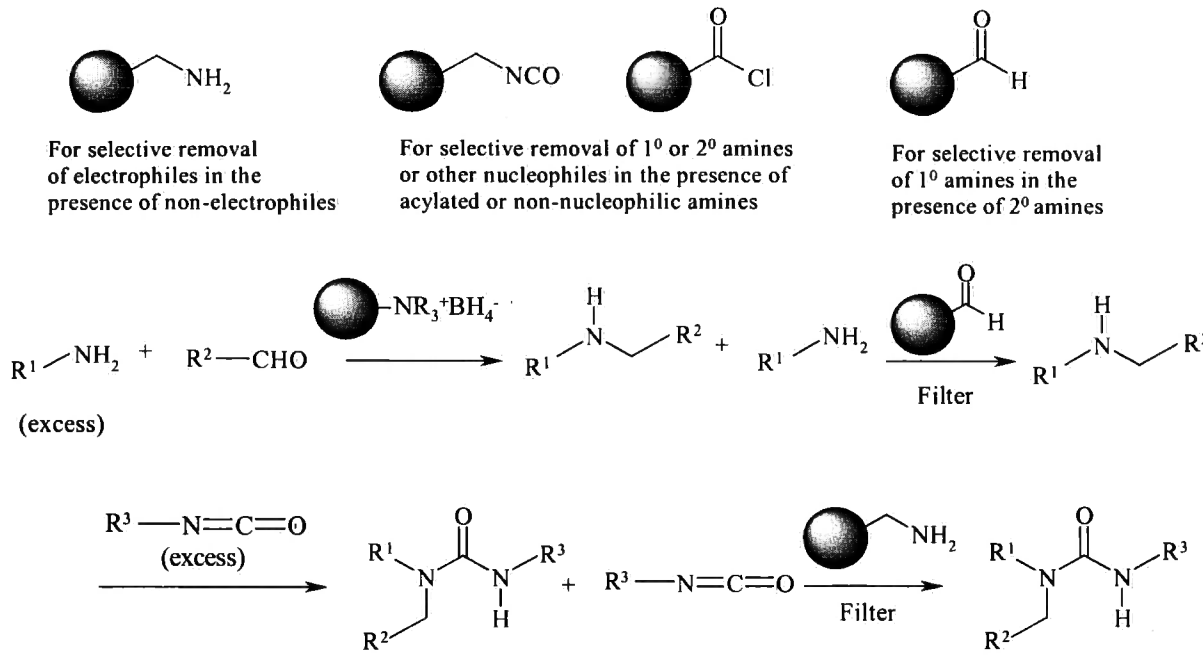


Figure 1.22 Polymer-supported scavenging reagents

In 2000, Nicewonger and co-workers[26] reported the use of polymer-supported tris(2-aminoethyl)amine for the rapid quenching of *trans*-β-styrene sulfonyl chloride. Merrifield resin was first reacted with an excess of the trisamine reagent to yield aminated polystyrene, which was then reacted with 50 μmol of *trans*-β-styrene sulfonyl chloride for 15 minutes. The maximum amount of scavenging achieved was 0.53 mmol g^{-1} (*Figure 1.23*).

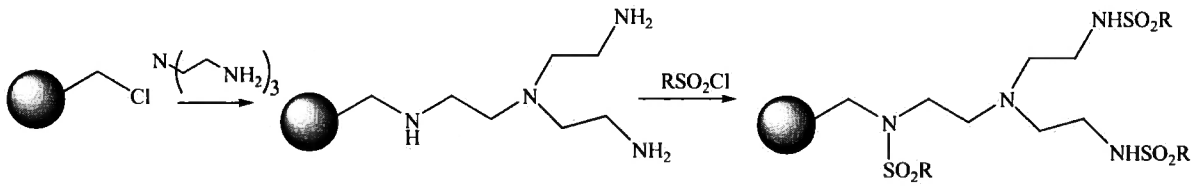


Figure 1.23 Scavenging of trans-β-styrene sulfonyl chloride with polymer-supported tris(2-aminoethyl)amine

More recently, Krajnc and Toplak[27] reported the chemical modification of poly(styrene-*co*-acryloyl chloride) beads with N, O, S and C nucleophiles to produce polymer-supported reagents. The base resin and poly(styrene-co-acrylic acid) were also tested as scavenger resins for the removal of excess benzylamine. The quenching

activity of the acrylic acid was found to be much slower than that of the acid chloride, which had a total scavenging ability of 4.73 mmol g^{-1} resin.

1.5 Developments in Solid Phase Supports

Supports of varying macroscopic shape have successfully been employed for solid phase synthesis, and as discussed, the most common type have been spherical particles in the form of polymer beads. Some of the original alternative insoluble supports included sheets[28] and crown-shaped pins,[29] which found application in the synthesis of peptides. However, it is evident that these materials and others are far from ideal in several aspects, and that there is significant scope to develop improved supports. This section reviews the literature on the various types of supports developed in an attempt to overcome the difficulties with earlier supports.

1.5.1 Developments in Bead Supports

1.5.1.1 Polystyrene-Based Beads

In 1986, Bayer[30] reported a major breakthrough in support technology with the development of PEG - polystyrene resin beads. Commercially known as TentaGel, these resins were initially exploited in peptide synthesis and are currently used widely for SPOS. They are prepared by grafting ethylene oxide to hydroxyl-functionalised styrene-DVB resin, containing 1-2% cross-linker. TentaGel typically consists of 70% PEG and 30% cross-linked resin, and offers versatility in terms of its broad solvent compatibility, uniformity in size, high flexibility and ease of functional end group accessibility (0.15-0.3 mmol g^{-1}). In order to increase the capacity and improve the stability of TentaGel, a similar support was introduced several years later under the name ArgoGel.[31] This differs from TentaGel in that it has been designed with a junction at the polystyrene-graft linkage through the use of a polystyrene diol. This was reported to double the resulting substitution level to 0.4 mmol g^{-1} (*Figure 1.24*). The main disadvantages associated with PEG-grafted polystyrene supports are the low loadings and the release of PEG upon treatment with TFA or upon heating.[32] In addition, the high levels of PEG required to generate the broad solvation properties tend to make the support tacky and difficult to dry.

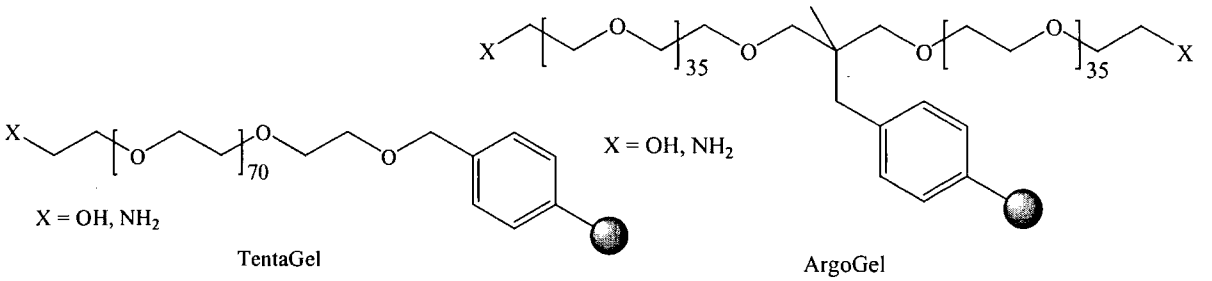
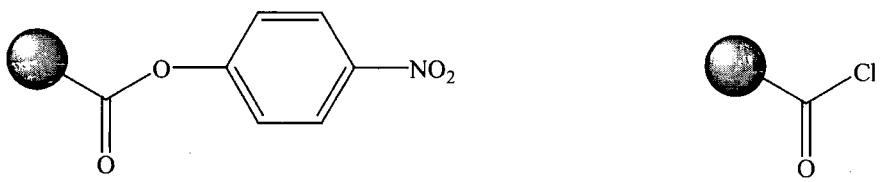


Figure 1.24 Structures of TentaGel and ArgoGel supports

More recent attempts to improve the solvent compatibility characteristics of polystyrene-based resins have involved copolymerising styrene with more polar monomers. Krajnc *et al.*[33] reported the preparation of poly(styrene-*co*-*p*-nitrophenylacrylate) beads, which were subsequently transformed into amino, amino acid and bifunctional amino derivatives. In an attempt to produce a much more reactive cross-linked polymer carrier, they later used this resin to produce poly(styrene-*co*-acryloyl chloride) beads, which have found application as base resins for preparing polymer-supported reagents and as polymer-supported scavengers for nucleophiles (*Figure 1.25*) (section 1.4.1).



poly(styrene-*co*-*p*-nitrophenyl acrylate) poly(styrene-*co*-acryloyl chloride)

Figure 1.25 Structures of acrylate-based supports used in SPOS applications

In an attempt to tailor the physicochemical properties of polystyrene-based supports and hence improve their suitability for organic synthesis, many groups investigated alternative cross-linking agents. Itsuno *et al.*[34] first introduced the idea of using more flexible cross-linkers than DVB, in 1989. In this work, PEG molecules of various molecular weights were capped by two styrene groups to produce bifunctional linker molecules, which were then used to cross-link polystyrene resins (*Figure 1.26*). The beads formed were found to swell to a greater extent than those containing DVB.

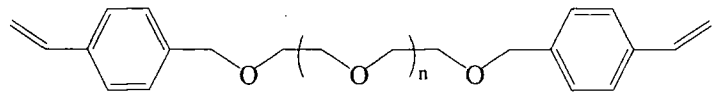


Figure 1.26 Bifunctional cross-linker

A decade later, Janda and co-workers[35] developed a class of resin beads containing flexible tetrahydrofuran-derived cross-linkers, specifically for use in SPOS (known commercially as Janda*Jels*). They reasoned that the use of cross-linker moieties closely matching the solvents used in solution phase synthesis, would allow for increased swelling and solvation characteristics. By copolymerising different mole fractions of the cross-linkers shown in *Figure 1.27*, with styrene and 4-vinylbenzyl chloride (VBC), various resins were prepared containing benzyl chloride functionality. The increased flexibility and polarity of the cross-linkers resulted in an increased interaction between the solvent and the resin. Furthermore, the resins were reported to be stable in the presence of a variety of reagents and have successfully been utilised in both library synthesis and in the preparation of solid-supported catalysts.

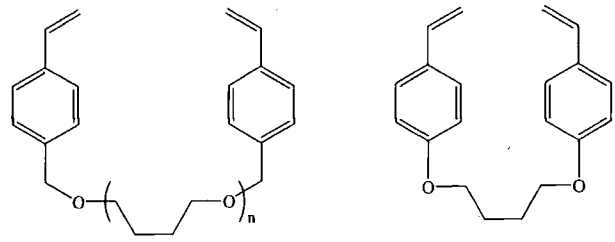


Figure 1.27 Flexible tetrahydrofuran-derived cross-linkers

With the aims of reducing the hydrophobicity of the polystyrene matrix and synthesising peptides with high purity and homogeneity, Pillai *et al.*[36] created polystyrene beads cross-linked with 1,4-butanediol dimethacrylate. Chloromethyl groups were introduced into the resins following polymerisation, and these were later functionalised to obtain both aminomethyl and hydroxymethyl resins. The beads were reported to have excellent swelling properties in all types of solvent and proved effective in the synthesis of polypeptides. Unfortunately, the presence of ester linkages in the cross-linker rendered this type of support less useful in the synthesis of small organic molecules.

In 2001, Janda and co-workers[1] reported the development of novel regio-reactive resin beads as high-loading supports for SPOS applications. The resins contained a new cross-linker bearing a secondary alcohol functionality. Copolymerisation of the cross-linker, with styrene and VBC, produced resins with two orthogonal functional groups, a pendant benzyl chloride functionality on the polymer backbone (1 mmol g^{-1}) and a secondary alcohol on the cross-linker (0.17 mmol g^{-1}) (*Figure 1.28*). In comparative studies with Merrifield resin, the regio-reactive beads were found to swell to a much greater extent.

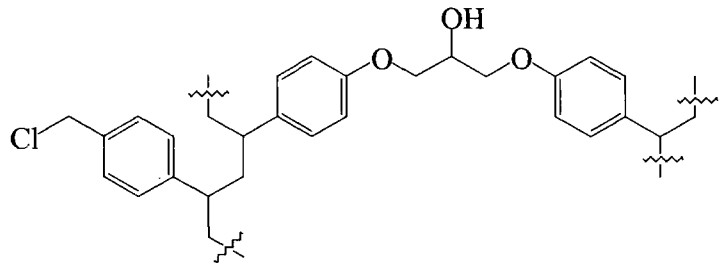


Figure 1.28 Structure of novel regio-reactive resins developed for use in SPOS

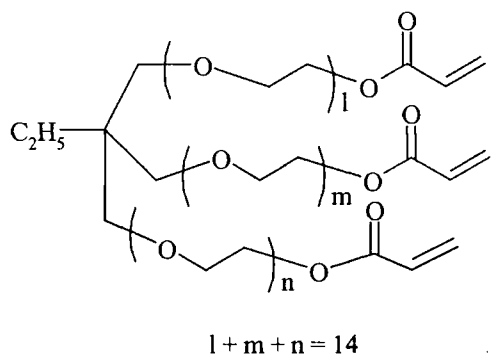
1.5.1.2 Polyacrylamide-Based Beads

In 1975, Sheppard and colleagues[37] experimented with dimethylacrylamide-based resins whose solvation characteristics matched those of the oligopeptide products more closely than polystyrene. Unfortunately, the beads were essentially gel-type and proved too soft and compressible for most applications. To address these problems, highly cross-linked polyacrylamide resins such as Pepsyn were introduced. These exhibited strong swelling properties in a variety of solvents, but unfortunately, they were too unstable for packing in columns for continuous flow synthesis. In 1981, the same group were able to prepare the first composite support in which rigid kieselguhr particles (macroporous silicon dioxide) were saturated with the soft, originally developed, poly(dimethylacrylamide) gel. Meldal *et al.*[38] later developed polyacrylamide beads cross-linked with PEG as supports for SPOS, peptide synthesis and on-bead enzymatic assays. Referred to as PEGA, both high capacity (0.4 - 0.8 mmol g^{-1}) and low capacity (0.2 - 0.4 mmol g^{-1}) forms of the support were produced. PEGA beads displayed excellent swelling properties and chemical stability in a wide range of solvents and reagents. However, the main disadvantage of such supports was their limited mechanical stability, which resulted in problems during filtration of the

polymer. Meldal and Renil[39] later recognised the need to eliminate the amide groups from the polymer backbone if the support was to be suitable for a broader range of organic reactions. They reasoned that the polymer support should be inert, and this was made possible through the introduction of polyoxyethylene-polyoxypropylene (POEPOP) and polyoxyethylene-polystyrene (POEPS) supports, in which all the amide linkages were replaced with more stable ether linkages.

1.5.1.3 Polyacrylate-Based Beads

In 1996, Kempe and co-workers[40] reported the development of cross-linked ethoxylate acrylate resin (CLEAR) supports. Prepared by copolymerisation of trimethylolpropane ethoxylate triacrylate branched cross-linker (*Figure 1.29*) with various monomers and other cross-linkers, CLEAR resins were found to be successful in peptide synthesis under batch and continuous-flow conditions. Their utility in SPOS applications has also been reported.[23] Bulk and suspension modes of polymerisation were used to produce both ground and spherical bead forms, with superior swelling properties and enhanced mechanical stability.



l + m + n = 14

Figure 1.29 Trimethylolpropane ethoxylate triacrylate branched cross-linker

It is evident from the vast array of literature published on polymer supports that common goals exist when attempting to produce the ideal support. In the majority of cases, attempts to improve the performance of polymer beads have focussed on improving the swelling characteristics, increasing the capacity, improving the mechanical and chemical stability and improving the handling. However, many believe that the true justification for using solid supports in organic synthesis lies in automation, and hence it is the ability to adapt a support to continuous flow processes that is of utmost importance. Flow-through techniques offer many advantages over

batch systems such as, fast reaction kinetics, high reactivity and high throughput. Bead-type polymers have been widely used as packed beds, however columns and reactors containing such materials have experienced some limitations.[41] Problems such as slow diffusional mass transport of soluble reagents into the stagnant liquid in the pores of the beads is evident, as well as the existence of large empty spaces between the packed particles. Only the active sites close to the bead surface tend to be accessible by the reagent solution. In order to improve the mass transfer characteristics of these systems, perfused beads containing larger pores were developed in the early 1990s, which enabled a small portion of the mobile phase to flow through them.[42] Separation media consisting of a rigid porous silica matrix impregnated with a soft hydrogel were also reported to have superior mass transfer properties.[43] Silica is considered to be well suited for continuous-flow applications due to the fact that its volume stays constant and diffusion rates are high.

Ideally a system containing little or no interparticular void volume is required to enable good convective flow through the medium and hence fast reactions. A medium possessing no voids would involve a single continuous piece of porous material. To overcome the problem of interparticular void volume within columns, systems in which a membrane has been used,[44] and stacked thin membranes based on modified cellulose,[45] cellulose acetate,[46] spun poly(ether-urethane-urea) and Nylon[47] have been reported.

1.5.2 Developments in Monolithic Supports

In the early 1990s, Fréchet *et al.*[48] launched a novel form of continuous medium based on rigid macroporous polymer monoliths. Designed for use in the flow-through mode, this new class of material was produced by a simple moulding process involving polymerisation of a solution of monomer and cross-linker within an unstirred tubular cast (*Figure 1.30*). The organic phase consisted of polyvinyl and monovinyl monomers, as well as initiator and porogen. The resultant monoliths were reported to contain both small pores (< 200 nm diameter) and large pores (> 600 nm diameter), resulting in a porosity of 30-90%. The authors reasoned that the monoliths should contain large pores for convection as well as a connected network of smaller pores for diffusion.

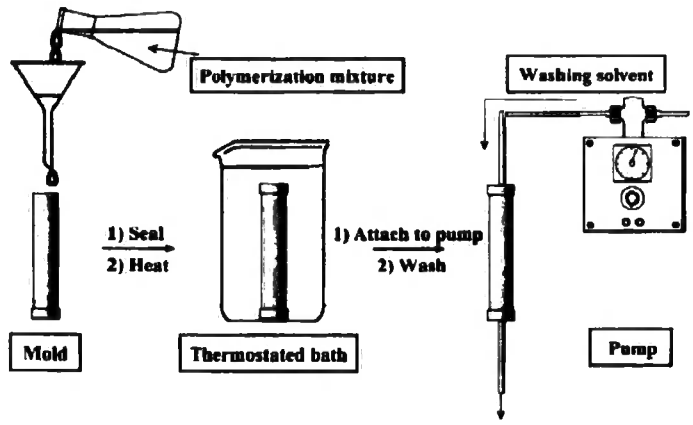


Figure 1.30 Schematic of moulding and flow-through processes[42]

More recently, Sinner and Buchmeiser[49] developed a new method for obtaining functionalised monolithic columns for micro-applications such as CLC and CEC. They prepared continuous matrices inside borosilicate columns by ring-opening metathesis polymerisation of monomers such as norbornene and dicyclopentadiene in the presence of cross-linker and porogen. By varying the monomer ratio, the type of porogenic solvent employed and the polymerisation temperature, monoliths with pore sizes of 30 μm and specific surface areas of 210 m^2g^{-1} were reported. For the same applications, Chirica and Remcho[50] prepared monolithic columns via a templated porosity technique. A monomeric solution, typically containing DVB and styrene, was flushed through a capillary packed with silica beads and then polymerised. Subsequent washing of the polymeric rod with sodium hydroxide, offered a completely porous monolith, without the need for a porogenic solvent.

With the aim of creating an almost work-up free method for automated solution-phase synthesis, Kirschning and co-workers[51] recently demonstrated the preparation of polyvinylchlorobenzene glass composites (cross-linked with 2-20% DVB), known as PASSflow supports, for use in flow-through processes. The composites were prepared by precipitation polymerisation inside the pore volume of highly porous glass rods. The matrix exhibited a small bead-type structure and possessed a high surface area. The composite was loaded with chemical functionalities such as immobilised reagents and catalysts. As a result of the high porosity and the presence of functionalised polymer inside the pores of the monoliths, good convective flow of the soluble organic reactants was observed (*Figure 1.31*).

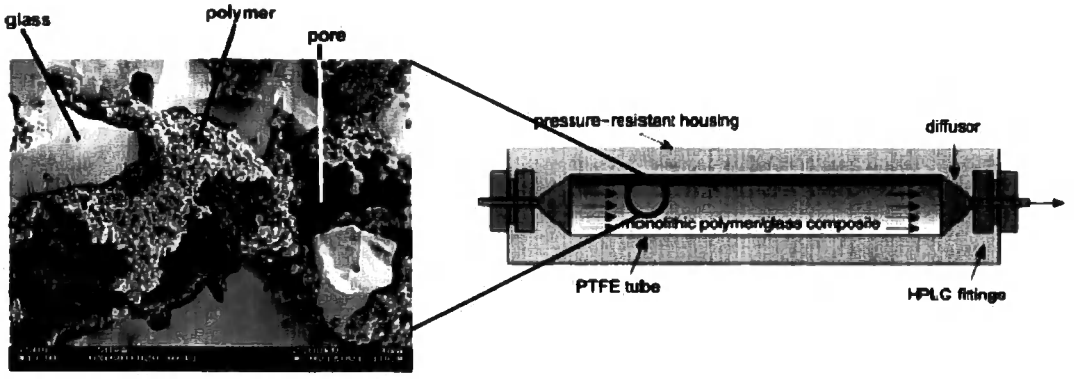


Figure 1.31 SEM of glass composite and schematic of flow-through system[52]

1.5.2.1 Grafting Technique

It would appear that for flow-through synthesis to occur successfully, the monolith must be highly loaded and allow good accessibility of the soluble reactants to the active sites. To achieve high flow rates and low backpressures, the monolith is required to contain an abundance of large pores, however this results in only a small internal surface area being available for reaction within the pores. Such a small surface area limits the amount of reactive functionalities and hence reduces the overall capacity of the monolith. Preparing monoliths with larger surface areas solves this problem, however an increase in surface area generally results in a less permeable support. Therefore, there are two conflicting demands placed on monolithic supports when used in flow-through mode.

In an attempt to increase the density of functional groups on the surface of a support and retain its high permeability, Fréchet *et al.*[52] introduced a grafting technique. The pore surface of an insoluble macroporous chloromethylstyrene copolymer was first chemically modified with a free-radical initiator and then this was used to initiate the polymerisation of an added functional monomer. This approach was reported to increase significantly the number of functionalities emanating from the reaction sites located on the internal surface of the monolith, without restricting flow through the pores. By carefully controlling the porous properties of the monolith, a mean pore diameter of 1 μm was found to enable flow at low back pressure, and a surface area of ~ 8.5 m^2 g^{-1} was reported to be sufficient for the intended grafting.

In similar work, Sinner and Buchmeiser[49] took advantage of the living character of ring opening metathesis polymerisation to perform in situ derivatisation with a suitable ROMP-active monomer. By pumping solutions of monomer through

the monolith active with initiator, grafting of the monomer onto the surface of the support was achieved. Depending on the type of monomer employed, the pores could be provided with a variety of typical functional groups such as carboxylic acid and tertiary amine.

1.5.2.2 Alternative Monolithic Shapes

In order to make the handling of supports more convenient and to optimise the advantages of automation, many groups have recently investigated the production of single polymer particulates or monoliths of varying shape and size. Sherrington and co-workers[22] produced small polymer discs, cut from monolithic rods and cylinders. The monoliths were prepared in glass test tubes by polymerisation of styrene and DVB. PEG cross-linkers were later introduced as alternatives to DVB, and in swelling studies the PEG-based discs were reported to be the most resistant to osmotic shock. Reactive VBC monomer was also introduced and the resultant cross-linked discs tested in SPOS. Their solvent compatibility was found to decrease with increasing loading of functional monomer, and apart from some minor mechanical damage to their edges, the discs were reported to be viable supports for Suzuki cross-coupling reactions (section 1.3.2). In 2000, Janda *et al.*[53] described the preparation of novel polymeric monoliths based on Euclidean shapes, upon which combinatorial split/pool synthesis was performed. Monolithic rods were produced inside glass moulds via the polymerisation of styrene, VBC and flexible cross-linker, 1,4-bis(vinylphenoxy)butane. The monoliths were then cut into the desired shapes using a stencil, and were reported to swell up to five times their original volume in a variety of solvents while still retaining their form. The loading capacity of one of the polymers was found to be four thousand times greater than that of a typical resin bead. The variety of shapes allowed for simple encoding and deconvolution of mixtures of products from a single reaction, which in turn, enabled the efficient production of a library of twenty-four different urea compounds.

More recently, Atrash *et al.*[54] reported the preparation of novel 'resin plugs' and demonstrated their usefulness as supports in organic synthesis and in work-up procedures. Based on composites of polyethylene and polystyrene, the cylindrical plugs were prepared by a resin sintering technique, within an inert polymer matrix. The porous materials were found to maintain their original shape and size, in all solvents except hot toluene. Furthermore, they were stable towards strong acids and

bases, and robust towards stirring. Similarly, the utility of Fréchet's grafting technique was demonstrated on macroporous polymer discs. Poly(chloromethylstyrene-*co*-divinylbenzene) monoliths were prepared inside shrinkable polyethylene moulds and sealed within glass tubes. After polymerisation, the monoliths were sliced to afford discs encircled with polyethylene rings, giving the polymers significant mechanical stability. The discs were activated by graft polymerisation of 4-vinyl-2,2-dimethylazlactone and other types of monomer, onto their surface. Initially, the usefulness of the grafted monolithic discs as reactive filtration devices was tested in the scavenging of excess reagents from reaction mixtures. The solutions were pumped through the monolithic devices, which were placed inside cartridges. By performing the scavenging under flow-through, the reactive filtration media required only a short residence time and hence work-up procedures were more efficient. In a continuation of this work,[55] the grafted discs were successfully utilised as acylating resins, under flow-through conditions, for the conversion of amines to amides.

An alternative method for the production of highly porous, permeable monoliths is to polymerise the continuous phase of a high internal phase emulsion (HIPE). The resulting material, termed PolyHIPE,[56] has a fully interconnected, open-cellular structure and is highly permeable as a result. Surface areas as high as 550 m^2 g^{-1} have been reported[57] with these novel materials, hence high capacity can be achieved without employing a grafting technique.

1.6 High Internal Phase Emulsions (HIPEs) and PolyHIPEs

From a technological perspective, porous polymeric foams are important materials and have been produced by a variety of processes ranging from phase separation to gas blowing. Although these materials have found uses in many applications, their structure is fairly irregular and difficult to control.[58] In response to this, high internal phase emulsions (HIPEs) have been developed for producing porous materials, which exhibit a much more regular and defined structure. HIPEs are described as concentrated systems possessing a large volume of dispersed phase. More specifically, they contain an internal (droplet) phase volume ratio of greater than 74.05%, this figure representing the maximum volume that can be occupied by uniform spheres when packed into a given space in the most efficient packing arrangement.[59] Since the internal phase occupies greater than 74% of the total

emulsion volume, the droplets are considered to be either non-uniform i.e. polydisperse or deformed into non-spherical, polyhedral cells.[60] Indeed, Lissant and Mayhan[61] studied the shape of the internal phase droplets on cured HIPEs using scanning electron microscopy (SEM) and found fairly monodisperse polyhedral droplets at high internal phase volumes (*Figure 1.32*).

1.6.1 Formation of PolyHIPEs from HIPEs

HIPEs are formed in the presence of two immiscible liquids, one of which constitutes the internal phase, and the other, the continuous phase. Like standard emulsions they can be obtained in either normal (oil-in-water, o/w) or inverse (water-in-oil, w/o) forms. In order to obtain foams, HIPEs are formed by the slow, drop-wise addition of the internal phase to a solution of surfactant and monomer in the continuous phase, under constant agitation. Upon polymerisation, the continuous phase is cured around the internal phase droplets. At high internal phase volumes and during the polymerisation step, holes are formed in the thin films separating the droplets and the structure formed is open cell (*Figure 1.32*).

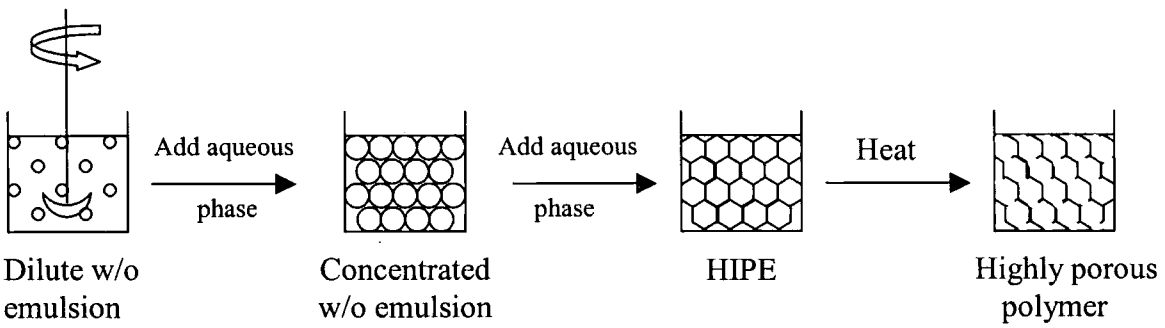


Figure 1.32 Schematic of PolyHIPE preparation

Consequently, the aqueous phase is removed by extraction of the resultant PolyHIPE material in a Soxhlet apparatus with water and a lower alcohol. Vacuum drying then yields a highly porous monolith of very low bulk density (~0.1 g cm^{-3}) (*Figure 1.33*). HIPE formation depends largely on the nature and concentration of the surfactant employed, the nature of the continuous phase and the presence of salts in the aqueous phase. Generally, the more hydrophobic the oil phase, the more stable the emulsion produced.

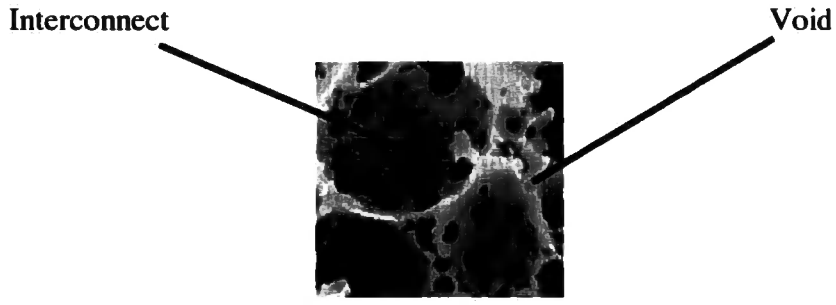


Figure 1.33 SEM of poly(vinylbenzyl chloride-co-divinylbenzene) PolyHIPE

1.6.2 PolyHIPE Surfactants and Electrolytes

As a general rule, the surfactant must be soluble only in the continuous phase or inversion to the corresponding dilute emulsion will occur. In w/o HIPEs, the main function of the surfactant is to stabilise the emulsion. It achieves this by forming a rigid film at the interface between the water and oil phases, thus lowering the interfacial tension between the two. Scientists at Unilever[62] found that the surfactant used to form HIPEs must possess a low hydrophilic-lypophilic balance (HLB) value, ideally between 2 and 6. The optimum surfactant was reported to be sorbitan monooleate (Span 80) which has an HLB number of 4.3 (*Figure 1.34*).

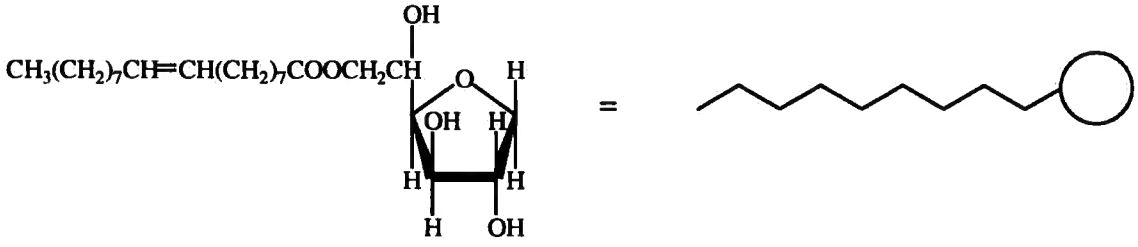


Figure 1.34 Sorbitan monooleate (Span 80)

Span 80 is a non-ionic surfactant, containing a large polar 'head' group and a long hydrophobic 'tail'. In order to form a rigid film at the interface between the water and oil phases, and hence stabilise the emulsion, strong interactions (electrostatic or hydrogen-bonding) are required between adjacent surfactant molecules (*Figure 1.35*).

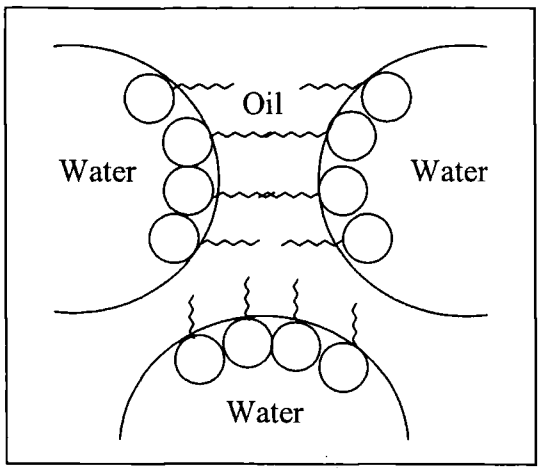


Figure 1.35 Schematic of non-ionic surfactant molecules at water/oil interface in a HIPE

The type of surfactant and surfactant concentration employed help to determine whether an open- or closed-cell HIPE is formed. Below 5% surfactant, relative to the total oil phase, Williams[63] described the polymers as closed-cell and as a result, aqueous phase was retained inside the pores yielding high-density materials. However, above 7%, open cell foams were obtained which exhibited fully interconnected structures. It has since been suggested by Cameron *et al.*[64] that higher surfactant concentrations lead to the formation of thinner films separating the emulsion droplets and hence, upon curing, shrinkage results in a number of interconnects between the voids.

The addition of salts, such as $CaCl_2$, to the aqueous phase of w/o HIPEs has the effect of stabilising the emulsions in a number of ways.[65] Firstly, Ostwald ripening (the process by which larger droplets grow at the expense of smaller ones) is inhibited due to the decreased solubility of the aqueous phase in the oil phase, and secondly, the attractive forces between adjacent aqueous droplets are lowered resulting in an increased resistance to coalescence.

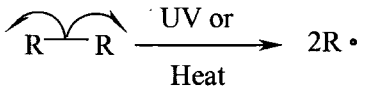
1.6.3 PolyHIPE Properties

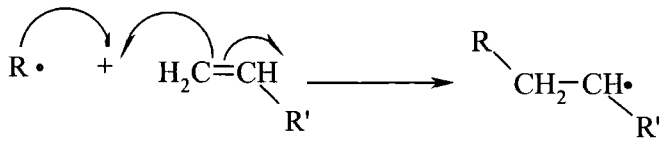
PolyHIPE materials exhibit a variety of desirable properties rendering them useful for a wide range of applications. Properties such as void size, interconnect size and porosity can all be controlled efficiently by a number of factors. An increase in the salt concentration of the aqueous phase has the effect of increasing both the size

and number of interconnects,[66] while an increase in both the cross-linker and surfactant concentration tends to cause a reduction in the average void size.[67] Void sizes often range from 5 and 100 μm, however, this tends to result in PolyHIPEs with low surface areas (~5 m^2 g^{-1}). Hainey *et al.*[68] reported that this property could be increased to 350 m^2 g^{-1} by a combination of three factors; by adding a porogen such as toluene in a 1:1 ratio relative to the monomer content; by using a high level of cross-linker such as DVB (80%); and by increasing the surfactant concentration (33 wt% relative to the total organic phase). In more recent work, Barbetta *et al.*[69] reported that PolyHIPEs with surface areas of 550 m^2 g^{-1} could be prepared by employing 2-chloro-ethyl benzene (CEB) as a solvent.

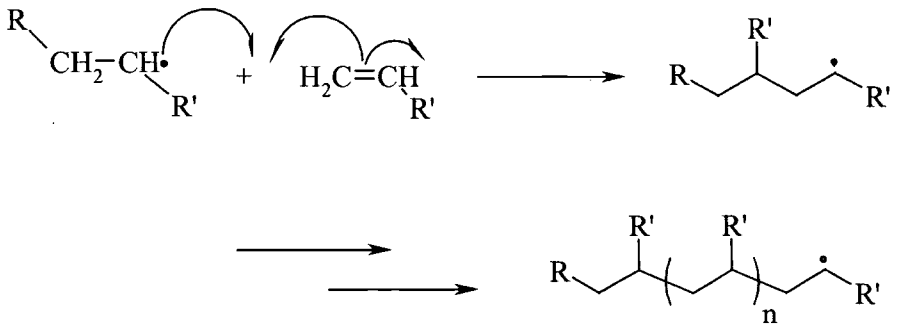
A variety of monomers can be employed in PolyHIPE formation. However, in order to produce the most stable emulsion, it is desirable to use those which are either sufficiently hydrophilic or hydrophobic, and stable in the presence of water. The monomers are polymerised via a free-radical process involving a series of elementary reactions comprising initiation, propagation, termination and monomer transfer (*Figure 1.36*).

1) Initiation

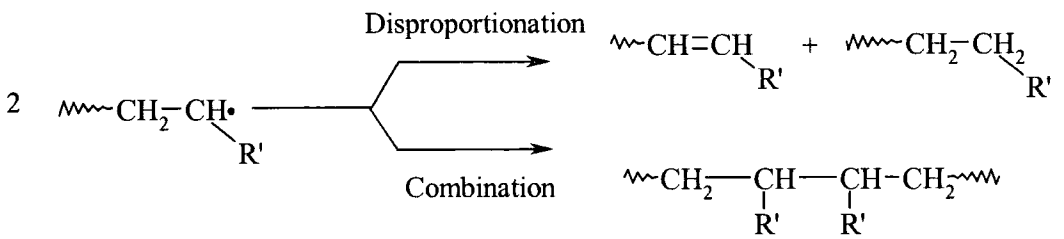




2) Propagation



3) Termination by disproportionation or combination



4) Transfer to monomer

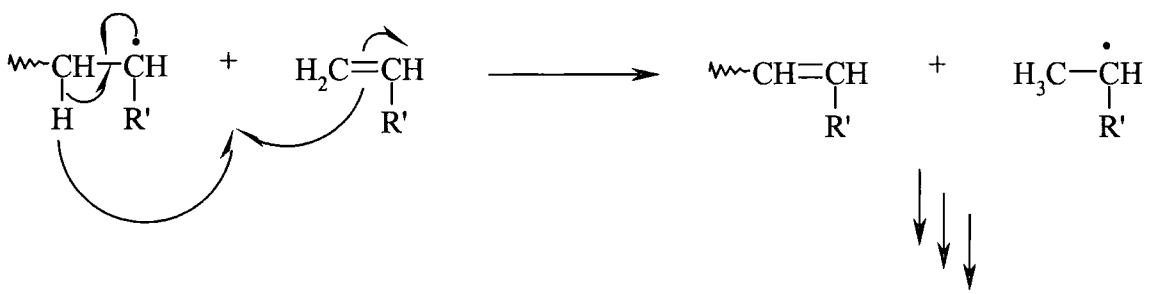


Figure 1.36 Reaction mechanism of free-radical addition polymerisation

A water-soluble free-radical initiator, such as potassium persulfate, can be used to initiate polymerisation as well as standard UV and redox curing agents (*Figure 1.37*).

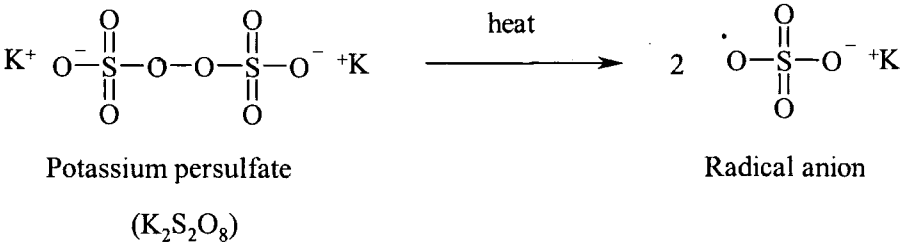


Figure 1.37 Potassium persulfate radical addition initiator

1.6.4 General Applications of PolyHIPE

In the early 1960s, Bartl and von Bonin[70] produced a series of publications on the preparation of highly porous polystyrene and poly(methylmethacrylate) materials from the polymerisation of high internal phase emulsions. However, it wasn't until twenty years later, that Unilever re-introduced these materials and created the trade name PolyHIPE. They disclosed work on styrene-DVB systems utilising Span 80 as the surfactant and potassium persulfate as the initiator.[71] The synthesis of the PolyHIPEs using a variety of monomers was also demonstrated, and the utility of the materials as absorbent substrates for spillage treatment was tested. Since this 'original proof of principle', poly(styrene/DVB) PolyHIPEs have found application as membranes,[72] filter bodies[73] and as stationary phases for HPLC.[74] More recently, these materials have successfully been employed as substrates for cell and tissue growth. In 2001, Busby *et al.*[75] developed polyester-based PolyHIPEs as substrates for tissue engineering.

The hydrophobic monomer 4-VBC (*Figure 1.38*) has also been used to produce PolyHIPE foams containing reactive chloromethyl groups, which are easily modified by reaction with a variety of nucleophiles.

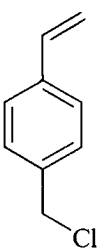


Figure 1.38 4-vinylbenzyl chloride monomer

In 1987, workers at Unilever[76] produced their final patent in a series in which they disclosed the functionalisation of poly(VBC-*co*-DVB) PolyHIPE monoliths with amines, sulfates and carboxylates. The amine-immobilised groups were further modified to obtain amine salts and oxides, while the sulfides were modified to yield supported sulfonates. The immobilised carboxylate groups, obtained by oxidation of the chloromethyl groups, were used to demonstrate the utility of the polymers as ion-exchange resins. Alexandratos and co-workers[77] recently exploited VBC-DVB PolyHIPEs in the form of cylindrical particles as supports for ion-complexing ligands. The particles were functionalised with trialkylphosphite and tetraalkyl vinylidene diphosphonate, and used to scavenge metal ions such as Eu(II), Fe(III), Cu(II) and Pd(II). In a comparable batch study with gel-type beads, PolyHIPE foams displayed greater accessibility and hence greater ion uptake as a result of their porosity and water content.

1.6.5 Applications of PolyHIPE in Solid Phase Synthesis and Supported Catalysis

Sherrington and Small[78] employed poly(styrene-*co*-DVB) PolyHIPE as a rigid, porous scaffold onto which a soft polyacrylamide-based gel could be chemically bound. They successfully demonstrated the use of the composite in low-pressure, continuous-flow solid phase peptide synthesis. PolyHIPE, used in the form of granules, was initially functionalised to afford vinyl groups on its internal surface and these groups were further derivatised to obtain amino groups. Acryloyl groups were then introduced and the matrix was impregnated with the secondary acrylamide gel using a solution of N,N'–dimethylacrylamide, acryloylsarcosine methyl ester, cross-linker and initiator. Upon polymerisation, the soft gel was grafted onto the support producing a robust composite with a loading of > 1 mmol g^{-1} and exhibiting excellent flow properties.

In an attempt to create bioreactor systems, Schoo and co-workers[79] prepared PolyHIPE discs as carrier materials for the immobilisation of the catalyst flavin (10-ethyl-isoalloxazine). A continuous flow system was used to bind flavin onto the discs via three different synthesis routes. The first method involved direct attachment of flavin onto chloromethylated PolyHIPE, the second method consisted of depositing a polyelectrolyte complex of flavin-containing polycations and poly(sodiumstyrenesulfonate) within styrene/DVB PolyHIPE, and the third route

involved complexing flavin-containing polycations onto a sulfonated PolyHIPE surface. The latter method was found to produce the greatest catalytic activity per flavin moiety in the continuous aerobic oxidation of 1-benzyl-1,4-dihydronicotinamide (BNAH).

With the aim of achieving greater uniformity upon chemical modification and to a reasonable level of substitution, Cameron *et al.*[80] employed mild, hydrophobic reagents and homogeneous reaction conditions to sulfonate, nitrate and brominate poly(styrene/DVB) PolyHIPE cubes and large cylindrical monoliths (*Figure 1.39*). An average degree of sulfonation of 2.4 mmol g^{-1} (42% conversion) coupled with reasonably uniform modification was reported using lauroyl sulfate in cyclohexane. Nitration via ammonium nitrate and trifluoroacetic anhydride was reported to occur to a lesser extent (average of 1.8 mmol g^{-1}), and was accompanied by a similar amount of uniformity in modification as with sulfonation. The bromination process was shown to produce the most successful results yielding completely uniform substitution, to a level of 3.7 mmol g^{-1}. The modification was performed with bromine and tin chloride as the Lewis acid catalyst.

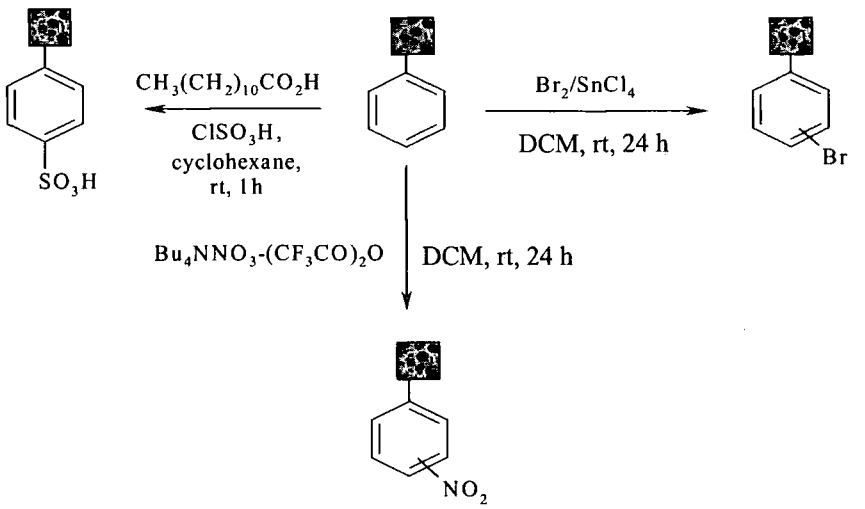


Figure 1.39 Sulfonation, bromination and nitration of poly(styrene/DVB) PolyHIPE

Recently, Ottens *et al.*[81] employed sulfonated PolyHIPEs as acid catalysts in the hydration of cyclohexene to cyclohexanol under two-phase reaction conditions. In parallel reactions with acidic ion-exchange resin beads, PolyHIPE was found to perform comparably, making it an attractive alternative to beads as a packing material.

Mercier and co-workers[82] took advantage of the high level of unreacted vinyl groups in poly(styrene/DVB) PolyHIPEs (3 mmol g^{-1}, 45 mol%) (*Figure 1.40*) to prepare a wide variety of immobilised reactive groups. They demonstrated that in the presence of a free-radical initiator, compounds such as hydrogen bromide and thiols were able to undergo an anti-Markovnikov addition to the residual vinyl groups. Other reactions such as hydroboration with a BH_3-THF complex followed by oxidation with H_2O_2, successfully produced primary alcohol derivatives. Comparisons in functionalisation success were made between a batch and continuous flow method (*Figure 1.41*) and in general, the batch system was found to produce superior results. The main drawback associated with this flow-through method is the sheer size and volume of the system. As a result of this, a larger amount of material is required to perform the flow-through successfully, which increases the overall cost of the procedure.

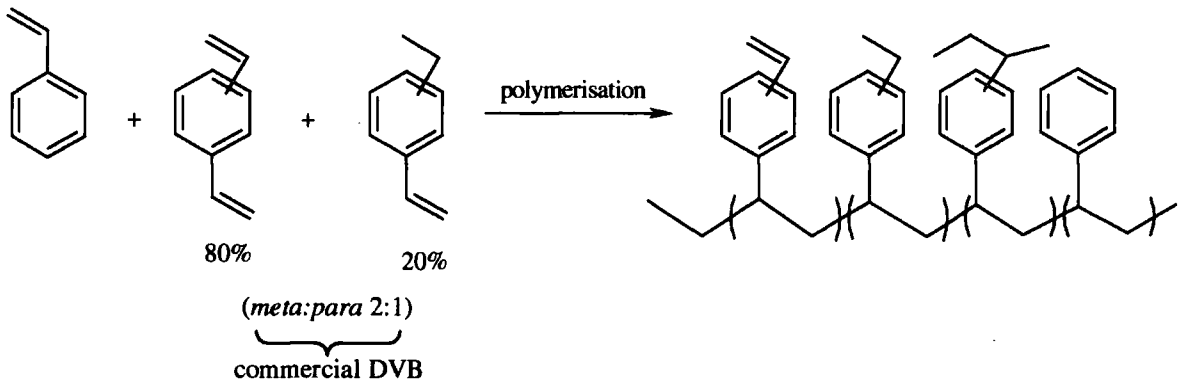


Figure 1.40 Unreacted vinyl groups in poly(styrene/DVB) PolyHIPEs

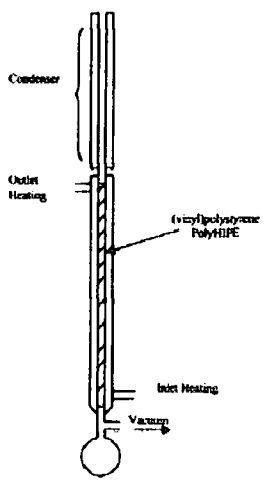


Figure 1.41 Apparatus used in the continuous flow method[85]

In a continuation of this work, Mercier and co-workers[83] demonstrated the modification of vinyl groups using a wider range of thiol and disulfide reagents, resulting in a host of PolyHIPE-bound reactive groups (capacities of 0.5 - 2.0 mmol g^{-1}) (*Figure 1.42*). These functional groups were elaborated further to obtain reactive functionalities with potential as hydrogen-atom transfer mediators, resin-bound ligands and scavengers for electrophiles and nucleophiles. For each chemical modification, a comparison with poly(DVB-*co*-ethylbenzene) beads was made. The lowest conversions with PolyHIPE were found to be comparable to the lowest conversions obtained with beads. Therefore, the authors reasoned that the success of functionalisation largely depended on the type of thiol and solvent employed, and to a lesser extent on the polymer structure.

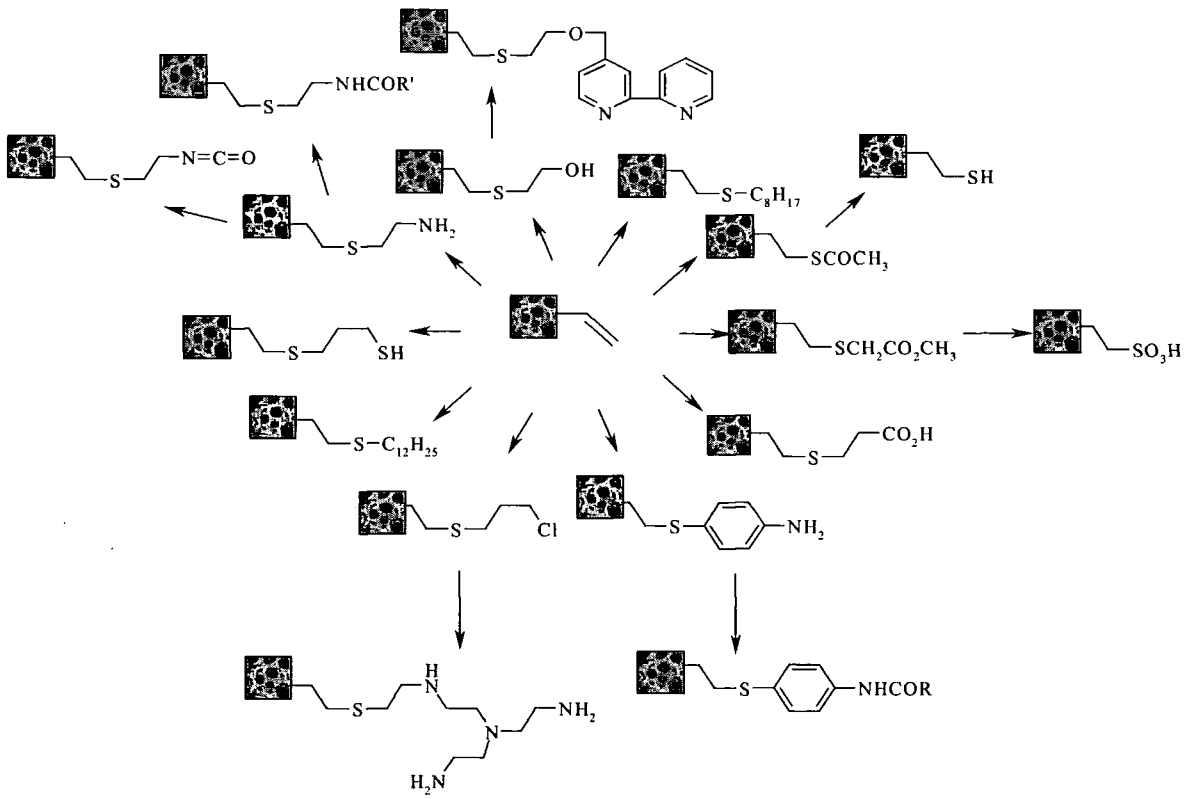


Figure 1.42 Functionalisation of (vinyl)polystyrene PolyHIPE by thiols

In parallel work, Mercier *et al.*[84] reported the development of a radical cyclisation catalyst supported on PolyHIPE, bearing the functionality shown (*Figure 1.43*). The catalyst was then used in the radical cyclisation of 1-bromo-2-(prop-2-enyloxy)benzene. In the presence of $NaBH_4$ and DME, a cyclic product bearing 5

carbons (1) was produced in 89% yield, together with a minor dehalogenation product (2) (*Figure 1.44*).

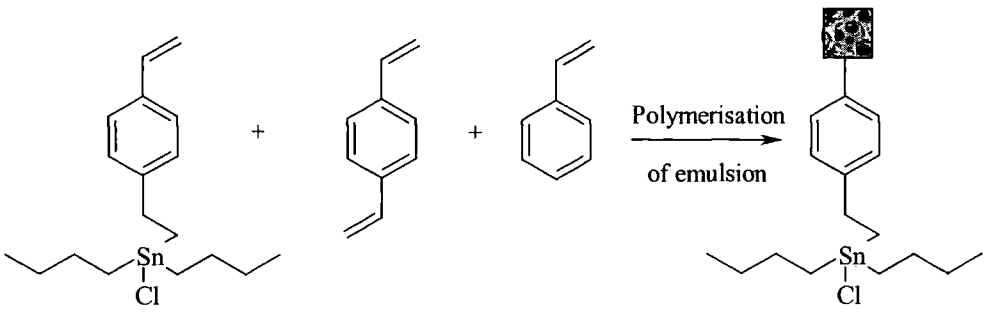


Figure 1.43 Preparation of the PolyHIPE-supported catalyst

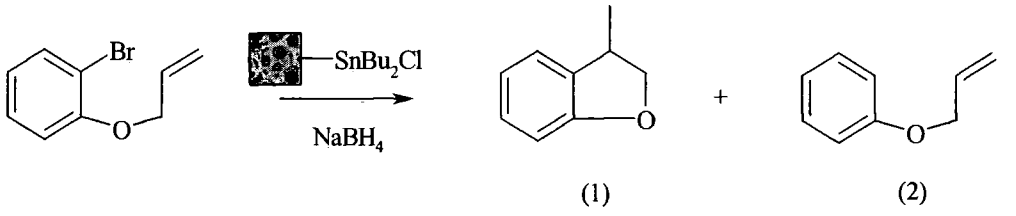


Figure 1.44 Radical cyclisation reaction of 1-bromo-2(prop-2-enyloxy)benzene

The same research group reported the synthesis of PolyHIPE-supported tin hydride and thiol for the reduction of alkyl bromides under free-radical conditions. The reduction of compounds such as 6-bromohex-1-ene (*Figure 1.45*) was performed using two methodologies under batch conditions; one using supported tin hydride (*Figure 1.46*) as the reducing agent and the other using supported thiol (*Figure 1.47*) as a polarity reversal catalyst, in the presence of triethylsilane as the reducing agent. PolyHIPE-supported organotin hydride was found to prevent tin contamination normally observed with tributyltin hydride, and facilitate product separation.

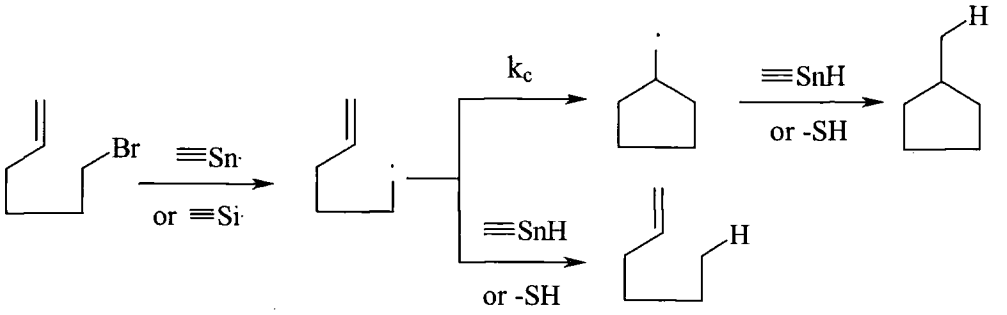


Figure 1.45 Radical-reduction mechanism of 6-bromohex-1-ene

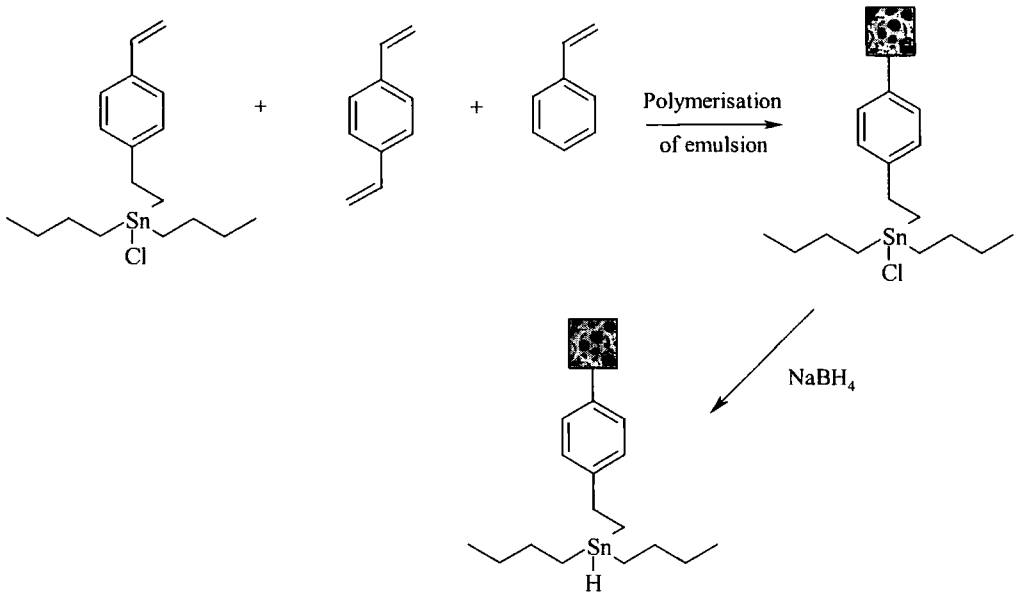


Figure 1.46 Preparation of PolyHIPE-supported organotin hydride

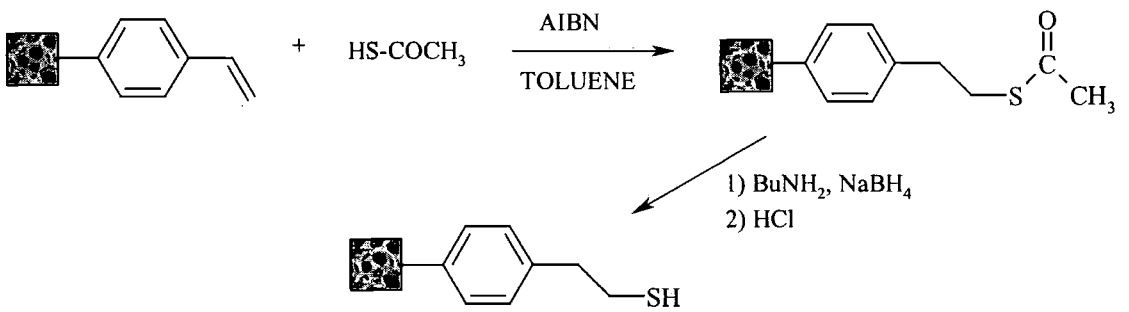


Figure 1.47 Preparation of PolyHIPE-supported thiol

1.7 Aims of Work

The objectives of this work were to prepare Merrifield-type PolyHIPE foams with high loadings of reactive chloromethyl functionality (> 4 mmol g^{-1} polymer), and to modify these chemically to obtain both conventional and novel immobilised linker systems for use in organic synthesis programmes. Further aims of the work were to test the utility of VBC-based PolyHIPEs as supports in the synthesis of small molecules. The Suzuki cross-coupling reaction has been chosen to demonstrate this, employing PolyHIPE in both batch and continuous-flow modes of operation. It is hoped that comparisons with commercial polymer beads will serve as a measure of PolyHIPE's success as a support in SPOS applications.

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Chapter 2

Preparation, Characterisation and Amine-Functionalisation of Poly(4-Vinylbenzyl Chloride-*co*-Divinylbenzene) PolyHIPE

2.1 Overview

Reactive polymer supports, such as those containing chloromethyl groups, can be prepared by two different strategies. The first involves the incorporation of functionalities after polymerisation via chemical modification of the resultant polymer, and the second, more convenient route, involves the direct copolymerisation of monomers bearing the desired functionalities. In solid phase synthesis, common reactive groups for the reversible attachment of intermediates on a support are chloromethyl and hydroxymethyl groups. Standard polystyrene supports do not enable the covalent, reversible attachment of intermediates unless they are functionalised with such groups. Pendant aminomethyl functionalities are more commonly used as non-cleavable points of attachment for linkers or for scavenging

applications in polymer assisted solution phase (PASP) synthesis. The first part of this chapter describes the preparation of PolyHIPE containing a high proportion of pendant chloromethyl groups and outlines the various methods employed in its characterisation. An investigation into the stability of the VBC monomer used in the preparation of these materials will follow. The second part describes the various attempts made to modify chemically the chloromethyl functionalities of the PolyHIPE with aminomethyl groups, in both batch and flow-through reactions.

2.2 Introduction

Electrophilic aromatic substitution, involving reactions such as nitration, sulfonation, and Friedel-Crafts, is one of the earliest reported means by which cross-linked polystyrene supports were chemically transformed. Chloromethyl polystyrene (Merrifield resin) has been synthesised by chloromethylation of polystyrene,[1] by copolymerisation of 4-chloromethylstyrene with styrene,[2] and by chlorination of poly(4-methylstyrene).[3] It has been found, however, that the direct chloromethylation route cannot achieve high loadings of reactive groups[4] and the reagent used in the process, chloromethyl methyl ether, is very carcinogenic. Due to interstrand cross-linking by Friedel-Crafts alkylation competing with the chloromethylation stage of the reaction, highly cross-linked polymers with poor swelling properties are produced. The functionality and extent of cross-linking can be controlled more carefully in supports produced by the copolymerisation route. Greater chemical homogeneity, improved swelling properties and faster reactions are just some of the advantages associated with this method. With the intention of producing a support with a high loading of reactive chloromethyl groups, in a simple and efficient manner, the polymerisation of HIPEs containing the hydrophobic monomer 4-vinylbenzyl chloride was undertaken.

Further aims were to functionalise the materials, in batch and flow-through reactions, to obtain PolyHIPE-immobilised amine linkers. It was hoped that the monolithic format would simplify reagent transfer and improve polymer handling for use in automated systems. Furthermore, the flow-through reactions were expected to produce supports with higher loadings of functionalised groups as a result of convective flow and hence, increased reactivity. Workers at Unilever[5] have previously described the amine modification of polyVBC monoliths, and demonstrated their efficiency as ion-exchange resins. Tertiary amine reagents were

used to produce the amine derivatives, which were modified to quaternary ammonium groups, amine salts, amine oxides, and sulfonates. Other examples of the use of VBC-containing PolyHIPEs have been outlined in sections 1.6.4 and 1.6.5, however, none of these describe the synthesis and post-functionalisation of VBC/DVB PolyHIPE for the immobilisation of amine linkers for use in SPOS applications.

Aminomethyl resins have been synthesised previously by amidomethylation of polystyrene with N-(hydroxymethyl)phthalimide, followed by hydrolysis.[6] As with chloromethylation, high loadings cannot be obtained by amidomethylation due to increased intermolecular aggregation.[7] Other routes to this resin have involved reaction of chloromethyl polystyrene with excess of ammonia,[8] or with potassium phthalimide to yield phthalimidomethyl resin, which affords the amine upon hydrazinolysis (Gabriel synthesis) (*Figure 2.1*).[9] Aminomethylated polystyrene beads have previously been used to scavenge activated carboxylic acids,[10] sulfonyl halides[11] and isocyanates.[12] With the intention of preparing PolyHIPE with a high loading of reactive aminomethyl groups for use in scavenging applications, a study of its reaction with N-containing species was undertaken.

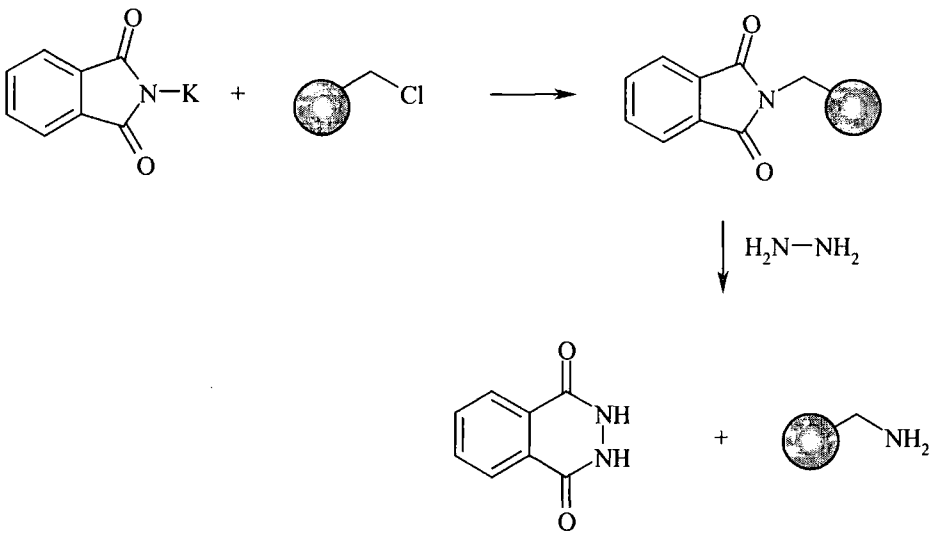


Figure 2.1 Preparation of aminomethyl resin via the Gabriel synthesis

2.3 Preparation and Characterisation of PolyVBC/DVB PolyHIPE

2.3.1 PolyHIPE Preparation

Initially, emulsions were prepared with VBC and DVB monomers in the ratio of 64:36 by weight. The equipment used consisted of a 3-necked flask, fitted with a

pressure-equalising dropping funnel and a nitrogen inlet. Stirring was provided by an overhead mechanical stirrer, which ensured a constant speed of 300 rpm (*Figure 2.2*). The intention was to functionalise the resultant PolyHIPEs as granular and cubic (*ca.* 1 cm^3) forms in batch reactions, and as monolithic columns in PTFE reactor tubes for flow-through reactions (*Figure 2.3*).

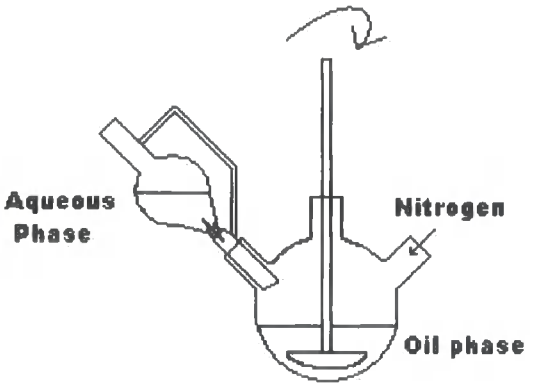


Figure 2.2 Schematic of the apparatus used in HIPE Synthesis

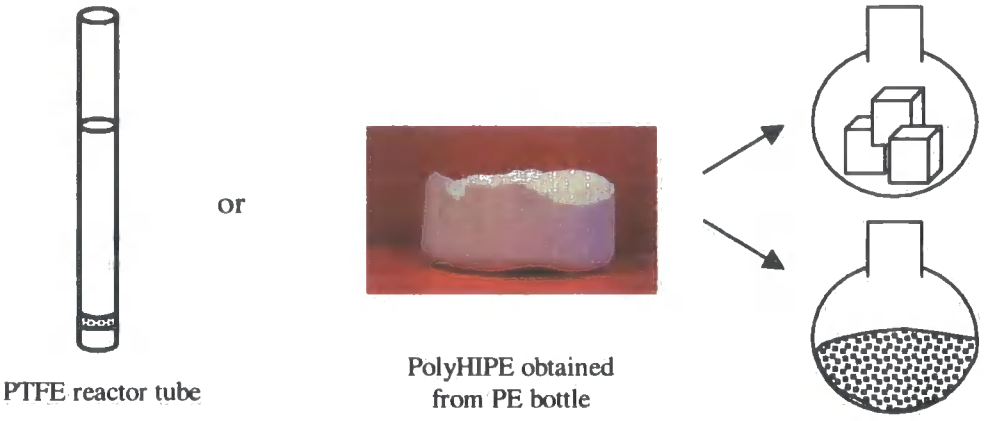


Figure 2.3 Schematic and photograph of the various PolyHIPE forms

HIPEs were prepared without the use of a porogen in order to avoid shrinkage of the foams when polymerised inside columns and reactor tubes. This prevents channelling of the reagent solution around the outer surfaces of the monoliths under flow-through. A commercial grade solution of divinylbenzene cross-linker (80% *m*- and *p*-DVB, 20% *m*- and *p*-ethylstyrene) was used to prepare the PolyHIPEs, resulting in residual vinyl and ethyl groups within the matrix (*Figure 2.4*).

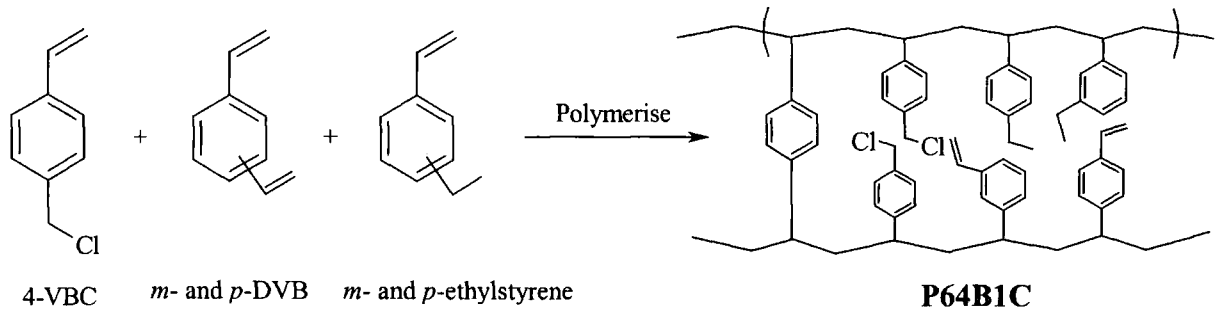
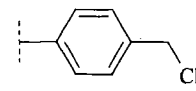
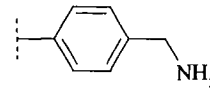
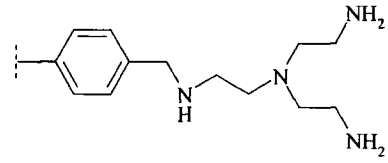


Figure 2.4 Synthesis of poly(VBC/DVB) PolyHIPE

2.3.2 Nomenclature of Polymer Supports

The code used to identify the various VBC/DVB supports and their functionalised forms is based on four parts. The first part indicates the type of support, the second part describes the percentage by weight of VBC monomer used, the third part indicates the experiment batch and the form in which the support was functionalised and the final part describes the reactive functionality it contains (*Table 2.1*). The support type is represented by a letter *e.g.* **P**olyHIPE (**P**) and **B**ead (**B**). In the second part, the amount of VBC monomer used to produce the PolyHIPE is indicated by the percentage weight number *e.g.* **64**. The third part indicates the batch and form of PolyHIPE with the term $\mathbf{B}x_y$, where x is the batch number and subscript y represents a granular, cubic or monolithic form. No subscript letter is shown when reference is made to the basic PolyHIPE foam or beads. Finally, the main reactive functionality of interest is denoted by letters: **C**hloromethyl (**C**); **A**minomethyl (**A**); or Tris**A**minomethyl (**TA**).

Table 2.1 Identification code for supports

Support Code			
Support type	% wt VBC	Batch and form	Functionality
PolyHIPE P  **Bead B** 	64% = **64** 78% = **78**	$\mathbf{B}x_y$ x = **1, 2, 3...** y = **g, c, m** **g** = granular **c** = cubic **m** = monolithic	 **C**  **A**  **TA**

For example, this work began with the preparation of a PolyHIPE containing 64 wt% VBC monomer, therefore, the first foam produced was given the name **P64B1C** (*Figure 2.4*). A portion of this material was later ground into granules, **P64B1$_g$C**, and functionalised to obtain an immobilised primary amine, **P64B1$_g$A**.

2.3.3 PolyHIPE Characterisation

2.3.3.1 Surface Area Measurements

The surface area of **P64B1C** was measured by an automated gas adsorption analyser in order to determine the ease of accessibility of the chloromethyl groups to reagents within the matrix. A wide variety of adsorption isotherms can be obtained for different gas-solid systems, and they can be conveniently grouped into six classes in the IUPAC classification (*Figure 2.5*).[13] The isotherm is a measure of the molar quantity of gas taken up or released at a constant temperature, by a clean solid surface, as a function of gas pressure, P. The pressure is expressed as a relative pressure (the actual pressure, P, divided by the vapour pressure, P_0, of adsorbing gas).

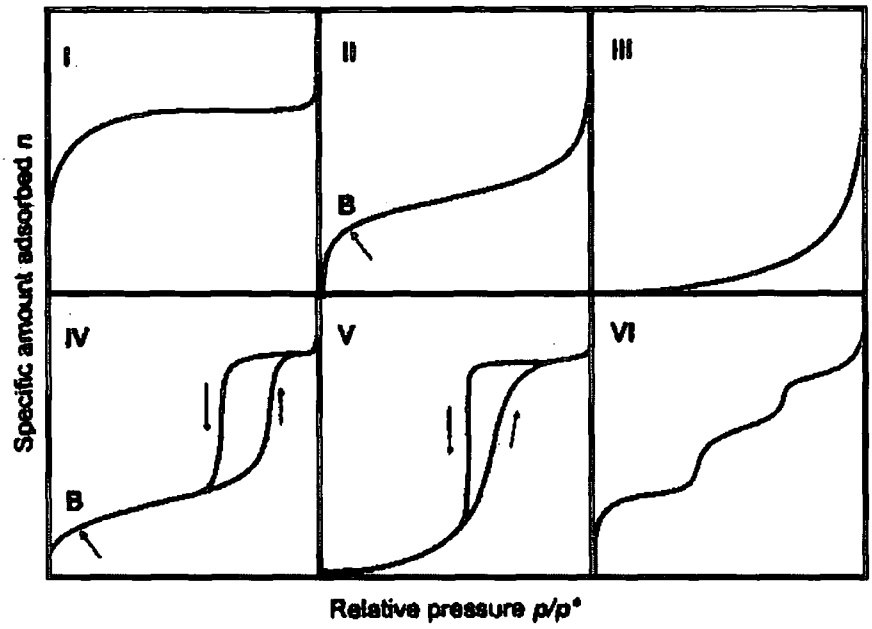


Figure 2.5 The six main types of gas physisorption isotherms, according to the IUPAC classification

Type I: characteristic of materials with extremely small pores (microporous)

Type II: characteristic of non-porous materials or adsorbents containing relatively large pores (macroporous)

Types III & V: indicative of weak-adsorbent-adsorbate interactions

Type IV: related to type II, but also displays a hysteresis loop

Type VI: characteristic of a non-porous surface with an almost completely uniform surface

The specific surface area of the PolyHIPE sample was determined by applying the Brunauer, Emmett and Teller (BET) model to the N_2 sorption data.[14] **P64B1C** was found to have a BET average surface area of 15.7 ± 2.7 m^2g^{-1} (analysis was performed in duplicate). This value was expected for a PolyHIPE prepared without the use of a porogen, and was considered to be sufficiently high to allow for a good degree of accessibility.

2.3.3.2 Scanning Electron Microscopy (SEM)

An SEM image of a VBC/DVB PolyHIPE shows an open-cellular, fully interconnected structure with average void diameters in the region of 6 μm (*Figure 2.6*).

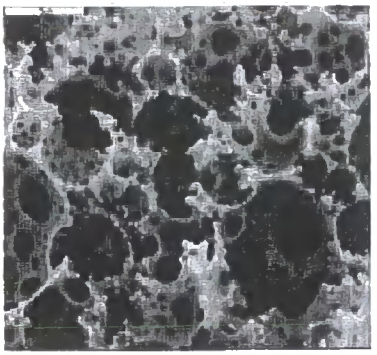


Figure 2.6 Scanning electron micrograph of VBC/DVB PolyHIPE (ratio of VBC/DVB = 63:37; pore volume 90%). Scale bar represents 5 μm[15]

2.3.3.3 Analytical Methods

Combustion elemental analysis was used primarily to determine the amount of chlorine present in the cross-linked PolyHIPEs, and FTIR analysis (KBr disc) was employed as a fast detection method for the presence of certain functional groups *i.e.* Cl and NH_2. Solid state ^{13}C NMR was also used for this purpose, but with the additional aim of quantifying the functionalities from the peak intensities.

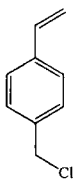
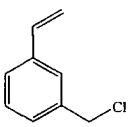
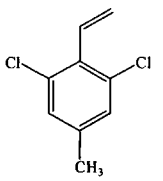
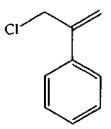
2.3.4 Investigation into the Stability of VBC Monomer

P64B1C was found to have a chlorine content of 9.50%, which corresponded to a loading of 2.68 mmol $-CH_2Cl$ groups g^{-1} of PolyHIPE. A sharp peak in the FTIR spectrum at 1265 cm^{-1} was attributed to the chloride precursor, further supporting the presence of these reactive groups in the polymer. However, after calculating the theoretical chlorine level for the material, based on 64 wt% VBC (Appendix 1), it was surprising to find that the sample contained 6.2% less chlorine than expected. This result was obtained after a re-wash of the sample to ensure complete removal of any inorganic salts, which may have been trapped within the matrix. A number of factors were postulated as the cause of the discrepancy in the results:

- inaccurate elemental analysis data
- impurities in VBC monomer
- hydrolysis of VBC monomer over time
- hydrolysis of VBC monomer during PolyHIPE formation

Inaccurate elemental analysis data was ruled out as a possible reason for the inconsistency as a sample of benzyl chloride, with a chlorine content of 28.06%, was analysed and found to contain 28.15% chlorine. This is clearly within the experimental error of this technique (± 0.1%). VBC monomer is commercially supplied as a 90% pure liquid, therefore, determination of the remaining 10% was vital in this investigation. After a request to the supplier for information regarding the nature and amounts of impurities present, the following data was obtained (*Table 2.2*).

Table 2.2 Composition of commercial 4-VBC monomer

Compound	Structure	Abundance (wt%)
4-vinylbenzyl chloride		90
3-vinylbenzyl chloride		5
dichloromethyl styrene		3
α-chloromethyl styrene		2

All of these compounds contain chlorine and hence, should theoretically contribute to the overall chlorine content of the PolyHIPE. Therefore, the loss in chlorine could not be attributed to the impurities in the VBC monomer. Since this particular monomer is very reactive, one other factor that was considered was the hydrolysis of the chloromethyl groups over time. Both ^{1}H and ^{13}C NMR spectra of the monomer were obtained and examined for the presence of hydroxymethyl groups. Both were found to be free of any peaks related to the hydrolysis products.

In order to determine whether hydrolysis of the monomer had taken place during polymerisation, **P64B1C** was analysed using solid state ^{13}C NMR. As a consequence of hydrolysis, the PolyHIPE structure was expected to contain the additional hydroxymethyl group as shown in *Figure 2.7.*

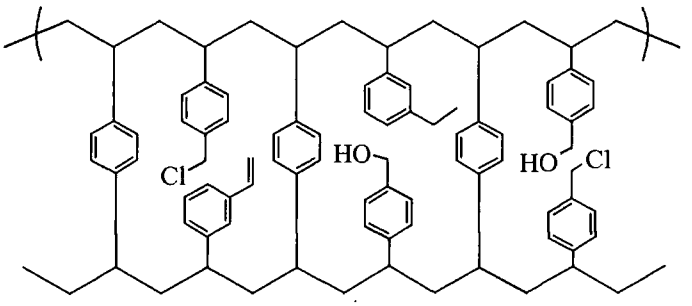


Figure 2.7 Structure of hydrolysed PolyHIPE

The chemical shifts of the chloromethyl and hydroxymethyl carbons were initially estimated, from correlation tables[16] to be δ_c 50 ppm and δ_c 68 ppm, respectively. Since these groups appear within a similar range, it was initially difficult to distinguish between them, therefore, the sample was analysed with the sidebands suppressed to enable easier identification. A sharp peak at δ_c 46.7 ppm was thought to be the chloromethyl carbons, and a weaker peak at δ_c 65.5 ppm was assumed to be hydroxymethyl carbons (*Figure 2.8*). The small peak at δ_c 29 ppm was thought to represent the ethyl carbon, $-\underline{C}H_2CH_3$, of ethyl styrene.

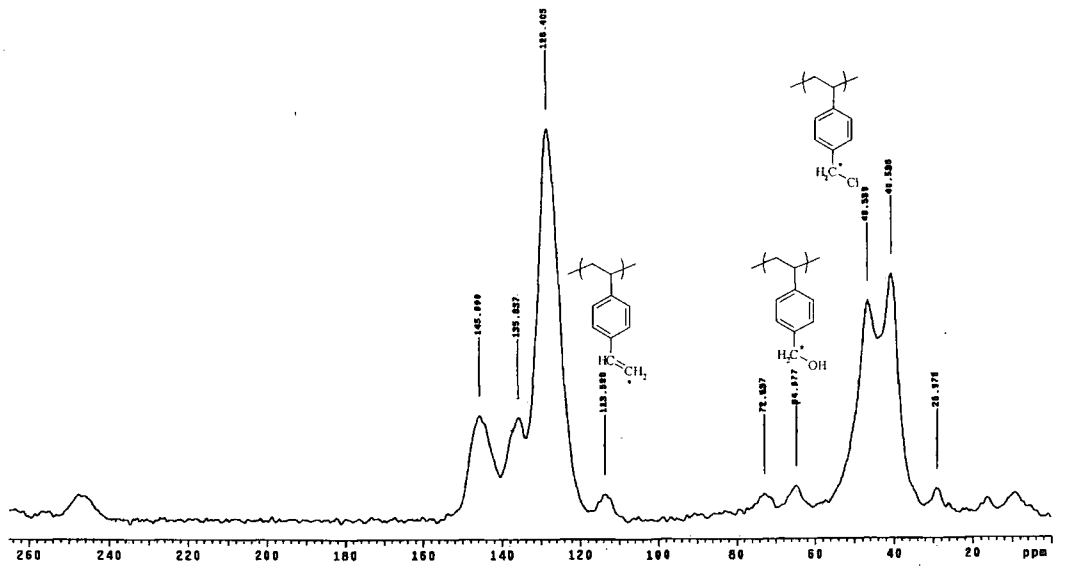


Figure 2.8 Solid state ^{13}C NMR spectrum of ***P64B1C***

In order to obtain further evidence of the formation of the hydrolysis product, solution state ^{13}C NMR spectra were obtained for benzyl alcohol and benzyl chloride (*Figure 2.9*). The signal for the pendant hydroxymethyl carbons was found to appear at δ_c 65.0 ppm and the signal for the corresponding chloromethyl carbons was evident at δ_c 46.6 ppm. This confirmed that the hydrolysis product was indeed present in the PolyHIPE sample.

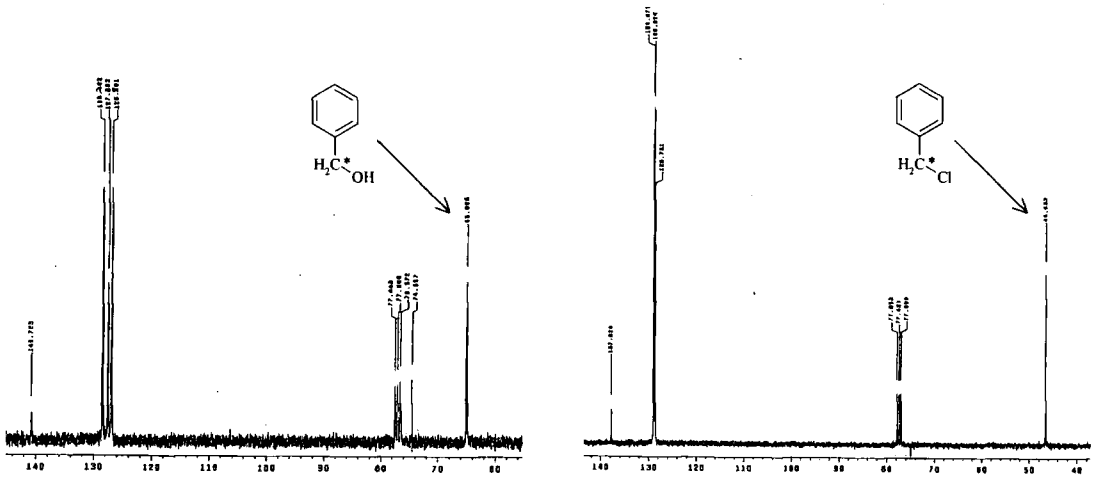


Figure 2.9 Solution state ^{13}C NMR spectra of benzyl alcohol and benzyl chloride

Obtaining a quantitative measure of the hydrolysis in **P64B1C**, via cross-polarisation (CP) and direct-polarisation (DP) experiments, proved to more

complicated. CP produces the best signal-to-noise ratio in any given time and records data much more quickly than the DP experiment, however, the relative intensities are not necessarily quantitative. DP allows intensities to be quantified, but it does not have the other advantages that CP provides. Unfortunately, the minor signals in the DP spectrum could not be seen, therefore, for the purposes of this study, the intensities in the CP spectrum were treated as quantitative. A deconvolution of the whole of the CP spectrum was carried out and it was revealed that the intensity of the δ_c 65 ppm signal ($-CH_2OH$) was 1.7 ± 0.7% of the total signal. For comparison, the intensity of the δ_c 114 ppm signal, representing unreacted vinyl groups ($-CH=CH_2$), was found to be 1.3% of the total signal.

From this investigation, it was found that a percentage of the chloromethyl groups (*ca.* 2.4% at most) had hydrolysed to the corresponding hydroxymethyl groups during the polymerisation stage. Although this figure did not account for the full chlorine loss, the data did provide a clearer picture of the PolyHIPE structure and the reactions occurring within the matrix. The hydrolysed groups were not expected to interfere with future functionalisation reactions on the materials.

2.4 Preparation of Amine-Functionalised PolyVBC/DVB PolyHIPE

Amine-functionalised PolyHIPE in granular form, has previously been prepared for derivatisation to obtain solid phase peptide supports.[17] However, functionalisation was achieved by the Gabriel synthesis,[18] which involves harsh conditions. In an attempt to obtain PolyHIPE-immobilised aminomethyl groups under milder reaction conditions and in a shorter time, a number of amination procedures were investigated. Initially, a functionalisation procedure involving potassium 1,1,3,3-tetramethyldisilazide reagent was studied. Itsuno and co-workers[19] reported the successful conversion of alkyl halides to amines using the silyl-protected nitrogen nucleophile, however, several attempts to convert the chloromethyl groups of PolyHIPE into primary amine groups via this route, proved largely unsuccessful. The most promising conversion obtained was a rather disappointing 15%.

An alternative functionalisation method involved heating VBC/DVB PolyHIPE under reflux with 0.5 M ammonium hydroxide solution in THF/water (50:50), for 24 h. Unfortunately, this procedure had no effect on the chloromethyl groups of the PolyHIPE material. Upon further examination of the literature, an amine

functionalisation method involving the Delépine reaction,[20] was discovered and subsequently employed in the batch syntheses. This simple procedure, based on hexamethylenetetramine reagent, proved to be the most successful of the functionalisation methods attempted.

2.4.1 Batch Reactions Involving Hexamethylenetetramine Reagent

Hexamethylenetetramine was allowed to react with the pendant chloromethyl groups of PolyHIPE, yielding quaternary salts. In protic media the salts decompose to give various products depending on the pH of the solution. In strongly acidic media (ethanol/conc. HCl) primary amines are formed with formaldehyde being removed as volatile formaldehyde diethylacetal (*Figure 2.10)*. The amine functionalisation was initially attempted on granular PolyHIPE, **P64B1$_g$C**, in a batch system. Since the literature procedure had to be adapted to the solid phase, it was decided to develop new conditions for the reaction. A greater excess of reagents was employed to drive the reaction to completion, and several water washes were included after the first step of the synthesis, to remove any NaCl salt trapped in the polymer matrix as a result of the Finkelstein displacement. Decomposition with conc. HCl in the second stage was allowed to take place over 24 hours instead of the reported 2 hours, to ensure complete conversion to the primary amine. As a consequence of the new conditions, the nitrogen content of **P64B1$_g$A** was found to be 0.93%, which corresponded to a conversion of chloromethyl groups of 24%, and a loading of 0.66 mmol $-CH_2NH_2$ groups g^{-1}. A second estimation of the loading was obtained by Fmoc analysis.

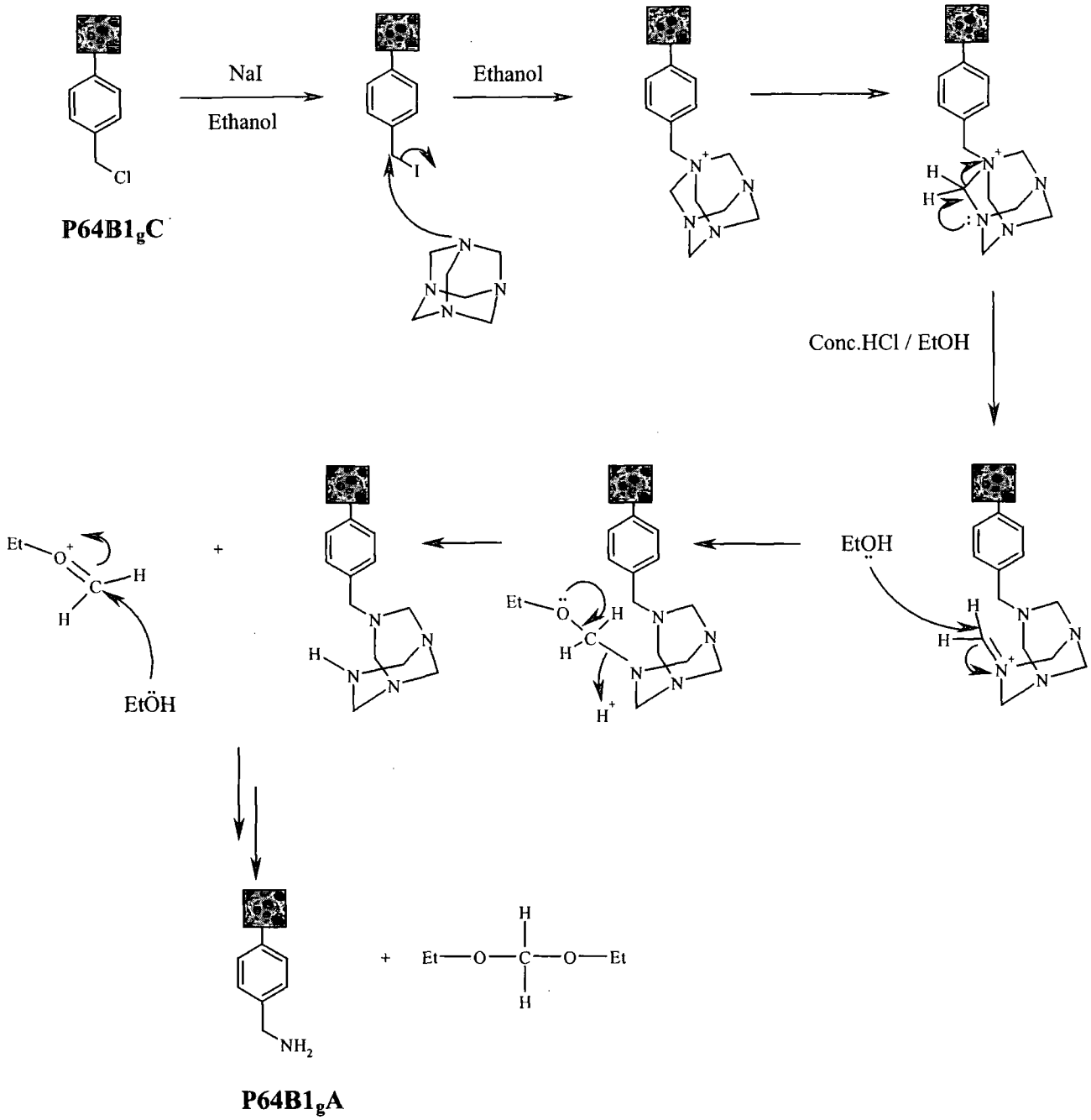


Figure 2.10 Synthesis of ***P64B1$_g$A*** *and mechanism of formaldehyde diethylacetal formation*

2.4.2 Fmoc Assay

An indication of the loading of aminomethyl groups on a support can be ascertained by obtaining an Fmoc number. The Fmoc group was developed by Carpino in 1972[21] and proved popular because of its ease of removal and the formation of a readily detectable by-product [9-(1-piperidinylmethyl)fluorine] (*Figure 2.11*).

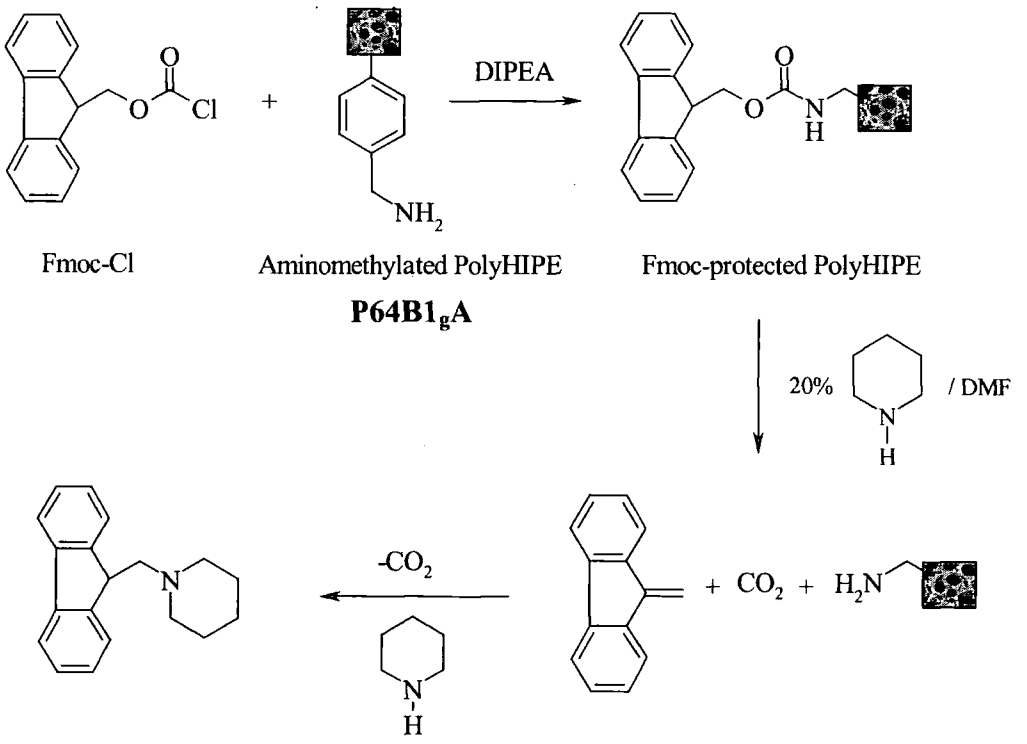


Figure 2.11 Synthesis involved in Fmoc analysis

The piperidine adduct absorbs UV at 301 nm, allowing for quantification through an adaptation of Beer's law (*Eq.1*).

$$\text{Loading in mmol g}^{-1} = \overbrace{\left(\frac{UV\ value}{7800}\right)}^{\text{Concentration in cell}} \text{ x } Dilution \text{ x } \left(\frac{Flask\ volume(mL)}{Wt.\ of\ sample(g)}\right) \qquad (1)$$

When the molecular weight of the Fmoc group is taken into consideration, a normalised Fmoc value can be obtained (Appendix 2). A normalised Fmoc number was determined for **P64B1$_g$A** to confirm the elemental analysis data. The technique was performed in triplicate to yield an average normalised Fmoc number of 0.59 mmol aminomethyl groups g^{-1}. This value was found to agree favourably with the value measured by elemental analysis (0.66 mmol g^{-1}), hence the technique is a reliable means for supporting the elemental data.

A broad peak at 3422 cm^{-1} in the FTIR spectrum confirmed the presence of the primary amine groups. However, the overall moderate conversion of chloromethyl groups was reflected in the existence of the sharp chloromethyl precursor peak at 1265 cm^{-1}. This modification was expected to benefit from the high surface area of the granular PolyHIPE, resulting in increased exposure of the functional groups and greater reactivity. However, the result obtained did not seem to mirror this. The conversion achieved was considered to be moderate for a polymer-supported batch reaction and a reasonable starting point upon which to optimise the reaction further.

2.4.3 Strategy for Flow-Through HMTA Syntheses

In order to increase the loading of the support, flow-through syntheses were carried out using a Quest parallel synthesiser. PolyHIPE was polymerised inside fritted PTFE reactor tubes to yield monoliths, **P64B2$_m$C**. For comparison, the granular form, **P64B2$_g$C**, was used to fill an adjacent reactor tube in the Quest. It was hoped that this would provide an indication of the best PolyHIPE form for optimum interaction and hence, functionalisation over a given time. The Quest apparatus allows for 20 reactions to be performed in parallel and provides simultaneous heating and stirring, as well as *in situ* washing. A flow of compressed gas automatically delivers solvent from large vessels to the reactor tubes and so it was proposed that the same delivery process could be applied to a solution of reagents. It was found, however, that the automatic delivery system could not provide flow at a sufficiently low rate, therefore, an experiment was designed which allowed the reagent solution to pass through the monoliths under gravity (*Figure 2.12*).

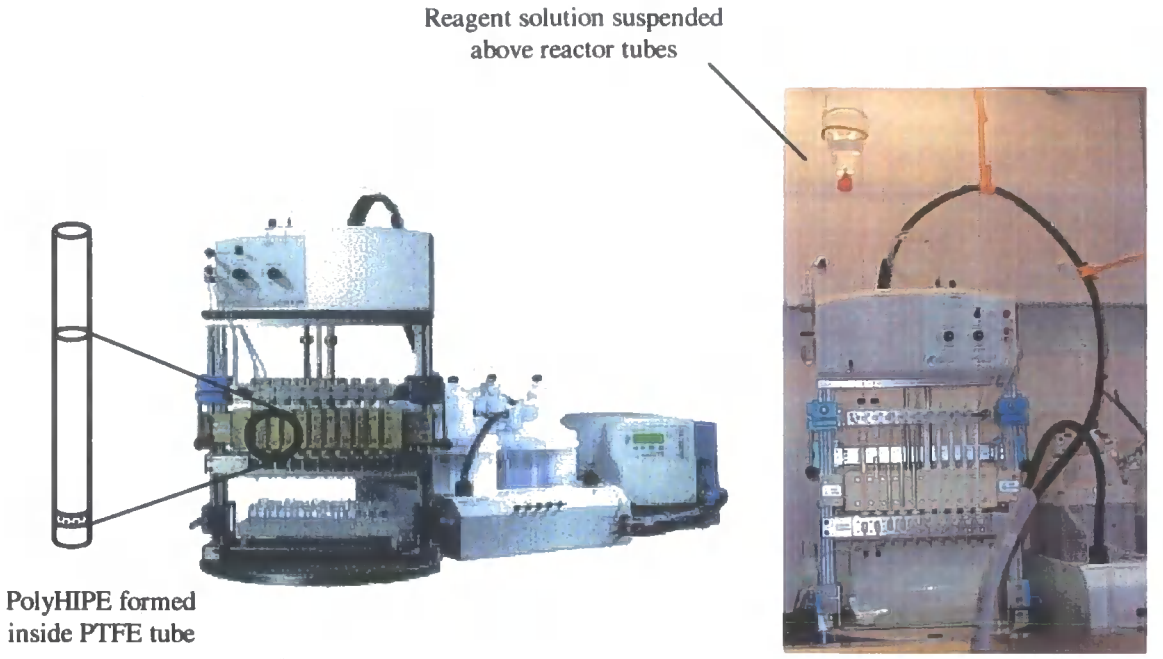


Figure 2.12 Quest apparatus for flow-through functionalisations

Two portions of PTFE tubing were inserted into the inverted conical flask, which contained the reagent solution. The exits of the tubing were then fed into the respective reactor tubes, thereby allowing the solution to drip through the supports under gravity. The outlets of the tubes were fitted with further sections of tubing, and fed into a second conical flask. The optimised conditions were applied and at each stage of the reaction, the reagent solution was allowed to pass through the samples over a 24 hour period. The flow-rate was recorded as 12 mL per hour. The flow-through modification of the monolith resulted in a 38% conversion of $-CH_2Cl$ groups producing **P64B2$_m$A** with 1.26 mmol $-CH_2NH_2$ groups g^{-1}. **P64B2$_g$A** was found to have a similar loading of 1.15 mmol g^{-1}. The modifications under flow were significantly more successful than the initial batch reaction, with the monolith yielding a slightly higher loading than the granular support. This was the first demonstration of the benefits of flow-through modification over batch modification.

The reaction conditions were then optimised in a further attempt to improve the capacities of the supports. It was believed that longer reaction times and heated conditions would ensure complete chemical transformation and hence, increased functionalisation. Test batch reactions were performed on **P64B2$_g$C** and **P64B2$_c$C**, using a Radleys Carousel reactor station. Five and ten equivalents of reagents were studied, and the reactions were carried out at 60 °C rather than at room temperature. The modification performed with five equivalents on **P64B2$_g$C** was found to produce

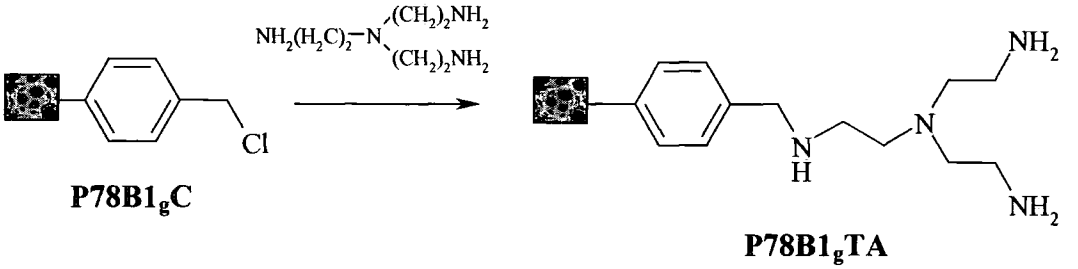
the best conversion and was therefore used in the flow-through syntheses. Using identical reaction procedures to those described previously, the loading of optimised product **P64B2$_g$A** was increased to 1.49 mmol $-CH_2NH_2$ groups g^{-1} (44% conversion). At first, **P64B2$_m$A** appeared to have undergone a 75% conversion, yielding an average nitrogen content of 3.52%, however, a correspondingly high chlorine level of 7.89% suggested that chloride salts were present in the sample. Therefore, the material was treated with triethylamine in order to remove the impurities and this had the effect of reducing the average nitrogen level to 2.22% and the chlorine content to 4.44%. The monolith had a loading of 1.6 mmol $-CH_2NH_2$ groups g^{-1}, as a result of a 48% conversion of chloromethyl groups. FTIR analysis confirmed that the correct product had been obtained.

Compared to the optimised batch reactions, on this occasion only the monolithic support was functionalised to a greater extent. This confirms the original hypothesis that flow-through modification of a monolith results in a greater extent of functionalisation than that of single particulate materials. This is due to the effect of the reagent solution being forced into the large pores of the PolyHIPE and accessing more of the reactive sites. It is not clear why the reactions did not exceed 50% conversion. It appears that only surface chloromethyl groups have been modified and those in the interior of the matrix have been unaffected. It could be said that some of the pendant chloromethyl groups are not easily accessed as a result of steric hindrance from neighbouring groups in the PolyHIPE material. Also, the groups are directly bonded to the polymer backbone and as a result, they lack a certain amount of flexibility. This must in turn affect their movement in solution and ultimately reduce their interaction with reagent molecules. Interestingly, in solution, this reaction was reported to convert chloromethyl groups of 1-chloro-4-chloromethyl benzene in 74% yield. Perhaps the moderate performance of the reaction is further exemplified on the solid phase. The ability of these functionalised PolyHIPEs as scavenger resins was not demonstrated, instead, it was decided to increase the loading of reactive aminomethyl groups on the PolyHIPE by immobilisation of a different linker.

2.4.4 Attempts to Increase the Capacity of PolyHIPE

Since the highest loading of primary amine groups achieved by the Delépine reaction was 1.66 mmol g^{-1}, an alternative reactive amine moiety was investigated in an attempt to increase the capacity of aminomethylated PolyHIPE. In this work,

P78B1$_g$C with a higher chlorine content of 15.7% (4.27 mmol $-CH_2Cl$ groups g^{-1}) was employed, and tris-(2-aminoethyl)amine reagent was chosen as the reactive species (*Figure 2.13*). This reagent bears a high number of amine groups g^{-1} making it ideal for scavenging applications and suitable for immobilising linkers. Furthermore, the immobilisation of this reagent is straightforward and has already proven to be successful on polymer beads. Bead-bound trisamine has been used to scavenge a variety of species ranging from acid chlorides to α,β-unsaturated ketones.[22] To avoid any additional cross-linking between two amine functionalities immobilised on the support the reaction was performed at 45 °C instead of at the reported temperature of 60 °C.



P78B1$_g$C **P78B1$_g$TA**

Figure 2.13 Synthesis of trisamine-immobilised PolyHIPE

Initially the reaction was performed in batch mode and the functionalised product **P78B1$_g$TA** was found to contain 8.67% N (52% conversion), which corresponded to an impressive loading of 4.67 mmol $-NH/NH_2$ groups g^{-1}. A broad peak at 3422 cm^{-1} together with peaks at 2818 cm^{-1} and 1670 cm^{-1} in the FTIR spectrum (*Figure 2.14*) confirmed that both $-NH_2$ and –NH groups were present. Furthermore, the signal for the chloride precursor was no longer detected. However, despite the use of a lower reaction temperature, a small residual chlorine level and a lower than expected nitrogen content suggested that additional cross-linking was still occurring and hence, complete conversion to the product had not taken place.

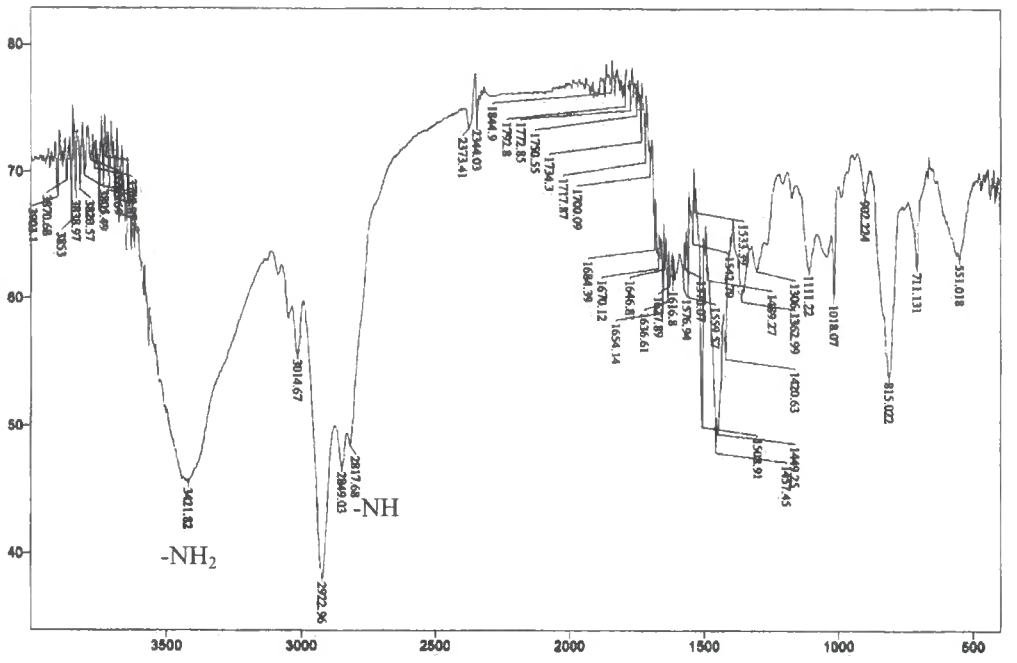


Figure 2.14 FTIR spectrum of ***P78B1$_g$TA***

In parallel work by Krajnc,[23] the synthesis was successfully adapted to flow-through in the Quest, producing PolyHIPE monoliths with loadings of 5.6 mmol – NH/NH_2 groups g^{-1}. Under identical flow-through conditions, the highly loaded supports scavenged a greater amount of 4-chlorobenzoyl chloride in a given time than commercial trisamine beads (*Figure 2.15*).

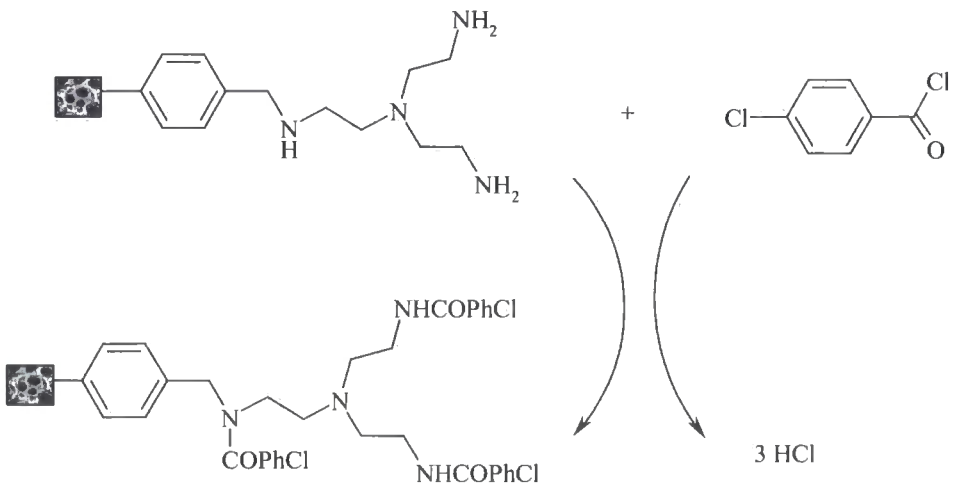


Figure 2.15 Scavenging of 4-chlorobenzoyl chloride by the tris(2-aminoethyl)amine derivative of PolyHIPE

2.5 Conclusions

PolyHIPE materials with loadings of chloromethyl groups as high as 4.3 mmol g^{-1} have been synthesised by the direct copolymerisation of VBC and DVB. Subsequent characterisation revealed that the VBC monomer was susceptible to hydrolysis during the polymerisation, however, this was estimated by solid state ^{13}C NMR to be very slight. Different forms of the PolyHIPEs were then reacted with N-containing reagents in an attempt to produce supported linkers and scavenger resins. Supports with loadings ranging from 0.66 to 4.67 mmol aminomethyl groups g^{-1} were obtained. As a consequence of the Delépine reactions, the monolithic form modified under flow-through was functionalised to the greatest extent resulting in a support with 1.66 mmol aminomethyl groups g^{-1}. This was later superseded by the highly-loaded trisamine PolyHIPE, which has shown to be a highly efficient scavenger of acid chlorides.

2.6 Experimental

2.6.1 Chemicals

Starting materials were purchased from Aldrich, Lancaster, Acros, BDH, Fluka and Novabiochem. Divinylbenzene (80 vol% *m*- and *p*-divinylbenzene, the remainder *m*- and *p*-ethylstyrene) and 4-vinylbenzyl chloride were purified by passing through a column of basic alumina. All other materials were used without further purification. Absolute ethanol and DMF (HPLC grade) were used as solvents for the reactions.

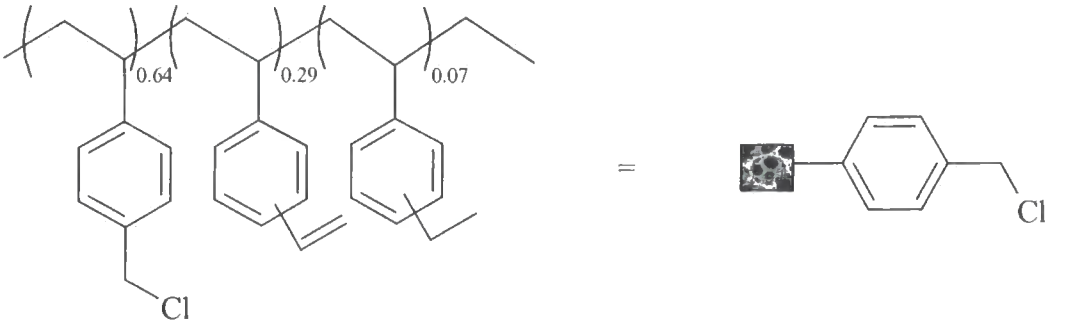
2.6.2 Characterisation

Combustion elemental analysis data (C, H and N) were obtained from an Exeter Analyser CE-440. A Dionex Ion Chromatograph Analyser DX-120 was employed for chlorine determination. FTIR spectra (KBr dics) were recorded on a Perkin Elmer 1600 Series FTIR Spectrometer. NMR spectra were recorded on a Varian Unity-300 (^1H at 299.9 MHz and ^{13}C at 75.4 MHz) using $CDCl_3$ (Aldrich) as solvent. Solid State ^{13}C NMR spectra were obtained in cross-polarisation and direct polarisation modes using a Varian Unity-plus 300 spectrometer at 75.4 MHz. Chemical shifts (δ) are reported in parts per million (ppm) with respect to an internal reference of tetramethylsilane (TMS). Surface area measurements were carried out in

duplicate using a Micromeritics Tristar 3000 Surface Area and Porosimetry Analyser. Scanning Electron Microscopy was performed at the University of Newcastle using a Hitachi S2400 electron microscope operating at 25kV. UV absorbencies were recorded on a Pye Unicam UV/VIS Spectrophotometer.

2.6.3 Procedures for the Preparation of Poly(4-Vinylbenzyl Chloride-*co*-Divinylbenzene) PolyHIPE

2.6.3.1 Preparation of P64B1C



P64B1C

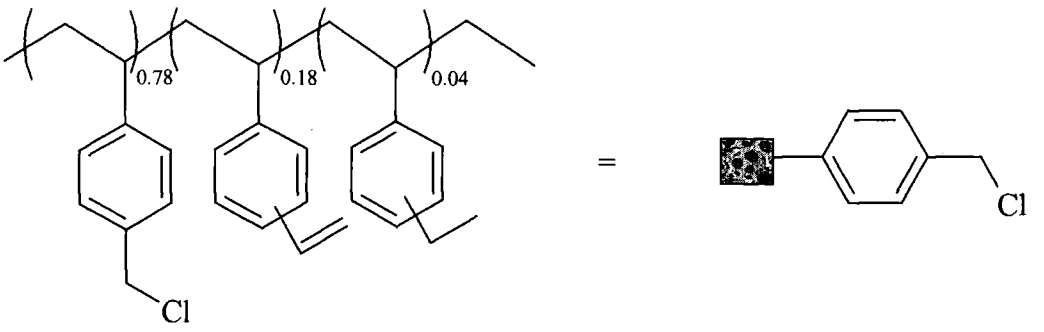
4-Vinylbenzyl choride (6.50 g, 0.04 mol), divinylbenzene (3.66 g, 0.03 mol) and Span 80 (1.97 g, 4.6 mmol) were placed in a 3-necked 250 mL round-bottomed flask, fitted with an overhead stirrer (glass rod fitted with a D-shaped PTFE paddle), a 100 mL pressure equalising dropping funnel (inserted into a side-neck) and a rubber septum. The mixture was purged with nitrogen gas for 15 min. The aqueous phase was prepared separately by dissolving potassium persulfate (0.2 g, 0.74 mmol) and calcium chloride dihydrate (1.0 g, 6.80 mmol) in de-ionised water (90 mL). This was added to the dropping funnel and purged with nitrogen for 15 min. The organic solution was stirred under nitrogen at *ca.* 300 rpm and the aqueous phase was added drop-wise under constant mechanical stirring. After complete addition of the aqueous phase, stirring was continued for 1 h to produce a homogeneous emulsion. The emulsion was poured into a PE bottle and polymerised in an oven at 60 °C for 48 h. PolyHIPE **P64B1C** was later retrieved by disassembling the bottle and extracted in a Soxhlet apparatus with de-ionised water for 24 h and IPA for a further 24 h. The monolith was dried *in vacuo* at 50 °C for 48 h. The material was later re-washed in a Soxhlet apparatus with de-ionised water for 24 h to ensure complete removal of

inorganic salts. The sample was dried *in vacuo* at 50 °C for 48 h. Granular PolyHIPE **P64B1$_g$C** was obtained by grinding sections of the monolith in a coffee grinder. Cubic pieces of PolyHIPE **P64B1$_c$C** (*ca.* 1cm^3) were cut from the monolith using a scalpel. Found C, 78.9; H, 7.0; Cl, 9.5%. Calculated for $(C_9H_9Cl)_{0.64}(C_{10}H_{10})_{0.29}(C_{10}H_{12})_{0.07}$, C, 77.7; H, 6.6; Cl, 15.7% (Appendix 1). IR (KBr disc) υ_{max}/cm^{-1} 3400br (OH), 2924s and 2853w (CH), 1610w and 1510m (aryl C=C), 1265s (CCl), 835s (*p*-disubstituted benzene ring). ^{13}C NMR (75.4 MHz, solid state) δ 15.8 (-$CH_2\underline{C}H_3$), 29.4 (-$\underline{C}H_2CH_3$), 40.7 (quaternary C), 46.7 (-$\underline{C}H_2Cl$), 65.5 (-$\underline{C}H_2OH$), 113.8 (-CH=$\underline{C}H_2$), 128.3 (aromatic C-H), 135.9 (-$\underline{C}H$=CH_2), 145.6 (aromatic C-R).

2.6.3.2 Preparation of P64B2C

P64B2C was prepared as outlined in section 2.6.3.1. Quantities used were; 4-VBC (5.1 g, 0.03 mol), DVB (2.9 g, 0.024 mol), Span 80 (1.55 g, 3.6 mmol), aqueous phase (70.5 mL). The emulsion was poured into a 100 mL glass syringe, containing a pressure release vent, and injected into fritted PTFE reactor tubes. The tubes were tapped several times to allow the emulsion to spread uniformly and to remove any air bubbles. The remaining HIPE was poured into a PE bottle and polymerised, together with the HIPE-filled tubes in an oven at 60 °C for 48 h. The polymer was washed as in 2.6.3.1. The reactor tubes containing **P64B2$_m$C** were fitted into the Quest, and de-ionised water was passed through them continuously for 30 min, followed by IPA (20 min) and methanol (10 min). All products were dried *in vacuo* at 50 °C for 48 h. Granular PolyHIPE **P64B2$_g$C** was obtained by grinding sections of the polymer in a coffee grinder. Cubic pieces of PolyHIPE **P64B2$_c$C** (*ca.* 1cm^3) were cut from **P64B2C** using a scalpel. Found C, 78.2; H, 6.9; Cl, 11.1%. Calculated for $(C_9H_9Cl)_{0.64}(C_{10}H_{10})_{0.29}(C_{10}H_{12})_{0.07}$, C, 77.7; H, 6.6; Cl, 15.7%. IR (KBr disc) υ_{max}/cm^{-1} 3402br (OH), 2924s and 2853w (CH), 1610w and 1510m (aryl C=C), 1265s (CCl), 835s (*p*-disubstituted benzene ring).

2.6.3.3 Preparation of P78B1C

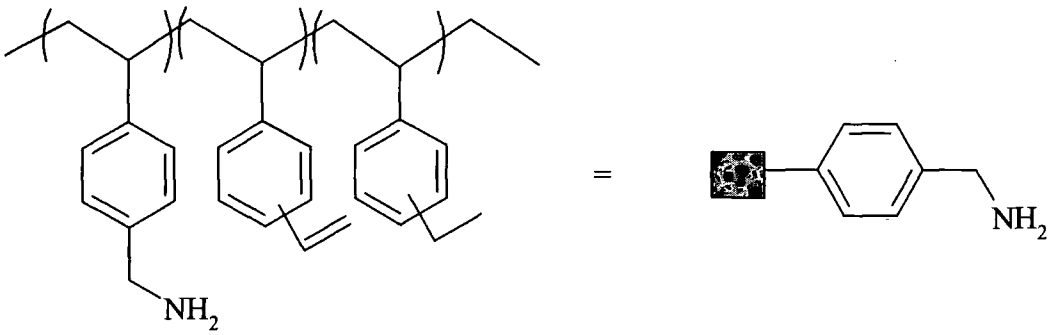


P78B1C

P78B1C was prepared as outlined in section 2.6.3.1. Quantities used were; 4-VBC (8.1 g, 0.05 mol), DVB (2.3 g, 0.019 mol), Span 80 (1.97 g, 4.6 mmol), aqueous phase (90 mL). **P78B1$_g$C** and **P78B1$_c$C** were obtained as described in section 2.6.3.1. Found C, 75.1; H, 6.3; Cl, 15.2%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3402br (OH), 2923s and 2852w (CH), 1610w and 1509m (aryl C=C), 1265s (CCl), 835s (*p*-disubstituted benzene ring).

2.6.4 Procedures for Batch Amine Functionalisations

2.6.4.1 Synthesis of P64B1$_g$A via Reaction with Silyl-Protected Nitrogen



P64B1$_g$A

In a 50 mL round-bottomed flask fitted with a rubber septum and vent, washed KH (0.18 g, 4.4 mmol) and dry THF (8.8 mL) were stirred under nitrogen. 1,1,3,3-tetramethyldisilazane (0.7 mL, 4 mmol) was added drop-wise at 0 °C and the mixture was stirred for 30 min to generate potassium 1,1,3,3-tetramethyldisilazide. **P64B1$_g$C**

(0.5 g, 1.33 mmol $-CH_2Cl$ groups) was added to a second 50 mL round-bottomed flask and flushed with nitrogen for 30 min. Potassium 1,1,3,3-tetramethyldisilazide was transferred to the flask containing **P64B1$_g$C** and the mixture was stirred gently under nitrogen for 24 h. The PolyHIPE was filtered and washed with THF (2 x 25 mL), THF/H_2O (1:1, 2 x 25 mL), THF/0.5M HCl (1:1, 2 x 25 mL), THF (1 x 25 mL), THF/1M NH_4OH (1:1, 2 x 25 mL), THF/H_2O (1:1, 2 x 25 mL) and MeOH (2 x 25 mL). The material was dried *in vacuo* at 50 °C for 48 h to provide **P64B1$_g$A** (0.38 g, 80% conversion by weight). Found N, 0.6; Cl, 9.0%. Calculated N, 3.9; Cl, 0% (15% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3446br (NH_2), 2923s and 2853m (CH), 1265s (CCl).

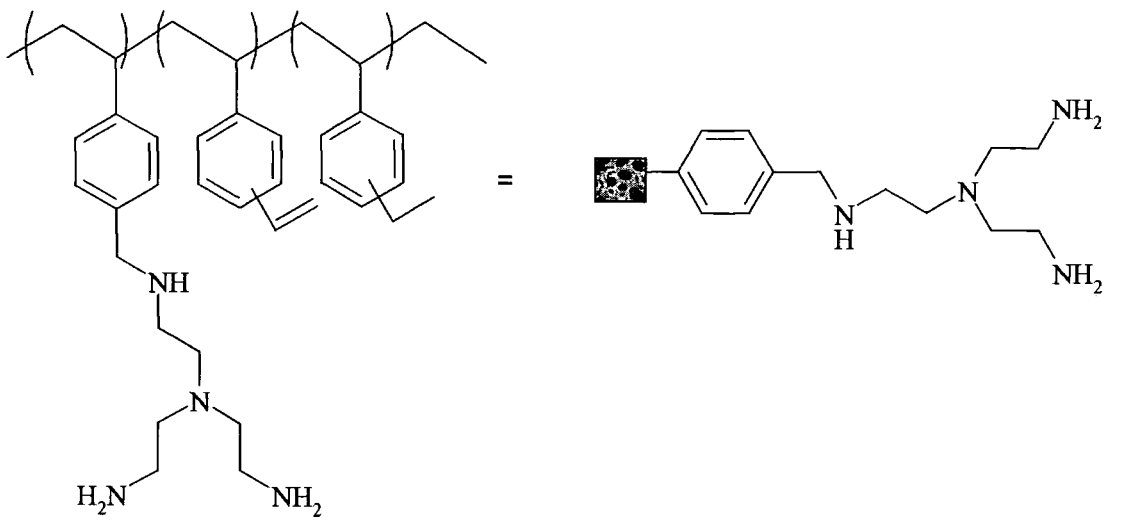
2.6.4.2 Synthesis of P64B1$_g$A via Reaction with Ammonium Hydroxide Solution

P64B1$_g$C (0.2 g, 0.53 mmol) and 0.5M NH_4OH (8.1 mL, THF/H_2O (50:50)) were placed in a 50 mL round-bottomed flask, fitted with a reflux condenser. The solution was stirred and heated at 70 °C for 24 h. The PolyHIPE was filtered and washed with THF (2 x 25 mL), THF/H_2O (1:1, 2 x 25 mL), THF (2 x 25 mL) and MeOH (2 x 25 mL). The material was dried *in vacuo* at 50 °C for 48 h to provide **P64B1$_g$A** (0.18 g, 95% conversion by weight). Found N, 0; Cl, 9.5%. Calculated N, 3.9; Cl, 0% (0% conversion).

2.6.4.3 Synthesis of P64B1$_g$A via the Delépine Reaction

In a 50 mL round-bottomed glass flask fitted with a rubber septum and vent, hexamethylenetetramine (0.44 g, 3 mmol), sodium iodide (0.45 g, 3 mmol) and PolyHIPE **P64B1$_g$C** (0.15 g, 0.4 mmol $-CH_2Cl$ groups) were stirred in ethanol (34 mL) at room temperature for 24 h. The resultant off-white product was filtered and washed with cold de-ionised water (5 x 25 mL), ethanol (5 x 25 mL) and diethyl ether (3 x 25 mL). The product was added to a second 50 mL round-bottomed flask, fitted with a reflux condenser, together with a solution of conc. HCl (1.8 mL) and ethanol (27.2 mL). The reaction mixture was heated at 90 °C for 24 h. After cooling, the support was filtered and washed as described above. The PolyHIPE was dried *in vacuo* at 50 °C for 48 h to give **P64B1$_g$A** (0.14 g, 100% conversion by weight) (Appendix 3). Found N, 0.9; Cl, 7.5%. Calculated N, 3.9; Cl, 0% (24% conversion) (Appendix 3). IR (KBr disc) υ_{max}/cm^{-1} 3422br (NH_2), 2924s and 2854m (CH), 1265s (CCl).

2.6.4.4 Synthesis of P78B1$_g$TA



P78B1$_g$TA

In a 2-necked 50 mL round-bottomed flask, fitted with rubber septa, **P78B1$_g$C** (0.5 g, 2.2 mmol $-CH_2Cl$ groups) was suspended in DMF (15 mL) and purged with nitrogen gas for 10 min. Tris(2-aminoethyl)amine (3.2 mL, 21.4 mmol) was added to the flask and the reaction was stirred gently under nitrogen at 45 °C for 48 h. The granules were filtered and washed with DMF (3 x 25 mL), MeOH (2 x 25 mL), NEt_3 (2 x 20 mL), MeOH (2 x 25 mL), MeOH/H_2O (1:1, 2 x 25 mL), MeOH (25 mL) and THF (2 x 25 mL). The PolyHIPE was dried *in vacuo* at 50 °C for 48 h to give **P78B1$_g$TA** (0.55g, 75% conversion by weight). Found N, 8.7; Cl, 0.8%. Calculated N, 16.3; Cl, 0% (53% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3422br (NH_2), 2923s and 2849m (CH), 2818s (NCH_2) 1670s (NH).

2.6.4.5 Procedure for the Determination of Fmoc Numbers for P64B1$_g$A

P64B1$_g$A (30 mg), 9-fluorenylmethyl chloroformate (Fmoc) (75 mg, 0.3 mmol), DIPEA (50 μL) and DCM (1 mL) were loaded into a 5 mL filter syringe tube fitted with a cap and stopper. The mixture was shaken using an agitating device for 1 h. The PolyHIPE was filtered and washed with DCM (5 x 5 mL) and diethyl ether (2 x 5 mL), and dried *in vacuo* at 50 °C for 24 h. In a 5 mL volumetric flask, the Fmoc-protected **P64B1$_g$A** (10 mg) was shaken in a 20% solution of piperidine/DMF (400 μL) for 30 min. Methanol was then added to the flask to obtain a 5 mL solution. A portion of solution (200 μL) was removed and diluted 25 times with methanol. UV readings of the diluted solution were recorded at 301 nm and 322 nm (background

reading). The Fmoc procedure was performed in duplicate in order to obtain an average Fmoc number.

2.6.5 Procedures for Flow-through Amine Functionalisations

2.6.5.1 Synthesis of P64B2$_m$A and P64B2$_g$A

Quest tubes containing **P64B2$_m$C** (1.2 g, 3.76 mmol $-CH_2Cl$ groups) and **P64B2$_g$C** (0.65 g, 2.04 mmol $-CH_2Cl$ groups) were inserted into the Quest apparatus and fitted with inlet and outlet PTFE tubing. A solution of hexamethylenetetramine (3.5 g, 24 mmol) and sodium iodide (3.6 g, 24 mmol) in ethanol (274 mL) was prepared in a 500 mL stoppered conical flask, and suspended in an inverted position above the apparatus. The inlet sections of tubing were fed from the tops of the tubes up into the conical flask. The reagent solution was allowed to drip into the tubes and through the supports over 24 h, after which time, 174 mL of solution had been delivered. The samples were washed by passing de-ionised water through them continuously for 30 min, followed by ethanol.

A solution of conc. HCl (20.1 mL) and ethanol (300 mL) was decanted into a solvent delivery bottle and flowed through the samples by means of compressed air (operated by the Quest system at its lowest flow-rate). The heating panel was set to 80 °C and delivery of the solution was continued for 24 h, after which, 150 mL of solution had passed through the samples. They were then washed with a continuous flow of ethanol (30 min) and diethyl ether (30 min). The monolith was dried *in vacuo* at 50 °C for 48 h to give **P64B2$_m$A** (1.1 g, 96% conversion by weight). Found N, 1.8; Cl, 9.4%. Calculated N, 4.7; Cl, 0% (38% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3422br (NH_2), 2924s and 2854m (CH), 1265s (CCl). The granular support was dried *in vacuo* at 50 °C for 48 h to give **P64B2$_g$A**. Found N, 1.6; Cl, 7.5%. Calculated N, 4.7; Cl, 0% (35% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3422br (NH_2), 2924s and 2854m (CH), 1265s (CCl).

2.6.5.2 Optimised Synthesis of P64B2$_m$A and P64B2$_g$A

Quest tubes containing **P64B2$_m$C** (0.59 g, 1.86 mmol $-CH_2Cl$ groups) and **P64B2$_g$C** (0.39 g, 1.22 mmol $-CH_2Cl$ groups) were inserted into the Quest apparatus. A solution of hexamethylenetetramine (3.83 g, 26 mmol) and sodium iodide (3.94 g, 26 mmol) in ethanol (300 mL) was prepared in a 500 mL conical flask, and decanted

into a solvent delivery bottle. The heating panel was set to 60 °C and the reagent solution was delivered to the PolyHIPE tubes, via a flow of compressed air, for 24 h. Taps were fitted at the exits of the tubes to control the flow-rate. The supports were immersed in reagent solution at 60 °C overnight. The solution was then drained from the tubes and the PolyHIPEs were flushed with ethanol continuously for 30 min, followed by ethanol/water (50:50).

A solution of conc. HCl (33.5 mL) and ethanol (500 mL) was decanted into a solvent delivery bottle and flowed through the samples at 80 °C for 24 h. The supports were then filtered and washed with a continuous flow of ethanol (30 min), ethanol/water (50:50) (30 min) and diethyl ether (30 min). The monolith was dried *in vacuo* at 50 °C for 48 h to give **P64B2$_g$A** (0.5 g, 89% conversion by weight). Found N, 2.1; Cl, 5.9%. Calculated N, 4.7; Cl, 0% (44% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3422br (NH_2), 2924s and 2854m (CH), 1265s (CCl). **P64B2$_m$A** was broken–up and stirred in triethylamine (10 mL) for 15 min and washed with MeOH:water (1:1, 40 mL), followed by MeOH:THF (1:1, 40 mL) to ensure complete removal of HCl salt. The sample was dried *in vacuo* at 50 °C for 48 h. Found N, 2.2; Cl, 4.4%. Calculated N, 4.7; Cl, 0% (48% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3422br (NH_2), 2924s and 2854m (CH), 1265w (CCl).

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Chapter 3

Poly(4-Vinylbenzyl Chloride-*co*-Divinylbenzene) PolyHIPEs as Supports in Batch and Flow-Through Suzuki Cross-Coupling Reactions

3.1 Overview

Biaryls [Ar^1-Ar^2] are an important class of organic compound. Polymers, liquid crystals, natural products and biologically active molecules are just some examples of systems containing the biaryl unit.[1] One of the most common catalytic methods used in its synthesis is the Suzuki cross-coupling reaction.[2] This reaction has been employed in organic synthesis programmes for many years, due to its mild reaction conditions, tolerance of a wide scope of functionalities, and the availability of diverse boronic acids.[3] Furthermore, the reaction is reported to progress in high yield at temperatures of 60-80 °C. It is not surprising therefore, that there has been a great deal of interest in adapting this reaction to the solid phase. This chapter begins with an account of the various attempts made to optimise and adapt the classical Suzuki

conditions to chloromethyl PolyHIPE supports in batch reactors. The coupling of substrates bearing different functionalities will follow, together with a comparative batch reaction employing chloromethyl polystyrene beads. The focus will then turn to flow-through Suzuki coupling utilising monolithic PolyHIPE in a variety of continuous flow techniques. A comparative flow-through experiment involving polymer beads will also be described.

3.2 Introduction

Frenette and Friesen[4] were the first to investigate the possibility that well-characterised reactions such as the Suzuki reaction could be developed and applied to the heterogeneous environment of solid phase reactions. Since then, a variety of solid phase Suzuki reactions employing elaborate supports and linker systems has been reported in the literature (reviewed in section 1.3.2). Common aims were to demonstrate the utility of the reaction for the SPOS of small molecule combinatorial libraries. All of these attempts were carried out in batch systems and the majority utilised polymer supports in the form of cross-linked polystyrene beads. Chloromethyl polystyrene (Merrifield resin) proved to be a highly successful support,[4] as did hydroxymethyl polystyrene (Wang resin)[5] and Rink amide TentaGel resin.[6] Indeed, most of the syntheses were reported to proceed with high conversions, however problems such as poor swelling[7] and in some cases, shattering of the supports as a result of osmotic shock[8] were also disclosed.

In order to overcome some of the shortcomings of bead-type supports and to improve procedures, the intention of this work was to perform flow-through Suzuki syntheses on monoliths of chloromethyl PolyHIPE, prepared inside columns and reactor tubes. In order to identify the optimum conditions for these reactions, an investigation into the suitability of PolyHIPE as a support in batch Suzuki couplings was initially undertaken. An examination of the literature suggested that this was the first demonstration of a flow-through Suzuki coupling, and PolyHIPE was considered to be an ideal support for this purpose. It was hoped that the highly porous structure of the material would result in greater reactive site accessibility and ultimately lead to higher yielding syntheses. Furthermore, monolithic PolyHIPEs prepared inside columns fully optimise the advantages of automation and offer additional advantages such as simpler reagent transfer and improved handling. Further aims of the work

were to compare the performance of PolyHIPE against macroporous polymer beads in both batch and flow-through reactions.

3.3 Suzuki Coupling on Poly(VBC/DVB) PolyHIPE

Mild reaction conditions and simple apparatus were just some of the reasons why the highly popular Suzuki cross-coupling reaction was chosen for this study. Symmetrical and unsymmetrical biaryls are typically prepared in the presence of boronic acids [$Ar^1B(OH)_2$], aryl halides [Ar^2X, X = halogen or triflate] and either a nickel or palladium catalyst. The complex, tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$, is one example of a catalyst that has found widespread application in Suzuki coupling reactions. The steps involved in the Suzuki coupling of a PolyHIPE-supported aryl iodide with 4-methoxybenzeneboronic acid are shown in *Figure 3.1*.

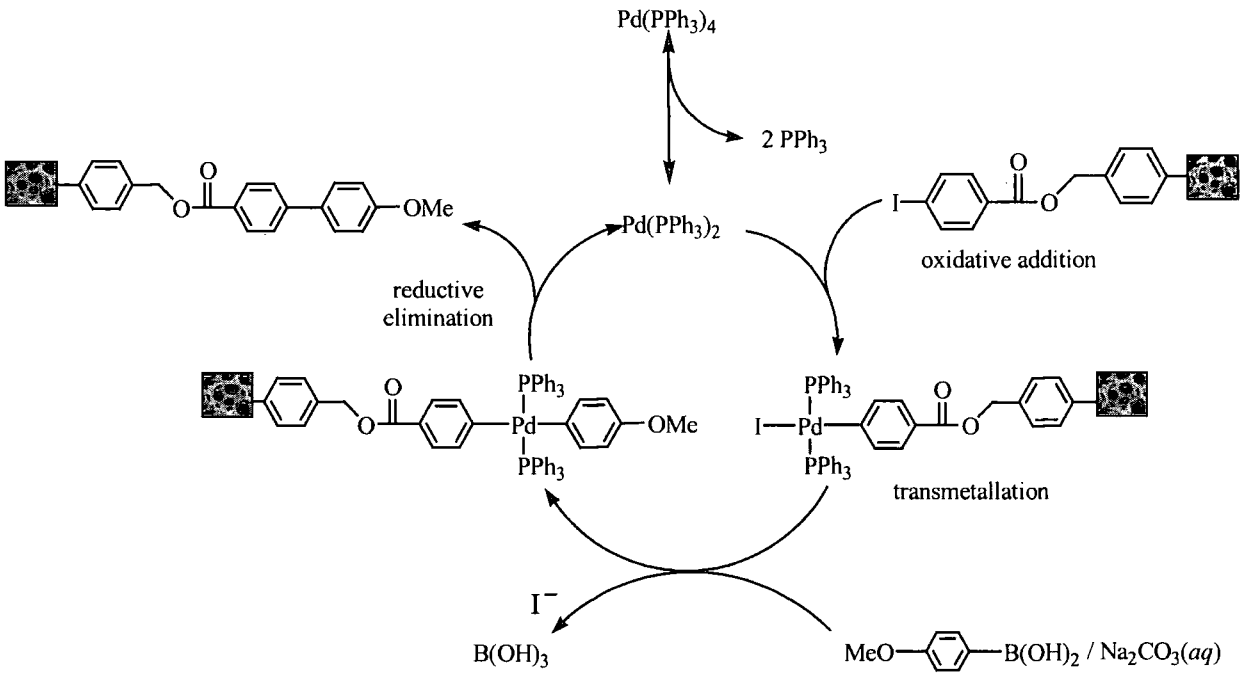


Figure 3.1 The Suzuki cross-coupling catalytic cycle

The first stage of the coupling reaction is known as oxidative addition.[9] This involves the addition of a molecule X-Y, to Pd(0), with cleavage of its covalent bond to create two new bonds. The most popular covalent bonds capable of undergoing oxidative addition to Pd(0) are C-X (X = halogen), particularly organic halides of sp^2 carbons. The rate of addition decreases in the following order: C-I > C-Br >> C-Cl

>>> C-F. The most commonly employed Pd(0) source in Suzuki reactions is $Pd(PPh_3)_4$. This saturated (four-coordinate, 18 electrons) Pd(0) complex undergoes reversible dissociation *in situ*, in solution, to give the unsaturated 14 electron species $Pd(PPh_3)_2$.[10] Essentially, the oxidative addition occurs with coordinatively unsaturated Pd(0) complexes. To avoid decomposition, this catalyst must be handled appropriately due to its light sensitivity and instability in air.

The second stage of the reaction is termed the transmetallation step. Organic compounds, M-R, of main group elements such as boron react with the complexes formed in the oxidative addition step. This results in the transfer of an organic group to Pd by exchange of X with R. Transmetallation between organopalladium (II) halides and organoboron compounds does not occur readily due to the low nucleophilicity of the organic group on the boron atom. However, the nucleophilicity of the organic group on boron can be enhanced by quaternisation with a negatively charged base. The driving force of the reaction is said to be the difference in electronegativity of the boron and palladium. The two processes[11] by which the aryl group on the boron atom of 4-methoxybenzeneboronic acid is believed to transfer to the PolyHIPE-supported palladium iodide species are shown in *Figures 3.2* and *3.3*.

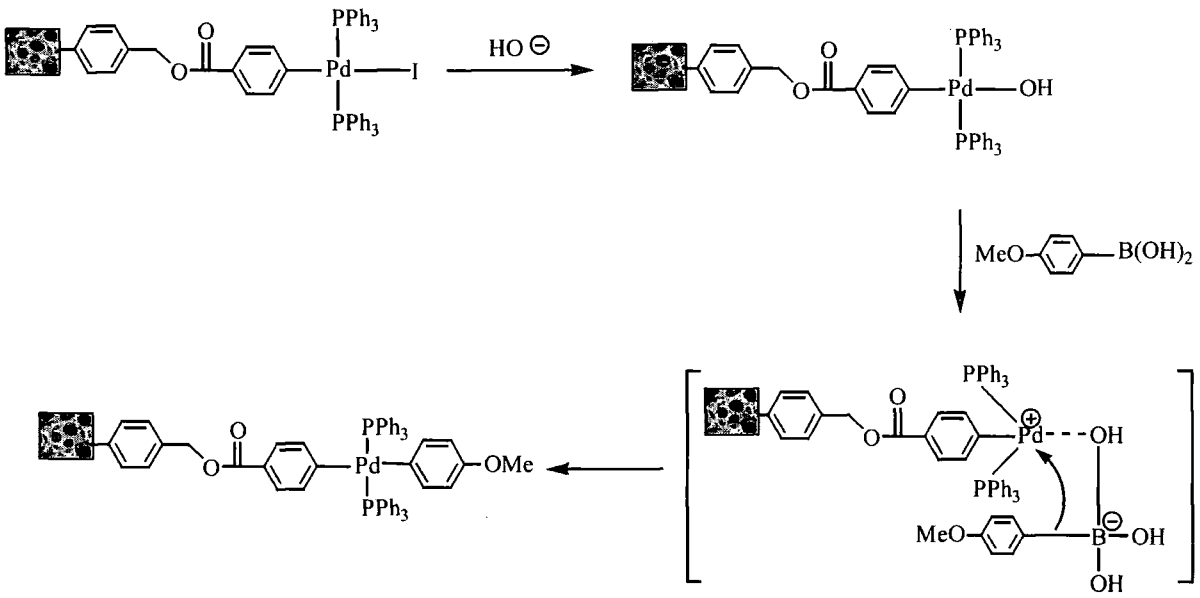


Figure 3.2 Transfer of the aryl group during transmetallation

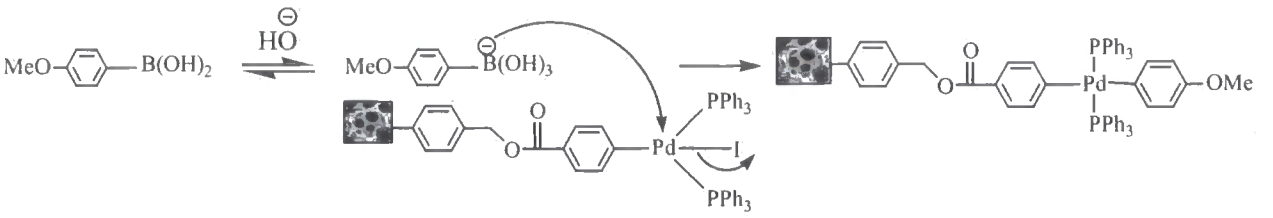
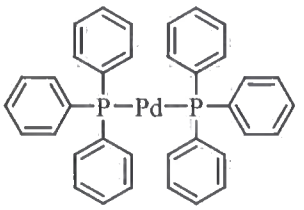


Figure 3.3 Alternative process for aryl group transfer

The final step in the synthesis is a decomposition involving a reductive elimination reaction. Two one-electron ligands of *cis* configuration are lost from the Pd centre and are combined to form a single elimination product.

3.3.1 Investigation into the Formation of By-Products in Suzuki Reactions

An investigation into the types of by-product formed in Suzuki cross-coupling reactions was undertaken to identify possible impurities contained in the final products of the batch and flow-through syntheses. In the transmetallation step, boron leaves the catalytic cycle with three hydroxyl groups attached ($B(OH)_3$, M_w = 62 g mol^{-1}) and iodide ions are produced as a result of the exchange reaction. Also, at the end of the coupling, regenerated $Pd(PPh_3)_2$ from the reductive elimination step could remain trapped inside the matrix (*Figure 3.4*). In polymer-supported couplings, the removal of residual palladium has proven to be a major problem, therefore, Argonaut Technologies have produced a polymer-supported palladium scavenger based on polystyrene -2,4,6-trimercaptotriazine.



M_w = 630 g mol^{-1}

Figure 3.4 Structure of the catalyst by-product $Pd(PPh_3)_2$

A review of the literature on the subject of Suzuki reaction impurities revealed that several side-reactions were possible. These included aryl-aryl exchange between Pd and a phosphine ligand, and the self-coupling of aryl boronic acids. One of the problems associated with the use of catalysts with arylphosphine ligands is the

formation of 'scrambled' products, in which the aryl group of the phosphine ligand becomes incorporated into the product. Kong et al.[12] demonstrated a facile two-way aryl migration between the metal centre and coordinated phosphine in Pd(II) complexes, which resulted in the formation of a completely different biaryl (*Figure 3.5*). In the PolyHIPE-supported couplings, one of the migrating aryls would theoretically be bound to the PolyHIPE, thereby preventing this exchange reaction from occurring. Furthermore, the exchange reaction was reported to be sensitive to air and only a complete degassing of the solution prior to heating was shown to prevent the side reaction from taking place. All of the PolyHIPE-supported couplings were performed in degassed solutions, therefore the probability of this side-reaction occurring was believed to be minimal.

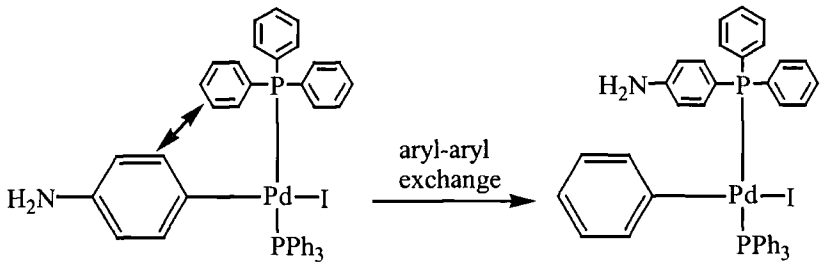


Figure 3.5 An example of aryl migration in Suzuki coupling reactions

Moreno-Manas and co-workers[13] showed that a palladium-catalysed Suzuki-type self-coupling of arylboronic acids was possible, whereby $Pd(PPh_3)_2$ inserts into the carbon-boron bond of the boronic acid (*Figure 3.6*). The formation of monosubstituted biaryls and phenols was also reported, and the presence of oxygen was found to accelerate the self-coupling. The PolyHIPE-supported couplings carried out in this work were performed under nitrogen, thereby limiting the formation of the self-coupled products. The structures of the by-products, which could theoretically form as a result of the self-coupling of the boronic acids employed in this work, are outlined in sections 3.4.1.3, 3.4.2.1 and 3.4.3.2.

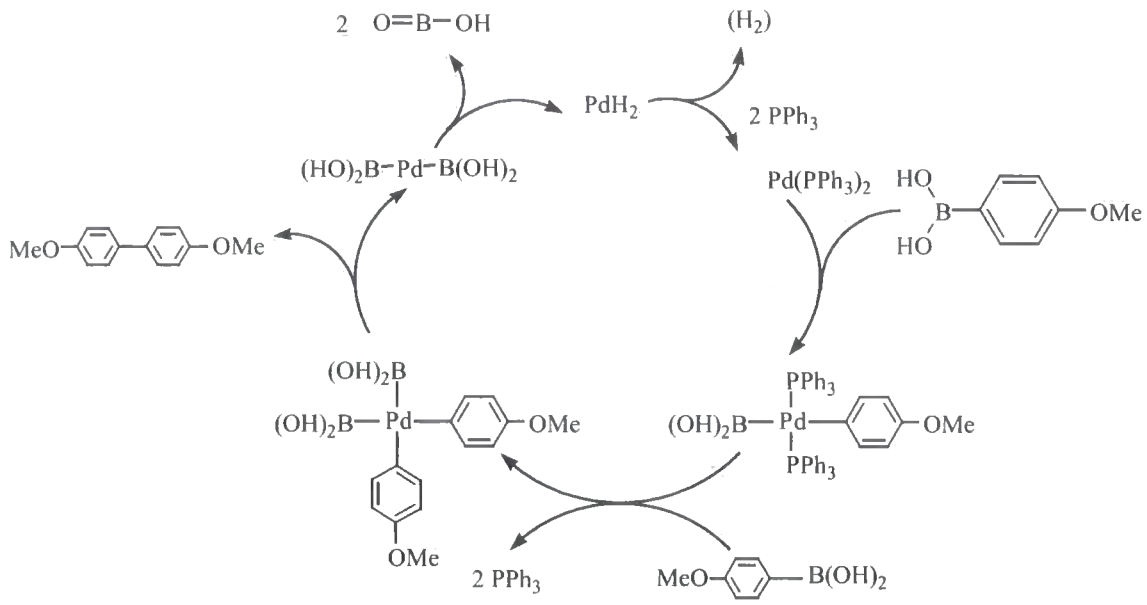


Figure 3.6 Self-coupling of 4-methoxybenzeneboronic acid

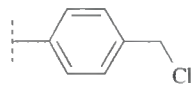
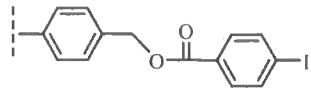
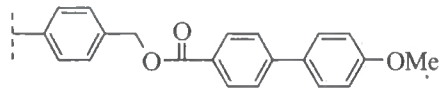
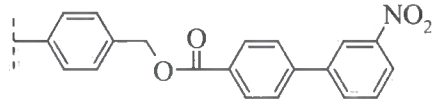
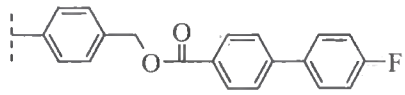
3.3.2 Nomenclature of Polymer Supports

The code used to identify the various VBC/DVB supports and their functionalised forms in this chapter, takes the same format as that described in section 2.3.2. The main reactive functionality of interest is denoted by letters: **C**hloromethyl (**C**); aryl **I**odine (**I**); biaryl **M**ethoxy (**M**); biaryl **N**itro (**N**); or biaryl **F**luorine (**F**) (*Table 3.1*). These letters are preceded by the numbers 1 or 2, which refer to the functionalisation attempt on that particular batch of support. This rule does not apply where reference is made to the basic **C**hloromethyl (**C**) supports. For example, 4-iodobenzoic acid was reacted with chloromethyl PolyHIPE, **P78B4$_g$C**, to yield **P78B4$_g$I1**. The same PolyHIPE batch was later used to prepare further amounts of the iodine-supported species, hence this functionalised PolyHIPE was referred to as **P78B4$_g$I2**.

3.3.3 Nomenclature of Biaryl Compounds

Single numbers have been used to identify the various small molecules synthesised. 4-Methoxy-biphenyl-4'-carboxylic acid methyl ester has been represented by **(1)**, 3-nitro-biphenyl-4'-carboxylic acid methyl ester by **(2)** and 4-fluoro-biphenyl-4'-carboxylic acid methyl ester by **(3)**. By-product 4-iodo-benzoic acid methyl ester has been represented by **(4)**.

Table 3.1 Identification code for supports

Support Code			
Support type	% wt VBC	Batch and form	Functionality
PolyHIPE P  **Bead B** 	78% = **78** 23% = **23**	**Bx_y** x = **1, 2, 3...** y = **g, c, m** **g** = granular **c** = cubic **m** = monolithic	 **C**  **IZ**  **MZ**  **NZ**  **FZ** **Z = 1 or 2**

3.4 Strategy for Batch Suzuki Couplings on Poly(VBC/DVB) PolyHIPE

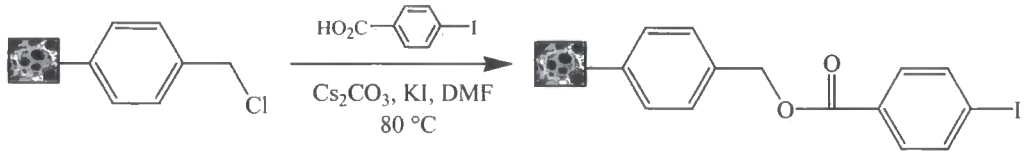
Work began by preparing poly(VBC/DVB) PolyHIPE with monomers in the ratio of 78:22 (VBC:DVB) by weight (the preparation and characterisation of PolyHIPE is discussed in chapter 2). Portions of the emulsion were polymerised inside PE bottles, PTFE reactor tubes and stainless steel columns, for use in batch and flow-through reactions. Sections of the PolyHIPE retrieved from the PE bottle were either ground into granules or cut into cubic pieces (*ca.* 1 cm^3) for comparative batch experiments. Since chloromethyl polystyrene beads (1.2 mmol -CH_2Cl groups g^{-1}) had already proven to be successful in the Suzuki reaction, it seemed logical to apply the reported conditions to VBC/DVB PolyHIPE foams. The literature procedure[4] involved reacting bead-bound aryl halide (1 mmol -I groups g^{-1}) with 0.05 eq of $Pd(Ph_3P)_4$ for 5 min, followed by the addition of the boronic acid substrate (2 eq) and

2M $Na_2CO_3(aq)$ (2.5 eq). The mixture was heated under reflux, in an argon atmosphere, overnight. When 4-methoxybenzeneboronic acid was coupled onto the beads, the yield of biaryl ester produced upon transesterification was reported to be greater than 95%. This excellent result prompted the use of the same boronic acid in the PolyHIPE reactions.

3.4.1 Synthesis of 4-Methoxy-Biphenyl-4'-Carboxylic Acid Methyl Ester

3.4.1.1 Application of Suzuki Conditions Reported for Polymer Beads

Firstly, granular and cubic forms of PolyHIPE **P78B2C**, with a loading of 4.37 mmol $-CH_2Cl$ groups g^{-1}, were reacted with 4-iodobenzoic acid in parallel batch reactions, according to the literature procedure (*Figure 3.7*).



P78B2$_g$C and P78B2$_c$C

P78B2$_g$I1 and P78B2$_c$I1

Figure 3.7 Attachment of 4-iodobenzoic acid to VBC/DVB PolyHIPE

Attachment of the carboxylic acid onto the chloromethyl groups was achieved by heating the PolyHIPEs in DMF with the cesium salt of the acid, in the presence of potassium iodide. This simple esterification yielded **P78B2$_g$I1** and **P78B2$_c$I1**, and allowed three modes of analysis. Firstly, the iodine and chlorine contents of the products were determined by elemental analysis, secondly, the presence of the carbonyl signal and disappearance of the chloride signal were monitored by FTIR analysis and thirdly, an increase in the weight of the PolyHIPEs was used to calculate conversions. The methods of analysis generally gave results that were reproducible and in good agreement. Conversions to iodine were found to be 69% for **P78B2$_g$I1** and 67% for **P78B2$_c$I1**, and strong peaks at 1720 cm^{-1} in the FTIR spectra were attributed to the presence of carbonyl groups in the newly formed ester bonds. The conversions by weight were calculated as 67% and 88% for the granular and cubic

forms respectively. The higher weight of the cubes was possibly due to incomplete drying of this form of the PolyHIPE. The conversions to iodine on the PolyHIPE supports were moderate compared to the 100% conversion reported for polymer beads.

P78B2$_g$I1 (1.56 mmol -I groups g^{-1}) and **P78B2$_c$I1** (1.52 mmol -I groups g^{-1}) were then employed in the coupling of 4-methoxybenzeneboronic acid under identical conditions to those outlined for the beads *(Figure 3.8)*. A slightly greater excess of reagents was used as a result of calculations being based on the theoretical iodine loading, rather than the actual loading which was determined shortly afterwards. Ultimately, this was expected to enhance the coupling rather than have a detrimental effect on it.

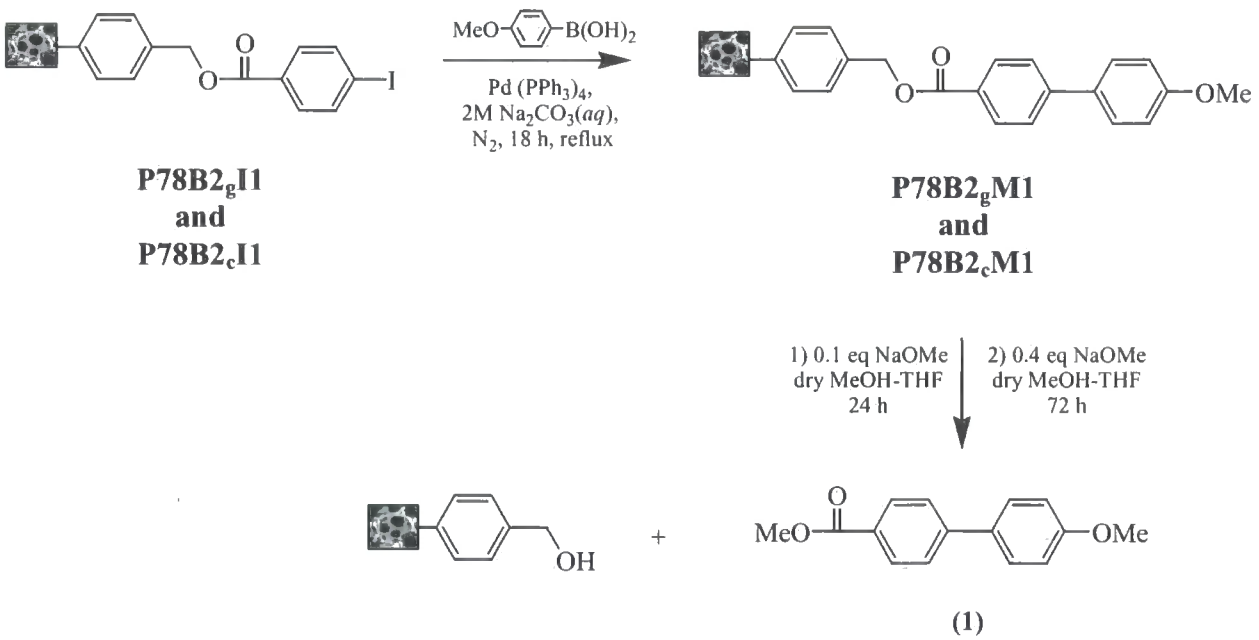


Figure 3.8 PolyHIPE-supported synthesis of 4-methoxy-biphenyl-4'-carboxylic acid methyl ester

Cleavage of **P78B2$_g$M1** was performed using 1M NaOMe and freshly dried solvents to prevent formation of the corresponding acid biaryl product. Interestingly, the purity of the biaryl ester produced from polymer beads was reported to be in excess of 90%, without the use of dry solvents in the transesterification step.[4] The yield of crude product obtained from the granular PolyHIPE was a rather disappointing 19% (based on the loading of iodine onto the PolyHIPE). ^{1}H NMR analysis showed that biaryl ester **(1)** had been obtained, as the major peaks were in

agreement with the values quoted in the literature for this compound.[14] However, there were also other peaks of lower intensity present which were thought to be by-products of the coupling reaction. In order to determine whether the coupled product had completely cleaved from the PolyHIPE support, an FTIR spectrum of the PolyHIPE after cleavage was obtained. Strong carbonyl signals were still present in the material suggesting that complete cleavage of the product had not taken place. The PolyHIPE support clearly required a longer residence time in the basic solution, to allow cleavage of the strong C-O bonds. Therefore, **P78B2$_g$M1** was subjected to a re-cleave using 0.4 eq of 1M NaOMe, for the extended time of 72 h. A similar amount of crude product was obtained as in the first cleave, resulting in a total crude yield of 38%. ^{1}H NMR analysis suggested that a greater amount of the pure biaryl ester had been obtained from the second cleave, as very few low intensity signals were present. This implied that the first cleavage had removed impurities and by-products trapped in the PolyHIPE matrix, resulting in 'cleaner' products in the second cleavage attempt.

P78B2$_c$M1 was similarly cleaved with 0.4 eq of 1M NaOMe for 72 h, producing a low yield of crude product (28%). The ^{1}H NMR spectrum of this product displayed the biaryl ester peaks and also various lower intensity signals, which suggested that the purity of the product was poor. Due to the discouraging yields and qualities of product obtained from these initial experiments, further characterisation to determine the nature of the impurities was not carried out at this stage. Rather, the focus of this initial work was to develop conditions that would result in optimum coupling and high yields.

3.4.1.2 Application of Classical Solution Phase Suzuki Conditions

Since the conditions reported for polymer beads proved to be largely unsuccessful for PolyHIPE materials, alternative coupling conditions were applied. The classical conditions employed in solution phase Suzuki reactions[15] were considered to be a logical starting point upon which to develop the PolyHIPE-supported reactions. Compared to the conditions reported for polymer beads, the solution phase conditions involved the use of dry solvents, an extended reaction time and a 1M $Na_2CO_3(aq)$ solution instead of 2M. The oxidative addition reaction was allowed to take place first, in the presence of dry solvents, to prevent the early onset of the transmetallation reaction which takes place once the aqueous base has been

added. One other significant modification was the replacement of commercially supplied catalyst $Pd(PPh_3)_4$ with a fresh batch prepared 'in house'.[16] Due to the sensitivity of palladium (0) complexes, the quality of commercially available catalysts of this type can vary substantially.[17] In addition, precautions were taken to avoid exposure of the reaction mixture to light. The filtrate and washings obtained upon cleavage of the supports, were passed through a column of celite to remove any residual palladium metal.

The procedure involved stirring PolyHIPE-bound iodine, **P78B3$_g$I1** (1.13 mmol -I groups g^{-1}) and **P78B3$_c$I1** (1.33 mmol -I groups g^{-1}), in degassed solutions of dry DME with 4-methoxybenzeneboronic acid (1.2 eq) and $Pd(Ph_3P)_4$ (0.06 eq) for 30 min. After this time, a degassed 1M solution of $Na_2CO_3(aq)$ (3.6 eq) was added to each flask and the mixtures were heated under reflux, in a nitrogen atmosphere, for 40 h. After being filtered, washed and dried, conversions by weight were found to be 92% for **P78B3$_g$M1** and 83% for **P78B3$_c$M1**. Upon cleavage with 0.5 eq of 1M NaOMe for 72 h, crude products were obtained in 89% yield from the granular support and 120% yield from the cubic support. The high yield of more than 100% from the latter support suggested that impurities were present. Furthermore, when $CDCl_3$ was added to the crude product it appeared that not all of the material had dissolved, implying that impurities were indeed present. ^1H and ^{13}C NMR spectra confirmed that the dissolved material was that of the pure biaryl ester product and the mass recovered from $CDCl_3$ revealed the actual yield of pure biaryl ester to be 22%. Similarly, an 18% yield of pure product was recovered from the granular support. Gas Chromatography-Mass Spectrometry (GC-MS) in electron ionisation mode confirmed the presence of the biaryl ester products (*m/z* 242).

The crude products were analysed by High Performance Liquid Chromatography (HPLC) in order to obtain a more accurate indication of their overall purities. The most abundant peaks in both spectra were found to have retention times of between 9 and 10 min, which was later confirmed to be the characteristic retention time range of compound **(1)** (section 3.4.1.3). The trace showed that **(1)** constituted 28% of the product obtained on the granular support and 34% of the product obtained on the cubic support. These values were slightly higher than those found by NMR analysis, however, a degree of inaccuracy was expected as a consequence of transferring the products from flasks to NMR tubes and then to pre-weighed vials.

By performing HPLC analysis on 4-methoxybenzeneboronic acid, it was deduced that both crude products were contaminated with up to 5% of the starting material. The boronic acid was found to have an overall purity of 83%, with a retention time of 3.3 min. A minor component, which comprised 13%, was detected at 4.4 min. It is known that most boronic acids readily undergo dehydration reactions to produce a cyclic anhydride and it was thought this by-product may have been present in the commercial acid used in the couplings. However, the presence of the anhydride was not believed to be a problem as it is considered to be equally effective in the Suzuki coupling reactions. The most abundant impurity was detected at earlier retention times of between 1.7 and 2.5 min in both crude products. Since the HPLC analysis was performed in reverse phase, this implied that the impurities were more polar in nature than the biaryl ester products.

These reactions were performed without the use of a high excess of boronic acid, therefore, it was thought that uncoupled iodine may have remained bound to the PolyHIPE, resulting in the formation of 4-iodo-benzoic acid methyl ester **(4)** upon cleavage with NaOMe (*Figure 3.9*).

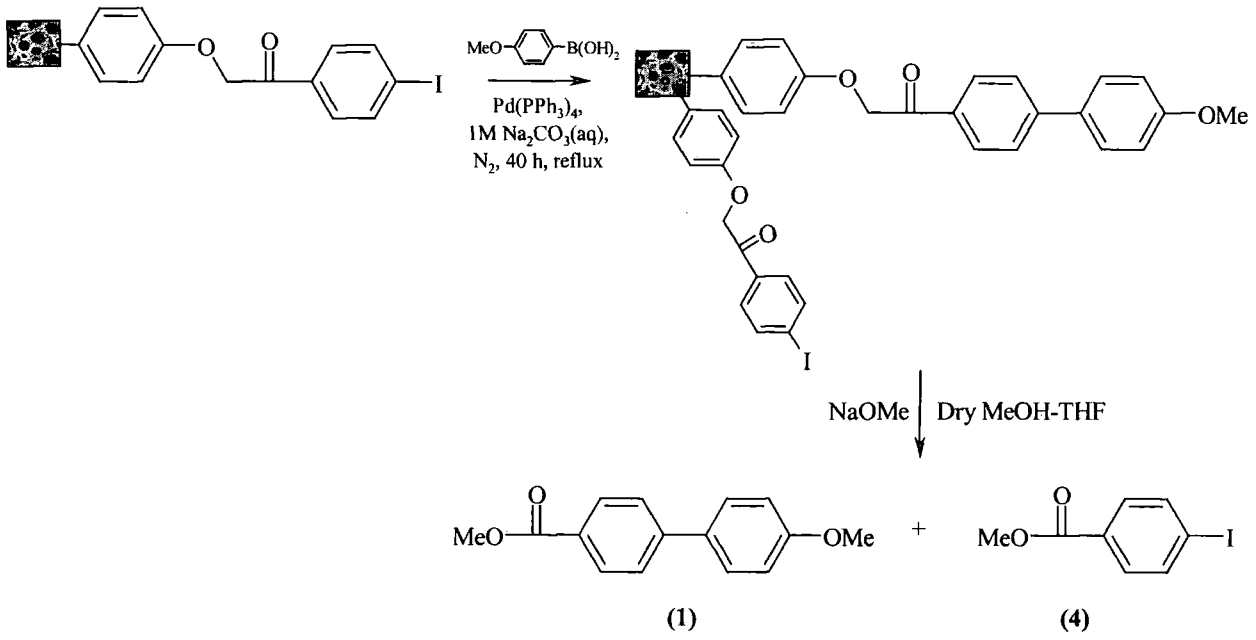
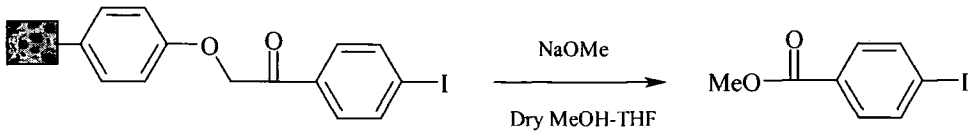


Figure 3.9 Synthesis of 4-iodo-benzoic acid methyl ester by-product

In order to isolate and identify this species, **P78B3$_g$I1** was cleaved directly with NaOMe (*Figure 3.10*) and the product was analysed by ^{1}H NMR spectroscopy and

HPLC. From analytical HPLC analysis, the product was found to contain one major compound and one minor compound.



P78B3$_g$I1 **(4)**

Figure 3.10 Cleavage of PolyHIPE-supported aryl iodide compound

The compound with the highest retention time (7.3 min) was believed to be 4-iodo-benzoic acid methyl ester, however it only comprised 21% of the total crude product. The major component had a retention time of 2.5 min, together with a relative abundance of 76%. This was suspected to be 4-iodobenzoic acid, due to this species being more polar in nature than the corresponding ester and hence, being detected first. Analytical HPLC analysis of a commercial sample of 4-iodobenzoic acid confirmed that this was indeed the acid. The retention time of the commercial acid was 2.8 min which is extremely close to that found for the major component. LC-MS analysis also confirmed the presence of 4-iodobenzoic acid in the sample. Peaks with retention times of 1.9 and 2.0 min in the LC trace were analysed in ES- mode and found to represent 247 (M-H), which corresponded to the molecular weight of the acid (248). The presence of 4-iodo-benzoic acid methyl ester **(4)** (corresponding to 21% by HPLC) was confirmed by mass spectrometry in electron ionisation mode (*m/z* (EI) 262) and by ^{1}H NMR.

These results were surprising and unexpected. The high level of 4-iodobenzoic acid in the cleaved product was attributed to a combination of factors. Firstly, unreacted acid could have remained in the PolyHIPE matrix from the initial conversion of chloromethyl groups to the iodine-supported species and secondly, hydrolysis of the ester bond may have occurred during the cleavage procedure. This, latter effect was thought to contribute less to the overall high amount of acid since dry solvents had been used in the cleavage reaction. However, hydrolysis would help to explain why a low percentage of **(4)** was retrieved. From this investigation, it was concluded that the main impurity in the reactions was unreacted 4-iodobenzoic acid. The formation of **(4)** was less evident from the HPLC data of the crude products, suggesting that the coupling was taking place successfully. The results implied that

substantial washing of the supports was required after each stage, in order to minimise the number of impurities in the final product. Furthermore, the data showed that the correct product was being produced and that further steps were necessary to drive the reactions to completion and improve product purity.

3.4.1.3 Application of Optimised Suzuki Conditions

In order to increase the purities of the biaryl products, higher concentrations of reagents and catalyst were employed. It was believed that this would drive the couplings to completion, resulting in fewer by-products. **P78B2$_g$I2** (1.50 mmol -I g^{-1}) and **P78B2$_c$I2** (1.35 mmol -I g^{-1}) were coupled with 4-methoxybenzeneboronic acid according to the procedure described in section 3.4.1.2. On this occasion an optimised version of the classical conditions was developed, involving 3.5 eq of boronic acid substrate, together with 0.17 eq of $Pd(PPh_3)_4$ and 10 eq of 1M $Na_2CO_3(aq)$ solution. Conversions to the PolyHIPE-immobilised biaryls appeared to take place successfully as evidenced by a high weight conversion of 83% for both **P78B2$_g$M2** and **P78B2$_c$M2**. Upon cleavage with 0.5 eq of 1M NaOMe for 72 h, the crude product yield was found to be 46% from the granular PolyHIPE and 87% from the cubic form. Since the yield from **P78B2$_g$M2** was much lower than expected, a second cleave of this PolyHIPE was conducted. As a result, the crude yield was increased to 95%.

^{1}H NMR analysis indicated that biaryl ester **(1)** had been obtained in high purity, and to confirm this, analytical and preparative HPLC analysis was performed on both products. Preparative HPLC of the crude product obtained from the granular support, showed that the biaryl ester comprised 70% of the total product. The yield of **(1)** was calculated from the mass of the fraction recovered as a percentage of the total amount. The structure of the isolated fraction (with a corresponding retention time of 9 min by analytical HPLC) was confirmed from the ^{1}H NMR spectrum to be the biaryl ester **(1)** (*Figure 3.11*). Integration of the peaks showed that the signals were present in the correct ratio.

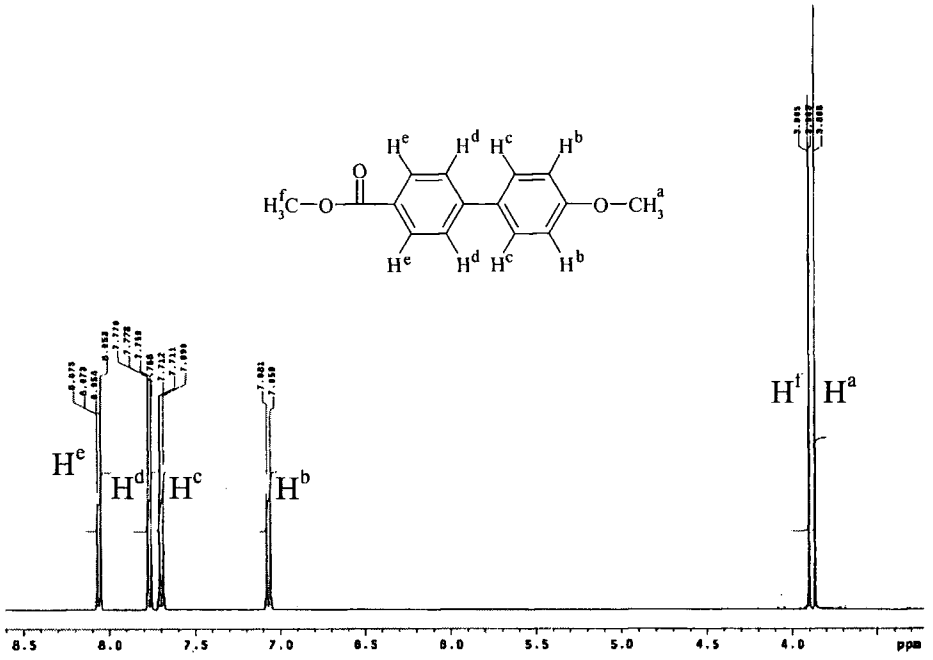


Figure 3.11 ^{1}H NMR spectrum of 4-methoxy-biphenyl-4'-carboxylic acid methyl ester (1)

Eleven signals were present in the ^{13}C NMR spectrum as expected. The major impurity in the product (with a corresponding retention time of 2 min by analytical HPLC) constituted 18% of the total, and when characterised by ^{1}H NMR, was found to display a lack of distinguishable signals. It was hoped that the preparative HPLC analysis would confirm that this fraction was 4-iodobenzoic acid, however, the spectrum inferred that an inorganic material was present. Therefore, a separate study was carried out in an attempt to determine the structures of the by-products in the Suzuki reaction (section 3.3.1). The majority of by-products proposed were not inorganic but rather contained aryl groups, particularly those formed during the self-coupling of 4-methoxybenzeneboronic acid (*Figure 3.12*). The cyclic trimeric anhydride, which accompanies the acid, is also shown.

MeO—⟨⟩—⟨⟩—OMe	MeO—⟨⟩—⟨⟩	MeOAr, ArOMe, ArOMe (cyclic B–O trimer)	MeO—⟨⟩—OH
M_w = 214.26 g mol^{-1}	M_w = 184.24 g mol^{-1}	M_w = 401.82 g mol^{-1}	M_w = 124.14 g mol^{-1}

Figure 3.12 Possible by-products from the self-coupling of 4-methoxybenzeneboronic acid

A small fraction of the product (12%) (with a corresponding retention time of 4 min by HPLC) was thought to be the carboxylic acid biaryl produced as a result of hydrolysis in the cleavage step. This occurs as a result of the presence of trace amounts of moisture in the reaction mixture. The disappearance of the singlet representing the methoxy ester protons in the ^{1}H NMR spectrum inferred that this was indeed the case, however, the signals in the aromatic region were complex and could not be assigned. Therefore, it could not be reported unambiguously that the acid had formed during the reaction.

The same analytical techniques were used to obtain information about the purity of compound **(1)** cleaved from the cubic PolyHIPE, **P78B2$_c$M2**. Recovery of the major component by preparative HPLC showed that it comprised 93% of the total product and NMR spectroscopy confirmed that the isolated fraction was the biaryl ester. The single impurity, which was found to make up the remaining 7% of the crude product (with a corresponding retention time of 4 min by analytical HPLC), was also analysed by ^{1}H NMR and found to have the same structure as the minor impurity obtained from the granular support. As in the previous case, it could not be determined that this was the corresponding acid biaryl. Interestingly, there was no evidence of the formation of the common impurity (retention time of 2 min) from the cubic support. From the results of the couplings on both supports, it appeared that the cubic PolyHIPE produced biaryl **(1)** in a higher overall purity than the corresponding granular form.

By using a higher concentration of reagents, the reactions were successfully driven to completion, producing very high yields of pure biaryl ester. These optimised conditions proved that PolyHIPE is a viable support for the batch coupling of an electron-rich boronic acid such as 4-methoxybenzeneboronic acid. However, in order to demonstrate the suitability of PolyHIPE with a wider range of substrates, it was decided to introduce two other acids into the synthesis programme. In order to obtain an indication of the success of coupling on the PolyHIPE supports, electron-deficient aryl boronic acids containing functional groups such as -F and -NO_2 were chosen, as these could be quantified by elemental analysis.

3.4.2 Preparation of 3-Nitro-Biphenyl-4'-Carboxylic Acid Methyl Ester

3.4.2.1 Application of Optimised Classical Suzuki Conditions

In parallel batch reactions, **P78B1$_g$I1** (1.68 mmol -I g^{-1}) and **P78B4$_c$I1** (1.66 mmol -I g^{-1}) were coupled with 3-nitrobenzeneboronic acid according to the optimised procedure developed in section 3.4.1.3 (*Figure 3.13*). 3-Nitro-biphenyl-4'-carboxylic acid methyl ester has already been synthesised by treatment of 3-nitro-biphenyl-4'-carboxylic acid with conc. H_2SO_4 in methanol.[18]

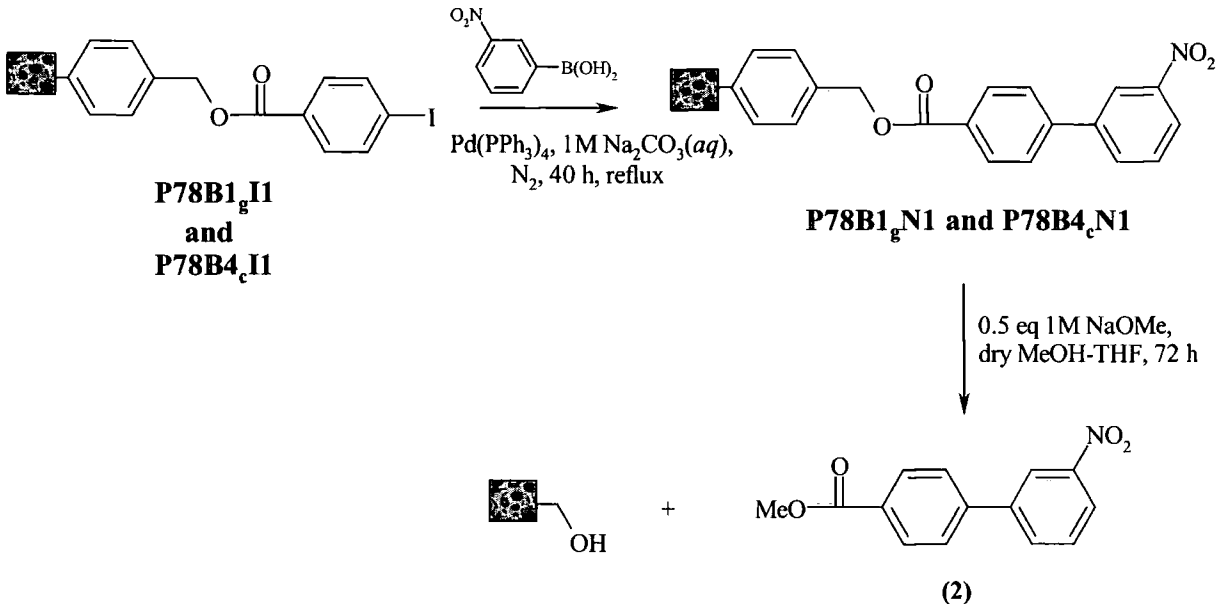


Figure 3.13 PolyHIPE-supported synthesis of 3-nitro-biphenyl-4'-carboxylic acid methyl ester

As in the previous coupling example, 3.5 eq of boronic acid substrate was employed, together with 0.17 eq of $Pd(PPh_3)_4$ and 10 eq of 1M $Na_2CO_3(aq)$ solution. The couplings appeared to proceed smoothly as evidenced by the high conversions by weight, 100% for **P78B1$_g$N1** and 95% for **P78B4$_c$N1**, and the correspondingly high conversions to nitrogen, 69% and 82% for **P78B1$_g$N1** and **P78B4$_c$N1**, respectively, as determined by nitrogen elemental analysis. The yields of crude product obtained from both forms of support after cleavage are summarised in *Table 3.2.*

Table 3.2 Crude yields obtained after cleavage

Functionalised PolyHIPE cleaved	Yield of crude product (%)	
	based on iodine loading	based on nitrogen loading
P78B1$_g$N1	70	100
P78B4$_c$N1	92	109

^{1}H NMR analysis of the crude product synthesised on the granular support, proved that biaryl **(2)** had been prepared in high purity, due to a lack of impurity peaks. From analytical HPLC analysis, the most abundant peak was detected at 7.2 min and comprised 63% of the crude product. This was believed to represent **(2)**, due to its high retention time (characteristic of the biaryl ester compound prepared previously) and its relatively high abundance. This was later confirmed to be compound **(2)** by preparative HPLC and NMR spectroscopy (section 3.4.2.2). The presence of **(2)** was also confirmed by mass spectrometry in electron ionisation mode (*m/z* (EI) 257).

By performing HPLC analysis on the starting material, 3-nitrobenzeneboronic acid, it was deduced that the crude product was contaminated with 10% of the acid. As in previous reactions, an impurity with a retention time of around 2 min (1.8 min in this case) was found to form the remainder of the product (23%). In an attempt to identify the impurity, the crude product from the granular support was analysed by LC-MS. The major peak in the LC trace, which was detected at 1.4 min, was believed to correspond to the peak at 1.8 min in the HPLC trace. However, when this peak was analysed by mass spectrometry in ES- mode, the only species detected were iodine (*m/z* 126.9) and a compound with *m/z* of 277. From the investigation into the possible by-products of the coupling reaction (section 3.3.1), this peak could not be attributed to any of the proposed impurities. The possible products from the self-coupling of 3-nitrobenzeneboronic acid and the cyclic trimeric anhydride, which accompanies the acid, are shown in *Figure 3.14*.

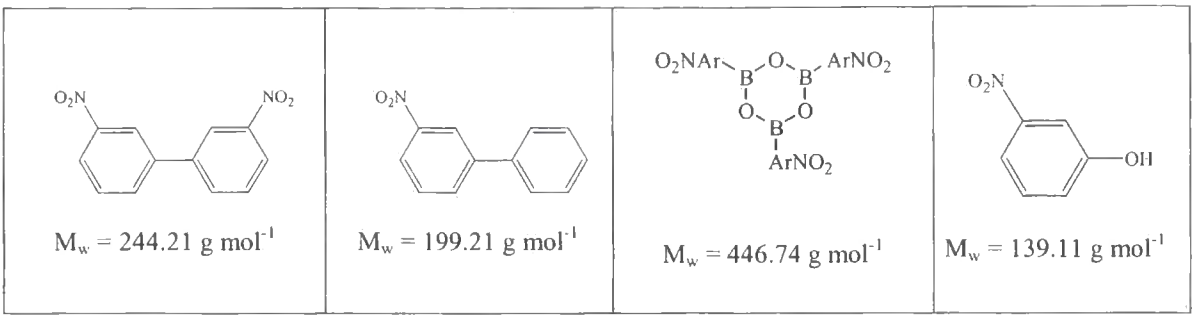


Figure 3.14 Possible by-products from the self-coupling of 3-nitrobenzeneboronic acid

When the LC spectrum was analysed in ES+ mode, the main peak was detected at 2.4 min. At this retention time, 5 peaks were resolved with molecular ions ranging from 279 to 391. Similarly, these peaks could not be attributed to any known by-products of the reaction, therefore, determination of the impurity was inconclusive at this stage. Starting material 4-iodobenzoic acid was ruled out as the source of the major impurity in this reaction as its retention time (2.5 min) is slightly higher than that of the impurity (1.8 min).

A ^{1}H NMR spectrum of the crude product synthesised on the cubic support, proved that the desired biaryl **(2)** had been synthesised in high purity. By analytical HPLC, the actual purity of the biaryl was revealed to be 55%. A further 10% of the crude was shown to be unreacted boronic acid and 17% contained the common impurity with a retention time of 1.8 min. These reactions were driven to completion by employing a high excess of reagents and also the supports were subjected to a rigorous washing procedure to remove any unreacted starting materials. Evidently, the washing procedure failed to remove all of the residual boronic acid from the supports, therefore the coupling of the boronic acid was repeated employing an improved washing procedure.

3.4.2.2 Application of Improved Version of Optimised Conditions

In an attempt to increase the purity of the nitro biaryl products, improvements were made to the optimised procedure to eliminate the formation of impurities and to remove certain by-products from the reactions. This involved substantial washing of the PolyHIPE-immobilised biaryl formed after coupling in a Soxhlet apparatus, to remove any residual boronic acid. Also, before cleavage, the support was thoroughly

dried under vacuum with heating, to remove any water held inside the matrix. It was believed that this would prevent formation of the corresponding hydrolysis product, the carboxylic acid biaryl, which was suspected to be a possible by-product of the reaction.

P78B4$_g$I2 (1.54 mmol -I g^{-1}) and **P78B1$_c$I2** (1.60 mmol -I g^{-1}) were coupled with 3-nitrobenzeneboronic acid according to the optimised conditions outlined in section 3.4.2.1. To remove excess boronic acid, the supports were washed in a Soxhlet apparatus in THF for 24 h after the coupling reaction and dried under vacuum at 50 °C for 24 h. Mass recovery and nitrogen analysis indicated that the couplings had proceeded successfully. The conversion to **P78B4$_g$N2** by weight was calculated to be 81%, and this was further supported by a conversion of 96% as determined by N elemental analysis. Similarly, the conversion to **P78B1$_c$N2** by weight was 83%, which was supported by a conversion of 100% by N elemental analysis. The crude yields of product obtained from both forms of support after cleavage are summarised in *Table 3.3.*

Table 3.3 Crude yields obtained after cleavage

Functionalised support cleaved	Yield of crude product (%)	
	based on iodine loading	based on nitrogen loading
P78B4$_g$N2	100	100
P78B1$_c$N2	74	72

^{1}H NMR analysis of the crude product synthesised on the granular support revealed that the biaryl **(2)** had been synthesised, and the clean quality of the spectrum suggested that the purity was high. Both preparative and analytical HPLC were used to determine the actual purity of the crude product. The major component isolated from the preparative procedure was shown to represent compound **(2)** by ^{1}H NMR (*Figure 3.15*).

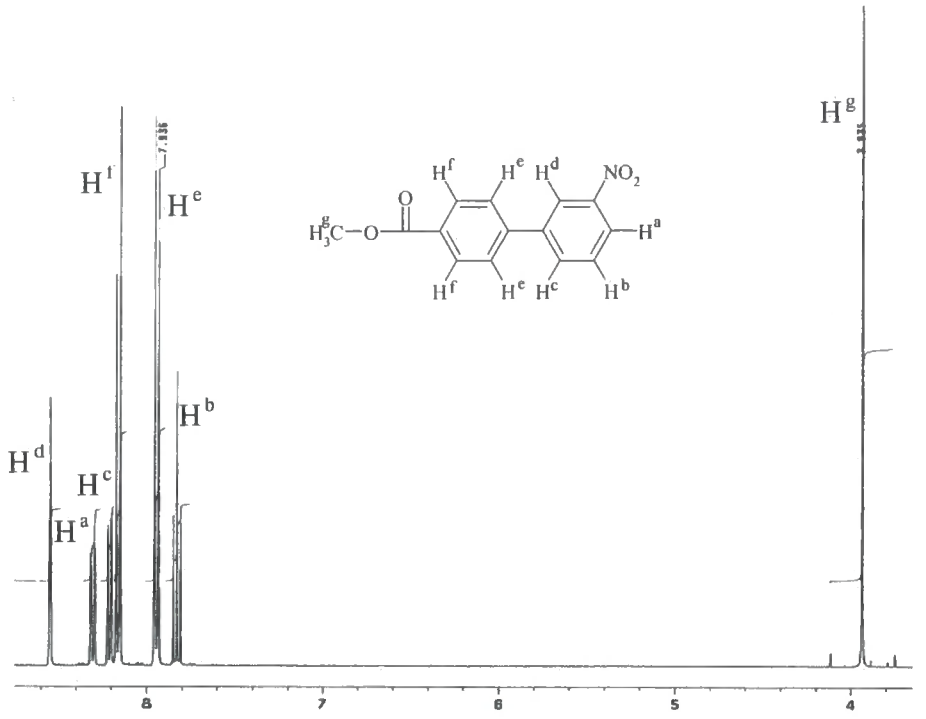


Figure 3.15 ^{1}H NMR spectrum of 3-nitro-biphenyl-4'-carboxylic acid methyl ester

Twelve signals were present in the ^{13}C NMR as expected. MS in electron ionisation mode further supported this data, displaying the molecular ion *m/z* 257. From the mass of **(2)** recovered from the preparative HPLC, the yield of the pure compound was calculated to be 72%. On this occasion, the impurity with a retention time of 1.3 min, which constituted the remaining 28% of the product, could be isolated and hence, characterised by various methods. A ^{1}H NMR spectrum revealed very little evidence about the structure of the impurity. There were no signals detected in the aromatic region, and only one doublet appeared at 3 ppm. From this data, the impurity was again assumed to be an inorganic residue from the reaction, which supported previous characterisation data of the fraction. The impurity was analysed by ^{11}B NMR spectroscopy to observe whether the by-product had formed as a result of the transmetallation step of the reaction. However, the analysis proved that there was no boron present in the impurity fraction. Further characterisation of the isolated impurity involved MS analysis, however identification of a single species was inconclusive due to the large number of peaks detected in ES+ mode. As in the previous example, LC-MS analysis of the crude product before separation of the impurity, revealed the presence of a species with $(M-H)^{-} = 277$, at a similar retention time to the impurity. This implied that the inorganic material had a molecular mass of

278, but as stated, attempts to match this with by-products of the reaction proved inconclusive.

A ^{1}H NMR spectrum of the crude product synthesised on the cubic PolyHIPE, confirmed that the nitro biaryl ester had been synthesised in very high purity. The crude product was then analysed by both preparative and analytical HPLC. From the mass of biaryl **(2)** recovered from the preparative procedure, the yield of pure product was calculated as 81%. ^{1}H and ^{13}C NMR analysis of this isolated fraction proved that this was indeed the desired product. The usual impurity was found to comprise 8% of the crude product, and when the isolated fraction was characterised by ^{1}H NMR, the spectrum was found to resemble that of the previous example *i.e.* an inorganic material. No further attempts were made to characterise the impurity due to the small amount of material available. As with 4-methoxybenzeneboronic acid, it appeared that PolyHIPE in the form of cubic pieces produced the pure biaryl product in a higher yield than the corresponding granular form.

3.4.3 Preparation of 4-Fluoro-Biphenyl-4'-Carboxylic Acid Methyl Ester

3.4.3.1 Application of Optimised Classical Suzuki Conditions

P78B1$_g$I1 (1.68 mmol -I g^{-1}) and **P78B1$_c$I2** (1.53 mmol -I g^{-1}) were coupled with 4-fluorobenzeneboronic acid according to the optimised procedure described in section 3.4.1.3 (*Figure 3.16*). Frenette and Friesen[4] used this boronic acid in their bead-supported Suzuki couplings and reported a yield of 4-fluoro-biphenyl-4'-carboxylic acid methyl ester **(3)** of 91%.

The couplings appeared to proceed smoothly as evidenced by the high conversions by weight, 90% for **P78B1$_g$F1** and 97% for **P78B1$_c$F2**, and the correspondingly high conversions to fluorine, 62% and 94% respectively, as determined by F elemental analysis. The coupling on the cubic support appeared to be significantly more successful than that of the granular support. The yields of crude product obtained from both forms of support after transesterification with NaOMe are summarised in *Table 3.4*.

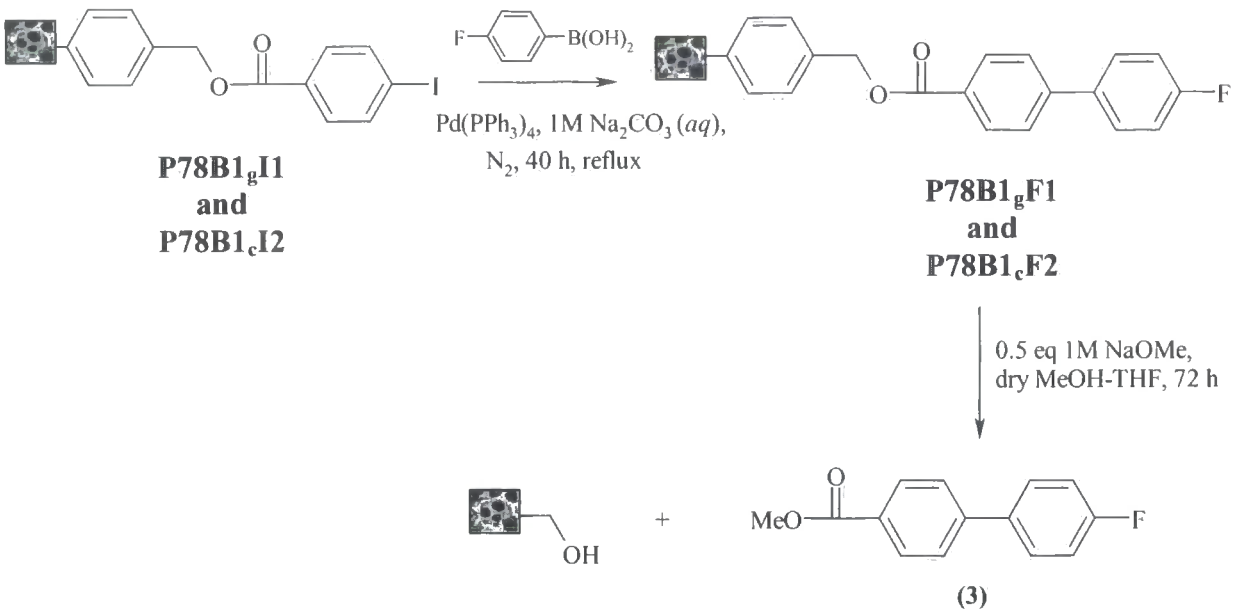


Figure 3.16 PolyHIPE-supported synthesis of 4-fluoro-biphenyl-4'-carboxylic acid methyl ester

Table 3.4 Crude yields obtained after cleavage

Functionalised PolyHIPE cleaved	Yield of crude product (%)	
	based on iodine loading	based on fluorine loading
P78B1$_g$F1	87	134
P78B1$_c$F2	104	105

^{1}H NMR analysis of the crude product cleaved from the granular support showed that compound **(3)** had been synthesised. The chemical shifts of the major peaks observed were in close agreement with the values estimated from correlation tables.[19] Also, integration of the peaks showed that the signals were present in the expected ratio. Analytical HPLC was performed on the crude product in order to obtain an accurate indication of the purity. The peak for biaryl **(3)** was believed to appear at around the same retention time as biaryl esters **(1)** and **(2)** produced in previous experiments, due to their overall similar structures. Upon inspection of this region of the trace, a peak was found at 8.5 min with a corresponding abundance of 32%, which was attributed to biaryl **(3)**. This was later confirmed by HPLC analysis and NMR spectroscopy (section 3.4.3.2). An HPLC spectrum of the starting material, 4-fluorobenzene boronic acid, revealed that the crude product synthesised on the

granular support contained 13% of this unreacted species. The most abundant peak however, was detected at 1.8 min and comprised 43% of the product. This was believed to be an inorganic residue from the reaction, which was later confirmed by NMR analysis of the isolated fraction.

From HPLC analysis of the crude product obtained on the cubic support, it was believed that the peak at 8.8 min, which constituted 40% of the total, represented biaryl ester **(3)**. Interestingly, a further 40% was detected with a similar retention time to the boronic acid starting material. On this occasion, the common impurity at 1.8 min was found to comprise only 12% of the total. Due to the high amount of unreacted boronic acid in the product, the conditions were modified further in an attempt to increase the overall purity of the material. As with the coupling of 3-nitrobenzeneboronic acid, the PolyHIPE-immobilised biaryl formed after coupling was washed in a Soxhlet apparatus, to remove any residual boronic acid. Also, before cleavage, the support was thoroughly dried under vacuum with heating, to remove any water held inside the matrix.

3.4.3.2 Application of Improved Version of Optimised Suzuki Conditions

P78B4$_g$I2 (1.54 mmol -I g^{-1}) and **P78B4$_c$I2** (1.57 mmol -I g^{-1}) were coupled with 4-fluorobenzeneboronic acid according to the improved conditions described. As with 3-nitrobenzeneboronic acid, mass recovery and elemental analysis were used as an indication of the success of coupling. The conversion to **P78B4$_g$F2** by weight was calculated to be 77%, and this was further supported by a conversion of 90% as determined by F elemental analysis. Similarly, the conversion to **P78B4$_c$F2** by weight was 83%, which was supported by a conversion of 96% as determined by F elemental analysis. As in the previous case, the coupling appeared to be more successful on the PolyHIPE in cubic form rather than granular form. The crude yields of product obtained from both forms of support after cleavage are summarised in *Table 3.5*.

Table 3.5 Crude yields obtained after cleavage

Functionalised PolyHIPE cleaved	Yield of crude product (%)	
	based on iodine loading	based on fluorine loading
P78B4$_g$F2	100	108
P78B4$_c$F2	105	104

^{1}H NMR analysis of the crude product synthesised on the granular support showed that compound **(3)** had been synthesised. The significant peaks were present in the spectrum together with peaks of weaker intensity. The purity of the crude material was analysed by both preparative and analytical HPLC. Three components were detected in the crude product. From the mass recovered by the preparative procedure, the pure yield of biaryl ester **(3)** was found to be 82%. ^{1}H NMR spectroscopy confirmed that the isolated fraction was indeed compound **(3)** (*Figure 3.17*).

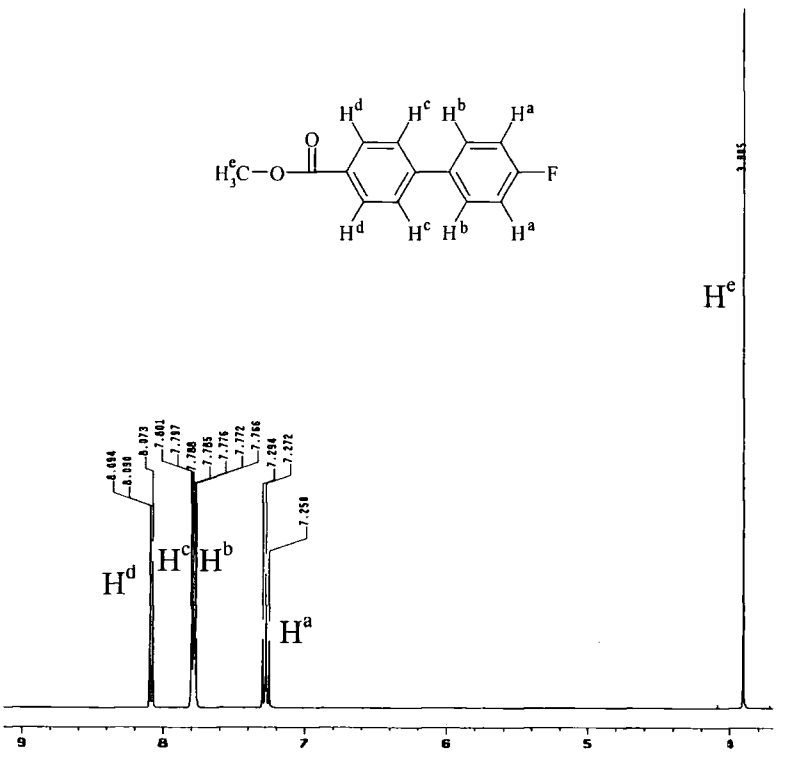


Figure 3.17 ^{1}H NMR spectrum of 4-fluoro-biphenyl-4'-carboxylic acid methyl ester

The ^{13}C NMR spectrum showed ten signals in total, four of which were doublets due to splitting by the fluorine atom. The quaternary carbon in the *ipso*

position was found to have a C-F coupling constant of 245 Hz, which is in agreement with the literature value quoted for this fragment.[20] The carbons in the *ortho* and *meta* positions were found to have 2nd and 3rd order C-F coupling constants of 21 Hz and 8 Hz respectively, which were also in agreement with the values quoted. Similarly, the quaternary carbon in the *para* position was split by the fluorine atom, resulting in a doublet with a 4th order coupling constant of 2.9 Hz. Part of this doublet was masked by a singlet, which was believed to represent the quaternary carbon on the adjacent phenyl ring. The NMR spectroscopy data was further supported by MS analysis of the fraction, which displayed the molecular ion *m/z* (EI) 230. An impurity with a retention time of 7.3 min (by preparative HPLC) constituted 12% of the crude product. When analysed by ^{1}H NMR, the isolated material exhibited multiplet signals in the aromatic region and also a singlet at 3.9 ppm, which was attributed to the methoxy ester protons. It was thought that this compound was formed as a result of the coupling of a different isomer of 4-flurobenzeneboronic acid. It was difficult to determine the structure of the compound by NMR spectroscopy alone, therefore, the fraction was analysed by MS. A spectrum produced in positive electron ionisation mode revealed that the material had a molecular ion of 336. This was further supported by the results of the electrospray spectrum which displayed signals at 359 (M+23), 391 (M+23+32) and 695 (2M+23). The molecular weight of the biaryl product is 230 g mol^{-1}, therefore, a product produced by a different isomer of the boronic acid should also have a molecular weight of 230 g mol^{-1}. However, this by-product had a greater molecular mass than the product. From the investigation undertaken into the possible by-products of the coupling reaction (section 3.3.1), this peak could not be attributed to any of the proposed impurities. The possible products from the self-coupling of 4-fluorobenzeneboronic acid and the cyclic trimeric anhydride, which accompanies the acid, are shown in *Figure 3.18*. A ^{19}F NMR spectrum of the isolated fraction was obtained in order to observe how many fluorine atoms were present. It appeared that no fluorine atoms were present in the by-product and due to the small amount of material isolated, a ^{13}C NMR spectrum could not be obtained. Hence, identification of the impurity was inconclusive.

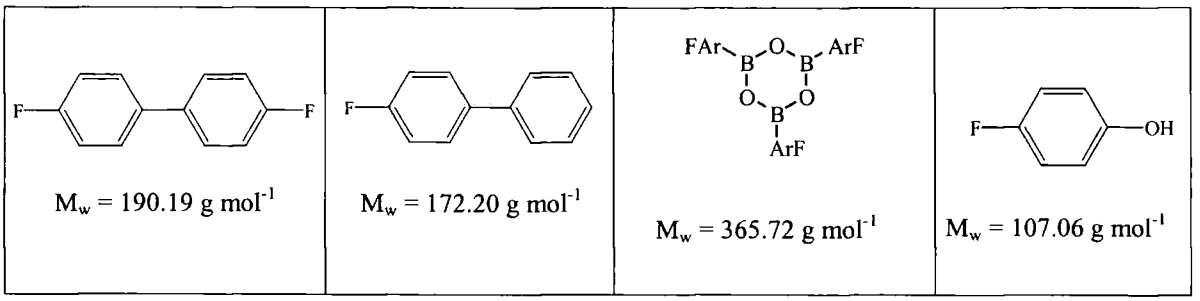


Figure 3.18 Possible by-products from the self-coupling of 4-fluorobenzeneboronic acid

Similar results were observed for the crude product synthesised on the cubic PolyHIPE. As before, the purity was determined by preparative and analytical HPLC. From the mass recovered by the preparative procedure, the yield of the pure biaryl **(3)** was calculated to be 73%. ^{1}H and ^{13}C NMR spectra confirmed that this fraction was indeed compound **(3)**. The fraction was re-analysed by analytical HPLC to verify that its retention time corresponded with that of the original HPLC of the crude sample, which it did. The common impurity was present in the crude product in 21% abundance. As before, this fraction was isolated and characterised by ^{1}H NMR and an identical spectrum was obtained as in previous reactions. Very few signals were displayed, supporting the theory that the impurity was an inorganic species. The impurity obtained from the granular support, with a retention time of 7.3 min (by preparative HPLC), was also evident in this product but to a lesser extent (6%). Unfortunately, the small amount of material available made attempts to characterise the impurity impossible.

3.4.4 Conclusions

Suzuki coupling conditions were developed and successfully applied in supported batch reactions involving granular and cubic forms of PolyHIPE. High yields of pure biaryls were obtained from the coupling of three different boronic acids (*Table 3.6*).

Table 3.6 Pure yields obtained from the coupling of various types of boronic acid on granular and cubic PolyHIPE

Boronic acid substituent	Yield of pure product (%)	
	Granular PolyHIPE	Cubic PolyHIPE
MeO-	70	93
NO_2-	72	81
F-	82	73

In the cases involving the methoxy- and nitro- boronic acids, higher yields of product were obtained with the cubic form of PolyHIPE than the granular form. This trend was reversed when 4-fluorobenzeneboronic acid was employed as the coupling substrate. In terms of the electronic effects of the substituents, it seemed that the electron-rich compound, 4-methoxybenzeneboronic acid, had coupled to the greatest extent and had produced the highest yield of pure biaryl product. The electron-deficient boronic acids performed comparably with each other, however, both yielded less pure product than the corresponding electron-rich acid. Electron-deficient boronic acids have also been reported to be less successful in solution phase Suzuki couplings.[13]

Identification of the major reaction impurity, which was detected in the majority of cleaved products, proved to be challenging. Separation of the impurity fraction by preparative HPLC, and subsequent analysis, revealed nothing more than an inorganic residue. This was possibly a by-product from the catalyst, $Pd(PPh_3)_4$, employed in the couplings.

3.5 Application of Optimised Batch Conditions to Argopore®-Cl Polymer Beads

The performance of PolyHIPE as a support in batch Suzuki coupling reactions was compared to that of commercial chloromethyl polymer beads (ArgoPore®-Cl) (*Figure 3.19*). It was believed that the highly porous, permeable nature of PolyHIPE would result in a greater overall conversion to the biaryl product.

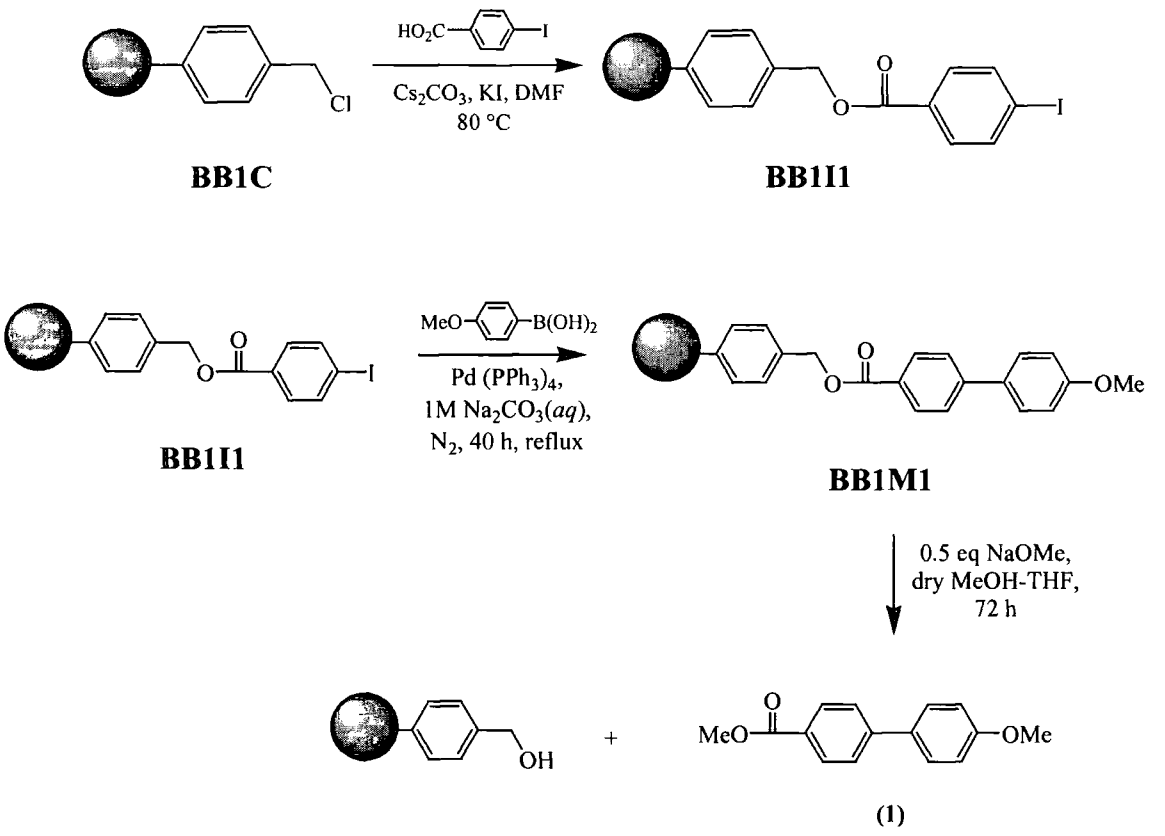


Figure 3.19 Bead-supported synthesis of 4-methoxy-biphenyl-4'-carboxylic acid methyl ester

Macroporous polystyrene beads (highly cross-linked with divinylbenzene and functionalised with chloromethyl functionality, to yield 1.2 mmol $-CH_2Cl$ groups g^{-1}) were reacted with 4-iodobenzoic acid under identical conditions to those applied to PolyHIPE. Mass recovery of the beads revealed a 79% yield of acid coupled product and a strong, sharp peak at 1725 cm^{-1} in the FTIR spectrum was attributed to the carbonyl peak of the newly formed ester bond, confirming that the attachment of the acid had taken place successfully. The conversion to iodine however, was calculated to be 59%, which is slightly lower than the average conversion obtained on PolyHIPE (65%).

The optimised conditions developed for PolyHIPE were utilised in the coupling of **BB1I1** (0.57 mmol -I groups g^{-1}) with 4-methoxybenzeneboronic acid. Conversion to the bead-bound coupled product **BB1M1** was calculated to be 70% and subsequent cleavage of the support with NaOMe resulted in a crude biaryl yield of 111% (based on the loading of iodine). The high yield inferred that impurities were present in the product, however, these were not apparent from the ^{1}H and ^{13}C NMR

spectra of the material. High performance liquid chromatography (HPLC) analysis revealed that the biaryl ester **(1)** (retention time of 8.9 min) accounted for 65% of the crude product and a single impurity with a retention time of 2.8 min constituted the remainder. In order to identify the impurity, the product was analysed by liquid chromatography-mass spectroscopy (LC-MS). In electro spray (ES-) mode, the spectrum showed a high intensity signal at 3.2 min with an *m/z* value of 227, which corresponds to $(M-H)^-$. This indicated that a molecular ion of 228 was present. This was discovered to be the molecular mass of the biaryl carboxylic acid product, suggesting that hydrolysis of the ester linkage had occurred during cleavage. Interestingly, the biaryl ester product was not detected by LC-MS in ES- or ES+ modes. Rather, its presence was confirmed by mass spectrometry in electron ionisation mode without chromatography (*m/z* (EI) 242).

In an attempt to obtain an accurate value for the pure yield of the biaryl ester product, preparative HPLC analysis was performed. Upon separation of the fractions, the pure yield of **(1)** was calculated to be 70%. NMR spectroscopy and HPLC analysis proved that the fraction at 8.3 min was indeed the biaryl ester **(1)** (*Figure 3.20*). This yield was found to match exactly with the pure yield of **(1)** synthesised on granular PolyHIPE, however, it was significantly lower than the pure yield obtained with cubic PolyHIPE (93%). The formation of the corresponding carboxylic acid biaryl suggested that the highly porous beads had retained a large amount of water, even after drying under vacuum, resulting in hydrolysis of the ester bond. Compared to both granular PolyHIPE and polymer beads, cubic PolyHIPE proved to be the most successful form of support in the batch Suzuki coupling reactions.

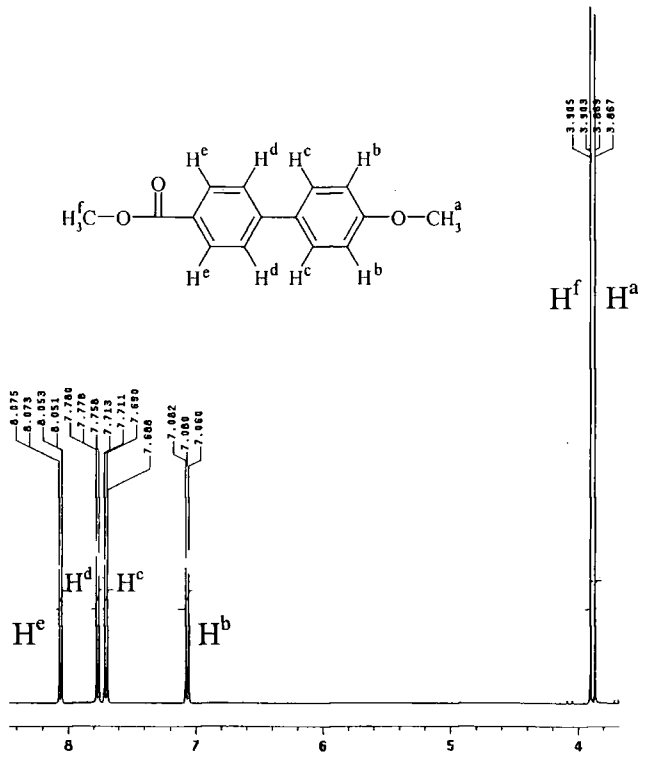


Figure 3.20 ^1H NMR spectrum of 4-methoxy-biphenyl-4'-carboxylic acid methyl ester (1) synthesised on beads

3.6 Strategies for Flow-Through Suzuki Cross-Coupling

Since both granular and cubic PolyHIPE proved to be successful supports for Suzuki coupling in batch systems, the intention was to demonstrate that the reaction could also be applied to PolyHIPE monoliths in flow-through systems. Continuous flow procedures involving macroporous monoliths and polymer composites have previously been discussed (section 1.5.2). Indeed, poly(styrene/DVB) PolyHIPE has been utilised in a flow-through method (section 1.6.5). In this study, VBC/DVB (78:22 wt%) HIPE was polymerised inside fritted PTFE tubes for use in the Quest parallel synthesiser (this flow-through method is described in chapter 2). The resultant PolyHIPE monoliths were found to have an average BET surface area (two runs) of 11.8 ± 2.1 m^2 g^{-1} and an average pore diameter of 16.1 ± 0.3 nm. PTFE tubes were also loaded with macroporous polymer beads for a comparative study in the Quest flow-through system. The average BET surface area of the beads was measured and found to be far greater than the PolyHIPE (785.1 ± 13.9 m^2 g^{-1}). However, the average pore diameter of the beads (8.4 ± 0.01 nm) was approximately half that of the PolyHIPE material.

3.6.1 PolyHIPE-Supported Flow-Through Suzuki Synthesis via the Quest System

The flow-through synthesis on the Quest began by attaching 4-iodobenzoic acid onto the chloromethyl groups of monolith **P78B3$_m$C** (3.7 mmol -CH_2Cl groups g^{-1}). A DMF solution of the acid, together with Cs_2CO_3 and KI, was used to fill the 'head-space' above the monolith, and this was allowed to flow-through the PolyHIPE under gravity at 80 °C. The reagent solution (10 mL) was collected over a 45 min period and manually recycled back into the top of the reactor tube. This procedure was repeated for 8 h at an approximate flow-rate of 0.2 mL min^{-1}. The PolyHIPE monolith was immersed in the reagent solution at 80 °C for a further 16 h. This resulted in a conversion to iodine of 74%, which was significantly higher than the average conversions obtained in the batch reactions (65%). The optimised coupling conditions, which were found to be the most efficient in batch reactions, were then applied to the flow-through coupling of 4-methoxybenzene boronic acid.

Dry DME was added to the head-space above monolith **P78B3$_m$I1** (1.6 mmol -I groups g^{-1}) and the Quest apparatus was darkened with aluminium foil and heated to 85 °C. Laboratory synthesised catalyst, $Pd(PPh_3)_4$, was added initially and allowed to penetrate the monolith for 5 min. Separately, 4-methoxybenzeneboronic acid was dissolved in a degassed solution of 1M $Na_2CO_3(aq)$ and a small amount of dry DME (to aid dissolution). This was added to the 'head-space' of the reactor tube and the reagent solution was passed through the monolith under low pressure (*ca.* 9 psi was applied by the Quest system) for 45 min. The retrieved solution was manually recycled back into the top of the reactor tube and either flowed through the monolith (*ca.* 0.2 mL min^{-1}) or allowed to saturate it (14 h), for a total of 36 h.

Cleavage of the material was achieved by flowing through a 2 M solution of NaOMe at 65 °C, for 24 h. This initial treatment resulted in a 21% yield of crude product **(1)**, the purity of which appeared to be high by ^1H NMR analysis. Analytical HPLC showed the actual purity of the product to be 60%. As with the batch reactions, it was necessary to re-cleave the PolyHIPE to ensure complete removal of the biaryl product. A second cleave resulted in the formation of additional crude product **(1)** (*Figure 3.21*), the purity of which was found to be 54% by analytical HPLC.

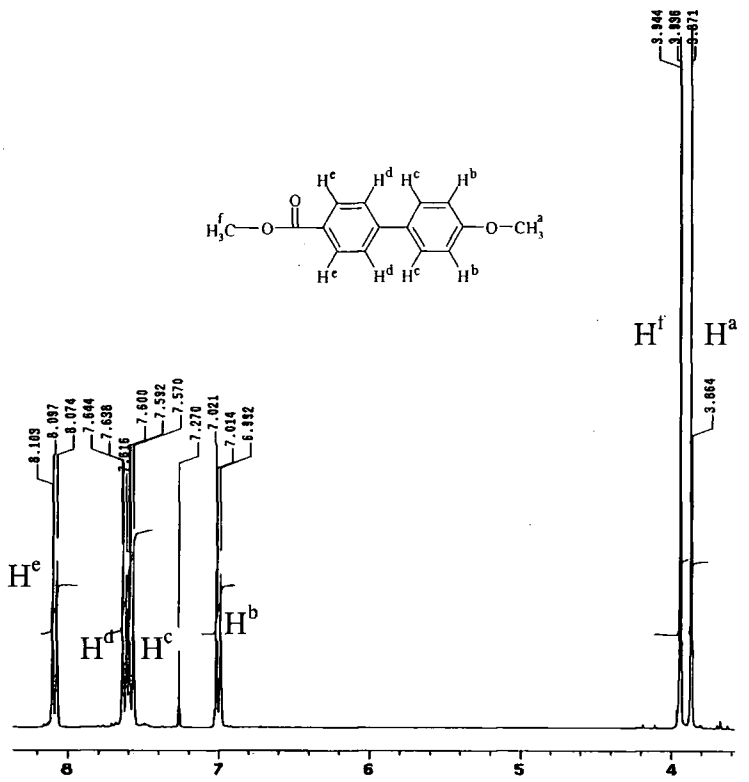


*Figure 3.21 ^1H NMR spectrum of crude product **(1)** obtained from the PolyHIPE-supported flow-through Suzuki synthesis*

Summarised in *Table 3.7*, are the cleavage conditions employed together with the amounts of crude product obtained. The total amount of crude product cleaved from the monolith was found to be 172 mg, which corresponded to a yield of 141%. The white crude product obtained from the last cleavage was found to dissolve only partially in $CDCl_3$. The undissolved solid was thought to be NaOMe, due to the high excess of the material used in the final cleavage. From the amounts of crude product obtained and their relative purities, the pure yield of **(1)** from the flow-through synthesis was estimated to be 63%.

Table 3.7 Crude amounts and purities obtained after cleavage

Cleavage conditions	Amount of crude product obtained (mg)	Purity by HPLC (%)
0.1 eq 2 M NaOMe, 24 h	25	60
0.1 eq 2 M NaOMe, 72 h	51	54
1.0 eq 2 M NaOMe, 24 h	96	35

3.6.2 Bead-Supported Flow-Through Suzuki Synthesis via the Quest System

Since the Quest system proved to be a viable means by which to demonstrate the Suzuki flow-through synthesis on a monolithic PolyHIPE support, a comparative study was undertaken with commercial polymer beads. In order to allow a fair comparison between the two types of support, identical conditions and procedures were applied to the beads as were employed in section 3.6.1. It was hoped that this experiment would highlight some of the problems associated with beads in flow-through applications, such as channelling of the reagent solution around the beads rather than through them. This would be reflected in the conversion at each stage and the overall amount of product from the reaction.

As with the PolyHIPE monolith, the flow-through synthesis began by attaching 4-iodobenzoic acid onto the chloromethyl groups of Argopore-Cl polymer beads (1.2 mmol $-CH_2Cl$ groups g^{-1}). A DMF solution of the acid, together with Cs_2CO_3 and KI, was used to fill the 'head-space' above the monolith, and this was allowed to flow-through the PolyHIPE under gravity at 80 °C. As with PolyHIPE, constant recycling and immersion of the reagent solution was performed over 24 h. This resulted in a very disappointing conversion to iodine groups of 42%, which was significantly lower than the corresponding conversion obtained with monolithic PolyHIPE. This was the first indication that incomplete reactions were occurring on the beads, possibly as a result of the channelling effect. The coupling of 4-methoxybenzene boronic acid to **BB1I2** was carried out in the established flow-through manner, and cleavage was performed in stages as with the PolyHIPE support. A slightly lower equivalent of reagents was used than that employed in the PolyHIPE flow-through synthesis due to the actual iodine content of the beads being slightly higher than the amount quoted initially by elemental analysis. This was not thought to have a detrimental effect as the reaction was still performed using an excess of reagents and catalyst.

The initial cleavage of **BB1M2** resulted in a 22% yield of crude product. ^1H NMR analysis showed that biaryl ester **(1)** had been obtained, however, there were also peaks of lower intensity apparent in the region between 7 and 8 ppm, which were thought to be impurities. Analytical HPLC revealed the actual purity of the product to be 48%. As with the PolyHIPE reaction, the beads were cleaved a further two times to ensure complete removal of the biaryl product. Summarised in *Table 3.8*, are the cleavage conditions employed together with the amounts of crude product obtained.

Figure 3.22 shows the ^{1}H NMR spectrum of the product obtained from the second cleave of the beads. The total amount of crude product cleaved was found to be 49 mg, which corresponded to a yield of 167% (based on the loading of iodine on the beads). The white crude product obtained from the last cleavage was found to dissolve only partially in $(CD_3)_2CO$. As in the PolyHIPE reaction, the undissolved solid was thought to be NaOMe, due to the high excess of the material used in the final cleavage. From the amounts of crude product obtained and their relative purities, the pure yield of **(1)** was estimated to be 95%, based on the loading of iodine.

Table 3.8 Crude amounts and purities obtained after cleavage of beads

Cleavage conditions	Amount of crude product obtained (mg)	Purity by HPLC (%)
0.1 eq 2 M NaOMe, 24 h	6	48
0.1 eq 2 M NaOMe, 72 h	15	71
1.0 eq 2 M NaOMe, 24 h	28	52

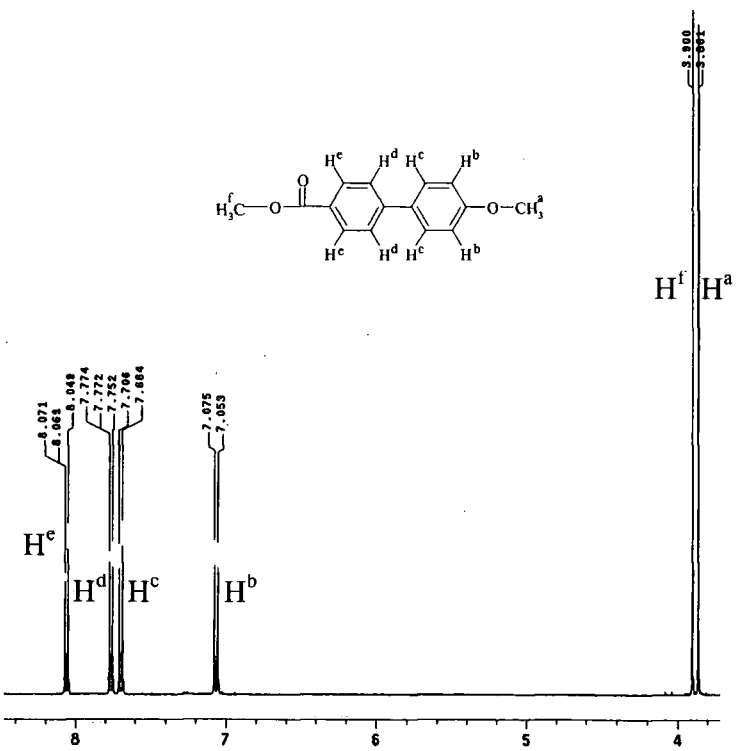


Figure 3.22 ^{1}H NMR spectrum of crude product (1) obtained from the bead-supported flow-through Suzuki synthesis

3.6.3 Conclusions on Quest Flow-Through Reactions

The yield of pure biaryl obtained from the flow-through reaction on the beads was found to be significantly higher than the yield obtained with the PolyHIPE monolith. However, a very small percentage of 4-iodobenzoic acid was loaded onto the beads in the first instance. As a consequence of the channelling effect, only the chloromethyl groups on the surface of the beads were believed to react, hence the low conversion to iodine. Due to the high accessibility of the surface groups to by-passing reagent solution, successful coupling on the beads was expected. Indeed, this was reflected in the high yield of product obtained. In order to compare the efficiencies of the two types of support, a more accurate approach involved examining the amount of material produced in each case. The same loading of chloromethyl groups was employed in each experiment, yet a significantly lower amount of pure product **(1)** (28 mg) was synthesised on the beads, than on the PolyHIPE monolith (76 mg). Therefore, under identical flow-through conditions, PolyHIPE converted a greater amount of chloromethyl groups into biaryl product than macroporous beads, making it a much more efficient form of support material.

3.7 Development of an Automatic Recyclable Flow-Through System

The Quest flow-through system was effective in demonstrating that HIPEs could be polymerised inside tubes to create monoliths suitable for use as supports in flow-through Suzuki cross-coupling reactions. However, a limitation of this system was that the reagent solution could not be automatically recycled or pumped through the monolith, rather, manual recycling of the solution was required. In order to optimise fully the advantages of automation and flow-through procedures, it seemed convenient to polymerise HIPE inside a column or tube which could be attached to a pump, allowing reagents to be pushed through the monolith under pressure. Ideally, the reagent solution was to be recycled through the monolith several times, to ensure complete reaction in a shorter time. It was believed that HIPEs could be polymerised inside stainless steel columns for this purpose, and that the reagent solution could be forced through the pores of the resultant monolith by means of an HPLC pump. Initially, a peristaltic pump was employed for this purpose, however, high backpressures and leakage as a result of loose fittings, made this approach unsuccessful.

3.7.1 Strategy for the Attachment of 4-Iodobenzoic Acid

With the intention of performing a comparative flow-through Suzuki synthesis with commercial beads (1.2 mmol -CH_2Cl groups g^{-1}), HIPE containing 23 wt% VBC monomer, **P23B1C**, was prepared, which provided a PolyHIPE with a loading of 1.39 mmol -CH_2Cl groups g^{-1}. The HIPE was injected into HPLC columns (*Figure 3.23*) and polymerised in a vertical position to ensure uniform packing of the emulsion. After polymerisation, each column was immersed in a hot water bath (60 °C) then subsequently flushed with hot water (20 mL, 1 mL min^{-1}, back pressure of 20 bar), and hot IPA/H_2O (50:50) (70 mL, 1.5 mL min^{-1}, back pressure of 30 bar), using a Kratos Spectroflow HPLC pump.

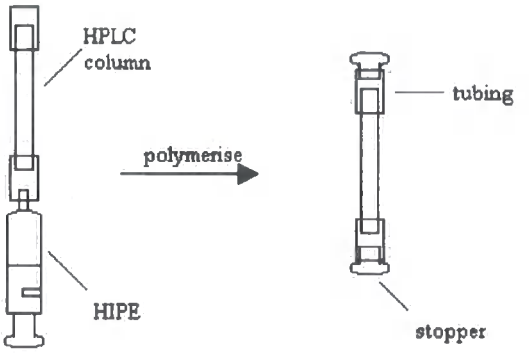


Figure 3.23 Preparation of VBC/DVB PolyHIPE inside a stainless steel HPLC column

The original system developed involved heating the reaction flask and pumping the reagent solution through a PolyHIPE-filled column immersed in a water bath. The outlet tubing of the column was subsequently fed back into the flask containing the reaction mixture, to be recycled back through the column (*Figure 3.24*).

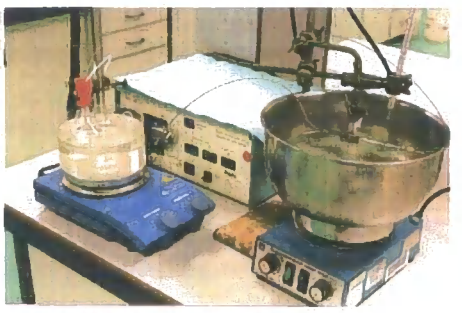


Figure 3.24 Photograph of the original automatic flow-through system developed

The initial intention of this work was to perform kinetic studies comparing the efficiencies of monolithic PolyHIPE with polymer beads under flow-through. The first stage involved loading the monolith with 4-iodobenzoic acid. In batch reactions, attachment of the carboxylic acid onto the chloromethyl groups was readily achieved by heating PolyHIPE in DMF with the cesium salt of the acid, in the presence of potassium iodide (*Figure 3.25*). In the flow-through system, it was believed that the extent of acid attachment could be determined by monitoring regularly the change in the concentration of the cesium salt in solution. UV analysis was used to construct a calibration curve of the carboxylate salt species (*Figure 3.26*), and this was then used to measure periodically the concentration of the species in solution at a fixed wavelength.

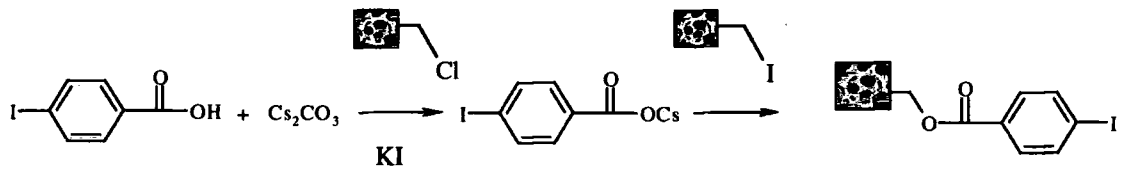


Figure 3.25 Reaction of cesium carboxylate salt with chloromethyl groups

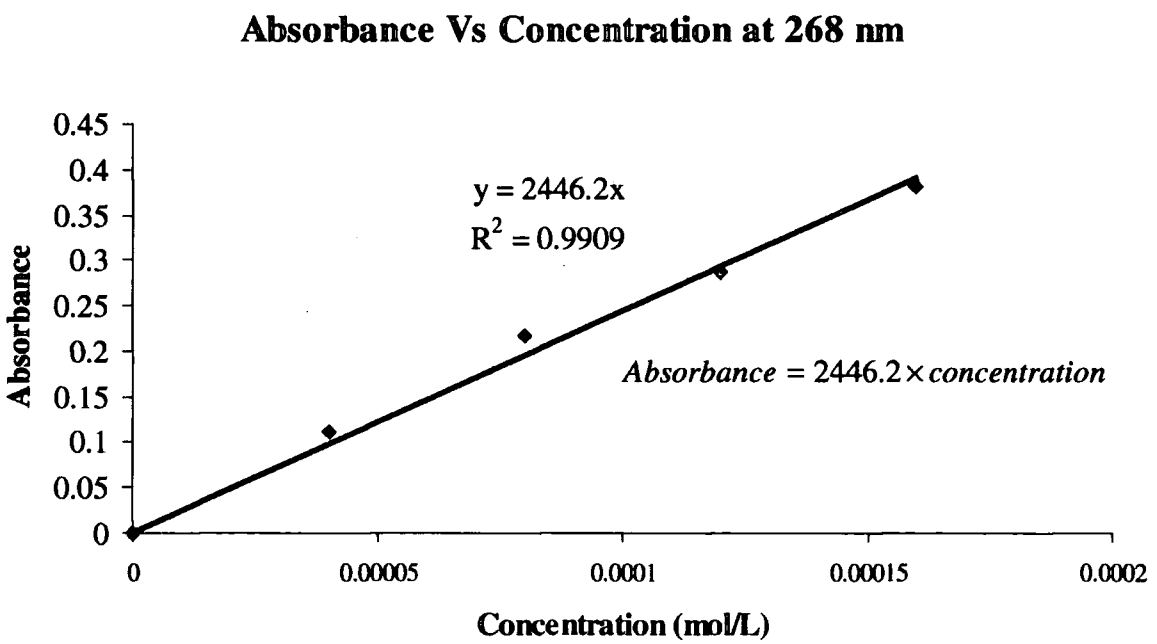


Figure 3.26 Calibration curve of cesium carboxylate salt in solution

The reaction solvent, DMF, was initially pumped through the HPLC column containing PolyHIPE, **P23B1$_m$C** (0.22 g, 0.32 mmol -CH_2Cl groups) to 'wet' the

monolith. Simultaneously, the acid-base reaction was initiated and allowed to continue for 1.5 h (this was the amount of time determined previously for the carboxylate salts to form). The concentration of the species in the system before the flow-through synthesis began was recorded as t_0. The reagent solution was then pumped continuously through the monolith (flow-rate set at 6 mL min^{-1}, back pressure of 3 bar) and back into the reaction flask, where it was sampled every 0.5 h. Unfortunately, few readings were recorded due to blockage of the pump system caused by particulates in the reaction flask. A number of modifications were then made to the flow-through system in an attempt to solve the insolubility problem. These included;

- increasing the reaction temperature
- employing a reaction flask fitted with a filtration device
- lagging of the tubing to avoid crystallisation of reagents

A dual-compartment flask fitted with a sinter filter was made to ensure that only clean solution was pumped through the monolith (*Figure 3.27*).

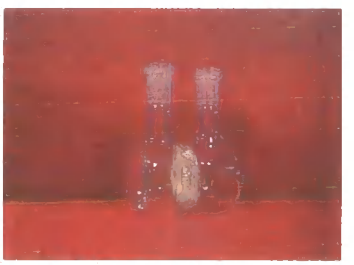


Figure 3.27 Dual compartment flask with filter frit

The temperatures of both the reaction flask and column were increased from 80 °C to 100 °C, and tubing was lagged with glass wool to minimise heat losses. These modifications appeared to improve the flow-through procedure as UV readings were successfully recorded over a 24 h period. However, an unexpected increase in the concentration of the carboxylate salt was plotted over this time (*Figure 3.28*), suggesting that another product was being formed during the reaction, which was interfering with the UV signals obtained.

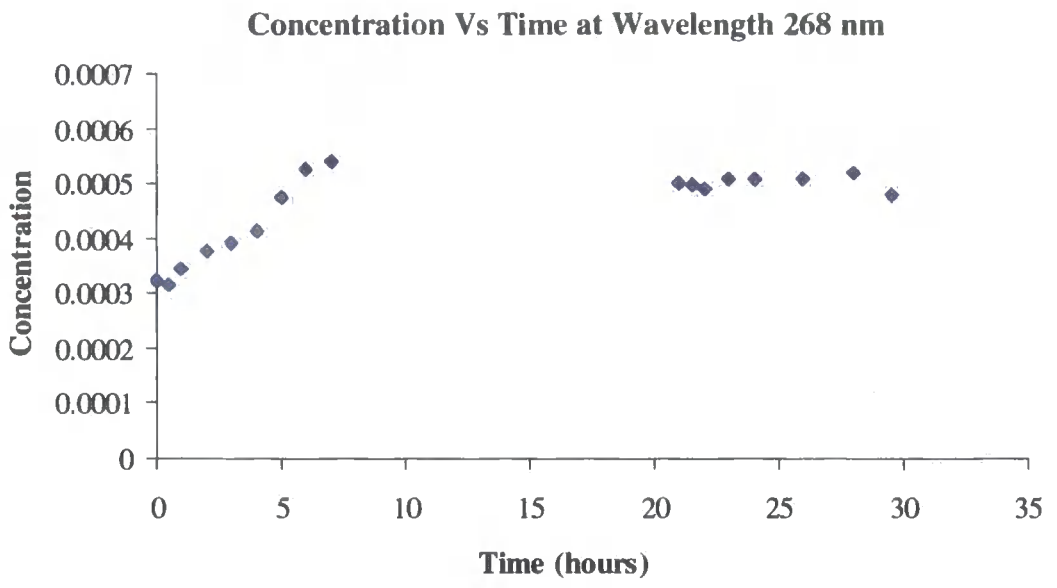


Figure 3.28 Graph of concentration of cesium carboxylate salt against flow-through time

3.7.2 Strategy for Automatic Flow-Through Suzuki Synthesis

Despite this surprising data, the flow-through coupling of 4-methoxybenzeneboronic acid was undertaken using the apparatus shown in *Figure 3.29.*

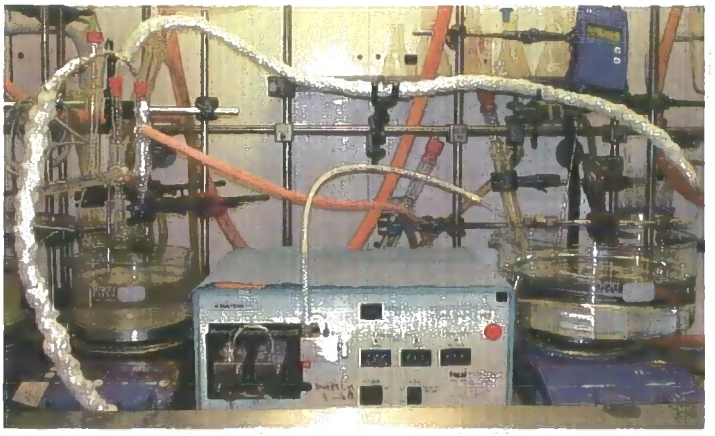


Figure 3.29 Apparatus used in the flow-through Suzuki Synthesis

Initially, the reaction solvent, DME, was flushed with nitrogen gas and pumped through the system. A DME solution of the reagents was added to one compartment of the flask and solution was pumped from the adjacent side into the column (4 mL min^{-1}, back pressure of 5 bar). This method seemed to be successful initially, until the

filter frit inside the flask became blocked with particulates, thus preventing solution from passing into the adjacent compartment. The surfaces of the frit were cleaned and the flow-rate was decreased to 2 mL min^{-1} to minimise build up of particulates on the frit. Further attempts to couple the boronic acid under flow-through eventually led to particulates entering the HPLC pump and blocking the system. Upon further inspection, it became apparent that an important valve had been damaged and was irreplaceable due to the age of the pump. This flow-through method had to be abandoned due to the high sensitivity of the HPLC pump to insoluble material. The system was clearly not suitable for the intended application. A more robust pump was required which, simultaneously, provided flow through the monolith in a closed-loop system.

3.8 Experimental

3.8.1 Chemicals

Starting materials were purchased from Aldrich, Lancaster and Acros. Divinylbenzene (80 vol% *m*- and *p*-divinylbenzene, the remainder *m*- and *p*-ethylstyrene), styrene and 4-vinylbenzyl chloride were purified by passing through a column of basic alumina. All other materials were used without further purification. ArgoPore®-Cl polymer beads were purchased from Argonaut and used as received. DMF (HPLC grade), DME, DME (anhydrous), methanol (anhydrous) and DMSO (anhydrous) were used as solvents for the reactions. The THF used was freshly distilled over benzophenone ketyl. Residual palladium was removed by passing through a column of Celite® 545 purchased from Aldrich.

3.8.2 Characterisation

Combustion elemental analysis data (C, H and N) were obtained from an Exeter Analyser CE-440. A Dionex Ion Chromatograph Analyser DX-120 was employed for chlorine, iodine and fluorine determination. FTIR spectra (KBr dics) were recorded on a Perkin Elmer 1600 Series FTIR Spectrometer. NMR spectra were recorded using either a Varian Mercury-200 (^1H at 200 MHz and ^{13}C at 50.2 MHz), a Varian Unity-300 (^1H at 299.9 MHz and ^{13}C at 75.4 MHz) or a Varian Mercury 400 (^1H at 400 MHz and ^{13}C at 100 MHz). Deuterated solvents were used as supplied from Aldrich ($CDCl_3$ and $(CD_3)_2SO$) and Apollo (CD_3COCD_3 and CD_3OD).

Chemical shifts (δ) are reported in parts per million (ppm) with respect to an internal reference of tetramethylsilane (TMS), and using residual solvent signals as secondary references.

For gas chromatography electron ionisation (GC EI), a Micromass Autospec instrument was used. A Micromass LCT instrument was employed for electrospray mass spectra (ES MS) and a Waters 600 LC instrument was used in conjunction with a Waters 2700 Autosampler, for liquid chromatography mass spectra (LC MS). Analytical and preparative high performance liquid chromatography (HPLC) was carried out using Varian Star instruments. Surface area measurements were carried out using a Micromeritics Tristar 3000 Surface Area and Porosimetry Analyser. UV absorbencies were recorded on a Pye Unicam UV/VIS Spectrophotometer.

3.8.3 Procedures for the Preparation of Poly(4-Vinylbenzyl Chloride-*co*-Divinylbenzene) PolyHIPE

3.8.3.1 Preparation of P78B1C

The quantities used in the preparation of PolyHIPE **P78B1C** are outlined in chapter 2 (section 2.6.3.3). Granular PolyHIPE **P78B1$_g$C** was obtained by grinding sections of the monolith in a coffee grinder, while cubic pieces, **P78B1$_c$C** (*ca.* 1cm^3), were cut from the monolith using a scalpel. Found C, 75.1; H, 6.3; Cl, 15.2%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3402br (OH), 2923s and 2852w (CH), 1610w and 1510m (aryl C=C), 1265s (CCl), 835s (*p*-disubstituted benzene ring).

3.8.3.2 Preparation of P78B2C

P78B2C was prepared according to the standard procedure described in chapter 2 (section 2.6.3.1). Quantities used were; 4-VBC (8.1 g, 0.05 mol), DVB (2.3 g, 0.019 mol), Span 80 (1.97 g, 4.6 mmol), aqueous phase (90 mL). **P78B2$_g$C** and **P78B2$_c$C** were obtained as described in section 3.8.3.1. Found C, 77.2; H, 6.7; Cl, 15.5%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3446br (OH), 2923s and 2852w (CH), 1610w and 1509m (aryl C=C), 1265m (CCl), 825m (*p*-disubstituted benzene ring).

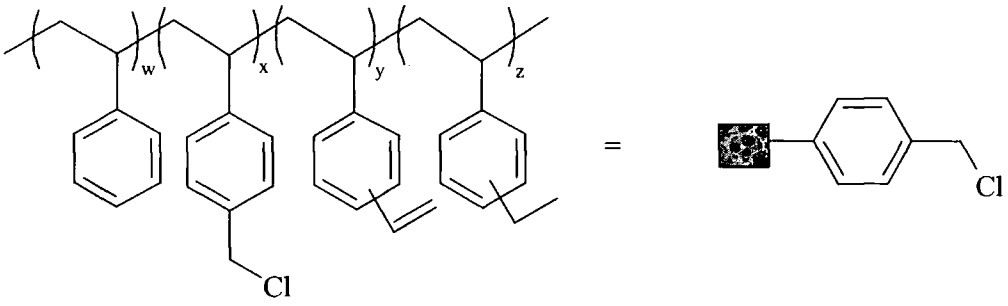
3.8.3.3 Preparation of P78B3C

P78B3C was prepared according to the standard procedure. Quantities used were; 4-VBC (8.1 g, 0.05 mol), DVB (2.3 g, 0.019 mol), Span 80 (1.97 g, 4.6 mmol), aqueous phase (90 mL). **P78B3$_g$C** and **P78B3$_c$C** were obtained as described previously and **P78B3$_m$C** was prepared inside Quest tubes according to the procedure described in chapter 2 (section 2.6.3.2). Found C, 72.2; H, 6.8; Cl, 14.0%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923s and 2853w (CH), 1610w and 1509m (aryl C=C), 1265m (CCl), 834m (*p*-disubstituted benzene ring).

3.8.3.4 Preparation of P78B4C

P78B4C was prepared according to the standard procedure. Quantities used were; 4-VBC (8.1 g, 0.05 mol), DVB (2.3 g, 0.019 mol), Span 80 (1.97 g, 4.6 mmol), aqueous phase (90 mL). **P78B4$_g$C** and **P78B4$_c$C** were obtained as described previously. Found C, 76.8; H, 6.5; Cl, 16.0%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3446br (OH), 2923s and 2852w (CH), 1610w and 1510m (aryl C=C), 1265s (CCl), 834m (*p*-disubstituted benzene ring).

3.8.3.5 Preparation of P23B1C



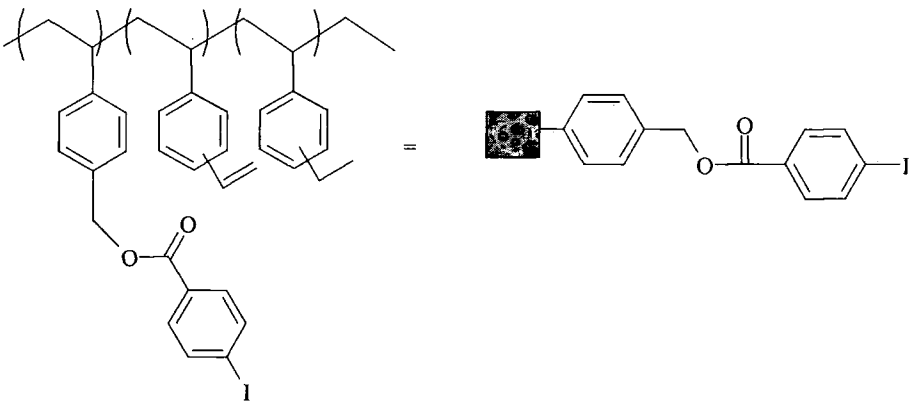
P23B1C

P23B1C was prepared according to the standard procedure. Quantities used were; 4-VBC (1.08 g, 7.1 mmol), DVB (1.14 g, 8.8 mmol), styrene (2.5 g, 0.02 mol), Span 80 (0.99 g, 2.3 mmol), aqueous phase (45 mL). The emulsion was poured into a 100 mL glass syringe, containing a pressure release vent, and injected into stainless steel HPLC columns (4.6 mm ID x 1/4' OD x 15 cm). The columns were tapped

several times to allow the emulsion to spread uniformly and to remove any air bubbles. The HIPEs were polymerised in a vertical position in an oven at 60 °C for 48 h. The columns containing monolith, **P23B1$_m$C**, were fitted with HPLC tubing and immersed in a hot water bath (60 °C). Hot water (20 mL, 1 mL min^{-1}) was pumped through each column followed by hot IPA/H_2O (50:50) (70 mL, 1.5 mL min^{-1}). One of the monoliths was dried *in vacuo* at 50 °C for 48 h for analysis purposes. Found C, 85.8; H, 7.4; Cl, 4.9%. Calculated for $(C_8H_8)_{0.53}(C_9H_9Cl)_{0.23}(C_{10}H_{10})_{0.19}(C_{10}H_{12})_{0.05}$, C, 84.8; H, 8.6; Cl, 6.6%. IR (KBr disc) υ_{max}/cm^{-1} 3446br (OH), 2923s and 2852w (CH), 1610w and 1510m (aryl C=C), 1265m(CCl), 834m (*p*-disubstituted benzene ring).

3.8.4 Procedures for the Batch Synthesis of Polymer-Supported 4-Iodobenzoic Acid

3.8.4.1 Synthesis of P78B2$_g$I1



P78B2$_g$I1

Granular PolyHIPE, **P78B2$_g$C** (0.5 g, 2.2 mmol –CH_2Cl groups) was placed in a 50 mL round-bottomed flask, to which cesium carbonate (2.15 g, 6.6 mmol), potassium iodide (0.18 g, 1.1 mmol), 4-iodobenzoic acid (0.82 g, 3.3 mmol) and DMF (20 mL) were added. The flask was fitted with a reflux condenser and the reaction mixture was heated at 80 °C for 24 h. The suspension was filtered and the PolyHIPE was washed thoroughly with DMF (3 x 25 mL), THF/H_2O (1:1, 2 x 25 mL), DCM (2 x 25 mL) and methanol (2 x 25 mL). The material was dried *in vacuo* at 50 °C for 24 h to give **P78B2$_g$I1** (0.65 g, 67% conversion by weight). Found I, 19.8; Cl, 1.1%. Calculated I, 28.8; Cl 0% (69% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3425br (OH),

2923s and 2853w (CH), 1721s (C=O), 1583m (aryl C=C), 1268s (CCl), 823w (*p*-disubstituted benzene ring), 580br (CI).

3.8.4.2 Synthesis of P78B2$_c$I1

The procedure was as described for the synthesis of **P78B2$_g$I1**, using cubic PolyHIPE **P78B2$_c$C** (0.5 g, 2.2 mmol $-CH_2Cl$ groups) as the support, to give **P78B2$_c$I1** (0.85 g, 88% conversion by weight). Found I, 19.3; Cl, 1.4%. Calculated I, 28.8; Cl 0% (67% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3425br (OH), 2923m and 2853w (CH), 1721s (C=O), 1586m (aryl C=C), 1268s (CCl), 823w (*p*-disubstituted benzene ring), 580br (CI).

3.8.4.3 Synthesis of P78B3$_g$I1

P78B3$_g$I1 was prepared as outlined in section 3.8.4.1. Quantities used were; **P78B3$_g$C** (1 g, 3.95 mmol $-CH_2Cl$ groups), Cs_2CO_3 (3.86 g, 11.85 mmol), KI (0.33 g, 1.98 mmol), 4-iodobenzoic acid (1.47 g, 5.93 mmol), DMF (35 mL). **P78B3$_g$I1** (1.22 g) was produced in 66% yield (conversion by weight). Found I, 14.4; Cl, 1.2%. Calculated I, 27.0; Cl 0% (53% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3422br (OH), 2923m and 2853w (CH), 1719s (C=O), 1586m (aryl C=C), 1268s (CCl), 822w (*p*-disubstituted benzene ring), 580br (CI).

3.8.4.4 Synthesis of P78B3$_c$I1

P78B3$_c$I1 was prepared as outlined in section 3.8.4.1. Quantities used were; **P78B3$_c$C** (1 g, 3.95 mmol $-CH_2Cl$ groups), Cs_2CO_3 (3.86 g, 11.85 mmol), KI (0.33 g, 1.98 mmol), 4-iodobenzoic acid (1.47 g, 5.93 mmol), DMF (35 mL). **P78B3$_c$I1** (1.49 g) was produced in 81% yield. Found I, 16.9; Cl, 1.4%. Calculated I, 27.0; Cl 0% (63% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2853w (CH), 1719s (C=O), 1586m (aryl C=C), 1268s (CCl), 822w (*p*-disubstituted benzene ring), 580br (CI).

3.8.4.5 Synthesis of P78B2$_g$I2

P78B2$_g$I2 was prepared as outlined in section 3.8.4.1. Quantities used were; **P78B2$_g$C** (0.5 g, 2.2 mmol $-CH_2Cl$ groups), Cs_2CO_3 (2.15 g, 6.6 mmol), KI (0.18 g, 1.1 mmol), 4-iodobenzoic acid (0.82 g, 3.3 mmol), DMF (20 mL). **P78B2$_g$I2** (0.75 g) was produced in 78% yield. Found I, 19.1; Cl, 1.3%. Calculated I, 28.8; Cl 0% (66%

conversion). IR (KBr disc) υ_{max}/cm^{-1} 3425br (OH), 2923m and 2853w (CH), 1721s (C=O), 1583m (aryl C=C), 1268s (CCl), 823w (*p*-disubstituted benzene ring), 580br (Cl).

3.8.4.6 Synthesis of P78B2$_c$I2

P78B2$_c$I2 was prepared as outlined in section 3.8.4.1. Quantities used were; **P78B2$_c$C** (0.5 g, 2.2 mmol –CH_2Cl groups), Cs_2CO_3 (2.15 g, 6.6 mmol), KI (0.18 g, 1.1 mmol), 4-iodobenzoic acid (0.82 g, 3.3 mmol), DMF (20 mL). **P78B2$_c$I2** (0.73 g) was produced in 76% yield. Found I, 17.2; Cl, 1.2%. Calculated I, 28.8; Cl 0% (60% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3425br (OH), 2923m and 2853w (CH), 1721s (C=O), 1586m (aryl C=C), 1268s (CCl), 823w (*p*-disubstituted benzene ring), 580br (Cl).

3.8.4.7 Synthesis of P78B1$_g$I1

P78B1$_g$I1 was prepared as outlined in section 3.8.4.1. Quantities used were; **P78B1$_g$C** (0.5 g, 2.14 mmol –CH_2Cl groups), Cs_2CO_3 (2.09 g, 6.4 mmol), KI (0.17 g, 1.07 mmol), 4-iodobenzoic acid (0.8 g, 3.21 mmol), DMF (20 mL). **P78B1$_g$I1** (0.77 g) was produced in 81% yield. Found I, 21.0; Cl, 0.78%. Calculated I, 28.5; Cl 0% (74% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3447br (OH), 2923m and 2853w (CH), 1719s (C=O), 1585m (aryl C=C), 1267s (CCl), 823w (*p*-disubstituted benzene ring), 587br (Cl).

3.8.4.8 Synthesis of P78B4$_c$I1

P78B4$_c$I1 was prepared as outlined in section 3.8.4.1. Quantities used were; **P78B4$_c$C** (0.5 g, 2.25 mmol –CH_2Cl groups), Cs_2CO_3 (2.2 g, 6.75 mmol), KI (0.18 g, 1.13 mmol), 4-iodobenzoic acid (0.84 g, 3.38 mmol), DMF (20 mL). **P78B4$_c$I1** (0.86 g) was produced in 88% yield. Found I, 21.1; Cl, 1.0%. Calculated I, 29.3; Cl 0% (72% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3447br (OH), 2923m and 2853w (CH), 1719s (C=O), 1585m (aryl C=C), 1267s (CCl), 823w (*p*-disubstituted benzene ring), 587br (Cl).

3.8.4.9 Synthesis of P78B4$_g$I2

P78B4$_g$I2 was prepared as outlined in section 3.8.4.1. Quantities used were; **P78B4$_g$C** (0.5 g, 2.25 mmol –CH_2Cl groups), Cs_2CO_3 (2.2 g, 6.75 mmol), KI (0.18 g,

1.1 mmol), 4-iodobenzoic acid (0.84 g, 3.38 mmol), DMF (20 mL). **P78B4$_g$I2** (0.83 g) was produced in 85% yield. Found I, 19.6; Cl, 1.8%. Calculated I, 29.3; Cl 0% (67% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2852w (CH), 1719s (C=O), 1586m (aryl C=C), 1268s (CCl), 823w (*p*-disubstituted benzene ring), 584br (CI).

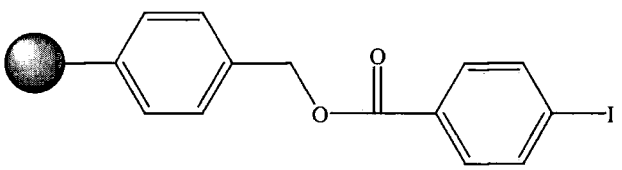
3.8.4.10 Synthesis of P78B4$_c$I2

P78B4$_c$I2 was prepared as outlined in section 3.8.4.1. Quantities used were; **P78B4$_c$C** (0.5 g, 2.25 mmol –CH_2Cl groups), Cs_2CO_3 (2.2 g, 6.75 mmol), KI (0.18 g, 1.1 mmol), 4-iodobenzoic acid (0.84 g, 3.38 mmol), DMF (20 mL). **P78B4$_c$I2** (0.90 g) was produced in 92% yield. Found I, 19.9; Cl, 1.9%. Calculated I, 29.3; Cl 0% (68% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2852w (CH), 1719s (C=O), 1586m (aryl C=C), 1268s (CCl), 823w (*p*-disubstituted benzene ring), 585br (CI).

3.8.4.11 Synthesis of P78B1$_c$I2

P78B1$_c$I2 was prepared as outlined in section 3.8.4.1. Quantities used were; **P78B1$_c$C** (0.5 g, 2.14 mmol –CH_2Cl groups), Cs_2CO_3 (2.09 g, 6.4 mmol), KI (0.17 g, 1.07 mmol), 4-iodobenzoic acid (0.8 g, 3.21 mmol), DMF (20 mL). **P78B1$_c$I2** (0.86 g) was produced in 90% yield (conversion by weight). Found I, 19.4; Cl, 1.3%. Calculated I, 28.5; Cl 0% (68% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3447br (OH), 2923m and 2852w (CH), 1719s (C=O), 1585m (aryl C=C), 1267s (CCl), 823w (*p*-disubstituted benzene ring), 584br (CI).

3.8.4.12 Synthesis of BB1I1

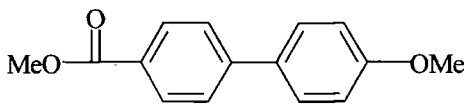


BB1I1

Macroporous chloromethyl polystyrene beads, **BB1C** (0.5 g, 0.6 mmol – CH_2Cl groups) were placed in a 50 mL round-bottomed flask, to which cesium

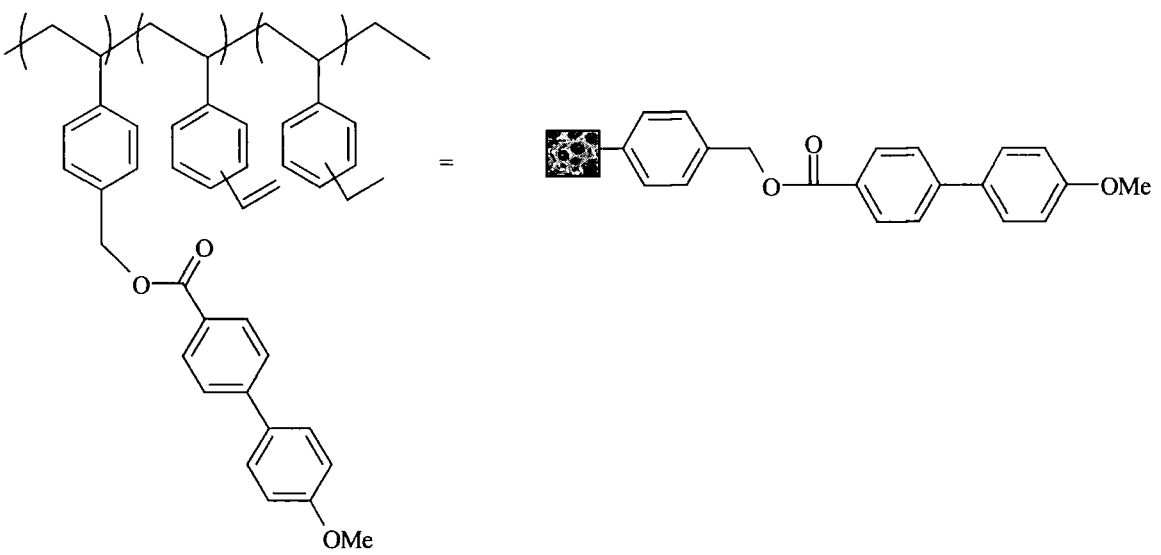
carbonate (0.59 g, 1.8 mmol), potassium iodide (50 mg, 0.3 mmol), 4-iodobenzoic acid (0.22 g, 0.9 mmol) and DMF (10 mL) were added. The flask was fitted with a reflux condenser and the reaction mixture was heated at 80 °C for 24 h. The beads were filtered and washed thoroughly with DMF (3 x 20 mL), THF/H_2O (1:1, 2 x 25 mL), DCM (2 x 20 ml) and methanol (3 x 20ml). The beads were dried *in vacuo* at 50 °C for 24 h to give **BB1I1** (0.49 g, 79% conversion by weight). Found I, 7.2; Cl, 0.9%. Calculated I, 12.2; Cl 0% (59% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3447br (OH), 2927m and 2856w (CH), 1725s (C=O), 1587m (aryl C=C), 1266s (CCl), 827w (*p*-disubstituted benzene ring), 548br (CI).

3.8.5 Procedures for the Batch Synthesis of 4-Methoxy-Biphenyl-4'-Carboxylic Acid Methyl Ester (1)



(1)

3.8.5.1 Synthesis of P78B2$_g$M1 via Suzuki Conditions Reported for Beads



P78B2$_g$M1

P78B2$_g$I1 (0.5 g, 0.78 mmol –I groups) was placed in a 2-necked 50 mL round-bottomed flask fitted with rubber septa. DME (18 mL) was transferred to the flask via syringe and the suspension was degassed with nitrogen gas for 30 min.

Commercially available catalyst $Pd(PPh_3)_4$ (0.13 g, 0.11 mmol) was added and the reaction mixture was stirred for 5 min. This was followed by the addition of 4-methoxybenzeneboronic acid (0.67 g, 4.4 mmol) and a 2M solution of $Na_2CO_3(aq)$ (2.73 mL, 5.46 mmol) via syringe. The flask was fitted with a condenser containing a nitrogen gas inlet and was heated under reflux at 95 °C for 24 h. After cooling, the mixture was diluted by addition of a 25% solution of ammonium acetate (15 mL), and stirred for 5 min. The PolyHIPE was filtered and washed successively with DME/H_2O (1:1, 10 mL), H_2O (20 mL), 0.2M HCl (20 mL), H_2O (20 mL), DME (20 mL), ethyl acetate (20 mL), ethyl acetate/MeOH (1:1, 20 mL) and MeOH (20 mL). This procedure will be referred to as the standard wash procedure in future experiments. The PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B2$_g$M1** (0.46 g, 96% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3431br (OH), 2923m and 2853w (CH), 1719s (C=O), 1604m (aryl C=C), 1268s (CCl), 1100m (CO), 827w (*p*-disubstituted benzene ring), 579w (CI).

3.8.5.2 Cleavage of P78B2$_g$M1 to Yield (1)

P78B2$_g$M1 (0.4 g, 0.62 mmol) was placed in a 50 mL round-bottomed flask to which a solution of 1M NaOMe in dry MeOH (0.18 mL, 0.18 mmol) and dry MeOH/THF (1:4, 18 mL) was added. The flask was fitted with a condenser and the mixture was heated under reflux at 70 °C for 24 h. The PolyHIPE was removed by filtration and washed with MeOH/THF (1:1, 10 mL), THF (10 mL) and MeOH (10 mL). The filtrate and washings were concentrated and the product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h. Due to incomplete cleavage, **P78B2$_g$M1** was cleaved for a second time using 1M NaOMe (0.18 mL, 0.18 mmol) and dry MeOH/THF (1:4, 18 mL). Crude product **(1)** was provided as an orange solid (0.057 g, 38% based on the loading of aryl iodide). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 7.00 (d, J=8.7 Hz, 2H), 7.61 (m, 4H), 8.09 (d, J=8.4 Hz, 2H).

3.8.5.3 Synthesis of P78B2$_c$M1

The procedure was as described for the synthesis of **P78B2$_g$M1**, using **P78B2$_c$I1** (0.6 g, 0.91 mmol –I groups), DME (20 mL), commercially available catalyst $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol), 4-methoxybenzeneboronic acid (0.79 g, 5.2 mmol) and 2M $Na_2CO_3(aq)$ (3.19 mL, 6.37 mmol). The PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B2$_c$M1** (0.5 g, 86% conversion by weight). IR

(KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2853w (CH), 1719s (C=O), 1605m (aryl C=C), 1268s (CCl), 1100m (CO), 823w (*p*-disubstituted benzene ring), 547w (CI).

3.8.5.4 Cleavage of P78B2$_c$M1 to Yield (1)

The procedure was as described for the cleavage of **P78B2$_g$M1**, only the reflux was performed over 72 h. This will now be referred to as the standard cleavage procedure. **P78B2$_c$M1** (0.45 g, 0.68 mmol) was cleaved using 1M NaOMe (0.2 mL, 0.20 mmol) and dry MeOH/THF (1:4, 20 mL). Crude product **(1)** was provided as an orange solid (0.046 g, 28% based on the loading of aryl iodide). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 7.00 (d, J=9.0 Hz, 2H), 7.61 (m, 4H), 8.09 (d, J=8.4 Hz, 2H). Lower intensity signals were also present in the spectrum between 7.00 and 8.00 ppm.

3.8.5.5 Synthesis of P78B3$_g$M1 via Classical Suzuki Conditions

P78B3$_g$I1 (0.25 g, 0.28 mmol –I groups) was placed in a 2-necked 50 mL round-bottomed flask fitted with rubber septa. Dry DME (6 mL) was transferred to the flask via syringe and the suspension was degassed with nitrogen gas for 30 min. The flask was wrapped in aluminium foil and supplied with a continuous flow of nitrogen. Freshly prepared $Pd(PPh_3)_4$ (19 mg, 0.017 mmol) and 4-methoxybenzeneboronic acid (52 mg, 0.34 mmol) were added, and the mixture was stirred thoroughly for 30 min. A 1M aqueous solution of Na_2CO_3 (1 mL, 1 mmol) was degassed and added via syringe. The flask was fitted with a condenser containing a nitrogen gas inlet and the mixture was heated under reflux at 95 °C for 40 h. After cooling, the mixture was diluted by addition of a solution of 25% ammonium actetate (4 mL) and stirred for 5 min. The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B3$_g$M1** (0.22 g, 92% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2853w (CH), 1718s (C=O), 1605m (aryl C=C), 1271s (CCl), 1250m and 1039m (CO) 828w (*p*-disubstituted benzene ring), 547br (CI).

3.8.5.6 Cleavage of P78B3$_g$M1 to Yield (1)

The standard cleavage procedure was applied to **P78B3$_g$M1** (0.2 g, 0.23 mmol), using a freshly prepared solution of 1M NaOMe in dry MeOH (0.11 mL, 0.11

mmol) and dry MeOH/THF (1:1, 6 mL). The PolyHIPE was removed by filtration through Celite and washed with MeOH/THF (1:1, 10 mL), THF (10 mL), and MeOH (10 mL). The solvent was removed using the rotary evaporator and the product was dried under vacuum (10^{-1} mbar), to provide an orange solid (0.049 g, 89% based on the loading of aryl iodide). The crude product had partially dissolved in $CDCl_3$ leaving impurities in the flask. ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 7.00 (d, J=9.0 Hz, 2H), 7.61 (m, 4H), 8.09 (d, J=8.4 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 52.1, 55.4, 114.3, 126.4, 128.0, 128.3, 130.1, 133.0, 145.2, 161.0, 167.0. 4-Methoxy-biphenyl-4'-carboxylic acid methyl ester **(1)** was recovered from $CDCl_3$ to yield a white solid (9.9 mg, 18% based on loading of aryl iodide). GC-MS (EI) *m/z* 242. Calculated for $C_{15}H_{14}O_3$ M_w = 242.27.

3.8.5.7 Synthesis of P78B3$_c$M1

The procedure was as described for the synthesis of **P78B3$_g$M1**, using **P78B3$_c$I1** (0.26 g, 0.33 mmol –I groups), dry DME (6 mL), freshly prepared catalyst $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), 4-methoxybenzeneboronic acid (60 mg, 0.40 mmol) and 1M $Na_2CO_3(aq)$ solution (1.2 mL, 1.16 mmol). The PolyHIPE was washed thoroughly and dried *in vacuo* at 50 °C for 24 h to give **P78B3$_c$M1** (0.20 g, 83% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2853w (CH), 1719s (C=O), 1605m (aryl C=C), 1269s (CCl), 1040m (CO) 827w (*p*-disubstituted benzene ring), 547br (CI).

3.8.5.8 Cleavage of P78B3$_c$M1 to Yield (1)

P78B3$_c$M1 (0.18 g, 0.24 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.12 mL, 0.12 mmol) and dry MeOH/THF (1:1, 6 mL). The product was dried under vacuum (10^{-1} mbar), to provide an orange solid (0.07 g, 120% based on the loading of aryl iodide). The crude product had partially dissolved in $CDCl_3$ leaving impurities in the flask. ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 7.00 (d, J=8.7 Hz, 2H), 7.61 (m, 4H), 8.09 (d, J=8.4 Hz, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 52.1, 55.4, 114.3, 126.4, 128.0, 128.3, 130.1, 133.0, 145.2, 161.0, 167.0. 4-Methoxy-biphenyl-4'-carboxylic acid methyl ester **(1)** was recovered from $CDCl_3$ to yield a white solid (12.8 mg, 22% based on loading of aryl iodide). GC-MS (EI) *m/z* 242. Calculated for $C_{15}H_{14}O_3$ M_w = 242.27.

3.8.5.9 Synthesis of P78B2$_g$M2 via Optimised Suzuki Conditions

The procedure was as described for the synthesis of **P78B3$_g$M1**, using **P78B2$_g$I2** (0.6 g, 0.90 mmol –I groups), dry DME (20 mL), freshly prepared $Pd(PPh_3)_4$ (0.18 g, 0.15 mmol), 4-methoxybenzeneboronic acid (0.48 g, 3.15 mmol) and 1M $Na_2CO_3(aq)$ (9 mL, 9 mmol). After reaction, the mixture was diluted by addition of a solution of 25% ammonium acetate (10 mL) and stirred for 5 min. The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B2$_g$M2** (0.49 g, 83% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3423br (OH), 2925m and 2853w (CH), 1718s (C=O), 1605s (aryl C=C), 1273s (CCl), 1251m and 1039m (CO) 828w (*p*-disubstituted benzene ring), 580br (CI).

3.8.5.10 Cleavage of P78B2$_g$M2 to Yield (1)

P78B2$_g$M2 (0.45 g, 0.68 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.2 mL, 0.2 mmol) and dry MeOH/THF (1:1, 20 mL). Due to incomplete cleavage, **P78B2$_g$M2** (0.32 g, 0.48 mmol) was treated with a second portion of 1M NaOMe (0.4 mL, 0.4 mmol), to provide crude product **(1)** as an orange solid (0.16 g combined, 95% based on the loading of aryl iodide). The crude product was purified by preparative HPLC to give pure **(1)** as a white solid (20.1 mg, 70%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.87 (s, 3H), 3.90 (s, 3H), 7.07 (d, J=8.8 Hz, 2H), 7.70 (m, 2H), 7.77 (m, 2H), 8.05 (d, J=9.2 Hz, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 52.3, 55.7, 115.3, 127.2, 129.1, 129.2, 130.8, 132.8, 146.0, 161.1, 167.1. MS (EI) *m/z* 242. Calculated for M_w = 242.27.

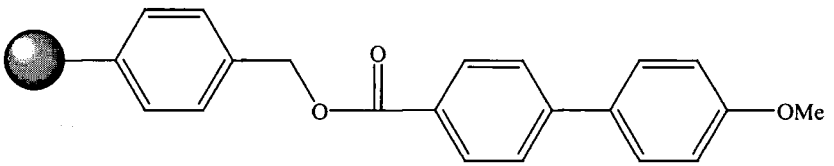
3.8.5.11 Synthesis of P78B2$_c$M2

The procedure was as described for the synthesis of **P78B2$_g$M2**, using **P78B2$_c$I2** (0.6 g, 0.81 mmol –I groups), dry DME (20 mL), freshly prepared catalyst $Pd(PPh_3)_4$ (0.16 g, 0.14 mmol), 4-methoxybenzeneboronic acid (0.43 g, 2.84 mmol) and 1M $Na_2CO_3(aq)$ (8 mL, 8 mmol). The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B2$_c$M2** (0.48 g, 83% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3423br (OH), 2925m and 2853w (CH), 1718s (C=O), 1605m (aryl C=C), 1273s (CCl), 1251m and 1039m (CO) 828w (*p*-disubstituted benzene ring), 580br (CI).

3.8.5.12 Cleavage of P78B2$_c$M2 to Yield (1)

P78B2$_c$M2 (0.45 g, 0.61 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.18 mL, 0.18 mmol) and dry MeOH/THF (1:1, 20 mL). The product was dried under vacuum (10^{-1} mbar), to provide crude product **(1)** as an orange solid (0.13 g, 87% based on the loading of aryl iodide). The crude product was purified by preparative HPLC to give pure **(1)** as a white solid (17.5 mg, 93%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.87 (s, 3H), 3.91 (s, 3H), 7.07 (d, J=8.8 Hz, 2H), 7.70 (m, 2H), 7.77 (m, 2H), 8.06 (d, J=8.4 Hz, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 52.3, 55.7, 115.3, 127.2, 129.1, 129.2, 130.8, 132.8, 146.0, 161.1, 167.1. MS (EI) *m/z* 242. Calculated for M_w = 242.27.

3.8.5.13 Synthesis of BB1M1 via Improved Suzuki Conditions



BB1M1

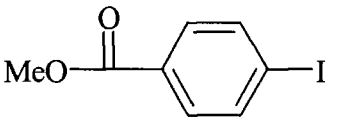
Polymer beads, **BB1I1** (0.3 g, 0.17 mmol –I groups) were placed in a 2-necked 50 mL round-bottomed flask fitted with rubber septa. Dry DME (8 mL) was transferred to the flask via syringe and the suspension was degassed with nitrogen gas for 30 min. The flask was wrapped in aluminium foil and supplied with a continuous flow of nitrogen. Freshly prepared $Pd(PPh_3)_4$ (33 mg, 0.03 mmol) and 4-methoxybenzeneboronic acid (91 mg, 0.60 mmol) were added, and the mixture was stirred thoroughly for 30 min. A 1M aqueous solution of Na_2CO_3 (1.7 mL, 1.7 mmol) was degassed and added via syringe. The flask was fitted with a condenser containing a nitrogen gas inlet and the mixture was heated under reflux at 95 °C for 40 h. After cooling, the mixture was diluted by addition of a solution of 25% ammonium actetate (10 mL) and stirred for 5 min. The beads were filtered and subjected to the standard wash procedure before being placed in a cellulose extraction thimble and extracted in a Soxhlet apparatus with THF for 24 h. The beads were dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to give **BB1M1** (0.21 g, 70% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3426br (OH), 2925m and 2853w (CH), 1721s (C=O), 1605m (aryl

C=C), 1270s (CCl), 1251s and 1039m (CO) 827m (*p*-disubstituted benzene ring), 545br (CI).

3.8.5.14 Cleavage of BB1M1 to Yield (1)

BB1M1 (0.2 g, 0.11 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.05 mL, 0.05 mmol) and dry MeOH/THF (1:3, 8 mL). The product was dried under vacuum (10^{-1} mbar), to provide crude product **(1)** as an orange solid (0.03 g, 111% based on the loading of aryl iodide). The crude product was purified by preparative HPLC to give pure **(1)** as a white solid (18.9 mg, 70%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.87 (s, 3H), 3.90 (s, 3H), 7.07 (d, J=8.8 Hz, 2H), 7.70 (m, 2H), 7.77 (m, 2H), 8.05 (d, J=8.8 Hz, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 52.3, 55.7, 115.3, 127.2, 129.1, 129.2, 130.8, 132.8, 146.0, 161.1, 167.1. MS (EI) *m/z* 242. Calculated for $C_{15}H_{14}O_3$ M_w = 242.27.

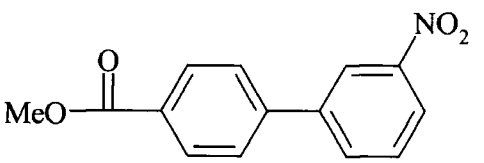
3.8.6 Procedure for the Synthesis of 4-Iodo-Benzoic Acid Methyl Ester (4)



(4)

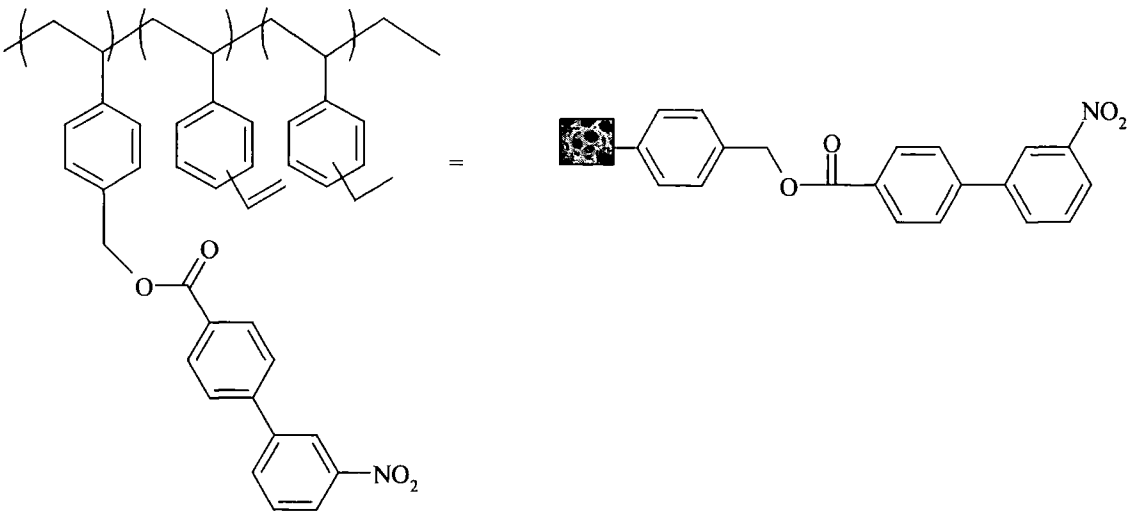
P78B3$_g$I1 (0.15 g, 0.17 mmol –I groups) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.07 mL, 0.07 mmol) and dry MeOH/THF (1:2, 15 mL). The product was dried under vacuum (10^{-1} mbar), to provide crude product **(4)** as a white solid (0.05 g, 111% based on the loading of aryl iodide). ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 3.89 (s, 3H), 7.65 (d, J=8.4 Hz, 2H), 7.94 (d, J=8.6 Hz, 2H). MS (EI) *m/z* 262. Calculated for $C_8H_7O_2I$ M_w = 262.04.

3.8.7 Procedures for the Batch Synthesis of 3-Nitro-Biphenyl-4'-Carboxylic Acid Methyl Ester (2)



(2)

3.8.7.1 Synthesis of P78B1$_g$N1 via Optimised Suzuki Conditions



P78B1$_g$N1

The procedure was as described for the synthesis of **P78B2$_g$M2**, using **P78B1$_g$I1** (0.3 g, 0.5 mmol –I groups), dry DME (12 mL), freshly prepared $Pd(PPh_3)_4$ (99 mg, 0.086 mmol), 3-nitrobenzeneboronic acid (0.29 g, 1.76 mmol) and 1M $Na_2CO_3(aq)$ (5.0 mL, 5.04 mmol). The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B1$_g$N1** (0.30 g, 102% conversion by weight). Found N, 1.6%. Calculated N, 2.4% (69% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2924m and 2853w (CH), 1718s (C=O), 1605m (aryl C=C), 1533m and 1349m (conj. NO_2), 1272s (CCl), 807w (*p*-disubstituted benzene ring), 735w (*m*-disubstituted benzene ring).

3.8.7.2 Cleavage of P78B1$_g$N1 to Yield (2)

P78B1$_g$N1 (0.25 g, 0.42 mmol) was placed in a 50 mL round-bottomed flask to which a solution of 1M NaOMe in dry MeOH (0.17 mL, 0.18 mmol) and dry MeOH/THF (1:3, 20 mL) was added. The flask was fitted with a condenser and the mixture was heated under reflux at 70 °C for 72 h. The PolyHIPE was removed by filtration and washed with MeOH/THF (1:1, 10 mL), THF (10 mL) and MeOH (10 mL). The filtrate and washings were concentrated and the product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h to provide product **(2)** as a yellow solid (0.075 g, 70% based on the loading of aryl iodide and 100% based on the loading of coupled nitrogen). ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 3.92 (s, 3H), 7.83 (t, J=8.0 Hz, 1H), 7.94 (d, J=8.6 Hz, 2H), 8.16 (d, J=8.8 Hz, 2H), 8.21 (ddd, $J_{b,c}$=7.8 Hz and $J_{a,c}$=$J_{d,c}$=1 Hz,

1H), 8.31 (ddd, $J_{b,a}$=8.0 Hz and $J_{c,a}$=$J_{d,a}$=1 Hz, 1H), 8.54 (t, J=2.0 Hz, 1H). MS (EI) *m/z* 257. Calculated for $C_{14}H_{11}NO_4$ M_w = 257.24.

3.8.7.3 Synthesis of P78B4$_c$N1

The procedure was as described for the synthesis of **P78B1$_g$N1**, using **P78B4$_c$I1** (0.3 g, 0.5 mmol –I groups), dry DME (12 mL), freshly prepared $Pd(PPh_3)_4$ (98 mg, 0.085 mmol), 3-nitrobenzeneboronic acid (0.29 g, 1.74 mmol) and 1M Na_2CO_3(*aq*) (5.0 mL, 5.0 mmol). The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B4$_c$N1** (0.28 g, 95% conversion by weight). Found N, 1.9%. Calculated N, 2.3% (82% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2853w (CH), 1718s (C=O), 1609m (aryl C=C), 1532m and 1349m (conj. NO_2), 1272s (CCl), 811w (*p*-disubstituted benzene ring), 735w (*m*-disubstituted benzene ring).

3.8.7.4 Cleavage of P78B4$_c$N1 to Yield (2)

P78B4$_c$N1 (0.25 g, 0.42 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.17 mL, 0.17 mmol) and dry MeOH/THF (1:3, 20 mL). The product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to provide crude product **(2)** as a yellow solid (0.096 g, 92% based on the loading of aryl iodide and 109% based on the loading of coupled nitrogen). ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 3.93 (s, 3H), 7.83 (t, J=8.0 Hz, 1H), 7.94 (d, J=8.6 Hz, 2H), 8.16 (d, J=8.6 Hz, 2H), 8.21 (ddd, $J_{b,c}$=8.2 Hz and $J_{a,c}$=$J_{d,c}$=1 Hz, 1H), 8.31 (ddd, $J_{b,a}$=8.0 Hz and $J_{c,a}$=$J_{d,a}$=1 Hz, 1H), 8.54 (t, J=2.0 Hz, 1H). MS (EI) *m/z* 257. Calculated for $C_{14}H_{11}NO_4$ M_w = 257.24.

3.8.7.5 Synthesis of P78B4$_g$N2 via Improved Suzuki Conditions

The procedure was as described for the synthesis of **P78B1$_g$N1**, using **P78B4$_g$I2** (0.35 g, 0.54 mmol –I groups), dry DME (12 mL), freshly prepared $Pd(PPh_3)_4$ (106 mg, 0.09 mmol), 3-nitrobenzeneboronic acid (0.31 g, 1.89 mmol) and 1M Na_2CO_3(*aq*) (5.4 mL, 5.4 mmol). The PolyHIPE was filtered and subjected to the standard wash procedure before being placed in a cellulose extraction thimble and extracted in a Soxhlet apparatus with THF for 24 h. The polymer was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to give **P78B4$_g$N2** (0.28 g, 81% conversion by weight). Found N, 2.1%. Calculated N, 2.2% (96% conversion). IR (KBr disc)

υ_{max}/cm^{-1} 3430br (OH), 2924m and 2853w (CH), 1719s (C=O), 1609w (aryl C=C), 1532m and 1349m (conj. NO_2), 1273s (CCl), 811w (*p*-disubstituted benzene ring), 735w (*m*-disubstituted benzene ring).

3.8.7.6 Cleavage of P78B4$_g$N2 to Yield (2)

P78B4$_g$N2 (0.25 g, 0.39 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.15 mL, 0.15 mmol) and dry MeOH/THF (1:3, 20 mL). The product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to provide crude product **(2)** as a yellow solid (0.098 g, 100% based on the loading of aryl iodide and 100% based on the loading of coupled nitrogen). The crude product was purified by preparative HPLC to give pure **(2)** as a white solid (18.5 mg, 72%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.93 (s, 3H), 7.82 (t, J=8.2 Hz, 1H), 7.94 (d, J=8.8 Hz, 2H), 8.15 (d, J=8.8 Hz, 2H), 8.20 (ddd, $J_{b,c}$=7.6 Hz and $J_{a,c}$=$J_{d,c}$=1 Hz, 1H), 8.30 (ddd, $J_{b,a}$=8.4 Hz and $J_{c,a}$=$J_{d,a}$=1 Hz, 1H), 8.54 (t, J=2 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 52.5, 122.6, 123.7, 128.3, 131.0, 131.1, 131.3, 134.3, 142.2, 143.7, 149.9, 166.9. MS (EI) *m/z* 257. Calculated for $C_{14}H_{11}NO_4$ M_w = 257.24.

3.8.7.7 Synthesis of P78B1$_c$N2

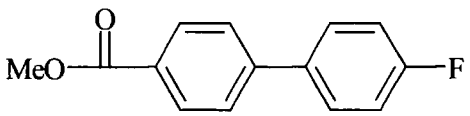
The procedure was as described for the synthesis of **P78B4$_g$N2**, using **P78B1$_c$I2** (0.35 g, 0.56 mmol –I groups), dry DME (12 mL), freshly prepared $Pd(PPh_3)_4$ (110 mg, 0.095 mmol), 3-nitrobenzeneboronic acid (0.33 g, 1.96 mmol) and 1M $Na_2CO_3(aq)$ (5.6 mL, 5.6 mmol). The PolyHIPE was filtered and subjected to the standard wash procedure before being placed in a cellulose extraction thimble and extracted in a Soxhlet apparatus with THF for 24 h. The polymer was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to give **P78B1$_c$N2** (0.29 g, 83% conversion by weight). Found N, 2.3%. Calculated N, 2.3% (100% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2853w (CH), 1719s (C=O), 1610w (aryl C=C), 1532m and 1349m (conj. NO_2), 1273s (CCl), 809w (*p*-disubstituted benzene ring), 735w (*m*-disubstituted benzene ring).

3.8.7.8 Cleavage of P78B1$_c$N2 to Yield (2)

P78B1$_c$N2 (0.25 g, 0.40 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.16 mL, 0.16 mmol) and dry MeOH/THF (1:3, 20 mL). The product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to

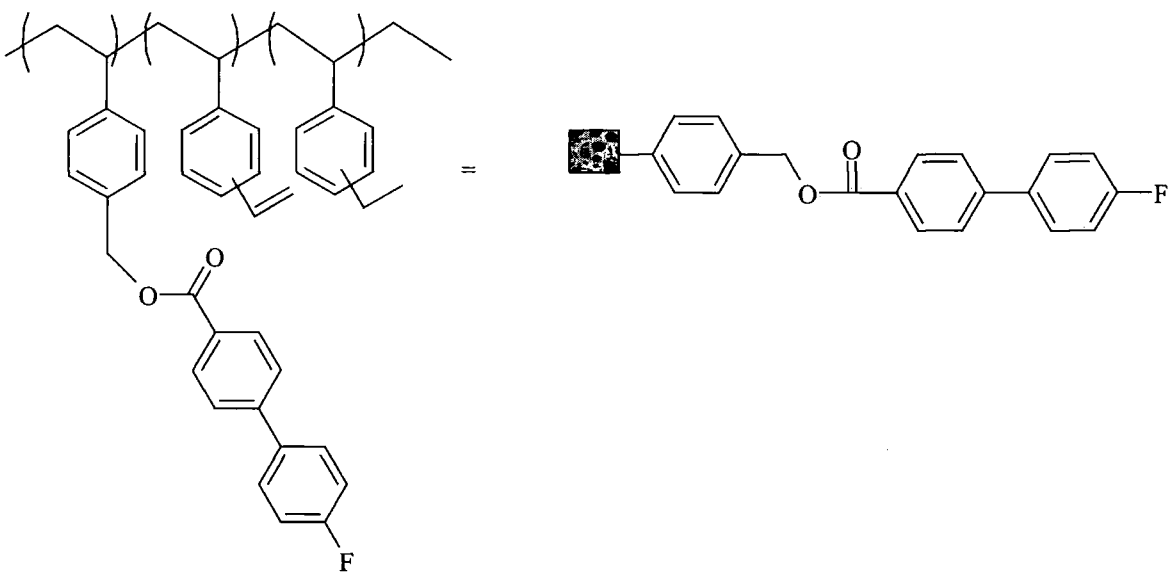
provide crude product **(2)** as a yellow solid (0.074 g, 74% based on the loading of aryl iodide and 72% based on the loading of coupled nitrogen). The crude product was purified by preparative HPLC to give pure 3-nitro-biphenyl-4'-carboxylic acid methyl ester **(2)** as a white solid (10.6 mg, 81%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.93 (s, 3H), 7.82 (t, J=8.2 Hz, 1H), 7.94 (d, J=8.8 Hz, 2H), 8.15 (d, J=8.4 Hz, 2H), 8.20 (ddd, $J_{b,c}$=7.6 Hz and $J_{a,c}$=$J_{d,c}$=1 Hz, 1H), 8.30 (ddd, $J_{b,a}$=8.4 Hz and $J_{c,a}$=$J_{d,a}$=1 Hz, 1H), 8.54 (t, J=2.2 Hz, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 52.5, 122.6, 123.7, 128.3, 131.0, 131.1, 131.3, 134.3, 142.2, 143.7, 149.9, 166.9. MS (EI) *m/z* 257. Calculated for $C_{14}H_{11}NO_4$ M_w = 257.24.

3.8.8 Procedures for the Batch Synthesis of 4-Fluoro-Biphenyl-4'-Carboxylic Acid Methyl Ester (3)



(3)

3.8.8.1 Synthesis of P78B1$_g$F1 via Optimised Suzuki Conditions



P78B1$_g$F1

The procedure was as described for the synthesis of **P78B1$_g$N1**, using **P78B1$_g$I1** (0.4 g, 0.67 mmol –I groups), dry DME (15 mL), freshly prepared $Pd(PPh_3)_4$ (132 mg, 0.11 mmol), 4-fluorobenzeneboronic acid (0.33 g, 2.35 mmol) and 1M $Na_2CO_3(aq)$ (6.7 mL, 6.7 mmol). The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B1$_g$F1** (0.34 g, 90% conversion by weight). Found F, 2.1%. Calculated F, 3.4% (62% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3426br (OH), 2924m and 2853w (CH), 1718s (C=O), 1610m (aryl C=C), 1273s (CCl), 831m (*p*-disubstituted benzene ring), 772m (CF).

3.8.8.2 Cleavage of P78B1$_g$F1 to Yield (3)

P78B1$_g$F1 (0.3 g, 0.5 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.20 mL, 0.20 mmol) and dry MeOH/THF (1:3, 20 mL). The product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to provide crude product **(3)** as a white solid (0.1 g, 87% based on the loading of aryl iodide and 134% based on the loading of coupled fluorine). ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 3.91 (s, 3H), 7.27 (t, J=8.8 Hz, 2H), 7.78 (m, 4H), 8.09 (d, J=8.6 Hz, 2H).

3.8.8.3 Synthesis of P78B1$_c$F2 via Optimised Suzuki Conditions

The procedure was as described for the synthesis of **P78B1$_g$F1**, using **P78B1$_c$I2** (0.4 g, 0.61 mmol –I groups), dry DME (15 mL), freshly prepared $Pd(PPh_3)_4$ (120 mg, 0.10 mmol), 4-fluorobenzeneboronic acid (0.3 g, 2.14 mmol) and 1M $Na_2CO_3(aq)$ (6.1 mL, 6.1 mmol). The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B1$_c$F2** (0.37 g, 97% conversion by weight). Found F, 2.9%. Calculated F, 3.1% (94% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3426br (OH), 2923m and 2853w (CH), 1718s (C=O), 1610m (aryl C=C), 1273s (CCl), 833m (*p*-disubstituted benzene ring), 772m (CF).

3.8.8.4 Cleavage of P78B1$_c$F2 to Yield (3)

P78B1$_c$F2 (0.3 g, 0.46 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.18 mL, 0.18 mmol) and dry MeOH/THF (1:3, 20 mL). The product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to provide crude product **(3)** as a white solid (0.11 g, 104% based on the loading of aryl iodide

and 105% based on the loading of coupled fluorine). ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 3.90 (s, 3H), 7.27 (t, J=8.8 Hz, 2H), 7.78 (m, 4H), 8.09 (d, J=8.8 Hz, 2H).

3.8.8.5 Synthesis of P78B4$_g$F2 via Improved Suzuki Conditions

The procedure was as described for the synthesis of **P78B4$_g$N2,** using **P78B4$_g$I2** (0.35 g, 0.54 mmol –I groups), dry DME (12 mL), freshly prepared $Pd(PPh_3)_4$ (106 mg, 0.09 mmol), 4-fluorobenzeneboronic acid (0.26 g, 1.89 mmol) and 1M $Na_2CO_3(aq)$ (5.4 mL, 5.4 mmol). The PolyHIPE was filtered and subjected to the standard wash procedure before being placed in a cellulose extraction thimble and extracted in a Soxhlet apparatus with THF for 24 h. The polymer was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to give **P78B4$_g$F2** (0.26 g, 77% conversion by weight). Found F, 2.8%. Calculated F, 3.1% (90% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2924m and 2853w (CH), 1719s (C=O), 1608m (aryl C=C), 1273s (CCl), 831m (*p*-disubstituted benzene ring), 772m (CF).

3.8.8.6 Cleavage of P78B4$_g$F2 to Yield (3)

P78B4$_g$F2 (0.22 g, 0.34 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.14 mL, 0.14 mmol) and dry MeOH/THF (1:3, 20 mL). The product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to provide crude product **(3)** as an orange solid (0.079 g, 100% based on the loading of aryl iodide and 108% based on the loading of coupled fluorine). The crude product was purified by preparative HPLC to give pure **(3)** as a white solid (13.4 mg, 82%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.91 (s, 3H), 7.27 (t, J=8.8 Hz, 2H), 7.78 (M, 4H), 8.09 (d, J=8.4 Hz, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 52.4, 116.7 (d, $^2J_{CF}$=21.2 Hz, 2C), 127.8, 130.0 (d, $^3J_{CF}$=8.1 Hz, 2C), 130.8, 136.9 (d, $^4J_{CF}$=2.9 Hz, 1C), 137.0, 145.2, 163.9 (d, $^1J_{CF}$=245.9 Hz, 1C), 167.0. MS (EI) *m/z* 230. Calculated for $C_{14}H_{11}FO_2$ M_w = 230.24.

3.8.8.7 Synthesis of P78B4$_c$F2 via Improved Suzuki Conditions

The procedure was as described for the synthesis of **P78B4$_g$F2**, using **P78B4$_c$I2** (0.35 g, 0.55 mmol –I groups), dry DME (12 mL), freshly prepared $Pd(PPh_3)_4$ (108 mg, 0.095 mmol), 4-fluorobenzeneboronic acid (0.27 g, 1.92 mmol) and 1M $Na_2CO_3(aq)$ (5.5 mL, 5.5 mmol). The PolyHIPE was filtered and subjected to the standard wash procedure before being placed in a cellulose extraction thimble

and extracted in a Soxhlet apparatus with THF for 24 h. The polymer was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to give **P78B4$_c$F2** (0.28 g, 83% conversion by weight). Found F, 3.0%. Calculated F, 3.1% (96% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3426br (OH), 2924m and 2853w (CH), 1719s (C=O), 1608m (aryl C=C), 1273s (CCl), 831m (*p*-disubstituted benzene ring), 772m (CF).

3.8.8.8 Cleavage of P78B4$_c$F2 to Yield (3)

P78B4$_c$F2 (0.23 g, 0.36 mmol) was cleaved according to the standard cleavage procedure, using 1M NaOMe (0.14 mL, 0.14 mmol) and dry MeOH/THF (1:3, 20 mL). The product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to provide crude product **(3)** as an orange solid (0.087 g, 105% based on the loading of aryl iodide and 104% based on the loading of coupled fluorine). The crude product was purified by preparative HPLC to give pure **(3)** as a white solid (14 mg, 73%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.91 (s, 3H), 7.27 (t, J=9.0 Hz, 2H), 7.78 (m, 4H), 8.09 (d, J=8.0 Hz, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 52.4, 116.7 (d, $^2J_{CF}$=21.2 Hz, 2C), 127.8, 130.0 (d, $^3J_{CF}$=8.1 Hz, 2C), 130.8, 136.9 (d, $^4J_{CF}$=2.9 Hz, 1C), 137.0, 145.2, 163.9 (d, $^1J_{CF}$=245.9 Hz, 1C), 167.0. MS (EI) *m/z* 230. Calculated for $C_{14}H_{11}FO_2$ M_w = 230.24.

3.8.9 Procedures for the Flow-Through Synthesis of 4-Methoxy-Biphenyl-4'-Carboxylic Acid Methyl Ester (1) using the Quest System

3.8.9.1 Flow-Through Synthesis of P78B3$_m$I1

A 10 mL fritted PTFE reaction vessel containing **P78B3$_m$C** (0.14 g, 0.62 mmol –CH_2Cl groups) was set in an Argonaut Quest 210 Parallel Synthesiser, to which was added DMF (8 mL). The reaction vessel was heated to 80 °C and the solvent was allowed to diffuse into the monolith for 15 min. The solvent was later drained from the vessel using a compressed flow of nitrogen. Cesium carbonate (2.44 g, 7.47 mmol), potassium iodide (0.2 g, 1.26 mmol) and 4-iodobenzoic acid (0.92 g, 3.69 mmol) were placed in a 100 mL conical flask fitted with a stopper, to which was added DMF (10 mL). The resultant slurry was sonicated at room temperature in the presence of water (2 mL) to dissolve carboxylate salts. This was then added to the heated reaction vessel via Pasteur pipette and allowed to flow through the monolith and into a collecting flask at a rate of *ca.* 18 mL h^{-1}. The solution was manually

recycled through the monolith for a total of 9 h. The monolith was then immersed in the solution at 80 °C for a further 15 h. The PolyHIPE was washed thoroughly by flowing through DMF (30 min), THF/H_2O (1:1) (30 min) and methanol (30 min). The monolith and reaction vessel were dried *in vacuo* at 50 °C for 24 h to provide **P78B3$_m$I1** (0.24 g, 96% conversion by weight). Found I, 20.2; Cl, 1.3%. Calculated I, 27.3; Cl 0% (74% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2852w (CH), 1721s (C=O), 1586m (aryl C=C), 1268s (CCl), 823w (*p*-disubstituted benzene ring), 584br (CI).

3.8.9.2 Flow-Through Synthesis of P78B3$_m$M1

A tube containing **P78B3$_m$I1** (0.24 g, 0.38 mmol -I groups) was set in the Quest 210 and the apparatus and collection flask were covered with aluminium foil to create a darkened environment. Dry DME (10 mL) was injected into the tube, which was sealed under nitrogen and approximately 5 mL of solvent was allowed to flow through in order to wet the monolith. Freshly prepared $Pd(PPh_3)_4$ (124 mg, 0.11 mmol) was added to the tube and allowed to diffuse into the monolith for 10 min before another 2 mL of DME was withdrawn into the collection flask. Separately, 4-methoxybenzeneboronic acid (0.34 g, 2.18 mmol) and dry DME (5 mL) were added to 1M $Na_2CO_3(aq)$ (7.3 mL, 7.3 mmol) and the mixture was injected into the reactor tube via syringe. The solution of reagents was passed through the monolith at a flowrate of 15 mL h^{-1}, at 85 °C and was manually recycled every hour (overnight, the monolith was immersed in the reagent solution at 85 °C). The procedure was performed for a total of 68 h. The PolyHIPE was neutralised with 25% NH_4OAc (7.5 mL), washed using the usual wash procedure and dried *in vacuo* at 50 °C for 48 h, to produce **P78B3$_m$M1** (0.32 g, 133% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3447br (OH), 2925m and 2853w (CH), 1718s (C=O), 1605m (aryl C=C), 1272s (CCl), 1251m and 1039w (CO) 828m (*p*-disubstituted benzene ring), 551br (CI).

3.8.9.3 Flow-Through Cleavage of P78B3$_m$M1 to Yield (1)

The product was cleaved initially from the monolith by passing a solution of 2M NaOMe (0.07 mL, 0.14 mmol) in dry MeOH/THF (1:4, 5 mL) through **P78B3$_m$M1** (0.32 g, 0.5 mmol) at a flowrate of 10 mL h^{-1}. The solution was flowed through the PolyHIPE at 60 °C for 8 h, and manually recycled every hour. The monolith was then immersed in the basic solution overnight, resulting in a total

cleavage time of 24 h. Due to incomplete cleavage, a fresh solution of 2M NaOMe (0.07 mL, 0.14 mmol) in dry MeOH/THF (1:4, 5 mL) was flowed through the monolith and manually recycled over an 8 h period. The monolith was then immersed in the basic solution overnight. The process of recycling and immersion took place over a total of 72 h. To ensure complete cleavage of the product, a third solution of 2M NaOMe (0.23 g Na in dry MeOH, 5 mL) (0.7 mL, 1.4 mmol) in dry MeOH (5 mL) was flowed through **P78B3$_m$M1** at 60°C for a total of 24 h. The monolith was washed each time with MeOH/THF (1:1, 10 mL), THF (10 mL) and MeOH (10 mL). The combined products provided crude 4-methoxy-biphenyl-4'-carboxylic acid methyl ester **(1)** as an orange solid (0.17 g, 141% based on the loading of aryl iodide). From analytical HPLC analysis, pure **(1)** was found to constitute 76 mg (63%). First cleave, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 7.00 (d, J=9.0 Hz, 2H), 7.60 (m, 4H), 8.08 (d, J=8.7 Hz, 2H). Second cleave, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 7.00 (d, J=8.7 Hz, 2H), 7.61 (m, 4H), 8.09 (d, J=8.7 Hz, 2H). Third cleave, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 7.01 (d, J=9.0 Hz, 2H), 7.61 (m, 4H), 8.09 (d, J=8.4 Hz, 2H).

3.8.9.4 Flow-Through Synthesis of BB1I2

A 10 mL fritted PTFE reaction vessel containing chloromethyl polystyrene beads **BB1C** (0.52 g, 0.62 mmol –CH_2Cl groups) was set in an Argonaut Quest 210 Parallel Synthesiser, to which was added DMF (10 mL). The reaction vessel was heated to 80 °C and the solvent was allowed to diffuse into the beads for 15 min. The solvent was then drained from the vessel using a compressed flow of nitrogen. Cesium carbonate (2.42 g, 7.43 mmol), potassium iodide (0.2 g, 1.26 mmol) and 4-iodobenzoic acid (0.92 g, 3.69 mmol) were placed in a 100 mL conical flask fitted with a stopper, to which was added DMF (10 mL). The resultant slurry was sonicated at room temperature in the presence of water (1 mL) to dissolve carboxylate salts. The reagent solution was added via pipette to the head-space above the beads and allowed to flow through them under gravity, into a collecting flask, at a rate of *ca.* 10 mL h^{-1}. The solution was manually recycled through the beads for a total of 9 h followed by immersion at 80 °C for a further 15 h. The beads were washed thoroughly by flowing through DMF (30 min), THF/H_2O (1:1) (30 min) and methanol (30 min). The beads were then dried *in vacuo* at 50 °C for 24 h to provide **BB1I2** (0.5 g, 77% conversion by weight). Found I, 5.1; Cl, 1.5%. Calculated I, 12.2; Cl 0%

(42% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3447br (OH), 2927m and 2856w (CH), 1724s (C=O), 1587m (aryl C=C), 1267s (CCl), 827w (*p*-disubstituted benzene ring), 584br (CI).

3.8.9.5 Flow-Through Synthesis of BB1M2

A tube containing **BB1I2** (0.5 g, 0.2 mmol -I groups) was set in the Quest 210 and the apparatus and collection flask were covered with aluminium foil. Dry DME (10 mL) was injected into the tube, which was sealed under nitrogen and approximately 2 mL of solvent was allowed to flow through in order to wet the beads. Freshly prepared $Pd(PPh_3)_4$ (39 mg, 0.03 mmol) was added to the tube and allowed to diffuse into the beads for 10 min before another 2 mL of DME was withdrawn into the collection flask. Separately, 4-methoxybenzeneboronic acid (0.10 g, 0.68 mmol) and dry DME (5 mL) were added to 1M $Na_2CO_3(aq)$ (2.3 mL, 2.3 mmol) and the mixture was injected into the reactor tube via syringe. The solution of reagents was passed through the beads at a flowrate of 15 mL h^{-1}, at 85 °C and was manually recycled every hour (overnight, the beads were immersed in the reagent solution at 85 °C). The procedure was performed for a total of 68 h. The beads were neutralised with 25% NH_4OAc (5 mL), washed using the usual wash procedure and dried *in vacuo* at 50 °C for 48 h, to produce **BB1M2** (0.40 g, 81% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3447br (OH), 2927s and 2853w (CH), 1718m (C=O), 1607m (aryl C=C), 1273m (CCl), 1251w (CO), 829s (*p*-disubstituted benzene ring).

3.8.9.6 Flow-Through Cleavage of BB1M2 to Yield (1)

The product was cleaved initially from the beads by passing a solution of 2M NaOMe (0.01 mL, 0.02 mmol) in dry MeOH/THF (1:4, 5 mL) through **BB1M2** (0.3 g, 0.12 mmol) at a flowrate of 10 mL h^{-1}. The solution was flowed through the beads at 60 °C for 8 h, and manually recycled every hour. The beads were then immersed in the basic solution overnight, resulting in a total cleavage time of 24 h. Due to incomplete cleavage, a fresh solution of 2M NaOMe (0.01 mL, 0.02 mmol) in dry MeOH/THF (1:4, 5 mL) was flowed through the beads and manually recycled over an 8 h period. The beads were then immersed in the basic solution overnight. The process of recycling and immersion took place over a total of 72 h. To ensure complete cleavage of the product, a third solution of 2M NaOMe (0.23 g Na in dry MeOH, 5 mL) (0.04 mL, 0.07 mmol) in dry MeOH (5 mL) was flowed through

BB1M2 at 60°C for a total of 24 h. The beads were washed each time with MeOH/THF (1:1, 10 mL), THF (10 mL) and MeOH (10 mL). The combined products provided crude 4-methoxy-biphenyl-4'-carboxylic acid methyl ester **(1)** as an orange solid (0.049 g, 167% based on the loading of aryl iodide). From analytical HPLC analysis, pure **(1)** was found to constitute 28 mg (95%). First cleave, ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.87 (s, 3H), 3.90 (s, 3H), 7.07 (d, J=8.8 Hz, 2H), 7.70 (m, 2H), 7.77 (m, 2H), 8.06 (d, J=8.4 Hz, 2H). Signals of lower intensity were also present in the spectrum between 7.00 and 8.00 ppm. Second cleave, ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.87 (s, 3H), 3.90 (s, 3H), 7.07 (d, J=8.8 Hz, 2H), 7.70 (m, 2H), 7.77 (m, 2H), 8.06 (d, J=8.4 Hz, 2H). Third cleave, ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.86 (s, 3H), 3.90 (s, 3H), 7.06 (d, J=8.8 Hz, 2H), 7.70 (m, 2H), 7.77 (m, 2H), 8.06 (d, J=8.8 Hz, 2H).

3.8.10 Flow-Through Suzuki Synthesis using the Automatic HPLC System

3.8.10.1 Attachment of 4-Iodobenzoic Acid

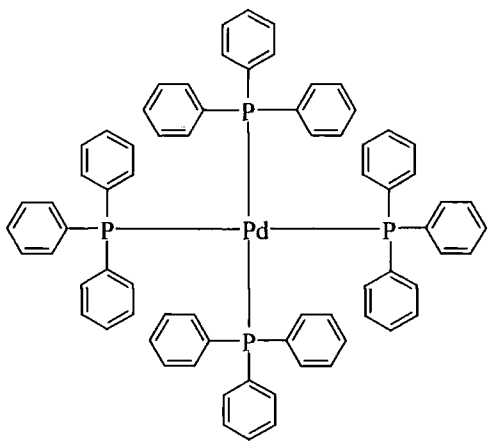
A stainless steel HPLC column containing **P23B1$_m$C** (0.22 g, 0.31 mmol – CH_2Cl groups) was fitted with PEEK tubing and connected to an HPLC pump. The tubing was insulated with glass wool and the column was immersed in a water bath at 100 °C. DMF was pumped around the system and through the column for 30 min. Cesium carbonate (0.31 g, 0.94 mmol), potassium iodide (26 mg, 0.16 mmol) and 4-iodobenzoic acid (0.12 g, 0.47 mmol) were placed in a 50 mL dual compartment glass flask, fitted with rubber septa, to which was added DMF (11.2 mL). The total amount of DMF used in the reaction was 15 mL, as 3.8 mL was calculated to reside inside the HPLC system and column. The flask containing the reagents was heated to 100 °C and the acid-base reaction was allowed to take place over 1.5 h. After this time, 30 μL was removed from the flask and diluted with DMF (5 mL). At this point, t_0, the UV absorbance of the solution was measured. The flow-rate of the pump was set at 6 mL min^{-1} and the reagent solution was allowed to flow through the monolith. The backpressure of the pump was 3 bar. Aliquots of reagent solution (30 μL) were removed from the flask at 30 min intervals and their absorbance recorded. The readings were taken over a period of 7 h and the reagent solution was allowed to flow through the monolith overnight. A further 8 readings were recorded the following

day. The flow-through reaction was stopped after a total of 31 h and the monolith was washed through with DMF (20 mL) and THF/H_2O (50:50) (20 mL).

3.8.10.2 Flow-Through Coupling of 4-Methoxybenzeneboronic Acid

DME (20 mL) was degassed with nitrogen and allowed to flow-through the column, which was immersed in a water bath at 100 °C, for 30 min. To a dual compartment flask covered with aluminium foil, was fitted condensers and rubber septa. DME (11.2 mL) was added to the flask and one condenser was provided with a flow of nitrogen while the other was vented. 4-Methoxybenzeneboronic acid (0.13 g, 0.84 mmol) and $Pd(PPh_3)_4$ (47.2 mg, 0.04 mmol) were added the flask and the mixture was stirred for 30 min. During this time a 1M solution of Na_2CO_3 was degassed with nitrogen for 30 min. The solution (2.4 mL) was added to the flask and the mixture was heated to 90 °C. The pump flow-rate was set to 6 mL min^{-1} and the reagent solution was allowed to flow through the monolith. The process was continued for 30 min until blockage of the system occurred and the HPLC pump ceased to operate.

3.8.11 Synthesis of Tetrakis(triphenylphosphine)palladium (0)



$Pd(PPh_3)_4$

Palladium dichloride (0.35 g, 2 mmol) and triphenylphosphine (0.26 g, 10 mmol) were placed in a two-necked, 50 mL round-bottomed flask. Anhydrous DMSO (25 mL) was added and the mixture was degassed with nitrogen for 20 min. The flask was then heated at 140 °C for 2 h under a nitrogen atmosphere. After this

time, the temperature of the reaction was increased to 145 °C and a clear solution was obtained. The solution was stirred vigorously for a further 30 min. The flask was then removed from the heat and hydrazine hydrate (0.39 mL, 8 mmol) was immediately added to the solution, via syringe. The solution was cooled to room temperature. The bright yellow crystals formed were filtered in a darkened environment and washed with ethanol (20 mL) and ether (20 mL), under a nitrogen atmosphere. The crystals were briefly dried under a continuous flow of nitrogen to yield **$Pd(PPh_3)_4$** (2.1 g, 91%).

3.9 References

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Chapter 4

Development of Hydroxymethyl-Functionalised PolyHIPE for Solid Phase Suzuki Cross-Coupling Reactions

4.1 Overview

Many solid phase organic syntheses require the use of a linker to attach the substrate to the polymeric support. Linkers should enable the easy attachment of the starting material to the polymer, be stable under a wide variety of reaction conditions, and yet enable selective cleavage at the end of the synthesis without damage to the product.[1] Several types of linker have been developed which meet these conflicting demands to varying extents (see section 1.3.1 for examples). Acid-labile benzyl alcohol linkers are the oldest and most commonly used linkers for the attachment of carboxylic acids. In 1973, Wang introduced the 4-alkoxybenzyl alcohol linker for use in solid phase synthesis.[2] The so-called Wang linker has since become one of the most popular linkers in SPOS. The first part of this chapter describes the preparation of Wang-functionalised PolyHIPE by the direct attachment of the 4-hydroxymethyl phenol linker (HMP), to granular and monolithic forms of chloromethyl PolyHIPE.

The actions taken to optimise the reaction and to quantify the resultant hydroxymethyl loadings are also outlined. An investigation into alternative reagents for the coupling of carboxylic acids onto Wang-functionalised PolyHIPE will follow, together with a description of a different route to Wang resin. The second part focuses on utilising the modified PolyHIPEs as supports in Suzuki coupling reactions, and introduces a novel, highly loaded PolyHIPE support. Its effectiveness in Suzuki coupling reactions will also be described.

4.2 Introduction

Wang resin (also known as HMP resin) refers to cross-linked polystyrene immobilised with Wang linker. As well as carboxylic acids, alcohols and phenols can be attached to this linker by various methods. Carbodiimides are generally used in the presence of catalysts for the attachment of acids to yield esters. DCC has been the most widely used reagent, but this compound is increasingly being replaced by DIC and the water-soluble EDCI (also known as EDC). MSNT reagent tends to be the coupling agent of choice in difficult circumstances, such as loading of 4-hydroxymethylbenzoic acid (HMBA) resins or when attaching amino acid derivatives which are prone to racemisation (*Figure 4.1*). More recently, novel methods for loading Wang resin have been reported. One such procedure involves transesterification of an ethyl ester with the resin lithium salt generated by pre-treatment of the polymer with LDA.[3] The Mitsunobu reaction is commonly used to attach alcohols and phenols to hydroxymethyl functionalised supports.

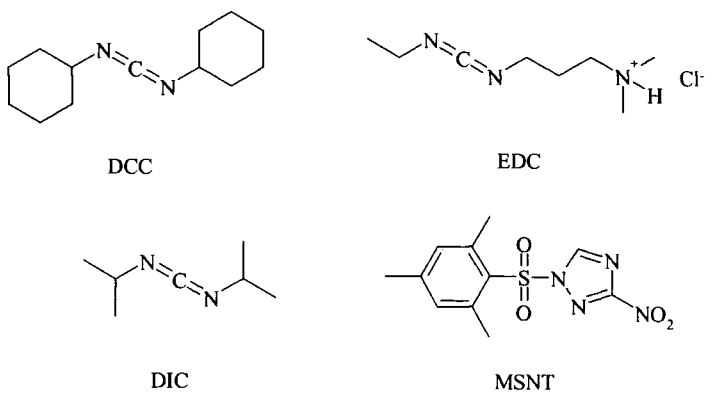


Figure 4.1 Carbodiimides and MSNT reagent used in solid phase synthesis

Esters of the Wang linker are difficult to cleave from the support by treatment with nucleophiles or with weak acids, but are readily hydrolysed by treatment with 50% TFA in DCM. Cleavage tends to occur via acidolysis of the benzylic C-O bonds (*Figure 4.2*).

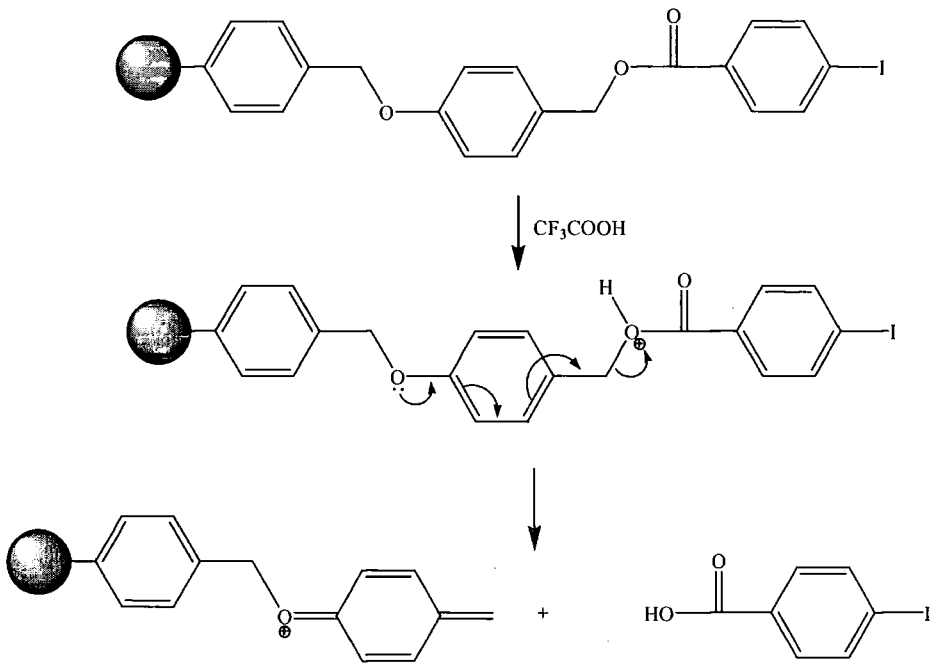
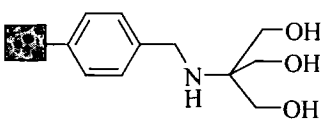


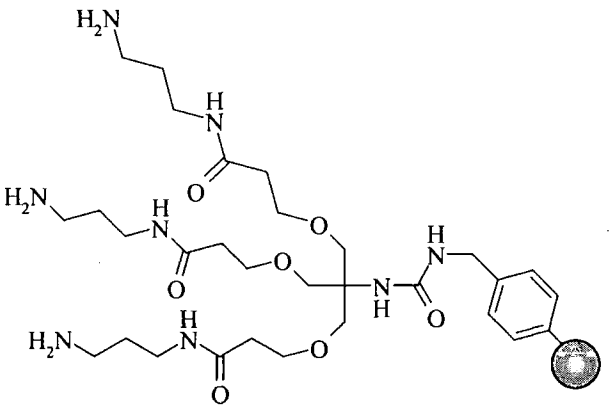
Figure 4.2 Acidolytic cleavage of TFA

Wang-functionalised polymer beads have successfully been employed in organic synthesis programmes ranging from Michael additions[4] and aldol reactions[5] to palladium-catalysed cross-couplings.[6] With the intention of preparing Wang-functionalised PolyHIPE for use in Suzuki cross-coupling reactions, various routes for the derivatisation of chloromethyl PolyHIPE were investigated. The aim was to functionalise PolyHIPE in batch as well as flow-through reactions, as it was believed that the monolithic format simplified reagent transfer and improved handling. Furthermore, previous flow-through functionalisations of PolyHIPE (chapter 2) had resulted in higher conversions than the corresponding batch reactions. The Suzuki reaction was chosen to demonstrate the utility of Wang-functionalised PolyHIPE, as this reaction had proven to be successful on chloromethyl PolyHIPE supports. Indeed, the mechanistic details of the synthesis have been described comprehensively in chapter 3.

Further aims were to perform solid phase Suzuki coupling utilising a novel PolyHIPE support. With a remarkably high loading of hydroxymethyl groups (7.7 mmol g^{-1}), trishydroxymethyl PolyHIPE was developed for the immobilisation of multiple reactive groups and for use in small molecule synthesis. Tris-OH is an example of a non-benzylic alcohol linker, which, like Wang linker, can be used for the immobilisation of carboxylic acids as esters. The advantage of such a linker is its stability towards electrophiles. Very few examples of the immobilisation of species onto multiple hydroxyl groups have been reported. Hodge *et al.*[7] utilised a polymer-supported diol for the removal of excess aldehydes and ketones from solution, while a diethanolamine support has recently been prepared for the immobilisation of boronic acids.[8] Bradley and Fromont produced similar high-loading resin beads in 2000.[9] Aminodendrimer polystyrene beads (*Figure 4.3*) were reported to be more polar than aminomethyl polystyrene beads, and were successfully employed as supports in peptide chemistry and Suzuki coupling (discussed in section 1.3.2).



Tris-OH PolyHIPE



Aminodendrimer polystyrene

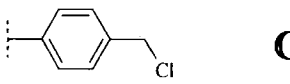
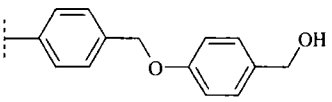
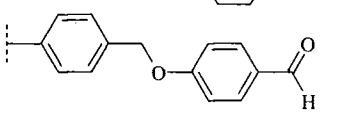
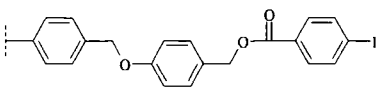
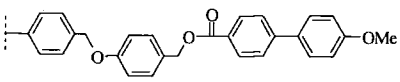
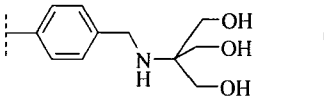
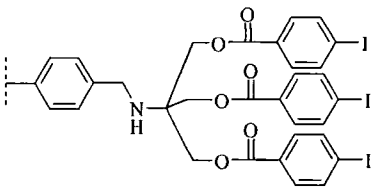
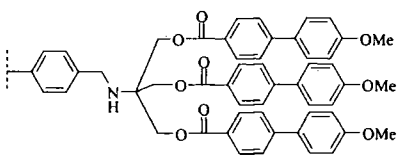
Figure 4.3 Highly loaded PolyHIPE and bead supports

4.3 Nomenclature of Polymer Supports

The code used to identify the various VBC/DVB supports and their functionalised forms in this chapter takes the same format as that described in section 2.3.2. The main reactive functionality of interest is denoted by letters: **C**hloromethyl (**C**); **W**ang **H**ydroxymethyl (**WH**); **B**enzyloxybenz**A**ldehyde (**BA**); **W**ang aryl **I**odine (**WI**); **W**ang biaryl **M**ethoxy (**WM**); **T**ris**H**ydroxymethyl (**TH**); **T**ris aryl **I**odine (**TI**); or **T**ris biaryl **M**ethoxy (**TM**) (*Table 4.1*). For example, PolyHIPE **P78B5$_m$C** was

reacted with HMP linker under flow-through conditions to produce **P78B5$_m$WH**. The support was then ground into a fine powder and esterified with 4-iodobenzoic acid to obtain an immobilised aryl iodine species, **P78B5$_g$WI**.

Table 4.1 Identification codes for polymer supports

Support Code			
Support type	% wt VBC	Batch and form	Functionality
PolyHIPE P  **Bead B** 	64% = **64** 78% = **78**	**Bx_y** x = **1, 2, 3...** y = **g, c, m** **g** = granular **c** = cubic **m** = monolithic	 **C**  **WH**  **BA**  **WI**  **WM**  **TH**  **TI**  **TM**

4.0.0 Nomenclature of Biaryl Compounds

Single numbers have been used to identify the small molecules synthesised. 4-Methoxy-biphenyl-4'-carboxylic acid methyl ester has been represented by (**1**) and 4-methoxy-biphenyl-4'-carboxylic acid has been represented by (**5**).

4.4 Preparation and Characterisation of Wang-Functionalised PolyVBC/DVB PolyHIPE

The original route to 4-(hydroxymethyl)phenoxymethyl poly(styrene-*co*-DVB) resin[2] involved reacting chloromethyl polystyrene with 4-alkoxybenzyl alcohol, however, this tended to produce resins with little homogeneity. Merrifield and Lu[10] later described an improved synthesis of Wang resin to avoid a number of competing reactions and side-products. This involved heating chloromethyl resin with 3 eq each of 4-(hydroxymethyl)phenol (HMP) and sodium methoxide in DMA for 8 h (*Figure 4.4*)

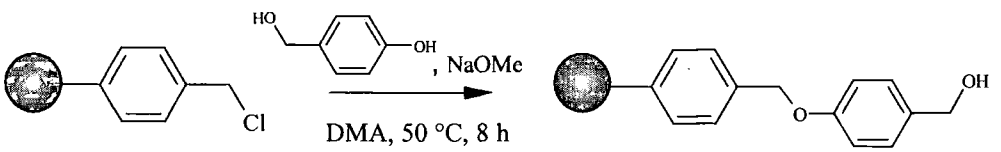


Figure 4.4 Synthesis of Wang Resin

These conditions were reported to avoid parallel reactions such as the displacement of chlorine by the benzyl alcohol anion (*Figure 4.5*), displacement by polymer-bound phenolate anions (*Figure 4.6*), or by the methoxide anion itself. In addition, at elevated temperatures and in the presence of base, it was proposed that HMP was able to undergo 1,6-elimination to 4-quinone methide.

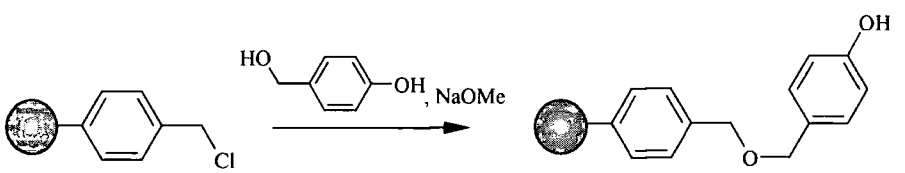


Figure 4.5 Displacement of chlorine by benzyl alcohol anion

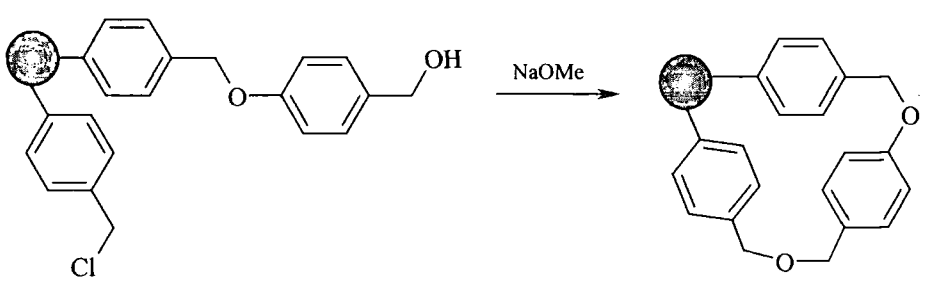


Figure 4.6 Displacement of chlorine by polymer-bound phenolate anions

4.4.1 Flow-Through HMP Functionalisations using Conditions Reported for Polymer Beads

The Quest Parallel Synthesiser has been shown to be an efficient device for performing flow-through syntheses and for obtaining functionalised supports with high loadings. Indeed, conversion by this method has often proven to be more successful than the corresponding batch method. Therefore, the improved conditions reported for the preparation of Wang resin were immediately applied to the flow-through functionalisation of PolyHIPE supports in the Quest apparatus. PolyHIPE was prepared inside fritted PTFE reactor tubes to yield monoliths, **P64B3$_m$C** (3.13 mmol -CH_2Cl groups g^{-1}), and for comparison, a granular form, **P64B2$_g$C** (3.14 mmol -CH_2Cl groups g^{-1}), was used to fill an adjacent reactor tube. On this occasion, a solution of the reagents was decanted into a Quest solvent delivery bottle and automatically delivered to **P64B3$_m$C**. Approximately 10 mL was allowed to flow-through the monolith under gravity at 50 °C, for 45 min, after which a fresh portion of reagent solution (10 mL) was delivered to the reactor tube. This process was repeated over a period of 8 h and as a result of the flow-through modification, the functionalised monolith, **P64B3$_m$WH**, was found to contain approximately 58% of the original chloromethyl sites, which corresponded to an estimated loading of 1.02 mmol $-CH_2OH$ groups g^{-1} (based on chlorine elemental analysis). Rather than flowing the reagent solution through the granular support, **P64B2$_g$C** was functionalised under batch conditions in the Quest, producing **P64B2$_g$WH** with an estimated loading of 0.95 mmol $-CH_2OH$ groups g^{-1} (61% unreacted chloromethyl sites). From the results obtained, it appeared that the batch functionalisation had performed comparably with the flow-through modification.

In an attempt to increase the number of hydroxymethyl groups on PolyHIPE supports, **P78B5$_m$C**, with a higher loading of chloromethyl groups (3.88 mmol $-CH_2Cl$ groups g^{-1}), was functionalised under flow-through. Using the procedure described for the modification of **P64B3$_m$C**, monolith **P78B5$_m$WH** was found to contain an estimated hydroxymethyl loading of 1.83 mmol -CH_2OH groups g^{-1}, which corresponded to a conversion of 63%. This was a significant improvement on previous loadings. In each functionalisation case, the hydroxymethyl loading was directly related to the change in the chlorine content of the support after modification. It was assumed, therefore, that the only reaction occurring was that of conversion to the desired Wang linker product. FTIR analysis of the functionalised support

displayed a broad peak at 3424 cm^{-1} and a sharp peak at 1241 cm^{-1} representing the hydroxyl and aryl ether groups, respectively. Interestingly, the spectra failed to show the characteristic chloride precursor peak at 1265 cm^{-1}, however, the presence of other strong peaks in the region may have masked the signal. In order to support the loadings found by elemental analysis, Fmoc analysis was performed on the functionalised supports.

4.4.2 Fmoc Assay

As with the aminomethylated PolyHIPE supports discussed in chapter 2, an indication of the loading of hydroxymethyl groups on a support can be ascertained by obtaining an Fmoc number (*Figure 4.7*) (see also *Equation 1* in section 2.4.2).

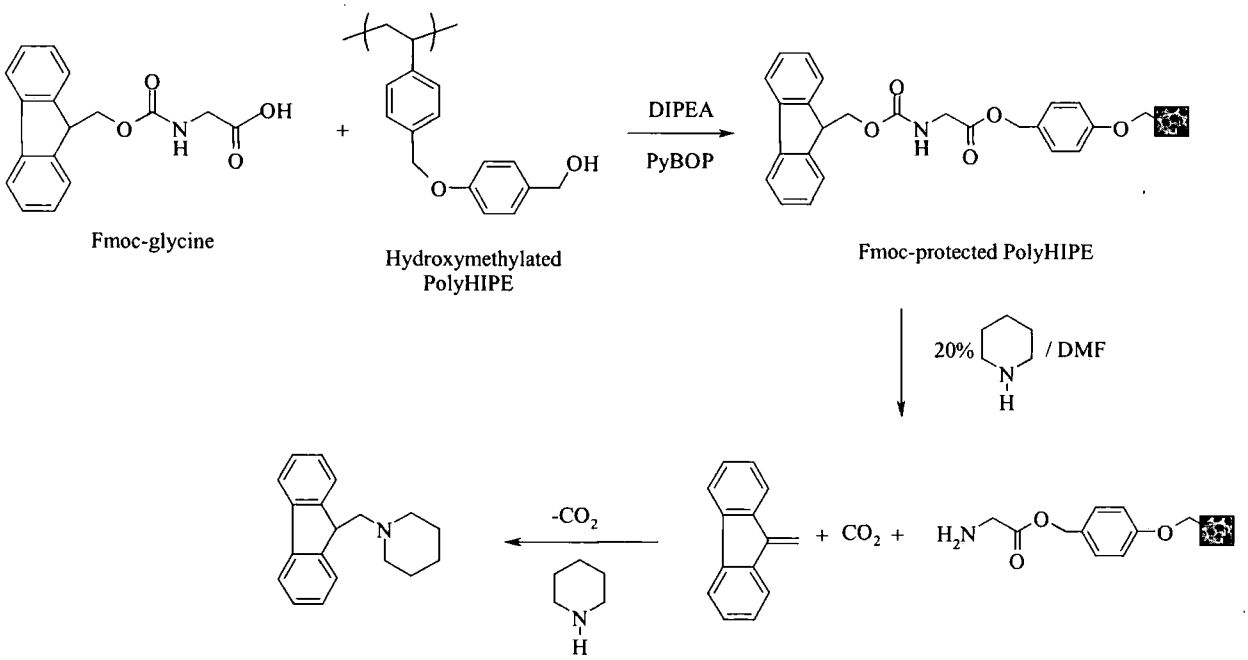


Figure 4.7 Synthesis involved in Fmoc analysis

Surprisingly, the normalised Fmoc numbers calculated for the functionalised supports were significantly lower than the loadings inferred by elemental analysis (*Table 4.2*). **P64B2$_g$WH** was reacted with Fmoc-glycine for a second time in an attempt to improve the result obtained, however, a very poor increase of 0.02 mmol g^{-1} was achieved.

Table 4.2 Loadings found by Fmoc and elemental analysis

Functionalised PolyHIPE	Average loading of -CH_2OH groups by Fmoc analysis (mmol g^{-1})	Average loading of -CH_2OH groups by elemental analysis (mmol g^{-1})
P64B3$_m$WH	0.1	1.02
P64B2$_g$WH	0.20 ± 0.03	0.95
P78B5$_m$WH	0.27 ± 0.02	1.83

The lower loadings of hydroxymethyl groups found by Fmoc analysis were possibly due to side-reactions taking place during the HMP modification. It was believed that the high loading of chloromethyl groups on the PolyHIPE may have resulted in additional reactions, and hence, the formation of a variety of different supported products. This would help to explain why the chlorine contents of the supports were reduced, and the loadings of hydroxymethyl groups were not as high as expected. This was thought to be the most reasonable explanation, however, it was also considered that this particular Fmoc procedure was not suitable for PolyHIPE materials and possibly required optimisation. Since the Wang-functionalised PolyHIPEs were to be utilised as supports in Suzuki cross-coupling reactions, it was believed that an accurate indication of the hydroxymethyl loading could be obtained by iodine elemental analysis upon attachment of 4-iodobenzoic acid.

4.4.3 Esterification of Wang-Functionalised PolyHIPE with 4-Iodobenzoic Acid

As discussed in chapter 3, the majority of solid-supported Suzuki couplings performed to date have exclusively employed cross-linked polystyrene beads as the support (see section 1.3.2 for a review of the literature). Guiles and co-workers[6] demonstrated the Suzuki coupling of phenylboronic acid with 4-iodobenzoic acid immobilised on Wang beads (0.89 mmol -CH_2OH groups g^{-1}). The acid was attached to the beads using the coupling reagents, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI) and N-hydroxybenzotriazole (HOBT). The subsequent coupling of the boronic acid was reported to take place at room temperature, in just 18 h and in 72% yield. In order to utilise Wang-functionalised PolyHIPE as a support in Suzuki reactions, routes for the attachment of 4-iodobenzoic acid were investigated. Initial experiments focussed on the use of EDCI/HOBT

chemistry, as this procedure had already proven to be successful in reactions involving beads.[6,11] Furthermore, EDCI was gradually replacing traditional coupling reagents such as DCC. Coupling by this route begins with attack on the EDCI by the acid, which is then displaced by HOBT. This activates the acid for nucleophilic attack by the hydroxyl groups on Wang resin (*Figure 4.8*).

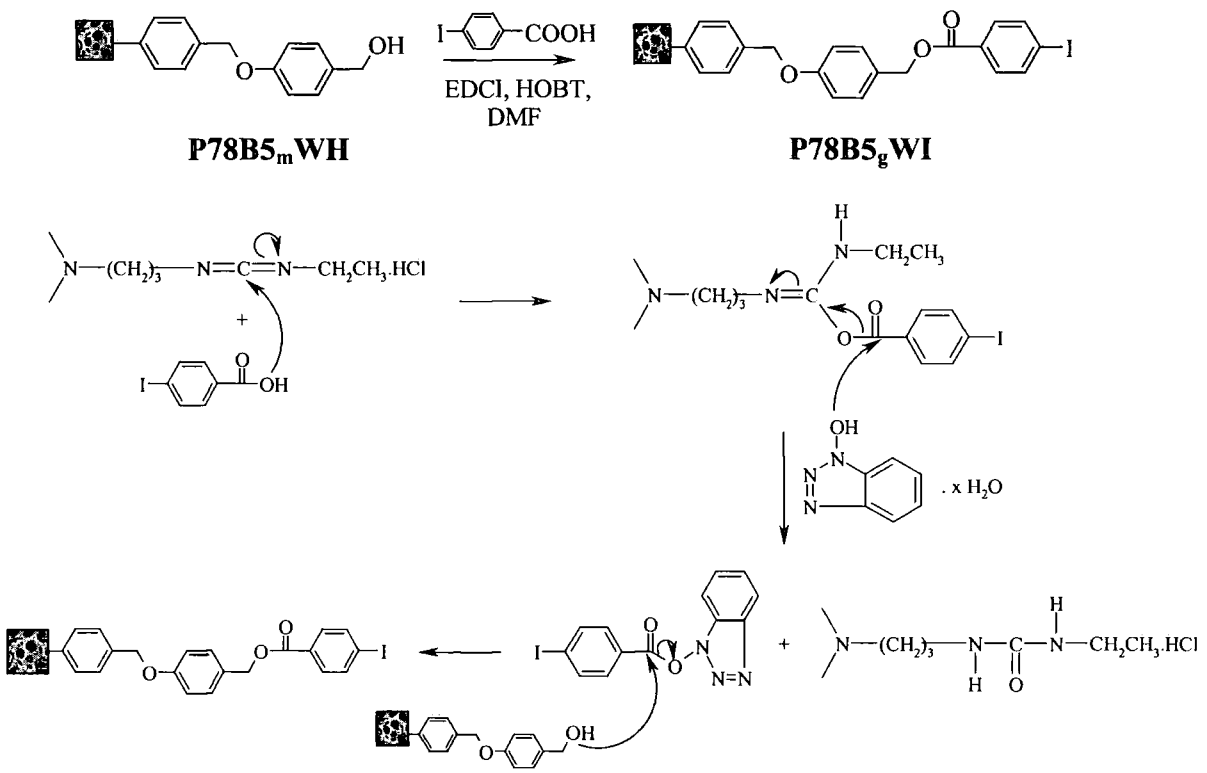


Figure 4.8 EDCI/HOBT-mediated coupling of Wang PolyHIPE and 4-iodobenzoic acid

The functionalised PolyHIPE used as the support in the esterification reaction was **P78B5$_m$WH** (1.83 mmol -CH_2OH groups g^{-1}). The monolith was finely ground for use in the batch reaction and the modification appeared to proceed well, as evidenced by a high iodine content in the functionalised support, **P78B5$_g$WI** (22.5%). An FTIR spectrum of the product displayed a strong signal at 1719 cm^{-1}, which was attributed to the carbonyl group of the ester linkage. Peaks at 1223 cm^{-1} and 1111 cm^{-1} were attributed to aryl ether and ether functionalities, respectively. These results were promising, however, it was believed that **P78B5$_g$WI** still contained unreacted 4-iodobenzoic acid, as complete conversion (based on 1.83 mmol -CH_2OH groups g^{-1}) would have resulted in 16.5% iodine, which is substantially lower than the actual

amount found on the support. Furthermore, from the mass of **P78B5$_g$WI** produced, the conversion by weight was found to be 152%. Therefore, to obtain an accurate indication of the success of acid attachment, the functionalised support was thoroughly re-washed and analysed for a second time. However, surprisingly, no iodine was found on the support.

The poor Fmoc results and unsuccessful esterification reaction implied that very few hydroxymethyl groups were present on the PolyHIPE support. This confirmed the suspicion that side-reactions were taking place during the HMP reaction. Therefore, the conditions reported in the literature[6] were optimised in an attempt to minimise the formation of by-products and to increase the loading of hydroxymethyl groups.

4.4.4 Flow-Through HMP Functionalisations using an Optimised Version of the Conditions Reported for Polymer Beads

To improve the overall success of modifications and to avoid side-reactions, optimised conditions were investigated and applied to PolyHIPE under flow-through, in the Quest system. In trial batch reactions, optimum results were obtained by employing a five times excess of reagents, by replacing DMA solvent with DMF, and by using a higher temperature (70 °C). Also, the reactions were performed over 24 h rather than 8 h. A solution of the reagents was flowed through granular and monolithic forms of **P64B4C** and **P78B2C**, using the procedure described in section 4.4.1. The functionalisation results are summarised in *Table 4.3*.

Table 4.3 Loadings obtained from optimised flow-through functionalisations

PolyHIPE support	Loading of chloromethyl groups before functionalisation (mmol g^{-1})	Functionalised PolyHIPE	Loading of chloromethyl groups after functionalisation (mmol g^{-1})	Estimated loading of hydroxymethyl groups (mmol g^{-1})
P64B4$_m$C	3.36	**P64B4$_m$WH**	0.93	1.88
P64B4$_g$C	3.36	**P64B4$_g$WH**	0.82	1.96
P78B2$_m$C	4.37	**P78B2$_m$WH**	0.62	2.71
P78B2$_g$C	4.37	**P78B2$_g$WH**	0.82	2.57

These results showed a significant increase in the loading of hydroxymethyl groups as a consequence of the optimised conditions. As expected, the extent of functionalisation was found to be greatest with the PolyHIPE in monolithic form, containing a high percentage of the VBC monomer. As in previous functionalisations, it was believed that this was due to the effect of the reagent solution being forced into the large pores of the PolyHIPE and accessing more of the reactive sites.

4.4.5 Batch HMP Functionalisations using Optimised Conditions

In comparative batch reactions employing a Radleys Carousel Reactor Station, granular and cubic forms of **P64B5C** and **P78B6C**, were functionalised using the optimised conditions described in section 4.4.4. The results are summarised in *Table 4.4*.

Table 4.4 Loadings obtained from optimised batch functionalisations

PolyHIPE support	Loading of chloromethyl groups before functionalisation (mmol g^{-1})	Functionalised PolyHIPE	Loading of chloromethyl groups after functionalisation (mmol g^{-1})	Estimated loading of hydroxymethyl groups (mmol g^{-1})
P64B5$_c$C	3.39	**P64B5$_c$WH**	1.15	1.73
P64B5$_g$C	3.39	**P64B5$_g$WH**	0.90	1.92
P78B6$_c$C	4.40	**P78B6$_c$WH**	1.20	2.31
P78B6$_g$C	4.40	**P78B6$_g$WH**	0.56	2.77

It appeared that the granular PolyHIPE supports were functionalised to a greater extent than the corresponding cubic forms. It was thought that this was due to increased exposure of the functional groups in the granular PolyHIPE, as a result of the higher surface area offered by this form. Compared to the modifications performed under flow-through, the batch reactions produced surprisingly similar results. The optimised conditions certainly appeared to produce supports with high loadings of hydroxymethyl groups and FTIR spectra showed the presence of hydroxyl and ether functionalities. However, an alternative analytical technique was greatly needed to quantify accurately the hydroxymethyl loadings of the supports and to

verify that the Fmoc loadings were indeed correct. Unfortunately, only esterification results and Fmoc numbers were available to confirm that the loadings were genuine.

4.4.6 Esterification and Fmoc Analysis of Wang-Functionalised PolyHIPE

Since functionalised PolyHIPEs, **P78B6$_c$WH** and **P78B6$_g$WH**, were estimated to contain high loadings of hydroxymethyl groups, these supports were employed in the attachment of 4-iodobenzoic acid. As in the previous esterification attempt, EDCI/HOBT coupling chemistry was employed, only on this occasion, a slightly greater excess of reagents was used to drive the reactions to completion. After two treatments, **P78B6$_c$WI** and **P78B6$_g$WI** were found to have iodine contents of 4% and 10%, respectively. These results corresponded to conversions of 23% and 45%, respectively and implied that supports with loadings in the region of 0.5 and 1.3 mmol -CH_2OH g^{-1} had been esterified. An Fmoc number was obtained for the parent HMP functionalised PolyHIPE, **P78B6$_g$WH**, in order to observe whether the loading implied by the esterification matched that of the Fmoc loading. The analysis revealed an average Fmoc loading of 0.39 mmol -CH_2OH groups g^{-1}, which was substantially lower than the loading estimated by elemental analysis (2.77 mmol -CH_2OH groups g^{-1}) and the loading implied by the esterification result (1.3 mmol -CH_2OH groups g^{-1}).

Even after optimising the HMP functionalisation procedure, the Fmoc number and esterification results still suggested that very few hydroxymethyl groups were present on the PolyHIPE supports. At this stage, the accuracy of the Fmoc technique was questioned. The procedure utilised on the PolyHIPEs was the same as that widely applied to polymer beads. Therefore, in order to test the reliability of the technique, commercial Wang resin beads, with a 'known' loading of 2.7 mmol -CH_2OH groups g^{-1}, were analysed. The beads were found to contain an average normalised loading of 2.11 ± 0.02 mmol -CH_2OH groups g^{-1}, which was significantly closer to the theoretical loading than any of the values measured on the PolyHIPE supports. Therefore, the technique proved to be reasonably accurate in determining the loading of polymer beads, but less successful with PolyHIPE materials. This result supported the original belief that the Fmoc procedure was unsuitable for PolyHIPE and possibly required optimisation. However, it seemed to be too much of a coincidence that the EDCI esterification reaction was also unsuitable for PolyHIPE materials. Once again, the data indicated that the HMP functionalisation had failed to produce exclusively the desired product.

4.4.7 Investigation into Alternative Bases for Wang Resin Synthesis

Since the PolyHIPEs used in the HMP functionalisations were highly loaded with reactive chloromethyl groups, there was a strong possibility that the unprotected resin-bound phenolate anions were displacing chlorine themselves, producing a cross-linking effect (*Figure 4.9*).

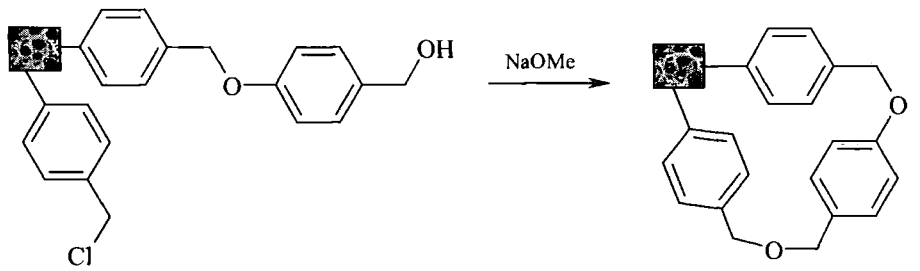


Figure 4.9 Cross-linking effect in highly loaded chloromethyl PolyHIPE

Furthermore, it was likely that the base, NaOMe, was directing the attack of the benzyl alcohol anion as well as the phenolic anion, resulting in a mixture of products. As a result, the aromatic hydroxyl groups would have been less reactive than the primary hydroxymethyl groups during the esterification reactions and the reactions involved in the Fmoc procedure, hence the low conversions (*Figure 4.10*).

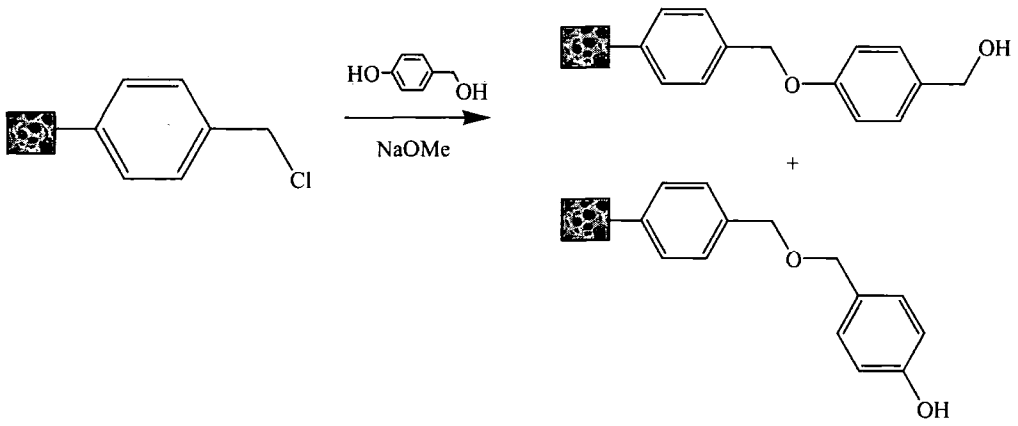


Figure 4.10 Mixture of products formed during HMP functionalisations

For these reasons, a variety of other organic bases was employed as replacements for NaOMe in the HMP reactions. Initial experiments focused on the use of the weak base triethylamine. In parallel reactions employing the optimised conditions, **P78B3$_g$C** was reacted with HMP reagent in the presence of NEt_3. Elemental analysis results suggested that a support with an estimated loading of 1.27 mmol $-CH_2OH$

groups g^{-1} had been produced. However, Fmoc analysis suggested that the support contained only 0.01 mmol -CH_2OH groups g^{-1}. FTIR analysis displayed a strong, broad peak at 3405 cm^{-1}, implying that high numbers of hydroxyl groups were present. However, these were not necessarily hydroxymethyl groups.

In an attempt to increase conversions, DIPEA was employed in an identical reaction to that performed with triethylamine. **P78B3$_g$C** was reacted with HMP reagent, and a PolyHIPE support with an estimated loading of 0.55 mmol -CH_2OH groups g^{-1} was obtained. As with triethylamine, the Fmoc number (0.06 mmol -CH_2OH groups g^{-1}) failed to match the estimated loading found by elemental analysis. Evidently, the alternative bases had failed to increase the loadings of Wang-functionalised PolyHIPE and were unsuccessful in improving the Fmoc results.

In a final attempt to obtain Wang-functionalised PolyHIPE, sodium hydride was employed as the base in the attachment of HMP linker. The reagent was first reacted with NaH to produce the phenoxide anion, and this was then added to granular and cubic PolyHIPE, **P78B3$_g$C** and **P78B3$_c$C**, in DMF. Initially, the original HMP functionalisation conditions reported in the literature[10] were utilised in the reactions, and after 8 h, **P78B3$_g$WH** was found to contain 1.84 mmol -CH_2OH groups g^{-1} (corresponding to 63% conversion) and **P78B3$_c$WH** contained 1.03 mmol -CH_2OH groups g^{-1} (corresponding to 35% conversion). Under the optimised conditions developed for PolyHIPE, the conversions were vastly improved compared to the other bases. The loadings of **P78B3$_g$WH** and **P78B3$_c$WH** were increased to 2.73 and 2.43 mmol -CH_2OH groups g^{-1}, respectively. In order to support the data, **P78B3$_g$WH** was esterified with 4-iodobenzoic acid. As in previous attempts, EDCI/HOBT coupling chemistry was used to attach the acid onto the Wang-functionalised support, however, on this occasion, no iodine was detected on **P78B3$_g$WI** after reaction.

Numerous attempts were made to attach HMP linker directly onto PolyHIPE, and indeed, elemental analysis data indicated that high loadings of hydroxymethyl groups had been obtained. However, Fmoc numbers were consistently lower than expected, as were conversions to iodoesters by the EDCI/HOBT esterification route. At this point, it was concluded that the esterification reactions involved in the Fmoc procedure and the attachment of 4-iodobenzoic acid were not compatible with PolyHIPE. Particularly in batch reactions involving PolyHIPE, it was likely that many of the pendant hydroxymethyl groups were hiding inside the matrix, hence, only surface –CH_2OH groups were reacting. Therefore, an alternative esterification route

involving MSNT/NMI reagents was investigated. MSNT is reported to be effective in difficult circumstances, such as loading of HMBA resins. Therefore, it was hoped that this reagent would be more successful in converting the pendant hydroxymethyl groups of PolyHIPE, which are thought to be less easily accessed as a result of steric hindrance from neighbouring pendant groups.

4.4.8 Esterification of Wang-Functionalised PolyHIPE via MSNT

In an investigation into ester formation, in which the alcohol or carboxylic acid component was immobilised on a solid support, MSNT reagent was found to produce the best results over DCC, DCC/HOBT and DCC/DMAP.[12] MSNT is particularly useful for the attachment of substituted amino acids, aromatic and hindered carboxylic acids, and in reactions involving unreactive linkers (*Figures 4.11 and 4.12*).

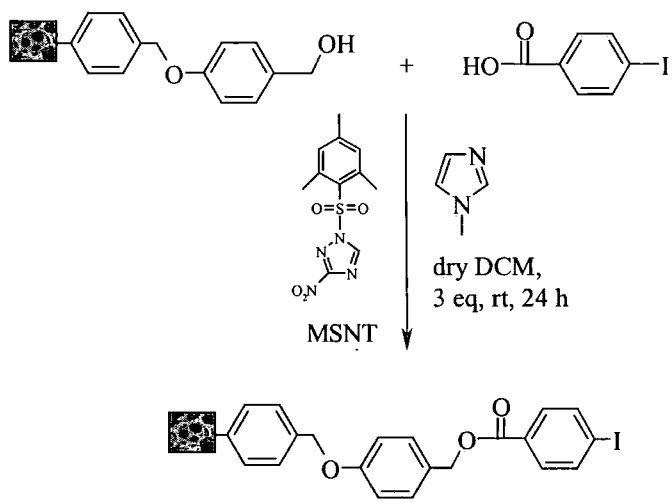


Figure 4.11 Reaction of 4-iodobenzoic acid with Wang linker using MSNT-mediated coupling

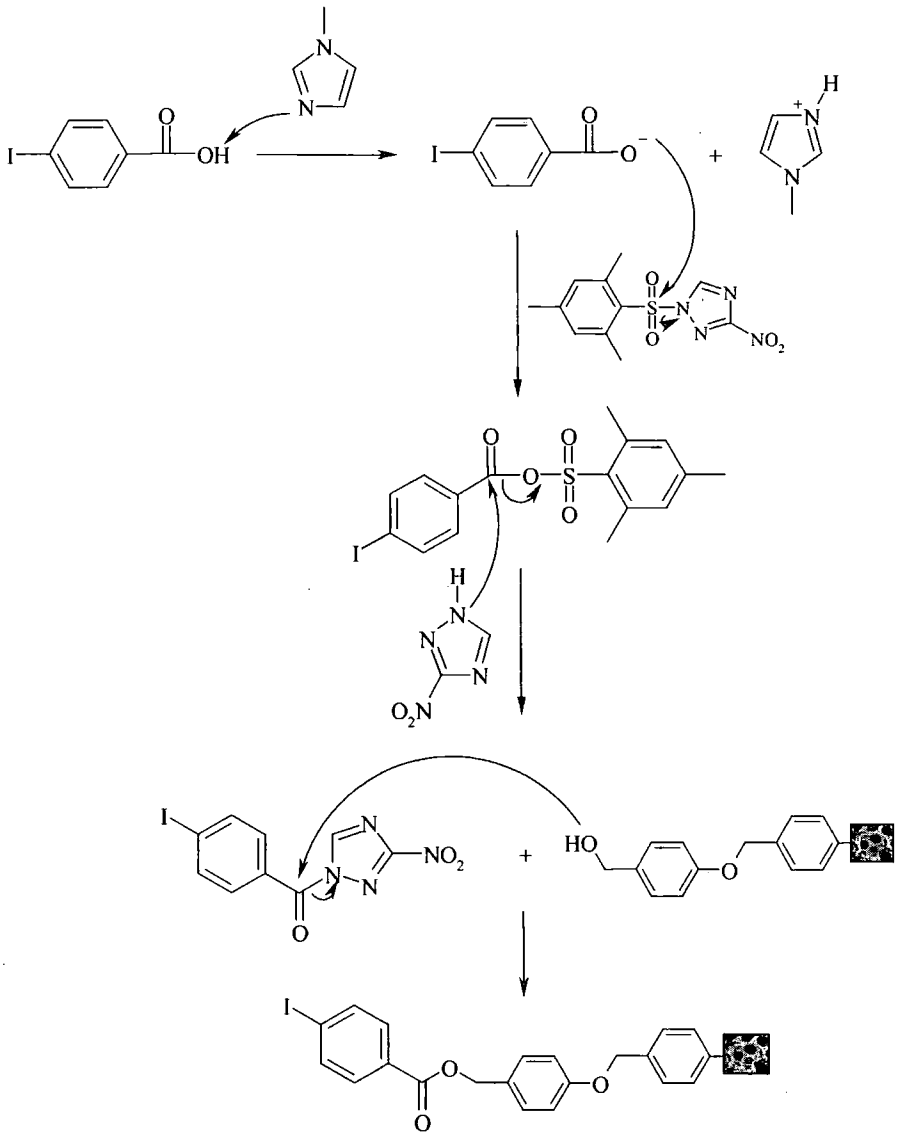


Figure 4.12 Mechanism of MSNT coupling

P78B3$_g$WH, prepared using NaH via the optimised conditions, was treated with MSNT/NMI reagents for 1 h, after which time the conversion by iodine analysis was found to be 30% and the FTIR spectrum revealed a strong carbonyl peak at 1718 cm^{-1}. This initial result was certainly more promising than the results of the recent couplings involving EDCI/HOBT. In batch reactions employing commercial Wang resin beads, the success of the MSNT/NMI route was compared to that of the EDCI/HOBT approach. Based on the loading of the beads (2.7 mmol -CH_2OH groups g^{-1}), complete conversion would have resulted in iodine contents of 21%. However, no iodine was found in **BB1WI** functionalised by the EDCI/HOBT route and 11.2% (corresponding to a conversion of 53%) was present in the batch treated with

MSNT/NMI reagents. These parallel reactions showed MSNT/NMI mediated coupling to be much more effective with Wang resins than the corresponding EDCI/HOBT protocol. Although the MSNT/NMI reaction was less successful with PolyHIPE than with beads, it was believed that optimisation of the reaction would eventually result in improved conversions.

4.4.9 Alternative Procedure for the Preparation of Wang-Functionalised PolyHIPE

With the introduction of the MSNT/NMI esterification route came an alternative procedure for the preparation of Wang-functionalised PolyHIPE.[13] This involved the initial attachment of 4-hydroxybenzaldehyde to the chloromethyl groups of PolyHIPE, followed by reduction to the primary alcohol (*Figure 4.13*).

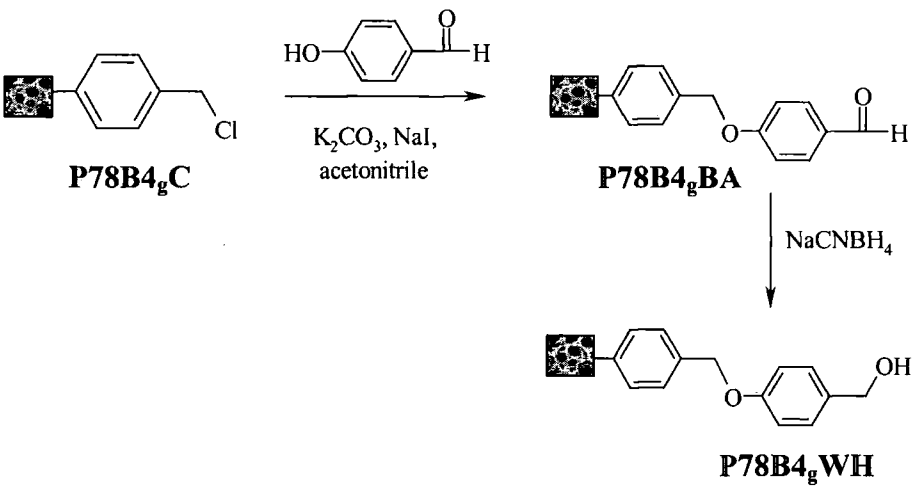


Figure 4.13 Alternative route to Wang-functionalised PolyHIPE

As an alternative to the direct attachment of the HMP linker, it was believed that this procedure avoided the formation of interfering by-products and allowed closer monitoring of the success of the reaction at each stage. The extent of conversion to the PolyHIPE-immobilised aldehyde was estimated from the loss in chlorine and confirmed by the presence of both carbonyl (1691 cm^{-1}) and aldehyde (2736 cm^{-1}) signals in the FTIR spectrum. The reduction of the carbonyl groups to primary alcohol groups was then monitored by the disappearance of the carbonyl signal by FTIR. Assuming complete reduction, the loading of hydroxymethyl groups on the support was believed to be directly proportional to the aldehyde loading.

This procedure also provided an efficient means by which to prepare PolyHIPE-immobilised aldehydes. Aldehyde functionalised beads have already found application in solid phase peptide and organic synthesis, and 4-benzyloxybenzaldehyde polystyrene (*Figure 4.14*) has proven to be an excellent polymer-supported scavenger reagent for removing amines, hydrazines, hydroxylamines and 1,2-aminothiols. Primary amines can be sequestered selectively in the presence of secondary amines making this scavenger particularly useful during the work-up of reductive alkylation reactions.

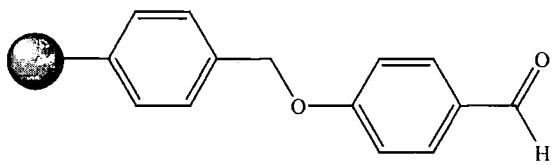


Figure 4.14 Structure of benzyloxybenzaldehyde polystyrene

In a batch reaction, **P78B4$_g$C** (4.5 mmol $-CH_2Cl$ groups g^{-1}) was heated under reflux with 4-hydroxybenzaldehyde, in the presence of K_2CO_3 and NaI, for 48 h. The resultant conversion to **P78B4$_g$BA** was found to be 97% (by elemental analysis) and the loading of aldehyde was calculated to be 3.14 mmol –CHO groups g^{-1}. FTIR analysis displayed strong signals at 1691 cm^{-1} and 2736 cm^{-1} representing carbonyl and aldehyde C-H stretching, respectively, and confirmed that the intermediate had been prepared. In order to identify the best reducing agent for optimum carbonyl reduction, **P78B4$_g$BA** was reduced using two different reagents, $NaBH_4$ and $NaCNBH_4$. The latter was employed in the procedure described in the literature, however, $NaBH_4$ was found to be the most successful for PolyHIPE materials, resulting in **P78B4$_g$WH** with an estimated hydroxymethyl loading of 3.14 mmol - CH_2OH groups g^{-1}. An FTIR spectrum of the product displayed a very broad peak at 3421 cm^{-1}, which was attributed to the primary hydroxyl functionality. The carbonyl peak was significantly reduced, however, not completely removed from the spectrum (*Figure 4.15*). This suggested that 100% reduction had not taken place and the actual hydroxymethyl loading was slightly less than that estimated.

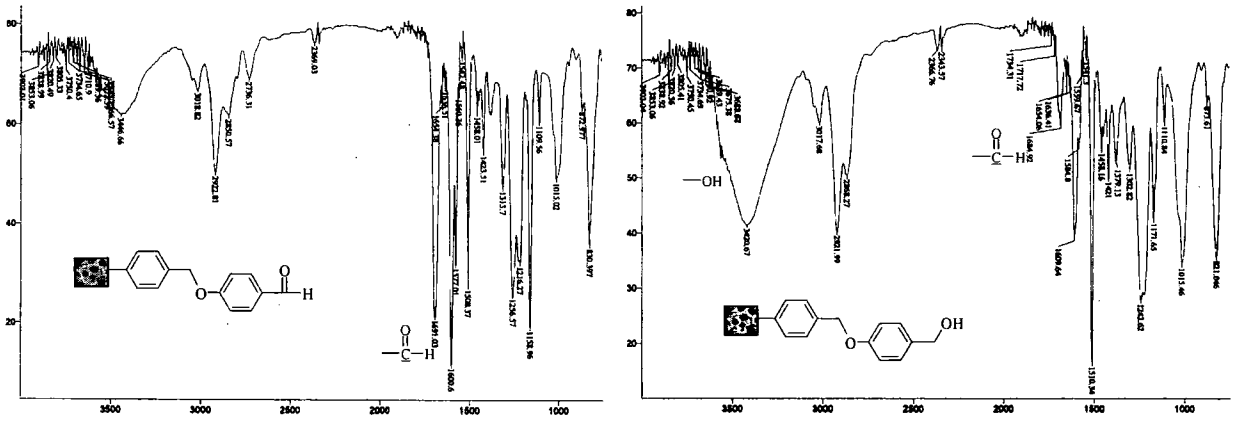


Figure 4.15 IR Spectra of PolyHIPE before and after reduction with $NaBH_4$

4.4.10 Optimisation of MSNT/NMI Coupling Reaction

The MSNT/NMI reaction was optimised in an attempt to improve the amount of 4-iodobenzoic acid loaded onto the PolyHIPE supports. The Wang-functionalised PolyHIPEs, prepared by the alternative derivatisation route, were employed in the study, as the estimated loadings were believed to be more accurate than those found from the direct HMP functionalisation route. Initially, the standard MSNT procedure was repeated using an extended reaction time of 2 h. This modification immediately increased the iodine conversion from 30% to 53%, and was believed to be a reasonable starting point upon which to optimise the reaction. The first parameter investigated, was the concentration of MSNT/NMI reagents. In parallel reactions, **P78B1$_g$WH** (3 mmol $-CH_2OH$ groups g^{-1}) was reacted at room temperature with 3, 5 and 10 equivalents of MSNT reagent. The greatest conversion, 69%, was achieved with 3 eq and was significantly higher than the conversion obtained with the standard conditions (*Table 4.5*)

Table 4.5 Conversions with increasing concentrations of MSNT

PolyHIPE loading (mmol g^{-1})	MSNT Concentration (eq)	Solvent	Temperature (°C)	Reaction time (h)	Conversion (%)
3.0	2	Dry DCM	20	2	53
3.0	3	Dry DCM	20	2	69
3.0	5	Dry DCM	20	2	68
3.0	10	Dry DCM	20	2	68

The optimum concentration of reagents (3 eq) was then applied in a temperature study, employing 20 °C (room temperature), 30 °C and reflux (40 °C) conditions. On this occasion, the greatest conversion was achieved when the reaction was performed under reflux (73%), however, this was not considered to be a substantial improvement on the conversion obtained at room temperature (69%) (*Table 4.6*).

Table 4.6 Conversions with increasing temperature

PolyHIPE loading (mmol g^{-1})	MSNT Concentration (eq)	Solvent	Temperature (°C)	Reaction time (h)	Conversion (%)
3.0	3	Dry DCM	20	2	69
3.0	3	Dry DCM	30	2	58
3.0	3	Dry DCM	40	2	73

In the final experiment, the effect of reaction time on the conversion to iodine was investigated. MSNT reagent (3 eq) was reacted at room temperature, with Wang-functionalised PolyHIPE, for 4, 6 and 24 h. The greatest conversion to iodine was obtained after 24 h (*Table 4.7*).

Table 4.7 Conversions with increasing reaction time

PolyHIPE loading (mmol g^{-1})	MSNT Concentration (eq)	Solvent	Temperature (°C)	Reaction time (h)	Conversion (%)
3.0	3	Dry DCM	20	2	62
3.0	3	Dry DCM	20	4	68
3.0	3	Dry DCM	20	6	64
3.0	3	Dry DCM	20	24	73

From the optimisation studies, the optimum conditions for the MSNT/NMI coupling of 4-iodobenzoic acid on Wang-functionalised PolyHIPE were found to be 3 eq of MSNT reagent, a reaction temperature of 20 °C and a duration of 24 h. It has often been found that PolyHIPE materials require longer reaction times to ensure

maximum conversion of their functional groups. FTIR spectra of the esterified PolyHIPEs revealed strong peaks at 1719 cm^{-1}, representing the ester carbonyl groups, and significantly reduced hydroxyl peaks.

4.4.11 Fmoc Analysis using MSNT/NMI Coupling

The results of the Fmoc analysis on Wang-functionalised PolyHIPE were consistently poor and it was often suspected that the procedure was unsuitable for PolyHIPE materials. The process involved activation of Fmoc-glycine by the coupling reagent PyBOP, and the subsequent attack of the hydroxyl groups of Wang-functionalised PolyHIPE. As with the EDCI/HOBT coupling, it was believed that PyBOP-mediated coupling was incompatible with PolyHIPE. Therefore, the MSNT/NMI route was employed in the attachment of Fmoc-glycine to the Wang-functionalised materials. An Fmoc procedure involving these reagents has been applied successfully to Wang polymer beads.[14] In parallel batch reactions, Fmoc analysis was performed on **P78B1$_g$WH** (3 mmol $-CH_2OH$ groups g^{-1}) and Wang beads (2.7 mmol $-CH_2OH$ groups g^{-1}) using the Fmoc conditions reported in the literature (2 h, 20 °C, 3 eq MSNT, 2.25 eq NMI). The average Fmoc loading of the beads was found to be 1.90 ± 0.15 mmol $-CH_2OH$ groups g^{-1}, which was slightly less than the average Fmoc loading obtained utilising the standard conditions (2.11 ± 0.02 mmol $-CH_2OH$ groups g^{-1}). Unfortunately, the PolyHIPE materials were found to have an average Fmoc loading of 0.66 ± 0.03 mmol $-CH_2OH$ groups g^{-1}, which was substantially lower than the loading estimated from elemental analysis.

In a similar batch reaction, the Fmoc analysis was repeated using the optimised MSNT/NMI coupling conditions developed for PolyHIPE (24 h, 20 °C, 3 eq MSNT, 12 eq NMI). However, as in the previous case, the PolyHIPE supports were found to have an average Fmoc loading of 0.65 ± 0.01 mmol $-CH_2OH$ groups g^{-1}. Again, this was a very disappointing and somewhat surprising result. It suggested that 23% of the hydroxymethyl groups had reacted with Fmoc-glycine leaving 77% of the groups unmodified. Since the Fmoc procedure was performed in two stages, it was unknown whether the coupling of Fmoc-glycine had been unsuccessful, or the cleavage to form the piperidine adduct. Therefore, to clarify the situation, the nitrogen contents of the Fmoc-coupled PolyHIPE and beads (*Figure 4.16*) were determined by elemental analysis.

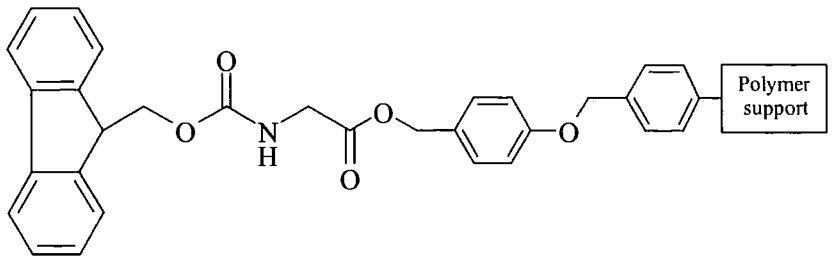


Figure 4.16 Fmoc-glycine protected polymer supports

Certainly, the results obtained were reflected in the Fmoc numbers obtained for these supports. The beads were found to have a nitrogen content of 1.95%, which corresponded to a conversion of 90%. On the contrary, the PolyHIPE material had a nitrogen content of 0.74%, which corresponded to a conversion of 32%. The nitrogen analysis proved that it was indeed the coupling of the Fmoc-glycine onto the PolyHIPE support which had failed to take place successfully.

In conclusion, several coupling reactions were undertaken in an attempt to couple Fmoc-glycine onto Wang-functionalised PolyHIPE supports. The MSNT/NMI route proved to be most successful for the Fmoc analysis of Wang beads, however, this route failed to predict the loading of the PolyHIPE supports. It was believed that this coupling route was successful for the attachment of small molecules such as 4-iodobenzoic acid onto PolyHIPE, yet, less suitable for the attachment of larger, bulkier compounds such as Fmoc-glycine. It was thought that the larger surface area of the polymer beads allowed for unimpeded access of the bulky reagent, and hence, increased Fmoc loadings.

4.5 Attempted Suzuki Coupling of Wang-Functionalised PolyHIPE

Since the attachment of 4-iodobenzoic acid to Wang-functionalised PolyHIPE had been demonstrated successfully (confirmed by iodine elemental analysis), the aim was to utilise this product in the solid phase Suzuki coupling of 4-methoxybenzeneboronic acid. To begin, the optimised MSNT/NMI conditions were applied to a slightly larger batch of **P78B1$_g$WH** than had been used in the optimisation investigation. As a result, a conversion of only 51%, as determined by iodine analysis, was observed. This result was disappointing, considering that 74% conversion had been achieved previously under these conditions, using a lesser amount of **P78B1$_g$WH**. The loading of iodine on **P78B1$_g$WI** (0.89 mmol –I groups g^{-}

[1]) was believed to be sufficient, however, to demonstrate that Suzuki coupling on Wang-functionalised PolyHIPE was viable.

Guiles and co-workers[6] reported that the Suzuki reaction could be performed at room temperature using Wang beads. However, Ruhland and co-workers' attempts to couple Wang-bound 4-iodobenzoic acid with phenylboronic acid, at ambient temperature, proved to be largely unsuccessful.[15] They found that heating of the reaction in DMF was necessary for coupling to occur. Therefore, a small-scale coupling reaction was attempted using the optimised conditions developed on chloromethyl PolyHIPE (section 3.4.1.3). The coupling seemed to proceed smoothly as evidenced by a high mass conversion to **P78B1$_g$WM** (95%) and the disappearance of the C-I signal (555 cm^{-1}) in the FTIR spectrum. **P78B1$_g$WM** was cleaved with trifluoroacetic acid in DCM (1:1) in order to obtain the biaryl product, 4-methoxy-biphenyl-4'-carboxylic acid (**5**) (*Figure 4.17*).

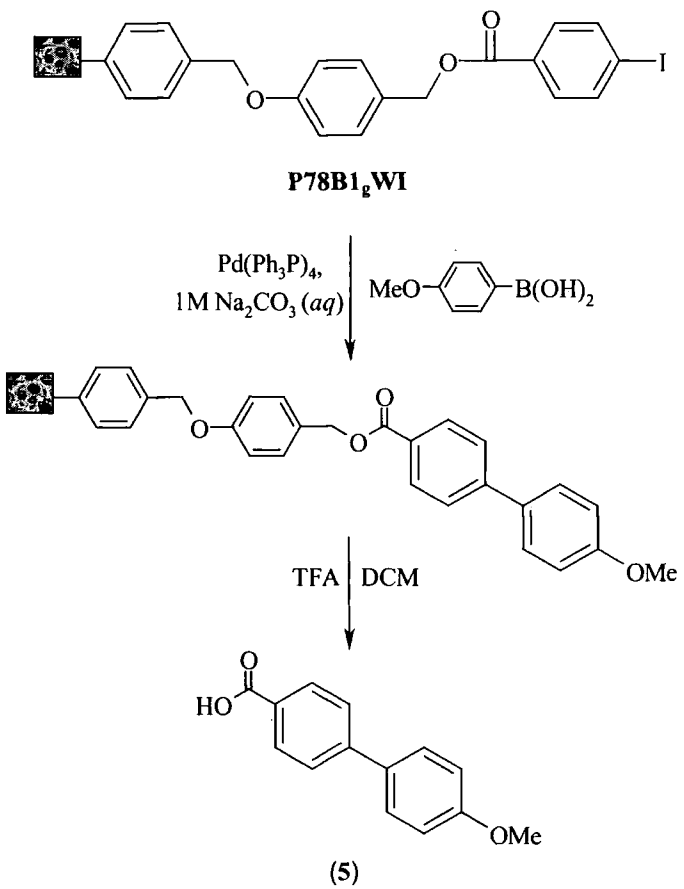


Figure 4.17 Solid-phase Suzuki coupling on Wang-functionalised PolyHIPE

The initial cleavage resulted in a 93% yield of crude product and the ^{1}H NMR spectrum displayed peaks which were in close agreement with the values quoted in the literature for this compound.[16] However, there were also other peaks of similar intensity in the aromatic region, which could not be easily assigned. The most abundant peaks, in the analytical HPLC trace of the crude product, were detected at 4.9 min (38%) and 5.7 min (39%). One other significant peak had a retention time of 3.7 min (12% abundance). In a previous Suzuki coupling attempt using polymer beads (section 3.5), 4-methoxy-biphenyl-4'-carboxylic acid was formed during cleavage with NaOMe, as a result of hydrolysis. On this occasion, the acid was found to have a retention time of 2.8 min by analytical HPLC, and was detected by LC-MS at 3.2 min. A species with a retention time of 2.9 min was also found in the crude product, however, its abundance was only 4.3%.

In an attempt to identify the major impurities, the crude product was analysed by LC-MS. The major peaks in the LC trace, which were detected at 4.4 min and 5.8 min, were believed to correspond to the signals at 4.9 min and 5.7 min in the analytical HPLC trace. When analysed in ES- mode, a species with *m/z* of 113 was found at 4.4 min and a species with *m/z* of 247 was found at 5.8 min. These were attributed to TFA $(M-H)^-$ and 4-iodobenzoic acid $(M-H)^-$. The product was also found to contain unreacted boronic acid in 5% abundance (3.1 min). In ES+ mode, a compound with *m/z* of 229 was detected at 3.5 min, which was thought to represent the biaryl acid product (**5**) $(M+H)^+$.

Despite the presence of various by-products, the LC-MS data suggested that a small amount of product had been obtained (12%). The FTIR spectrum of the PolyHIPE after cleavage displayed a strong carbonyl peak at 1718 cm^{-1}, suggesting that the biaryl product had not cleaved completely from the support. Therefore, **P78B1$_g$WM** was cleaved for a second time using a higher concentration of TFA and a reaction time of 1 h, rather than 30 min. The second treatment resulted in a further 20 mg of crude product, which increased the total crude yield to >100%. The ^{1}H NMR spectrum displayed the desired peaks, and it appeared that the crude product was contaminated with fewer impurities. Based on the results of the first cleavage, the analytical HPLC analysis of the second crude product showed that TFA was present in 55% abundance, together with 4-iodobenzoic acid (21% abundance). Interestingly, the amount of biaryl acid (**5**) had increased to 19%. In the LC-MS trace, a signal with *m/z* of 229 $(M+H)^+$, confirmed that the product was indeed present. Despite the re-

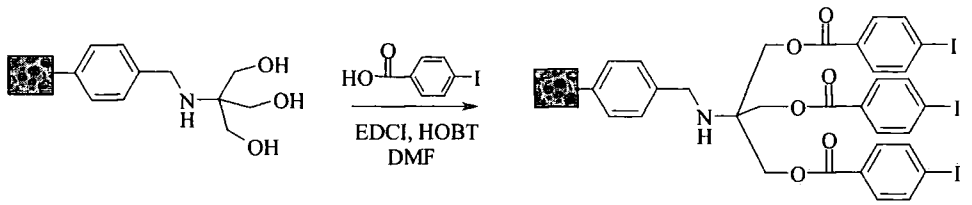
cleave using a higher concentration of TFA, the FTIR spectrum of the cleaved PolyHIPE still displayed a strong carbonyl peak at 1718 cm^{-1}.

From the analytical results, it was apparent that treatment with TFA was cleaving only a small amount of biaryl acid product each time. Furthermore, the purities of the products were poor due to the high concentrations of TFA utilised. This was the first attempt at Suzuki coupling on Wang-functionalised PolyHIPE and indeed the coupling of 4-methoxybenzeneboronic acid was believed to have taken place successfully. However, cleavage with TFA using the conditions reported for beads[6] proved to be less effective when applied to PolyHIPE material, and required optimisation to ensure complete recovery of the product.

4.6 Attempted Suzuki Coupling Using Highly Loaded Tris-OH Functionalised PolyHIPE

In parallel work by Krajnc *et al.*,[17] tris(hydroxymethyl)aminomethane was immobilised on VBC/DVB (78:22 wt%) PolyHIPE to obtain a highly loaded support with 7.7 mmol $-CH_2OH$ groups g^{-1} (based on nitrogen elemental analysis). It was proposed that this novel linker be used to attach 4-iodobenzoic acid to obtain a high number of immobilised halide groups for subsequent Suzuki coupling reactions. Theoretically, if all of the hydroxymethyl groups reacted with the acid, the maximum loading of iodine on the support would be 2.9 mmol –I groups g^{-1}.

As with the Wang-functionalised PolyHIPEs prepared, Fmoc analysis was performed on tris-OH PolyHIPE, **P78B7$_g$TH**, in an attempt to determine accurately the hydroxymethyl loading. However, as with previous efforts, the average Fmoc number was found to be significantly lower (1.22 ± 0.06 mmol $-CH_2OH$ groups g^{-1}) than the loading suggested by elemental analysis. This further supported the theory that the Fmoc procedure developed for Wang beads was unsuitable for PolyHIPE. Although EDCI/HOBT mediated esterification proved to be unsuccessful with Wang-functionalised PolyHIPE, it appeared to work well with tris-OH PolyHIPE for the attachment of 4-iodobenzoic acid. The resultant conversion to iodine was found to be 95% (*Figure 4.18*).



P78B7$_g$TH **P78B7$_g$TI**

Figure 4.18 Attachment of 4-iodobenzoic acid to trishydroxymethyl PolyHIPE

Upon closer inspection of the reagents and functionalities involved, it was thought that the secondary amine may have reacted with the acid to form a salt. Therefore, **P78B7$_g$TI** was washed with triethylamine in methanol (1:1) to remove any salt by-products (*Figure 4.19*). Indeed, this treatment reduced the iodine content of the support from 35% (94% conversion) to 29% (79% conversion).

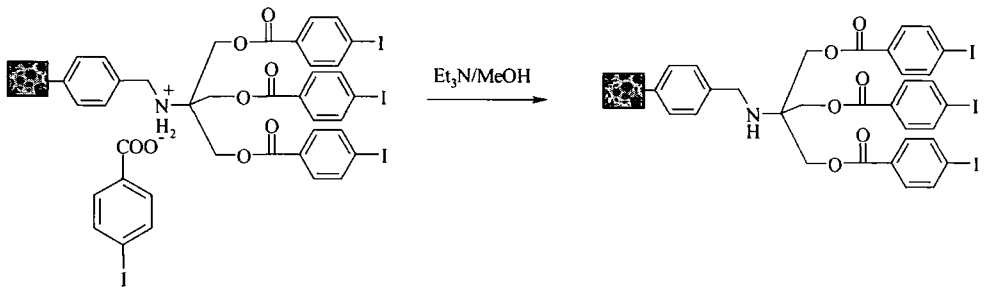


Figure 4.19 Removal of salts from tris-functionalised PolyHIPE

To verify the reproducibility of the esterification technique, a second batch of **P78B7$_g$TI** was prepared. Under identical reaction conditions, and following the same wash procedure, the conversion to **P78B7$_g$TI** was found to be 86%, which corresponded to a loading of 2.5 mmol –I groups g^{-1}.

The highly loaded supports were then used in Suzuki coupling reactions. Since this was the first time that the Suzuki reaction had been performed utilising a support with such a high loading of hydroxymethyl groups, parallel reactions involving two different sets of conditions were performed. The optimised conditions developed in section 3.4.1.3, and the room temperature conditions reported by Guiles and co-workers[6] were applied in the coupling of **P78B7$_g$TI** with 4-methoxybenzeneboronic acid (*Figure 4.20*). Rather than using 1M $Na_2CO_3(aq)$, the couplings were performed using potassium carbonate, as outlined in the literature procedure.

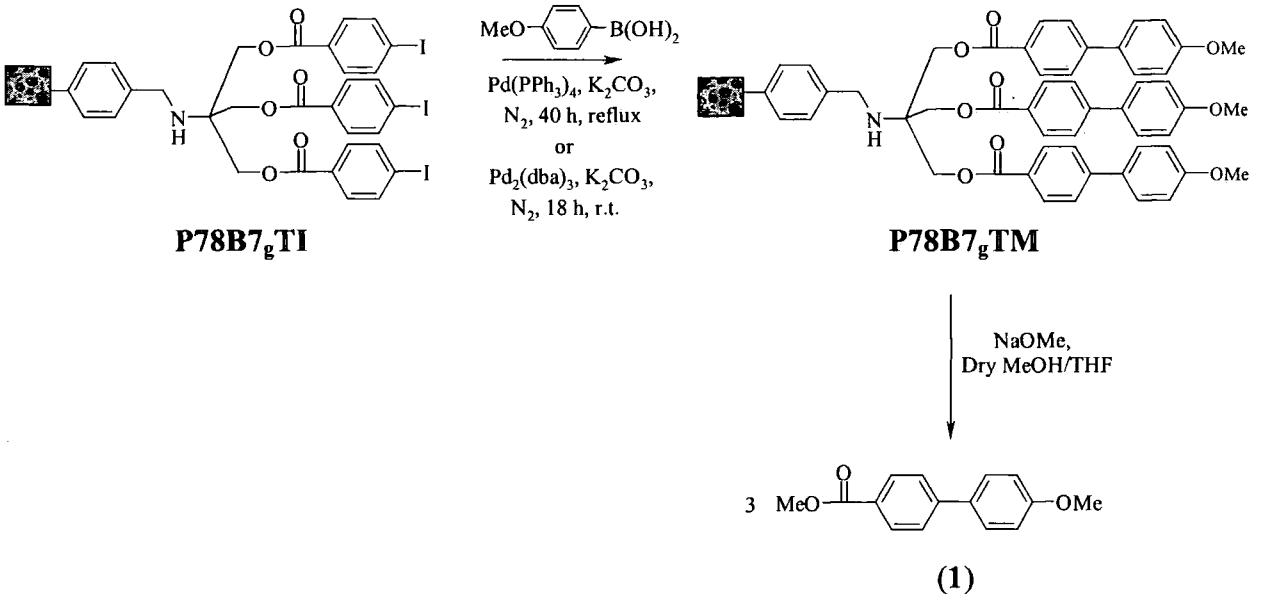


Figure 4.20 Solid-phase Suzuki coupling on tris-I functionalised PolyHIPE

After reaction, the weights of immobilised product were lower than expected, yielding conversions of 44% and 42% for the optimised and ambient couplings, respectively. Furthermore, the FTIR signals representing the carbonyl groups at the ester attachment points, were significantly reduced after coupling, suggesting that the loadings of immobilised product had decreased. Despite this, the materials were cleaved with NaOMe and crude yields of 34% and 21% (based on the original loading of iodine) were obtained for the optimised and ambient conditions, respectively. ^{1}H NMR analysis of the crude product obtained from the optimised conditions confirmed that biaryl ester (**1**) had been produced in high purity (*Figure 4.21*).

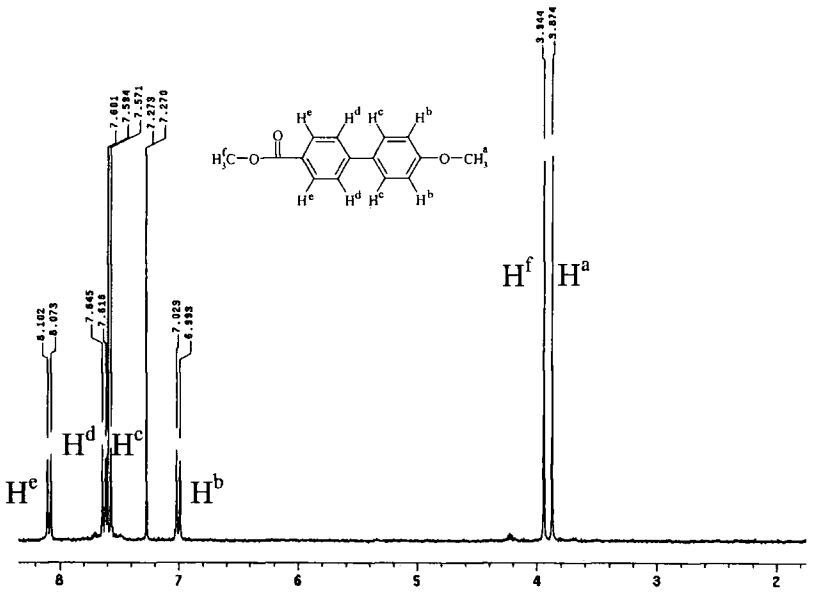


Figure 4.21 ^{1}H NMR spectrum of 4-methoxy-biphenyl-4'-carboxylic acid methyl ester (1)

The ^{1}H NMR spectrum of the crude product obtained from the ambient conditions also confirmed that biaryl ester **(1)** was present, however, there were also other peaks of similar intensity present in the aromatic region. This suggested that the quality of product produced by this route was not as high as with the optimised Suzuki conditions. The actual purities of the products were not determined, rather the intention of this work was to demonstrate that the Suzuki coupling reaction was viable on this type of support.

Unfortunately, the amounts of biaryl ester produced from the tris-OH PolyHIPE reactions did not exceed the quantities obtained from the direct Suzuki coupling on chloromethyl PolyHIPE. In fact, the yields produced by the latter route were significantly higher. The supports were supposedly highly loaded with 4-iodobenzoic acid, however, after coupling, it seemed that the loadings had decreased significantly. As with Wang-functionalised PolyHIPE, it was thought that unreacted 4-iodobenzoic acid was trapped within the matrix, and was producing a 'false' supported iodine content. Upon further reaction *i.e.* coupling and washing, the unreacted acid was gradually removed, leaving the actual 'bound' iodine. This explanation supports previous findings, that the EDCI/HOBT route was unsuccessful for PolyHIPE material and thorough washing of the supports, ideally in a Soxhlet apparatus was necessary, to remove residual 4-iodobenzoic acid.

4.7 Conclusions

In conclusion, the derivatisation of VBC/DVB PolyHIPE for the preparation of Wang resin proved to be challenging. The limited number of techniques for the determination of hydroxymethyl loading on a support, meant that functionalisation success was often uncertain. The direct HMP derivatisation route was complicated by competing side-reactions, while the EDCI esterification method often produced variable results. MSNT/NMI coupling was introduced in response to this, and an optimised version of the standard procedure certainly increased conversions and delivered reproducible results. The alternative Wang synthesis, involving aldehyde attachment followed by reduction, offered a greater amount of control. Side-reactions were eliminated and loadings of hydroxymethyl groups could be directly related to the success of aldehyde attachment. Successful MSNT coupling of 4-iodobenzoic acid and subsequent Suzuki coupling showed that Wang-functionalised PolyHIPE was a viable support for this application. Tris-OH PolyHIPE also showed potential as a support for Suzuki cross-coupling reactions. The highly loaded nature of this support renders it ideal for peptide synthesis and other SPOS applications.

4.8 Experimental

4.8.1 Chemicals

Starting materials were purchased from Aldrich, Lancaster, Acros, BDH and Novabiochem. Divinylbenzene (80 vol% *m*- and *p*-divinylbenzene, the remainder *m*- and *p*-ethylstyrene) and 4-vinylbenzyl chloride were purified by passing through a column of basic alumina. All other materials were used without further purification. Wang polymer beads were provided by GSK and were washed with DMF (anhydrous) and DCM (anhydrous) before use. DMA, DMF (anhydrous and HPLC grade), DME, DME (anhydrous), methanol (anhydrous), absolute ethanol, acetonitrile and DMSO (anhydrous) were used as solvents for the reactions. The THF used was freshly distilled over benzophenone ketyl. Similarly, the DCM used was freshly distilled over calcium hydride. Residual palladium was removed by passing through a column of Celite® 545 purchased from Aldrich. Tris-OH PolyHIPE, **P78B7$_g$TH**, was used as received.

4.8.2 Characterisation

Combustion elemental analysis data (C, H and N) were obtained from an Exeter Analyser CE-440. A Dionex Ion Chromatograph Analyser DX-120 was employed for chlorine and iodine determination. FTIR spectra (KBr dics) were recorded on a Perkin Elmer 1600 Series FTIR Spectrometer. NMR spectra were recorded using either a Varian Unity-300 (^{1}H at 299.9 MHz), a Varian Mercury 400 (^{1}H at 400 MHz) or a Varian Inova-500 (^{1}H at 500 MHz). Deuterated solvents were used as supplied from Aldrich ($CDCl_3$) and Apollo (CD_3COCD_3). Chemical shifts (δ) are reported in parts per million (ppm) with respect to an internal reference of tetramethylsilane (TMS), and using residual solvent signals as secondary references.

A Micromass LCT instrument was employed for electrospray mass spectra (ES MS) and a Waters 600 LC instrument was used in conjunction with a Waters 2700 Autosampler, for liquid chromatography mass spectra (LC MS). Analytical high performance liquid chromatography (HPLC) was carried out using a Varian Star instrument. UV absorbencies were recorded on a Pye Unicam UV/VIS Spectrophotometer.

4.8.3 Procedures for the Preparation of Poly(4-Vinylbenzyl Chloride-*co*-Divinylbenzene) PolyHIPE

4.8.3.1 Preparation of P64B2C

The quantities used in the preparation of PolyHIPE **P64B2C** are outlined in section 2.6.3.2. The granular form, **P64B2$_g$C**, was obtained as described in section 2.6.3.1. Found C, 78.2; H, 6.9; Cl, 11.1%. Calculated for $(C_9H_9Cl)_{0.64}(C_{10}H_{10})_{0.29}(C_{10}H_{12})_{0.07}$, C, 77.7; H, 6.6; Cl, 15.7%. IR (KBr disc) υ_{max}/cm^{-1} 3402br (OH), 2924s and 2853w (CH), 1610w and 1510m (aryl C=C), 1265s (CCl), 835m (*p*-disubstituted benzene ring).

4.8.3.2 Preparation of P64B3C

P64B3C was prepared according to the standard procedure outlined in section 2.6.3.1. Quantities used were; 4-VBC (3.25 g, 0.02 mol), DVB (1.83 g, 0.015 mol), Span 80 (0.99 g, 2.3 mmol), aqueous phase (45 mL). **P64B3$_g$C** was obtained as described in section 2.6.3.1, and **P64B3$_m$C** was prepared inside Quest tubes according to the procedure described in section 2.6.3.2. Found C, 78.6; H, 6.8; Cl, 11.1%.

Calculated for $(C_9H_9Cl)_{0.64}(C_{10}H_{10})_{0.29}(C_{10}H_{12})_{0.07}$, C, 77.7; H, 6.6; Cl, 15.7%. IR (KBr disc) υ_{max}/cm^{-1} 3400br (OH), 2924s and 2853w (CH), 1610w and 1510m (aryl C=C), 1265s (CCl), 835m (*p*-disubstituted benzene ring).

4.8.3.3 Preparation of P64B4C

P64B4C was prepared according to the standard procedure outlined in section 2.6.3.1. Quantities used were; 4-VBC (6.5 g, 0.04 mol), DVB (3.66 g, 0.03 mol), Span 80 (1.97 g, 4.6 mmol), aqueous phase (90 mL). **P64B4$_g$C** was obtained as described in section 2.6.3.1, and **P64B4$_m$C** was prepared inside Quest tubes according to the procedure described in section 2.6.3.2. Found C, 78.6; H, 6.8; Cl, 11.9%. Calculated for $(C_9H_9Cl)_{0.64}(C_{10}H_{10})_{0.29}(C_{10}H_{12})_{0.07}$, C, 77.7; H, 6.6; Cl, 15.7%. IR (KBr disc) υ_{max}/cm^{-1} 3400br (OH), 2924s and 2853w (CH), 1610w and 1510m (aryl C=C), 1265s (CCl), 835m (*p*-disubstituted benzene ring).

4.8.3.4 Preparation of P64B5C

P64B5C was prepared according to the standard procedure outlined in section 2.6.3.1. Quantities used were; 4-VBC (6.5 g, 0.04 mol), DVB (3.66 g, 0.03 mol), Span 80 (1.97 g, 4.6 mmol), aqueous phase (90 mL). Granular and cubic forms, **P64B5$_g$C** and **P64B5$_c$C**, were obtained as described in section 2.6.3.1. Found C, 76.6; H, 6.8; Cl, 12.0%. Calculated for $(C_9H_9Cl)_{0.64}(C_{10}H_{10})_{0.29}(C_{10}H_{12})_{0.07}$, C, 77.7; H, 6.6; Cl, 15.7%. IR (KBr disc) υ_{max}/cm^{-1} 3400br (OH), 2924s and 2853w (CH), 1611w and 1510m (aryl C=C), 1265s (CCl), 835m (*p*-disubstituted benzene ring).

4.8.3.5 Preparation of P78B2C

The quantities used in the preparation of PolyHIPE **P78B2C** are outlined in section 3.8.3.2. The granular form, **P78B2$_g$C**, was obtained as described in section 2.6.3.1, and the monolithic form, **P78B2$_m$C**, was prepared inside Quest tubes according to the procedure described in section 2.6.3.2. Found C, 77.2; H, 6.7; Cl, 15.5%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3446br (OH), 2923s and 2852w (CH), 1610w and 1509m (aryl C=C), 1265m (CCl), 825m (*p*-disubstituted benzene ring).

4.8.3.6 Preparation of P78B3C

The quantities used in the preparation of PolyHIPE **P78B3C** are outlined in section 3.8.3.3. **P78B3$_g$C** and **P78B3$_c$C** were obtained as described in section 2.6.3.1. Found C, 72.2; H, 6.8; Cl, 14.0%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923s and 2852w (CH), 1610w and 1509m (aryl C=C), 1265m (CCl), 834m (*p*-disubstituted benzene ring).

4.8.3.7 Preparation of P78B4C

The quantities used in the preparation of PolyHIPE **P78B4C** are outlined in section 3.8.3.4. The granular form, **P78B4$_g$C**, was obtained as described in section 2.6.3.1. Found C, 76.8; H, 6.5; Cl, 16.0%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3446br (OH), 2923s and 2852w (CH), 1610w and 1510m (aryl C=C), 1265s (CCl), 834m (*p*-disubstituted benzene ring).

4.8.3.8 Preparation of P78B5C

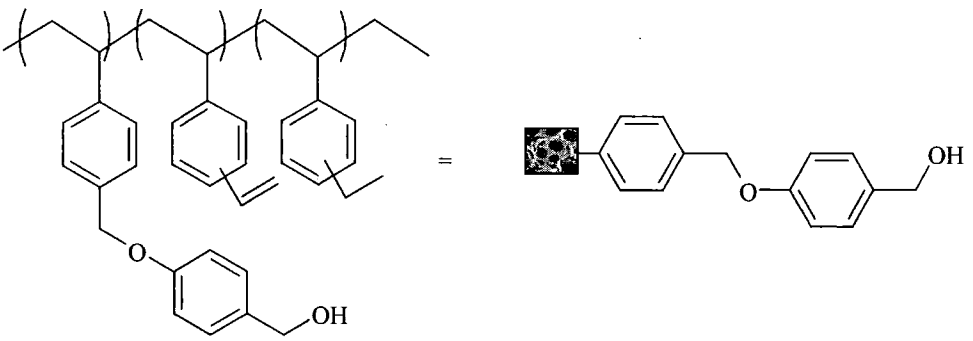
P78B5C was prepared according to the standard procedure outlined in section 2.6.3.1. Quantities used were; 4-VBC (4.06 g, 0.025 mol), DVB (1.14 g, 9.3 mmol), Span 80 (0.99 g, 2.3 mmol), aqueous phase (45 mL). Monolithic PolyHIPE, **P78B5$_m$C**, was prepared inside Quest tubes according to the procedure described in section 2.5.3.2. Found C, 76.8; H, 6.7; Cl, 13.8%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923s and 2852w (CH), 1610w and 1509m (aryl C=C), 1265s (CCl), 835m (*p*-disubstituted benzene ring).

4.8.3.9 Preparation of P78B6C

P78B6C was prepared according to the standard procedure outlined in section 2.6.3.1. Quantities used were; 4-VBC (8.1 g, 0.05 mol), DVB (2.3 g, 0.019 mol), Span 80 (1.97 g, 4.6 mmol), aqueous phase (90 mL). **P78B6$_g$C** and **P78B6$_c$C** were obtained as described in section 2.5.3.1. Found C, 75.4; H, 6.6; Cl, 15.6%. Calculated for $(C_9H_9Cl)_{0.78}(C_{10}H_{10})_{0.18}(C_{10}H_{12})_{0.04}$, C, 74.9; H, 6.3; Cl, 18.8%. IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923s and 2852w (CH), 1610w and 1509m (aryl C=C), 1265s (CCl), 835m (*p*-disubstituted benzene ring).

4.8.4 Procedures for HMP Functionalisations

4.8.4.1 Flow-Through Synthesis of P64B3$_m$WH and P78B5$_m$WH via Conditions Reported for Polymer Beads



P64B3$_m$WH

Quest tubes containing **P64B3$_m$C** (1.2 g, 3.72 mmol –CH_2Cl groups) and **P78B5$_m$C** (0.92 g, 3.57 mmol –CH_2Cl groups) were inserted into the Quest apparatus. A solution of 4-(hydroxymethyl) phenol (12 g, 96 mmol) and NaOMe (5.3 g, 95 mmol) in DMA (250 mL) was prepared in a 500 mL conical flask, and decanted into a Quest solvent delivery bottle (a large volume of reagent solution was prepared in order to supply five different monoliths). The reaction vessels were heated to 50 °C and *ca.* 10 mL of reagent solution was delivered to each tube. The solution was allowed to flow through the monoliths under gravity for 45 min, after which the tubes were drained and fresh reagent solution (10 mL) was delivered. The process was repeated over a period of 8 h. The monoliths were then flushed with THF (30 mL), THF/H_2O (1:1, 30 mL), THF (30 mL) and MeOH (30 mL), and dried *in vacuo* at 50 °C for 48 h. Functionalisation of **P64B3$_m$C** provided **P64B3$_m$WH** (1.25 g, 83% conversion by weight). Found Cl, 6.5%. Calculated Cl, 0% (42% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3424br (OH), 2923s and 2863m (CH), 1611m and 1511s (aryl C=C), 1241m (aryl C-O-C), 821m (*p*-disubstituted benzene ring). Functionalisation of **P78B5$_m$C** provided **P78B5$_m$WH** (1.1 g, 89% conversion by weight). Found Cl, 5.1%. Calculated Cl, 0% (63% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3424br (OH), 2923s and 2863m (CH), 1611m and 1511s (aryl C=C), 1241m (aryl C-O-C), 821m (*p*-disubstituted benzene ring).

4.8.4.2 Batch Synthesis of P64B2$_g$WH via Conditions Reported for Polymer Beads

A Quest tube containing granular PolyHIPE **P64B2$_g$C** (0.24 g, 0.75 mmol –CH_2Cl groups) was inserted into the Quest apparatus. A solution of 4-(hydroxymethyl) phenol (0.36 g, 2.88 mmol) and NaOMe (0.16 g, 2.88 mmol) in DMA (8 mL) was prepared in a 50 mL conical flask, and decanted into the Quest tube. The PolyHIPE and solution were mixed at 50 °C for 8 h. The granular support was then flushed with THF (30 mL), THF/H_2O (1:1, 30 mL), THF (30 mL) and MeOH (30 mL). The Quest tube containing the functionalised support was dried *in vacuo* at 50 °C for 48 h, to provide **P64B2$_g$WH** (0.23 g, 75% conversion by weight). Found Cl, 6.8%. Calculated Cl, 0% (39% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3420br (OH), 2923s and 2863m (CH), 1610m and 1510s (aryl C=C), 1241m (aryl C-O-C), 821m (*p*-disubstituted benzene ring).

4.8.4.3 Flow-Through Synthesis of P64B4$_m$WH and P78B2$_m$WH via Optimised Conditions

Quest tubes containing **P64B4$_m$C** (0.66 g, 2.2 mmol –CH_2Cl groups) and **P78B2$_m$C** (0.55 g, 2.4 mmol –CH_2Cl groups) were inserted into the Quest apparatus, and saturated with DMF. A solution of 4-(hydroxymethyl) phenol (22 g, 0.17 mol) and NaOMe (9.7 g, 0.17 mol) in DMF (500 mL) was prepared in a 1 L conical flask, and decanted into a Quest solvent delivery bottle (a large volume of reagent solution was prepared in order to supply four different monoliths and to allow flow-through to take place over 8 h). The DMF was drained from the monoliths and the reaction vessels were heated to 70 °C. Reagent solution was automatically delivered to the tubes and the flow through each monolith was controlled by exit taps (*ca.* 15 mL h^{-1}). The solution was passed through the monoliths for 8 h, and allowed to saturate them overnight. After a total reaction time of 24 h, the monoliths were flushed continuously with THF (30 min), THF/H_2O (1:1, 30 min), THF (30 min) and MeOH (30 min), and dried *in vacuo* at 50 °C for 48 h. Functionalisation of **P64B4$_m$C** provided **P64B4$_m$WH** (0.65 g, 76% conversion by weight). Found Cl, 3.3%. Calculated Cl, 0% (72% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3424br (OH), 2923m and 2864w (CH), 1610m and 1509s (aryl C=C), 1244m (aryl C-O-C), 824m (*p*-disubstituted benzene ring). Functionalisation of **P78B2$_m$C** provided **P78B2$_m$WH** (0.63 g, 83% conversion by weight). Found Cl, 2.2%. Calculated Cl, 0% (86%

conversion). IR (KBr disc) υ_{max}/cm^{-1} 3424br (OH), 2923m and 2864w (CH), 1610m and 1509s (aryl C=C), 1244m (aryl C-O-C), 824m (*p*-disubstituted benzene ring).

4.8.4.4 Flow-Through Synthesis of P64B4$_g$WH and P78B2$_g$WH via Optimised Conditions

Quest tubes containing **P64B4$_g$C** (0.34 g, 1.1 mmol $-CH_2Cl$ groups) and **P78B2$_g$C** (0.27 g, 1.2 mmol $-CH_2Cl$ groups) were inserted into the Quest apparatus. A solution of 4-(hydroxymethyl) phenol (14 g, 0.11 mol) and NaOMe (6.0 g, 0.11 mol) in DMF (300 mL) was prepared in a 500 mL conical flask, and decanted into a Quest solvent delivery bottle (a large volume of reagent solution was prepared in order to supply four different vessels and to allow flow-through to take place over 8 h). The heating panel was set to 70 °C and the reagent solution was automatically delivered to the vessels. Initially, the flow through the granular PolyHIPEs was very fast and difficult to control using the exit taps. All of the solution had passed through the supports within 2 h (the flow-rate through each vessel was *ca.* 38 mL h^{-1}). The solution was then decanted back into the solvent delivery bottle and allowed to flow through the supports for a second time. The flow-rate was slower on this occasion and carefully controlled using exit taps. The solution was passed through the granular PolyHIPEs for the remaining 6 h, and allowed to saturate them overnight. After a total reaction time of 24 h, the PolyHIPEs were flushed continuously with THF (30 min), THF/H_2O (1:1, 30 min), THF (30 min) and MeOH (30 min), and dried *in vacuo* at 50 °C for 48 h. Functionalisation of **P64B4$_g$C** provided **P64B4$_g$WH** (0.33 g, 75% conversion by weight). Found Cl, 2.9%. Calculated Cl, 0% (76% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3420br (OH), 2923m and 2864w (CH), 1610m and 1509s (aryl C=C), 1244m (aryl C-O-C), 820m (*p*-disubstituted benzene ring). Functionalisation of **P78B2$_g$C** provided **P78B2$_g$WH** (0.30 g, 80% conversion by weight). Found Cl, 2.9%. Calculated Cl, 0% (81% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3420br (OH), 2923m and 2864w (CH), 1610m and 1509s (aryl C=C), 1244m (aryl C-O-C), 820m (*p*-disubstituted benzene ring).

4.8.4.5 Batch Synthesis of P64B5$_g$WH and P78B6$_g$WH via Optimised Conditions

Carousel reactor vessels containing **P64B5$_g$C** (0.5 g, 1.95 mmol $-CH_2Cl$ groups) and **P78B6$_g$C** (0.5 g, 2.2 mmol $-CH_2Cl$ groups) were inserted into the reaction station. A solution of 4-HMP (0.63 g, 5 mmol) and NaOMe (0.28 g, 5 mmol)

in DMF (10 mL) was prepared and added to the vessel containing **P64B5$_g$C**. Similarly, a solution of 4-HMP (0.75 g, 6 mmol) and NaOMe (0.34 g, 6 mmol) in DMF (13 mL) was prepared and added to the vessel containing **P78B6$_g$C**. The mixtures were stirred at 70 °C for 24 h, before being filtered and washed with DMF (3 x 20 mL), THF/H_2O (1:1, 3 x 20 mL) and MeOH (3 x 20 mL). The PolyHIPEs were dried *in vacuo* at 50 °C for 48 h. Functionalisation of **P64B5$_g$C** provided **P64B5$_g$WH** (0.58 g, 89% conversion by weight). Found Cl, 3.2%. Calculated Cl, 0% (74% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3420br (OH), 2923m and 2864w (CH), 1610m and 1509s (aryl C=C), 1244m (aryl C-O-C), 820m (*p*-disubstituted benzene ring). Functionalisation of **P78B6$_g$C** provided **P78B6$_g$WH** (0.69 g, 93% conversion by weight). Found Cl, 2.0%. Calculated Cl, 0% (87% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3420br (OH), 2923m and 2864w (CH), 1610m and 1509s (aryl C=C), 1244m (aryl C-O-C), 820m (*p*-disubstituted benzene ring).

4.8.4.6 Batch Synthesis of P64B5$_c$WH and P78B6$_c$WH via Optimised Conditions

P64B5$_c$WH and **P78B6$_c$WH** were prepared according to the procedure described in section 4.8.4.5. The quantities used in the reaction involving **P64B5$_c$C** (0.5 g, 1.95 mmol –CH_2Cl groups) were the same as those used in the synthesis of **P64B5$_g$WH**. Similarly, the quantities used in the reaction involving **P78B6$_c$C** (0.5 g, 2.2 mmol –CH_2Cl groups) were the same as those used in the synthesis of **P78B6$_g$WH**. Functionalisation of **P64B5$_c$C** provided **P64B5$_c$WH** (0.64 g, 99% conversion by weight). Found Cl, 4.1%. Calculated Cl, 0% (66% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3424br (OH), 2923m and 2864w (CH), 1610m and 1509s (aryl C=C), 1241m (aryl C-O-C), 824m (*p*-disubstituted benzene ring). Functionalisation of **P78B6$_c$C** provided **P78B6$_c$WH** (0.69 g, 100% conversion by weight). Found Cl, 4.3%. Calculated Cl, 0% (73% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3424br (OH), 2923m and 2864w (CH), 1610m and 1509s (aryl C=C), 1241m (aryl C-O-C), 824m (*p*-disubstituted benzene ring).

4.8.4.7 Synthesis of P78B3$_g$WH using Triethylamine Base under Optimised Conditions

P78B3$_g$WH was synthesised according to the optimised procedure described in section 4.8.4.5, using NEt_3 rather than NaOMe. Quantities used were; **P78B3$_g$C** (0.1 g, 0.39 mmol –CH_2Cl groups), 4-HMP (0.25 g, 1.98 mmol), NEt_3 (0.2 g, 1.98

mmol), DMF (6 mL). The PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B3$_g$WH** (0.07 g, 52% conversion by weight). Found Cl, 8.0%. Calculated Cl, 0% (45% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3405br (OH), 2923s and 2864s (CH), 1610w and 1510m (aryl C=C), 1266w (CCl), 1217w (aryl C-O-C), 824m (*p*-disubstituted benzene ring).

4.8.4.8 Synthesis of P78B3$_g$WH using DIPEA Base under Optimised Conditions

P78B3$_g$WH was synthesised according to the optimised procedure described in section 4.8.4.5, using DIPEA rather than NaOMe. Quantities used were; **P78B3$_g$C** (0.07 g, 0.28 mmol –CH_2Cl groups), 4-HMP (0.18 g, 1.44 mmol), DIPEA (0.25 mL, 1.44 mmol), DMF (4.5 mL). The PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B3$_g$WH** (0.06 g, 63% conversion by weight). Found Cl, 11.4%. Calculated Cl, 0% (19% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3424br (OH), 2924s and 2864s (CH), 1610w and 1509m (aryl C=C), 1265s (CCl), 1217w (aryl C-O-C), 824m (*p*-disubstituted benzene ring).

4.8.4.9 Synthesis of P78B3$_g$WH using NaH Base under Standard HMP conditions

In a 2-necked 50 mL round-bottomed flask, fitted with rubber septa and a vent, 4-HMP (0.37 g, 2.96 mmol) and a degassed solution of DMA (12 mL) were flushed with nitrogen for 20 min. NaH (118.5 mg, 2.96 mmol) was slowly added to the flask and the mixture was stirred for 10 min. In a second 50 mL round-bottomed flask, fitted with a rubber septum and vent, **P78B3$_g$C** (0.25 g, 0.99 mmol –CH_2Cl groups) was immersed in DMA (12 mL). The flask was heated to 50 °C and flushed with nitrogen. The contents of the first flask were added to the flask containing the PolyHIPE material and the mixture was stirred under nitrogen at 50 °C for 8 h. The PolyHIPE was filtered and washed with THF (2 x 20 mL), THF/H_2O (1:1, 2 x 25 mL), THF (2 x 20 mL) and MeOH (1 x 20 mL). The material was dried *in vacuo* at 50 °C for 48 h, to provide **P78B3$_g$WH** (0.20 g, 61% conversion by weight). Found Cl, 5.2%. Calculated Cl, 0% (63% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3446br (OH), 2922s and 2864s (CH), 1611m and 1509s (aryl C=C), 1240m (aryl C-O-C), 821m (*p*-disubstituted benzene ring).

4.8.4.10 Synthesis of P78B3$_c$WH using NaH Base under Standard HMP Conditions

P78B3$_c$WH was synthesised according to the standard procedure described in section 4.8.4.9, using cubic PolyHIPE, **P78B3$_c$C**, and identical quantities of reagents and solvent. The material was dried *in vacuo* at 50 °C for 48 h, to provide **P78B3$_c$WH** (0.21 g, 64% conversion by weight). Found Cl, 9.1%. Calculated Cl, 0% (35% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2922s and 2864s (CH), 1610m and 1509s (aryl C=C), 1240m (aryl C-O-C), 821m (*p*-disubstituted benzene ring).

4.8.4.11 Synthesis of P78B3$_g$WH using NaH Base under Optimised Conditions

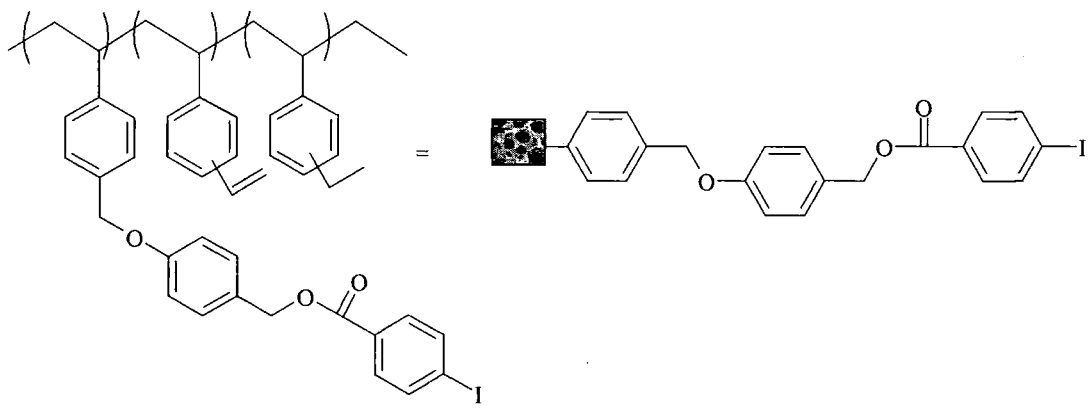
P78B3$_g$WH was synthesised using an optimised version of the procedure described in section 4.8.4.5. The reaction was performed at 70 °C rather than 50 °C, for the extended reaction time of 24 h. The quantities used were; **P78B3$_g$C** (0.25 g, 0.99 mmol –CH_2Cl groups), 4-HMP (0.61 g, 4.94 mmol), NaH (198 mg, 4.94 mmol), DMF (24 mL). The PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B3$_g$WH** (0.23 g, 70% conversion by weight). Found Cl, 0.93%. Calculated Cl, 0% (93% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923s and 2863s (CH), 1610m and 1509s (aryl C=C), 1241m (aryl C-O-C), 820m (*p*-disubstituted benzene ring).

4.8.4.12 Synthesis of P78B3$_c$WH using NaH Base under Optimised Conditions

P78B3$_c$WH was synthesised as described in section 4.8.4.11, using cubic PolyHIPE, **P78B3$_c$C** (0.25 g, 0.99 mmol –CH_2Cl groups), and identical quantities of reagents and solvent. The PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B3$_c$WH** (0.27 g, 81% conversion by weight). Found Cl, 2.4%. Calculated Cl, 0% (83% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923s and 2863s (CH), 1611m and 1510s (aryl C=C), 1241m (aryl C-O-C), 820m (*p*-disubstituted benzene ring).

4.8.5 Procedures for the Esterification of Wang-Functionalised Polymer Supports

4.8.5.1 Synthesis of P78B5$_g$WI using EDCI/HOBT Coupling Chemistry



P78B5$_g$WI

In a 50 mL round-bottomed glass flask fitted with a rubber septum and vent, EDCI (0.91 g, 6.3 mmol), HOBT (0.17 g, 1.3 mmol), 4-iodobenzoic acid (1.55 g, 6.3 mmol) and finely ground PolyHIPE, **P78B5$_m$WH** (0.5 g, 0.92 mmol -CH_2OH groups) were stirred in DMF (12 mL) at room temperature for 4 h. The PolyHIPE was filtered and washed with DMF (2 x 10 mL), DCM (6 x 5 mL) and MeOH (6 x 5 mL). The material was dried *in vacuo* at 50 °C for 48 h to give an off-white product (1.1 g, 152% conversion by weight). Found I, 22.5%. Calculated I, 16.4% (137% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3423br (OH), 2923s and 2864m (CH), 1782s and 1719s (C=O), 1612s and 1510s (aryl C=C), 1223s (aryl C-O-C), 1111m (CO), 825s (*p*-disubstituted benzene ring). Due to the high amount of iodine in the product, the PolyHIPE was re-washed with DMF (4 x 10 mL), DCM (2 x 10 mL) and MeOH (2 x 10 mL), and dried *in vacuo* at 50 °C for 24 h to give **P78B5$_g$WI** (0.45 g, 63% conversion by weight). Found I, 0%. Calculated I, 16.4% (0% conversion).

4.8.5.2 Synthesis of P78B6$_g$WI and P78B6$_c$WI using EDCI/HOBT

P78B6$_g$WI and **P78B6$_c$WI** were synthesised according to the procedure described in section 4.8.5.1. The quantities used in the functionalisation of **P78B6$_g$WH** (0.46 g, 1.27 mmol -CH_2OH groups) were; 4-iodobenzoic acid (2.2 g, 8.87 mmol), EDCI (1.7 g, 8.87 mmol), HOBT (0.24 g, 1.78 mmol), DMF (20 mL).

The quantities used in the functionalisation of **P78B6$_c$WH** (0.46 g, 1.06 mmol -CH_2OH groups g^{-1}) were; 4-iodobenzoic acid (1.8 g, 7.4 mmol), EDCI (1.4 g, 7.4 mmol), HOBT (0.2 g, 1.5 mmol), DMF (20 mL). The granular PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B6$_g$WI** (0.57 g, 68% conversion by weight). Found I, 10%. Calculated I, 22% (45% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2864m (CH), 1783s and 1720m (C=O), 1611w and 1510s (aryl C=C), 1227s (aryl C-O-C), 1111m (CO), 826m (*p*-disubstituted benzene ring). The PolyHIPE in cubic form was dried *in vacuo* at 50 °C for 24 h to give **P78B6$_c$WI** (0.75 g, 97% conversion by weight). Found I, 4.3%. Calculated I, 19% (23% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2925s (CH), 1783m and 1719m (C=O), 1510m (aryl C=C), 1228s (aryl C-O-C), 1111w (CO), 826m (*p*-disubstituted benzene ring), 555w (CI).

4.8.5.3 Synthesis of P78B3$_g$WI using EDCI/HOBT

P78B3$_g$WI was synthesised according to the procedure described in section 4.8.5.1. The quantities used in the functionalisation of **P78B3$_g$WH** (80 mg, 0.22 mmol -CH_2OH groups) were; 4-iodobenzoic acid (0.27 g, 1.09 mmol), EDCI (0.21 g, 1.09 mmol), HOBT (29.5 mg, 0.22 mmol), DMF (4 mL). The granular PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B3$_g$WI** (65 mg, 50% conversion by weight). Found I, 0%. Calculated I, 21% (0% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923s and 2864m (CH), 1718w (C=O), 1611m and 1510s (aryl C=C), 1241m (aryl C-O-C), 820m (*p*-disubstituted benzene ring), 557br (CI).

4.8.5.4 Synthesis of BB1WI using EDCI/HOBT

BB1WI was synthesised according to the procedure described in section 4.8.5.1. The quantities used were; **BB1WH** (80 mg, 0.22 mmol -CH_2OH groups), 4-iodobenzoic acid (0.27 g, 1.09 mmol), EDCI (0.21 g, 1.09 mmol), HOBT (29.5 mg, 0.22 mmol), DMF (4 mL). The beads were dried *in vacuo* at 50 °C for 24 h to give **BB1WI** (57 mg, 44% conversion by weight). Found I, 0%. Calculated I, 21% (0% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3436br (OH), 2922s and 2868m (CH), 1718w (C=O), 1610m and 1510s (aryl C=C), 1218m (aryl C-O-C), 822m (*p*-disubstituted benzene ring).

4.8.5.5 Synthesis of P78B3$_g$WI via MSNT/NMI Coupling

P78B3$_g$WH (80 mg, 0.22 mmol -CH_2Cl groups) was washed with dry DMF (2 x 5 mL) and dry DCM (2 x 5 mL) and placed in a 25 mL round-bottomed flask, fitted with a rubber septum and vent. In a second 25 mL round-bottomed flask, fitted with a rubber septum and vent, was placed 4-iodobenzoic acid (108 mg, 0.44 mmol), dry DCM (2 mL) and NMI (0.14 mL, 1.74 mmol). MSNT (129 mg, 0.44 mmol) was placed in a third 25 mL round-bottomed flask, fitted with a rubber septum and vent. The contents of flask 2, containing the 4-iodobenzoic acid solution, were added, via syringe, to flask 3 containing MSNT. The resultant solution was immediately added to **P78B3$_g$WH** in flask 1. The reaction was stirred gently at 20 °C for 1 h, after which, the PolyHIPE was filtered and thoroughly washed with dry DCM (3 x 5 mL) and dry DMF (3 x 5 mL). The material was dried *in vacuo* at 50 °C for 24 h to give **P78B3$_g$WI** (94 mg, 72% conversion by weight). Found I, 6.4%. Calculated I, 21.3% (30% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923s and 2864m (CH), 1718m (C=O), 1610m and 1510s (aryl C=C), 1243m (aryl C-O-C), 821m (*p*-disubstituted benzene ring), 551br (CI).

4.8.5.6 Synthesis of BB1WI using MSNT/NMI

BB1WI was synthesised according to the procedure described in section 4.8.5.5. The quantities used were; **BB1WH** (80 mg, 0.22 mmol -CH_2OH groups), 4-iodobenzoic acid (0.11 g, 0.43 mmol), NMI (137 μL, 1.73 mmol), MSNT (128 mg, 0.43 mmol), dry DCM (2 mL). The beads were dried *in vacuo* at 50 °C for 24 h to give **BB1WI** (94 mg, 72% conversion by weight). Found I, 11.9%. Calculated I, 21% (57% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3436br (OH), 2922s and 2868m (CH), 1718s (C=O), 1610m and 1510s (aryl C=C), 1243m (aryl C-O-C), 822m (*p*-disubstituted benzene ring), 551br (CI).

4.8.5.7 Synthesis of P78B4$_g$WI using MSNT/NMI

P78B4$_g$WI was synthesised using an optimised version of the procedure described in section 4.8.5.5. The reaction was performed for the extended reaction time of 2 h rather than 1 h. The quantities used were; **P78B4$_g$WH** (50 mg, 0.16 mmol –CH_2OH groups), 4-iodobenzoic acid (80 mg, 0.31 mmol), NMI (100 μL, 1.26 mmol), MSNT (93 mg, 0.31 mmol), dry DCM (2 mL). The PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B4$_g$WI** (57 mg, 66% conversion by weight).

Found I, 12%. Calculated I, 23% (53% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3447br (OH), 2923m and 2864w (CH), 1719s (C=O), 1611m and 1511s (aryl C=C), 1246s (aryl C-O-C), 824m (*p*-disubstituted benzene ring), 561br (CI).

4.8.6 Procedures Involved in the MSNT Optimisation Studies

4.8.6.1 Synthesis of P78B1$_g$WI using Three Equivalents of MSNT

P78B1$_g$WH (30 mg, 0.09 mmol -CH_2OH groups) was loaded into a 5 mL filter syringe tube fitted with a cap and stopper. The procedure described in section 4.8.5.7 was repeated using the following quantities; 4-iodobenzoic acid (67 mg, 0.27 mmol), NMI (90 μL, 1.08 mmol), MSNT (80 mg, 0.27 mmol), dry DCM (1.8 mL). The syringe tube was inserted into a rotating device and the contents were mixed at 20 °C for 2 h. The PolyHIPE was filtered and thoroughly washed with dry DCM (3 x 5 mL), dry DMF (3 x 5 mL) and MeOH (2 x 5 mL). The granular support was dried *in vacuo* at 50 °C for 24 h to provide **P78B1$_g$WI**. Found I, 15.5%. Calculated I, 22.5% (69% conversion).

4.8.6.2 Synthesis of P78B1$_g$WI using Five Equivalents of MSNT

P78B1$_g$WI was synthesised according to the procedure outlined in section 4.8.5.7. The quantities used were; **P78B1$_g$WH** (30 mg, 0.09 mmol -CH_2OH groups), 4-iodobenzoic acid (112 mg, 0.45 mmol), NMI (150 μL, 1.8 mmol), MSNT (133 mg, 0.45 mmol), dry DCM (3 mL). The granular support was dried *in vacuo* at 50 °C for 24 h to provide **P78B1$_g$WI**. Found I, 15.4%. Calculated I, 22.5% (68% conversion).

4.8.6.3 Synthesis of P78B1$_g$WI using Ten Equivalents of MSNT

P78B1$_g$WI was synthesised according to the procedure outlined in section 4.8.5.7. The quantities used were; **P78B1$_g$WH** (30 mg, 0.09 mmol -CH_2OH groups), 4-iodobenzoic acid (223 mg, 0.9 mmol), NMI (300 μL, 3.6 mmol), MSNT (267 mg, 0.9 mmol), dry DCM (6 mL). The granular support was dried *in vacuo* at 50 °C for 24 h to provide **P78B1$_g$WI**. Found I, 15.4%. Calculated I, 22.5% (68% conversion).

4.8.6.4 Synthesis of P78B1$_g$WI using Various Reaction Temperatures

P78B1$_g$WI was synthesised according to the procedure outlined in section 4.8.5.7, using reaction temperatures of 20 °C, 30 °C and 40 °C. In each reaction, the

quantities used were; **P78B1$_g$WH** (30 mg, 0.09 mmol -CH_2OH groups), 4-iodobenzoic acid (67 mg, 0.27 mmol), NMI (90 μL, 1.08 mmol), MSNT (80 mg, 0.27 mmol), dry DCM (1.8 mL). The granular supports were dried *in vacuo* at 50 °C for 24 h to provide **P78B1$_g$WI**. Found I, 15.5%. Calculated I, 22.5% (69% conversion) for **P78B1$_g$WI** synthesised at 20 °C. Found I, 13.4%. Calculated I, 22.5% (60% conversion) for **P78B1$_g$WI** synthesised at 30 °C. Found I, 16.5%. Calculated I, 22.5% (73% conversion) for **P78B1$_g$WI** synthesised at 40 °C.

4.8.6.5 Synthesis of P78B1$_g$WI using Various Reaction Times

P78B1$_g$WI was synthesised according to the procedure outlined in section 4.8.5.7, using reaction times of 4 h, 6 h and 24 h. In each reaction, the quantities used were; **P78B1$_g$WH** (30 mg, 0.09 mmol -CH_2OH groups), 4-iodobenzoic acid (67 mg, 0.27 mmol), NMI (90 μL, 1.08 mmol), MSNT (80 mg, 0.27 mmol), dry DCM (1.8 mL). The granular supports were dried *in vacuo* at 50 °C for 24 h to provide **P78B1$_g$WI**. Found I, 15.4%. Calculated I, 22.5% (68% conversion) for **P78B1$_g$WI** produced after 4 h. Found I, 14.4%. Calculated I, 22.5% (64% conversion) for **P78B1$_g$WI** produced after 6 h. Found I, 16.6%. Calculated I, 22.5% (73% conversion) for **P78B1$_g$WI** produced after 24 h. IR (KBr disc) υ_{max}/cm^{-1} 3429br (OH), 2923m and 2864w (CH), 1719s (C=O), 1611m and 1512s (aryl C=C), 1246s (aryl C-O-C), 824m (*p*-disubstituted benzene ring), 563br (CI).

4.8.6.6 Synthesis of P78B1$_g$WI for Suzuki Coupling

P78B1$_g$WI was synthesised according to the procedure described in section 4.8.6.5, using a reaction time of 24 h. The quantities used were; **P78B1$_g$WH** (75 mg, 0.22 mmol –CH_2OH groups), 4-iodobenzoic acid (116 mg, 0.67 mmol), NMI (224 μL, 2.68 mmol), MSNT (198 mg, 0.67 mmol), dry DCM (4.5 mL). The PolyHIPE was dried *in vacuo* at 50 °C for 24 h to give **P78B1$_g$WI** (110 mg, 87% conversion by weight). Found I, 11.4%. Calculated I, 22.5% (51% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3446br (OH), 2923m and 2864w (CH), 1719s (C=O), 1611m and 1512s (aryl C=C), 1246m (aryl C-O-C), 824m (*p*-disubstituted benzene ring), 555br (CI).

4.8.7 General Procedures for the Determination of Fmoc Numbers for HMP Functionalised Polymers

4.8.7.1 Attachment of Fmoc-Glycine using PyBOP-Mediated Coupling

HMP functionalised polymer (30-50 mg), N-α-Fmoc-glycine (Fmoc-Gly-OH) (2.9 eq), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) (2.9 eq), DIPEA (2 eq) and DMF (2 mL) were loaded into 5 mL filter syringe tubes fitted with caps and stoppers. The mixtures were shaken using an agitating device for 2 h. The polymers were filtered and washed with MeOH (5 x 5 mL), THF (2 x 5 mL), and Et_2O (2 x 5 mL), before being dried *in vacuo* at 50 °C for 24 h. In 5 mL volumetric flasks, the Fmoc-protected polymers (10 mg) were shaken in a 20% solution of piperidine/DMF (400 μL) for 40 min. Methanol was then added to the flasks to obtain 5 mL solutions. The solutions were diluted with methanol, depending on the loading expected, and UV readings were recorded at 301 nm and 322 nm (background reading). The Fmoc procedure was performed in duplicate, with each polymer support, in order to obtain an average Fmoc number.

4.8.7.2 Attachment of Fmoc-Glycine using MSNT-Fmoc Procedure

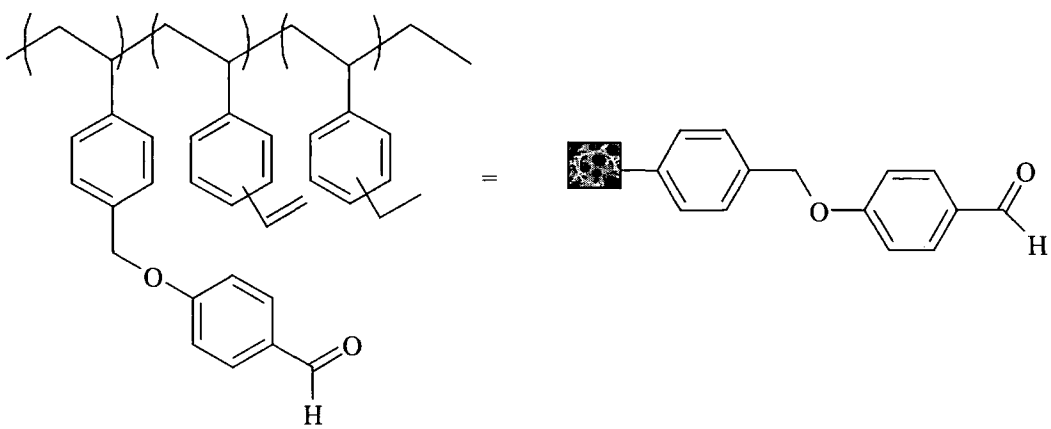
Polymer supports (30-50 mg) were loaded into 5 mL filter syringe tubes and washed with DMF and dry DCM before functionalisation. Fmoc-Glycine (3 eq) was placed in a 50 mL round-bottomed flask fitted with a rubber septum and vent. Dry DCM (3-4 mL) was added via syringe and the solution was degassed with nitrogen for 10 min. NMI (2.25 eq) was added via syringe and the solution was transferred to a stoppered 50 mL round-bottomed flask containing MSNT (3 eq). This solution was then added immediately via syringe to the filter tubes containing the supports. The tubes were shaken using an agitating device for 2 h. The polymer supports were filtered and washed with MeOH (5 x 5 mL), THF (2 x 5 mL), and Et_2O (2 x 5 mL), before being dried *in vacuo* at 50 °C for 24 h. In 5 mL volumetric flasks, the Fmoc-protected polymers (10 mg) were shaken in a 20% solution of piperidine/DMF (400 μL) for 40 min. Methanol was then added to the flasks to obtain 5 mL solutions. The solutions were diluted with methanol, depending on the loading expected, and UV readings were recorded at 301 nm and 322 nm (background reading). The Fmoc procedure was performed in duplicate, with each polymer support, in order to obtain an average Fmoc number.

4.8.7.3 Attachment of Fmoc-Glycine using Optimised MSNT Conditions

Fmoc analysis was performed according to the procedure described in section 4.8.7.2, using an extended reaction time of 24 h. The quantities used were; Wang-functionalised PolyHIPE (30-50 mg), Fmoc-Glycine (3 eq), NMI (12 eq), MSNT (3 eq).

4.8.8 Alternative Derivatisation Method for the Preparation of Wang-Functionalised PolyHIPE

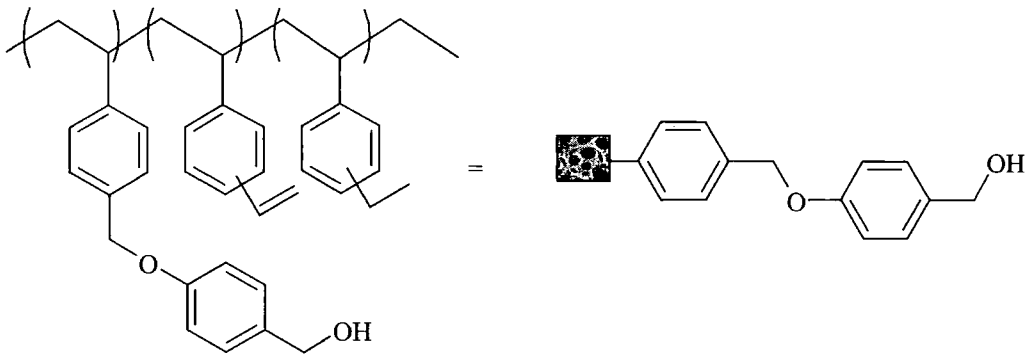
4.8.8.1 Synthesis of P78B4$_g$BA



P78B4$_g$BA

In a 50 mL round-bottomed flask fitted with a reflux condenser, **P78B4$_g$C** (0.3 g, 1.35 mmol –CH_2Cl groups), 4-hydroxybenzaldehyde (3.38 g, 27.7 mmol), K_2CO_3 (3.83 g, 27.7 mmol) and NaI (4.15 g, 27.7 mmol) were stirred in acetonitrile (30 mL). The mixture was heated under reflux at 92 °C for 48 h, after which time, the PolyHIPE was filtered and washed with DCM (2 x 25 mL), DMF (4 x 25 mL), MeOH (2 x 25 mL) and Et_2O (1 x 25 mL). The material was dried *in vacuo* at 50 °C for 72 h to give **P78B4$_g$BA** (0.34 mg, 83% conversion by weight). Found Cl, 0.5%. Calculated Cl, 0% (97% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3447br (OH), 2923m and 2851w (CH), 2736w (CHO), 1691s (HC=O), 1601s and 1508s (aryl C=C), 1257m (aryl C-O-C), 830m (*p*-disubstituted benzene ring).

4.8.8.2 Synthesis of P78B4$_g$WH via NaBH$_4$ Reduction



P78B4$_g$WH

To a 50 mL round-bottomed flask fitted with a rubber septum and vent, was charged **P78B4$_g$BA** (0.1 g, 0.31 mmol –C=O groups). Dry THF (4 mL), NMM (2 mL) and ethanol (2 mL) were added to the PolyHIPE via syringe, and the mixture was stirred and degassed with nitrogen gas for 20 min. Sodium borohydride (49.5 mg, 1.31 mmol) was slowly added to the flask, and the mixture was stirred under nitrogen for 24 h. The PolyHIPE was filtered and treated with water (5 x 30 mL), before being washed with MeOH (2 x 30 mL), THF (2 x 30 mL), THF (2 x 30 mL), H_2O (2 x 30 mL), THF (2 x 30 mL) and MeOH (2 x 30 mL). The support was dried under vacuum (10^{-1} mbar) at 50 °C for 4 h to provide **P78B4$_g$WH** (70 mg, 70% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2922s and 2852w (CH), 1685w (HC=O), 1610m and 1510s (aryl C=C), 1243s (aryl C-O-C), 821m (*p*-disubstituted benzene ring).

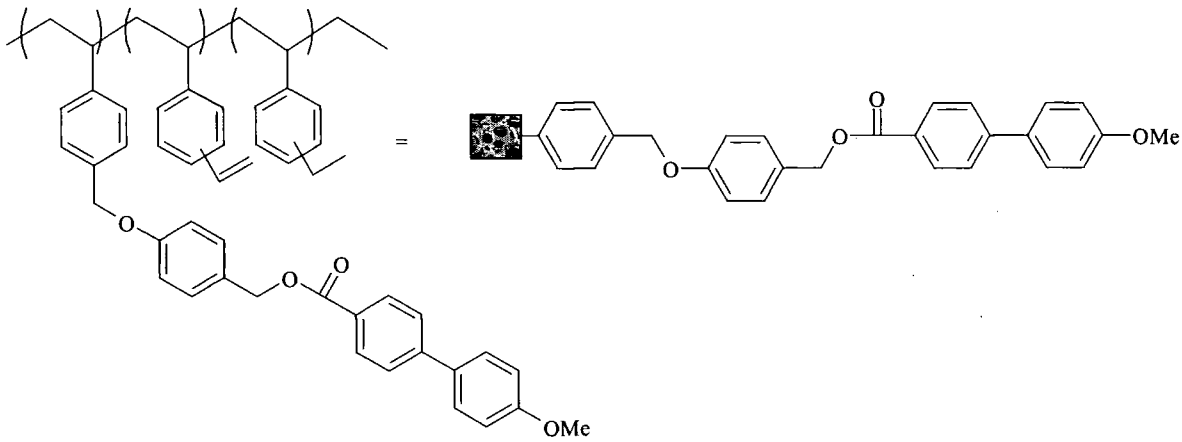
4.8.8.3 Synthesis of P78B4$_g$WH via NaCNBH$_4$ Reduction

To a 50 mL round-bottomed flask fitted with a rubber septum and vent, was charged **P78B4$_g$BA** (0.1 g, 0.31 mmol –C=O groups). Dry MeOH (5 mL) was added to the PolyHIPE via syringe, and the mixture was stirred and degassed with nitrogen gas for 20 min. Sodium cyanoborohydride (197 mg, 3.14 mmol) was slowly added to the flask, and the mixture was stirred gently. A trace of bromocresol green indicator was added to the reaction to monitor the pH of the solution. A 10 % solution of HCl in ethanol was prepared and added drop wise to the reaction in order to maintain the pH (the solution was initially blue, but steadily turned green on addition of the acid solution). The mixture was then stirred under nitrogen for 24 h. The PolyHIPE was filtered and washed with DCM (3 x 10 mL), DMF (1 x 25 mL), MeOH (1 x 25 mL)

and Et_2O (1 x 25 mL). The material was dried *in vacuo* at 50 °C for 24 h to provide **P78B4$_g$WH** (57 mg, 57% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3446br (OH), 2922m and 2852w (CH), 2736w (CHO), 1691s (HC=O), 1601s and 1509s (aryl C=C), 1255s (aryl C-O-C), 830m (*p*-disubstituted benzene ring).

4.8.9 Procedure for Solid Phase Suzuki Coupling utilising Wang-Functionalised PolyHIPE

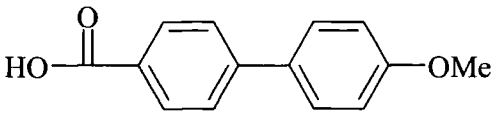
4.8.9.1 Synthesis of P78B1$_g$WM



P78B1$_g$WM

P78B1$_g$WM was synthesised according to the procedure described for **P78B3$_g$M1** (section 3.8.5.5), using **P78B1$_g$WI** (0.1 g, 0.09 mmol –I groups), dry DME (4 mL), freshly prepared $Pd(PPh_3)_4$ (18 mg, 0.015 mmol), 4-methoxybenzeneboronic acid (48 mg, 0.32 mmol) and 1M $Na_2CO_3(aq)$ (0.9 mL, 0.9 mmol). After reaction, the mixture was diluted by addition of a solution of 25% ammonium acetate (5 mL) and stirred for 5 min. The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B1$_g$WM** (93 mg, 95% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH), 2923m and 2853w (CH), 1718s (C=O), 1610m and 1511s (aryl C=C), 1246s (aryl C-O-C), 1099s (CO), 825w (*p*-disubstituted benzene ring).

4.8.9.2 Cleavage of P78B1$_g$WM to Yield (5)

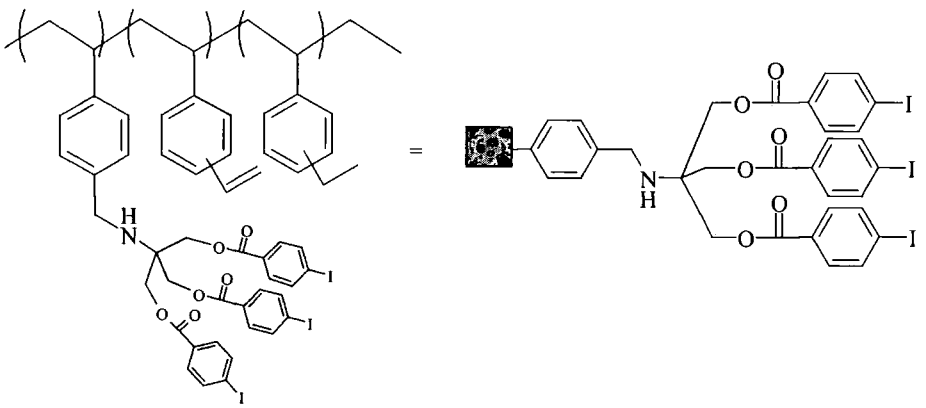


(5)

P78B1$_g$WM (90 mg, 0.08 mmol) was placed in a 25 mL round-bottomed flask fitted with a rubber septum and vent. A solution of TFA/DCM (1:1, 2 mL) was added and the mixture was stirred for 30 min. The PolyHIPE support was removed by filtration through Celite and washed with DCM/MeOH (1:1, 4 x 5 mL) and MeOH (2 x 5 mL). The filtrate and washings were concentrated and the product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to provide an orange solid (17 mg, 93% based on the loading of aryl iodide). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.87 (s, 3H), 7.07 (d, J=8.8 Hz, 2H), 7.70 (d, J=8.8 Hz, 2H), 7.76 (d, J=8.4 Hz, 2H), 8.08 (d, J=8.4 Hz, 2H). Signals of similar intensity were also present in the spectrum between 7.00 and 8.00 ppm. Due to incomplete cleavage, **P78B1$_g$WM** was cleaved for a second time using a solution of TFA/DCM (1:1, 4 mL) and an extended reaction time of 1 h. The filtrate and washings were concentrated and the product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to provide an orange solid (19.7 mg, total yield of 200% based on the loading of aryl iodide). ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 3.87 (s, 3H), 7.07 (d, J=8.5 Hz, 2H), 7.70 (d, J=8.5 Hz, 2H), 7.77 (d, J=8.0 Hz, 2H), 8.09 (d, J=7.5 Hz, 2H). Signals of similar intensity were also present in the spectrum between 7.00 and 8.00 ppm.

4.8.10 Procedures for the Esterification of Trishydroxymethyl-Functionalised PolyHIPE

4.8.10.1 Synthesis of P78B7$_g$TI



P78B7gTI

P78B7$_g$TI was synthesised according to the standard EDCI/HOBT procedure described in section 4.8.5.1. The quantities used were; **P78B7$_g$TH** (0.3 g, 2.31 mmol $-CH_2OH$ groups), 4-iodobenzoic acid (2.9 g, 11.6 mmol), EDCI (2.2 g, 11.6 mmol), HOBT (0.32 g, 2.3 mmol), DMF (20 mL). The PolyHIPE was filtered and washed with DMF (4 x 20 mL), DCM (2 x 20 mL) and MeOH (2 x 10 mL). The material was dried *in vacuo* at 50 °C for 24 h to give **P78B7$_g$TI** (1.2 g, 96% conversion by weight). Found I, 35.8%. Calculated I, 37.5% (95% conversion). **P78B7$_g$TI** (0.3 g, 0.85 mmol -I groups) was re-washed with NEt_3/MeOH (1:1, 2 x 10 mL) and MeOH (3 x 10 mL) to provide **P78B7$_g$TI** (143 mg, 48% conversion by weight). Found I, 29.7%. Calculated I, 37.5% (79% conversion). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH or NH), 2924m and 2853w (CH), 1782m and 1719s (C=O), 1637m and 1510s (aryl C=C), 825m (*p*-disubstituted benzene ring), 555br (CI).

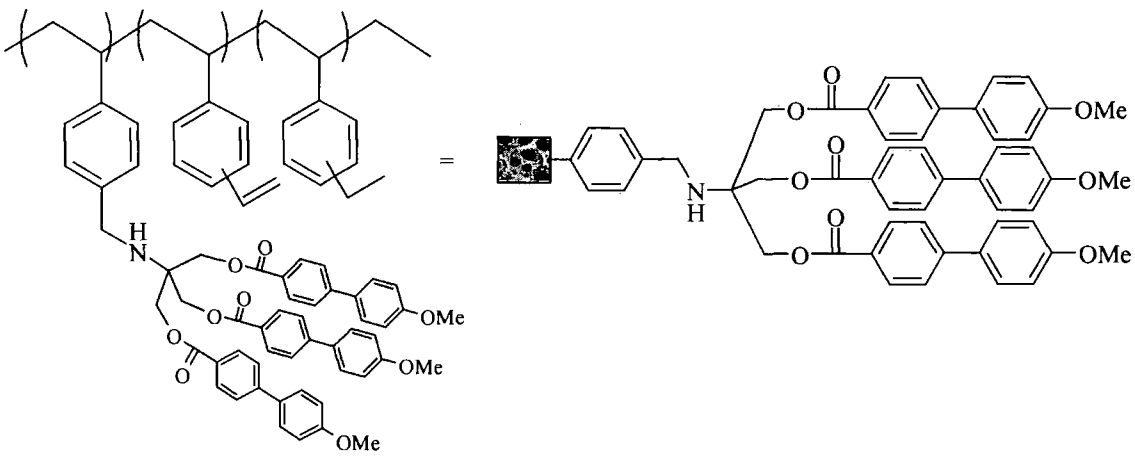
4.8.10.2 Synthesis of P78B7$_g$TI (Second Batch)

P78B7$_g$TI was synthesised as described in section 4.8.5.1. The quantities used were; **P78B7$_g$TH** (0.2 g, 1.54 mmol $-CH_2OH$ groups), 4-iodobenzoic acid (1.9 g, 7.7 mmol), EDCI (1.5 g, 7.7 mmol), HOBT (0.21 g, 1.5 mmol), DMF (13 mL). The PolyHIPE was filtered and washed with DMF (3 x 20 mL), DCM (2 x 20 mL), NEt_3/MeOH (1:1, 2 x 20 mL) and MeOH (2 x 10 mL). The material was dried *in*

vacuo at 50 °C for 24 h to give **P78B7$_g$TI** (0.61 g, 72% conversion by weight). Found I, 32%. Calculated I, 37.5% (85% conversion).

4.8.11 Procedures for Solid Phase Suzuki Coupling utilising Tris-OH Functionalised PolyHIPE

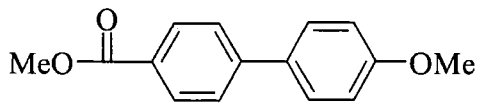
4.8.11.1 Synthesis of P78B7$_g$TM via Heated Conditions



P78B7$_g$TM

P78B7$_g$TM was synthesised according to the procedure described in section 3.8.5.5, using K_2CO_3 rather than $Na_2CO_3(aq)$, dry DMF rather than dry DME and a reaction temperature of 70 °C. The quantities used were; **P78B7$_g$TI** (0.25 g, 0.63 mmol –I groups), dry DMF (10 mL), freshly prepared $Pd(PPh_3)_4$ (122 mg, 0.11 mmol), 4-methoxybenzeneboronic acid (0.33 g, 2.2 mmol) and K_2CO_3 (0.55 g, 4 mmol). After reaction, the mixture was diluted by addition of a solution of 25% ammonium acetate (20 mL) and stirred for 5 min. The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B7$_g$TM** (94 mg, 44% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3421br (OH or NH), 2925m and 2853w (CH), 1718w (C=O), 1610w and 1510w (aryl C=C), 1056s (CO), 827w (*p*-disubstituted benzene ring).

4.8.11.2 Cleavage of P78B7$_g$TM to Yield (1)



(1)

P78B7$_g$TM (80 mg, 0.20 mmol) was cleaved according to the standard cleavage procedure (section 3.8.5.4) using 1M NaOMe (80 μL, 0.08 mmol) and dry MeOH/THF (1:3, 8 mL). The PolyHIPE support was removed by filtration through Celite and washed with MeOH/THF (1:1, 4 x 5 mL) and THF (2 x 5 mL). The filtrate and washings were concentrated and the product was dried under vacuum (10^{-1} mbar) at 50 °C for 2 h, to provide an orange solid (16.4 mg, 34% based on the loading of aryl iodide). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 7.00 (d, J=9.0 Hz, 2H), 7.61 (m, 4H), 8.09 (d, J=8.7 Hz, 2H).

4.8.11.3 Synthesis of P78B7$_g$TM via Ambient Conditions

P78B7$_g$TI (0.3 g, 0.76 mmol –I groups) was placed in a 2-necked 50 mL round-bottomed flask fitted with rubber septa. DMF (8 mL) was transferred to the flask via syringe and the suspension was degassed with nitrogen gas for 30 min. Commercially available catalyst tris-(dibenzylideneacetone)dipalladium (0) (55 mg, 0.06 mmol) and 4-methoxybenzeneboronic acid (0.17 g, 1.1 mmol) were added and the reaction mixture was stirred for 30 min. This was followed by the addition of K_2CO_3 (0.26 g, 1.9 mmol). The reaction was performed under a nitrogen atmosphere for 18 h. The resultant mixture was diluted by addition of a 25% solution of ammonium acetate (20 mL), and stirred for 5 min. The PolyHIPE was filtered and subjected to the standard wash procedure before being dried *in vacuo* at 50 °C for 24 h, to give **P78B7$_g$TM** (106 mg, 42% conversion by weight). IR (KBr disc) υ_{max}/cm^{-1} 3422br (OH or NH), 2925m and 2853w (CH), 1718w (C=O), 1637m and 1509m (aryl C=C), 1056s (CO), 827w (*p*-disubstituted benzene ring).

4.8.11.4 Cleavage of P78B7$_g$TM to Yield (1)

P78B7$_g$TM (80 mg, 0.20 mmol) was cleaved according to the procedure outlined in section 4.8.11.2, using identical quantities of reagents and solvent. The filtrate and washings were concentrated and the product was dried under vacuum (10^{-1}

mbar) at 50 °C for 2 h, to provide an orange solid (10.4 mg, 21% based on the loading of aryl iodide). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.94 (s, 3H), 7.00 (d, J=8.4 Hz, 2H), 7.61 (m, 4H), 8.09 (d, J=8.7 Hz, 2H). Signals of similar intensity were also present in the spectrum between 7.00 and 8.00 ppm.

4.8.12 Synthesis of Tetrakis(triphenylphosphine)palladium (0)

$Pd(PPh_3)_4$ was synthesised according to the procedure outlined in section 3.8.11.

4.9 References

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Chapter 5

Overall Conclusions and Recommendations for Future Work

5.1 Conclusions

The preparation and subsequent functionalisation of PolyHIPE monoliths with high loadings of chloromethyl groups has been described. The monoliths were synthesised by the direct copolymerisation of VBC and DVB, and their properties were determined by a variety of techniques. Characterisation of the PolyHIPEs revealed that the VBC monomer was susceptible to hydrolysis during polymerisation, resulting in the formation of hydroxymethyl functionalities. However, the concentration was estimated to be low by solid state ^{13}C NMR. In parallel batch reactions, granular PolyHIPE was reacted with TMDS, NH_4OH and HMTA reagents in an attempt to aminate the material and produce a PolyHIPE-supported amine linker. An optimised version of the HMTA procedure proved to be the most successful method, yet conversion was not as high as expected. When applied to monoliths in

flow-through mode however, conversions were significantly increased and supports with high loadings of aminomethyl groups (1.6 mmol g^{-1}) were obtained. The capacity of aminomethylated PolyHIPE was increased further with the introduction of the trisamine linker. This functionalised PolyHIPE showed excellent potential as a polymer-supported scavenger for PASP synthesis.

The suitability of chloromethyl PolyHIPE as a support in the Suzuki cross-coupling reaction was investigated. In batch reactions involving different boronic acids, the classical Suzuki conditions were optimised in order to maximise the yields and purities of product obtained. The highest yield of pure biaryl was produced using the cubic form of the PolyHIPE support and the electron-rich boronic acid, 4-methoxybenzene boronic acid. Identification of the major reaction impurity, which was detected in most of the cleaved products, proved to be challenging. Isolation and analysis of the species suggested that it was an inorganic residue, possibly from the catalyst employed in the couplings. In a comparative batch reaction involving polymer beads, it was believed that a large amount of moisture had been retained in the beads as a result of their high porosity. This led to the formation of the hydrolysis product, 4-methoxy-biphenyl-4'-carboxylic acid during cleavage with NaOMe. Fortunately, this effect was not observed in the reactions involving PolyHIPE.

In identical flow-through reactions employing monolithic PolyHIPE and macroporous beads, PolyHIPE was found to be a much more efficient form of support material, converting a greater amount of chloromethyl groups into biaryl product. Attempts to develop an automatic recyclable flow-through system proved unsuccessful. A more robust pump was needed to recycle the reagent solution through the monoliths in a closed-loop system.

The derivatisation of VBC/DVB PolyHIPE for the preparation of Wang resin was problematic. Various PolyHIPE forms were modified using an optimised version of the HMP procedure and conversions appeared to be high as evidenced by reductions in the chlorine elemental analysis results. However, attempts to functionalise the supports were unsuccessful and it was suspected that side-reactions had interfered with the HMP procedure. An alternative route to Wang resin, involving a two-step synthesis, proved to be more useful in that the success of the reaction could be monitored at each stage. The eventual immobilisation of 4-iodobenzoic acid utilising MSNT/NMI reagents and the subsequent Suzuki coupling, demonstrated that Wang PolyHIPE was suitable as a support in this application.

Similarly, the highly loaded tris-OH PolyHIPE proved to be a valuable support for Suzuki coupling, with the optimised conditions developed for chloromethyl PolyHIPE producing the greatest yield of product.

5.2 Recommendations for Future Work

The development of PolyHIPE monoliths bearing three basic linker moieties, chloromethyl (Merrifield), aminomethyl and hydroxymethyl (Wang), as well as the more elaborate, trisamine and trishydroxymethyl linkers, has been described. It would be beneficial if this series was expanded further to produce a full range of PolyHIPE-immobilised linkers for use in a broad range of organic transformations. Rink amide, Sasrin and HMPA are some examples of common linkers which could be attached to PolyHIPE. In the latter type, the linker part is attached to the bead support by means of a flexible spacer, which is believed to assist with the diffusion of reagents to the immobilised reactive sites by increasing their distance from the support. It would be interesting to compare the performance of PolyHIPEs containing HMPA linker and Wang linker, to observe whether this effect is true of a support such as PolyHIPE.

In the Suzuki reaction employing Wang-functionalised PolyHIPE, it appeared that the coupling reaction had taken place successfully. However, incomplete cleavage of the product was observed using TFA and the conditions reported for polymer beads. Therefore, the procedure should be optimised on PolyHIPE to ensure complete detachment of pure product from the support. The entire process should then be applied to monolithic PolyHIPE supports under flow-through as this would provide an excellent demonstration of the utility of PolyHIPE in a five-step organic synthesis.

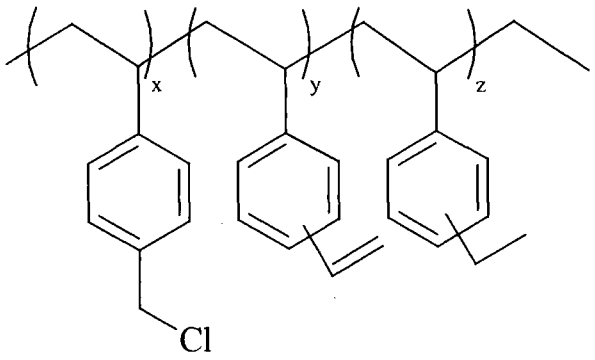
In the Suzuki reaction involving tris-OH PolyHIPE, it was believed that the EDCI/HOBT method had failed to attach a high concentration of 4-iodobenzoic acid. Therefore, this step should be repeated using MSNT/NMI reagents, as they proved to be successful with Wang-functionalised PolyHIPE. Subsequent Suzuki coupling using the optimised conditions should result in high yields of product.

From a review of the literature, it would seem advantageous to attach trifunctional dendrimer monomers to trisamine and tris-OH PolyHIPEs to enhance the loadings of these supports further. The robust nature and easy handling of PolyHIPE, would allow the resultant dendrimers to be used in a variety of synthetic applications.

APPENDIX

Appendix 1

Sample Calculation for the Theoretical Composition of P64B1C



P64B1C

Weight of 4-VBC monomer = 6.50 g

Weight of DVB monomer = 3.66 g (2.93 g *m*- and *p*-DVB, 0.73 g *m*- and *p*-ES)

Total weight of monomer in **P64B1C** = 10.16 g

Therefore, monomer ratios by weight are; x = 0.64, y = 0.29, z = 0.07

The amounts of carbon, hydrogen and chlorine in each monomer with respect to the monomer ratios are calculated as:

4-VBC (C_9H_9Cl): C, 69.1 g; H, 5.8 g; Cl, 22.7 g.

DVB ($C_{10}H_{10}$): C, 34.8 g; H, 2.9 g.

ES ($C_{10}H_{12}$): C, 8.4 g; H, 0.84 g.

Total carbon = 112.3 g, hydrogen = 9.5 g and chlorine = 22.7 g

Total amount = 144.5 g

Theoretical composition: C, 77.7%; H, 6.6%; Cl, 15.7%

Appendix 2

Sample Fmoc Calculation for P64B1$_g$A

UV absorbance (301 nm value – 322 nm value) = 0.339

Amount of Fmoc-protected **P64B1$_g$A** cleaved = 0.0104 g

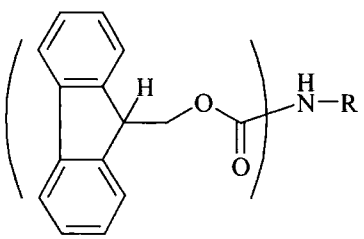
$$\text{Loading in mmol g}^{-1} = \overbrace{\left(\frac{UV\ value}{7800}\right)}^{\text{Concentration in cell}} \text{ x } Dilution \text{ x } \left(\frac{Flask\ volume(mL)}{Wt.of\ sample(g)}\right)$$

$$\text{Loading in mmol g}^{-1} = \left(\frac{0.339}{7800}\right) \text{ x } 25 \text{ x } \left(\frac{5}{0.0104}\right)$$

$$\text{Loading} = 0.522 \text{ mmol g}^{-1}$$

Normalised calculation for **P64B1$_g$A**:

The molecular weight of Fmoc was taken into consideration and a normalised value was obtained by working back to $-NH_2$.



M_w Fmoc = 223 g

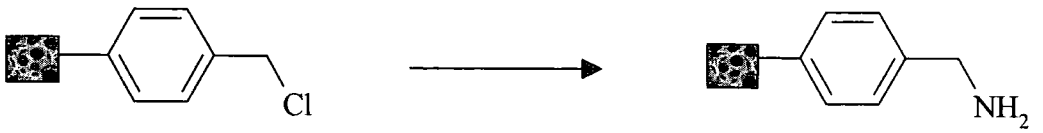
To obtain an accurate value for the amount of $-NH_2$ groups in the sample, the weight of the Fmoc group was subtracted from the Fmoc number. For 0.522 mmol, the amount subtracted was:

$$223 \text{ g x } (5.22 \text{ x } 10^{-4} \text{ mol}) = 0.116 \text{ g}$$

The actual value became 0.522 mmol in 0.884 g. So in 1 g of sample the amount of $-NH_2$ groups was calculated as 0.59 mmol.

Appendix 3

Sample Calculations for Yield of Functionalised PolyHIPE and Degree of Functionalisation



P64B1C

2.68 mmol $-CH_2Cl\ g^{-1}$

P64B1$_g$A

There are 2.68 mmol $-CH_2Cl$ groups in 1g of **P64B1C**, therefore 1 mmol of $-CH_2Cl$ groups are contained in 0.373 g of **P64B1C**. The average molecular weight per repeat unit of unmodified **P64B1C** is 373 g mol^{-1} (M_1). The average molecular weight per repeat unit of **P64B1$_g$A** is 354 g mol^{-1} (M_2).

$$M_2 = M_1 - 35.5 + 16$$

$$M_2 = 354\ g\ mol^{-1}$$

Calculation of theoretical weight of **P64B1$_g$A** (W_T):

$$W_T\ (g) = \frac{Weight\ of\ PolyHIPE\ before\ functionalisation\ (g)}{M_1\ (g\ mol^{-1})}\ x\ M_2 (g\ mol^{-1})$$

$$W_T = \frac{0.15\,g}{373\,g\ mol^{-1}} \times 354\,g\ mol^{-1}$$

$$W_T = 0.142\ g$$

$$\text{Yield}\ (\%) = \frac{Observed\ weight\ (W_O)(g)}{Theoretical\ weight\ (W_T)(g)}$$

$$\text{Yield of P64B1}_g\text{A} = \frac{0.142\,g}{0.142\,g} = 100\%$$

For **P64B1$_g$A**, the degree of functionalisation is calculated from n, the number of nitrogen atoms per modified repeat unit *i.e.* n=1.

$$\text{Degree of functionalisation (\%)} = \frac{n \times M_w}{M_2} \times 100\%$$

$$\text{Degree of functionalisation (\%)} = \frac{1 \times 14}{354} \times 100\%$$

$$= 3.95\% \text{ nitrogen}$$

Conversion (ρ) of chloromethyl groups to modified groups is given by:

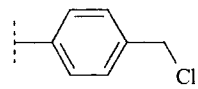
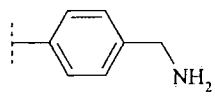
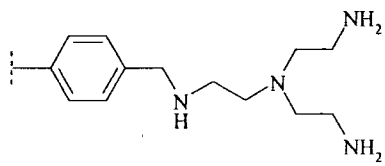
$$\rho = \frac{\textit{Degree of functionalisation found (\%)}}{\textit{Degree of functionalisation calculated (\%)}} \times 100\%$$

Based on combustion elemental analysis for nitrogen, the conversion to **P64B1$_g$A** was found to be:

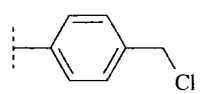
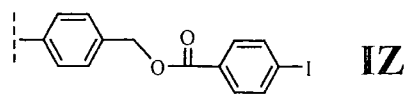
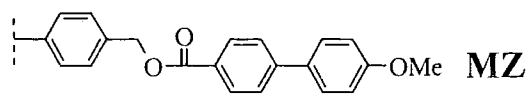
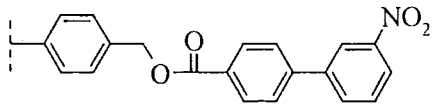
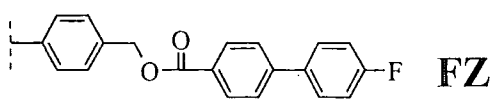
$$\rho = \frac{0.9}{3.95} \times 100\% = 23\%$$

$$\text{Loading of } -NH_2 \text{ groups } g^{-1} = \left(\frac{0.9}{14}\right) \div 100 \times 1000 = 0.64 \text{ mmol } -NH_2 \text{ groups } g^{-1}$$

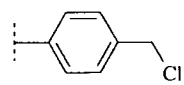
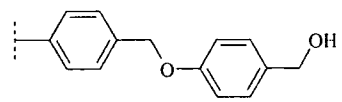
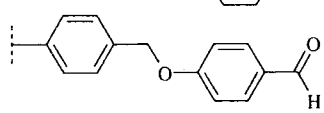
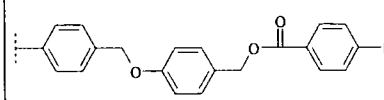
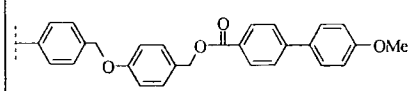
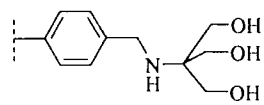
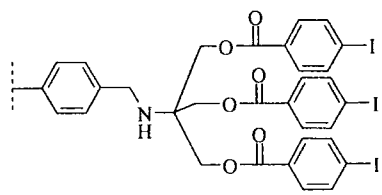
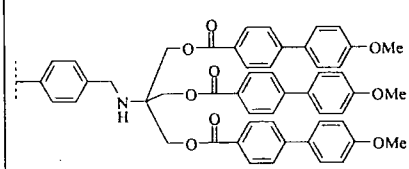
Identification Codes for Chapter 2

Support Code			
Support type	% wt VBC	Batch and form	Functionality
PolyHIPE P  **Bead B** 	64% = **64** 78% = **78**	**B**x_y x = **1, 2, 3…** y = **g, c, m** **g** = granular **c** = cubic **m** = monolithic	 **C**  **A**  **TA**

Identification Codes for Chapter 3

Support Code			
Support type	% wt VBC	Batch and form	Functionality
PolyHIPE P  **Bead B** 	78% = **78** 23% = **23**	**B**x_y x = **1, 2, 3…** y = **g, c, m** **g** = granular **c** = cubic **m** = monolithic	 **C**  **IZ**  **MZ**  **NZ**  **FZ** **Z = 1 or 2**

Identification Codes for Chapter 4

Support Code			
Support type	% wt VBC	Batch and form	Functionality
PolyHIPE P  **Bead B** 	64% = **64** 78% = **78**	**B**x_y x = **1, 2, 3**... y = **g, c, m** **g** = granular **c** = cubic **m** = monolithic	 **C**  **WH**  **BA**  **WI**  **WM**  **TH**  **TI**  **TM**