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PolyHIPE Supports in Batch and Flow-Through Suzuki Cross-Coupling Reactions

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As part of ongoing research efforts to discover alternative support materials to polymer beads for use in polymer-supported synthesis, particularly under flow-through conditions, this work involves the synthesis of PolyHIPE (High Internal Phase Emulsion) polymer monoliths. PolyHIPEs containing high loadings of chloromethyl groups were efficiently prepared by the direct copolymerization of 4-vinylbenzyl chloride and divinylbenzene monomers. The 'Merrifield' PolyHIPE proved 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 the PolyHIPE support in cubic form and utilizing an electron-rich boronic acid. In comparison to polymer beads, this material 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. It is suggested that the absence of channelling with PolyHIPE monoliths gives better performance under flow-through conditions than permanently porous beads.

Introduction

The first polymer-supported organic synthesis was reported over 40 years ago,[1] 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. To meet the growing demand for novel, biologically active compounds, synthetic chemists are expected to produce chemical entities in a faster, more efficient manner. This has introduced the new challenge of adapting solution phase reactions to the solid phase. Among the many reported organic reactions developed on solid supports are Pd-catalyzed cross-couplings,[2] as well as Diels−Alder, Wittig, and Michael reactions.[3] Of particular interest is the Suzuki coupling reaction, which has already proven to be effective in solid-phase synthesis.[4] Suzuki coupling yields a biaryl moiety, which is found in many molecules with interesting properties (including polymers, liquid crystals, natural products and biologically active compounds[5]).

While the development of synthetic 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.[6] The majority of solid phase organic syntheses (SPOS) performed to date have exclusively employed polymeric beads as the support.[7] These have tended to be gel-type and based on polystyrene-divinylbenzene (1−2%) copolymer resins. A major limitation of gel-type beads however is that most of the reactive sites (99%) are situated inside the bead particles and swelling in an organic solvent is necessary if the reactants are to access these readily. Alternatives to gel-type beads are rigid, permanently porous polymer beads. (The commonly applied term 'macroporous' is avoided, as it implies a pore size >50 nm, according to IUPAC definitions.) These are considered to improve functional group accessibility as they do not require preswelling and allow access to the interior by diffusion. However, limitations with this technology include a tendency for the beads to react primarily at the surface, and slow incomplete reactions as a consequence of the diffusion process.

Several articles have since detailed the development of novel composite resin beads, reported to overcome some of these problems. A major breakthrough was the development of polystyrene-poly(ethylene glycol) composite beads known as TentaGel.[8] Long PEG side-chains grafted onto the surface of the beads resulted in greater flexibility and accessibility of the functional end groups. However, the main shortcomings of this technology are the low loading capacities (0.2 mmolg⁻¹) and the easy cleavage of the grafted PEG chains. Following this initial work, a host of commercial bead supports such as JandaJels,[9] PEGA,[10] CLEAR,[11] ArgoGel, and ArgoPore resins[12] have since been developed.

It is evident from the array of literature published on polymer supports that common goals exist when attempting to produce an ideal support. In the majority of cases, attempts to improve the performance of polymer beads have focused 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.[13] Flow-through techniques offer many advantages over batch systems such as fast reaction kinetics, high reactivity, high throughput, minimal

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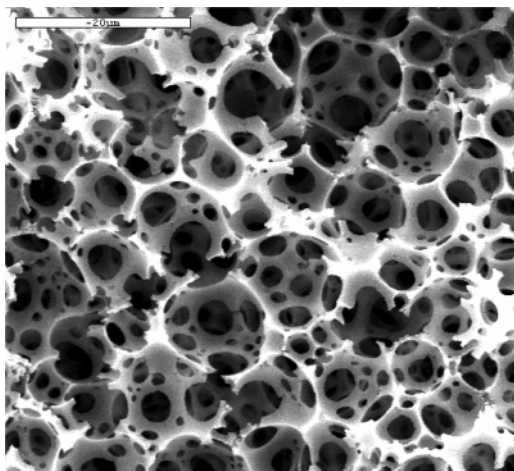‡ University of Maribor, Faculty of Chemistry and Chemical Engineering.

Figure 1. Scanning electron micrograph of typical PolyHIPE material.

workup and continuous operation. Bead-type polymers have been widely used in packed beds, however columns and reactors containing such materials have experienced some limitations.[14] When highly swollen, gel-type beads become soft and compressible under flow, and a channelling effect is observed with permanently porous beads, whereby the solution prefers to flow around the beads and into the interstitial voids, rather than through them. Only the active sites close to the bead surface tend to be accessible by the reagent solution.

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. In the early 1990s, Svec, Fréchet et al.[15] launched a novel form of continuous medium based on rigid permanently porous polymer monoliths. The monoliths were reported to contain both small (<200 nm diameter) and large pores (> 600 nm diameter), resulting in a porosity of 30−90%. The authors reasoned that the material should contain large pores for convection as well as a connected network of smaller pores for diffusion. With the aim of creating an almost workup free method for automated solution-phase synthesis, Kirschning and co-workers[16] recently demonstrated the preparation of poly(vinylbenzyl chloride)-glass composites (cross-linked with 2−20% DVB), known as PASSflow supports, for use in flow-through processes. The matrix exhibited a small bead-type structure and possessed a high surface area. The composite was loaded with chemical functionalities such as immobilized reagents and catalysts. As a result of the high porosity and the presence of functionalized polymer inside the pores of the monoliths, good convective flow of the soluble organic reactants was observed. In this case, technical problems such as channelling are avoided since the polymeric phase is wedged inside the microchannel pore system of the support.

An alternative method for the production of highly porous, permeable monoliths is to polymerize the continuous phase of a high internal phase emulsion (HIPE). The resulting material, termed PolyHIPE,[17] has a fully interconnected, open-cellular structure and is highly permeable as a result (Figure 1).

Surface areas approaching 700 m^2 g^{-1} have been reported[18] with these novel materials, hence high capacity can be achieved without employing a grafting technique. PolyHIPE polymers have been tested in a

wide variety of applications ranging from inert matrixes for the immobilization of cells[19] and enzymes[20] to precursors for supported reagents[21] and catalysts.[22] Mercier and co-workers[23] took advantage of the high level of unreacted vinyl groups in poly(styrene/DVB) PolyHIPEs (3 mmol g^{-1}, 45 mol %) to prepare a wide variety of immobilized reactive groups. Comparisons in fictionalization success were made between a batch and continuous flow method and in general, the batch system was found to produce superior results.

With the aim of preparing a reactive PolyHIPE material suitable for elaboration to provide supports for use in organic synthesis, we incorporated 4-vinylbenzyl chloride (VBC) monomer into PolyHIPE materials.[24] Chemical modification of the resulting monoliths with N-nucleophilic reagents to produce supported bases and scavenger resins has been described.[25] One of our further research aims was to demonstrate the utility of PolyHIPE materials as supports for SPOS applications such as the Suzuki biaryl cross-coupling reaction. Frenette and Friesen[3] were the first to investigate the possibility that well-characterized 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. 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 utilized polymer supports in the form of cross-linked polystyrene beads. Indeed, most of the syntheses were reported to proceed to high conversion, however problems such as poor swelling[26] and in some cases, shattering of the supports as a result of osmotic shock[27] were disclosed. In the quest to find an alternative support to polymer beads, Sherrington and co-workers[28] tested the utility of VBC-based polymer disks in the solid-phase Suzuki reaction. Coupling on the disk and subsequent cleavage resulted in an overall 10.5% conversion to product. 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.

In this work, flow-through Suzuki synthesis on monoliths of chloromethyl PolyHIPE, prepared inside Quest reactor tubes, was performed. 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 suggests that this is one of the first demonstrations of Suzuki coupling under flow-through conditions (Haswell et al. report microwave assisted Suzuki reactions using Pd supported on silica and alumina in microreactors[29]). PolyHIPE was considered to be an ideal support for this purpose due to its open and permeable structure. 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. Further aims of the work were to compare the performance of PolyHIPE against permanently porous polymer beads in both batch and flow-through reactions.

Experimental

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 (VBC) were purified by passing through a column of basic alumina. THF was freshly distilled over benzophenone ketyl. DMF (HPLC grade), DME, DME (anhydrous), methanol (anhydrous) and DMSO (anhydrous) were used as solvents for the reactions. All other reagents were used without further purification. ArgoPore-Cl polymer beads were purchased from Argonaut and used as received. Residual palladium was removed from Suzuki coupling reactions by passing through a column of Celite 545 purchased from Aldrich.

Characterization. Combustion elemental analysis data (C, H and N) were obtained from an Exeter Analyzer CE−440. A Dionex Ion Chromatograph Analyzer DX-120 was employed for chlorine, iodine and fluorine determination. FTIR spectra (KBr disks) were recorded on a Perkin-Elmer 1600 Series FTIR Spectrometer. NMR spectra were recorded using either a Varian Mercury-200 (^{1}H at 200 MHz and ^{13}C at 50.2 MHz), a Varian Unity-300 (^{1}H at 299.9 MHz and ^{13}C at 75.4 MHz) or a Varian Mercury 400 (^{1}H at 400 MHz and ^{13}C at 100 MHz) NMR spectrometer. Deuterated solvents were used as supplied from Aldrich (CDCl$_3$ and (CD$_3$)$_2$SO) and Apollo (CD$_3$COCD$_3$ and CD$_3$OD). 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−mass spectrometry (GC−MS), a Micromass Autospec instrument was used. A Micromass LCT instrument was employed for electrospray mass spectrometry (ES−MS) and a Waters 600 LC instrument was used in conjunction with a Waters 2700 Autosampler, for liquid chromatography mass spectrometry (LC-MS). Analytical and preparative high performance liquid chromatography (HPLC) were carried out using Varian Star instruments. MeOH/H$_2$O (90/10 v/v) was used as the eluent at a flowrate of 10 mLmin^{-1}. Samples were injected manually using a 500 μL injection loop and analytes were detected by UV (λ = 233 nm). Surface area measurements were carried out using a Micromeritics Tristar 3000 Surface Area and Porosimetry Analyzer. UV absorbencies were recorded on a Pye Unicam UV−vis Spectrophotometer.

PolyHIPE Preparation. PolyVBC PolyHIPE materials were prepared as described previously.[24e] Briefly, VBC (8.1 g, 0.05 mol), divinylbenzene (2.3 g, 0.019 mol) and Span 80 (1.97 g, 4.6 mmol) were placed in a three-necked 250 mL round-bottomed flask, fitted with an overhead stirrer (glass rod fitted with a D-shaped PTFE paddle), and 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 deionized water (90 mL), and the resulting solution was purged with nitrogen for 15 min. The organic solution was stirred under nitrogen at ca. 300 rpm, and the aqueous phase was added dropwise 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 polymerized in an oven at 60 °C for 48 h. The PolyHIPE was retrieved by disassembling the bottle and extracted in a Soxhlet apparatus with deionized water for 24 h and 2-propanol 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 deionized 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 was obtained by grinding sections of the monolith in a homogenizer. Cubic pieces of PolyHIPE (ca., 1 cm^3) were cut from the monolith using a scalpel. All PolyHIPE materials used in this study contained 78 mol % VBC (from the monomer feed ratio).

Batch Synthesis of PolyHIPE-Supported 4-Iodobenzoic Acid. A typical procedure is as follows: granular PolyHIPE (0.5 g, 2.2 mmol −CH$_2$Cl 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 × 25 mL), THF/H$_2$O (1:1, 2 × 25 mL), DCM (2 × 25 mL) and methanol (2 × 25 mL). The material was dried in vacuo at 50 °C for 24 h to give 4-iodobenzoate modified PolyHIPE (0.65 g, 67% conversion by weight). Found I, 19.8; Cl, 1.1%. Calculated I, 28.8; Cl 0% (69% conversion). IR (KBr disk) v_{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).

Batch Suzuki Coupling on PolyHIPE. The following example procedure is for the synthesis of **1** on a granular PolyHIPE support.

PolyHIPE possessing 4-iodobenzoate groups (0.6 g, 0.90 mmol −I) was placed in a two-necked 50 mL round-bottomed flask fitted with rubber septa. Dry DME (20 mL) was transferred to the flask via syringe and the suspension was degassed with nitrogen gas for 30 min. The flask was wrapped in aluminum foil and supplied with a continuous flow of nitrogen. Freshly prepared Pd-(PPh$_3$)$_4$ (0.18 g, 0.15 mmol) and 4-methoxybenzeneboronic acid (0.48 g, 3.15 mmol) were added, and the mixture was stirred thoroughly for 30 min. A 1 M aqueous solution of Na$_2$CO$_3$ (9 mL, 9 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 PolyHIPE was filtered, washed as above and dried in vacuo at 50 °C for 24 h, to give PolyHIPE functionalized with 4-methoxybiphenyl carboxylate moieties (0.49 g, 83% conversion by weight). IR (KBr disk) v_{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).

Batch Cleavage of Biaryl Compound 1 from PolyHIPE. Biaryl functionalized PolyHIPE (0.45 g, 0.68 mmol) was placed in a 50 mL round-bottomed flask to which a solution of 1 M NaOMe in dry MeOH (0.2 mL, 0.2 mmol) and dry MeOH/THF (1:1, 20 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 in vacuo at 50 °C for 2 h. Due to incomplete cleavage, the PolyHIPE (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$_3$)$_2$CO) 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$_3$)$_2$CO) 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 FW = 242.27).

Flow-Through Synthesis of Biaryl Compound 1 Using PolyHIPE Supports. A 10 mL fritted PTFE reaction vessel containing monolithic VBC PolyHIPE (0.14 g, 0.62 mmol $-$CH$_2$Cl groups$-$see Supporting Information for preparation procedure) was set in an argonaut Quest 210 Parallel Synthesizer, 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 result-ant 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 and allowed to flow through the monolith and into a collect-ing 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$_2$O (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 iodo-containing monolith (0.24 g, 96% conver-sion by weight). Found I, 20.2; Cl, 1.3%. Calculated I, 27.3; Cl 0% (74% conversion). IR (KBr disk) v_{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).

A tube containing 4-iodobenzoate modified PolyHIPE monolith (0.24 g, 0.38 mmol $-$I groups) was set in the Quest 210 and the apparatus and collection flask were covered with aluminum foil to create a darkened environment. Dry DME (10 mL) was injected into the tube, which was sealed under nitrogen and approxi-mately 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$_2$CO$_3$-(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 neutralized with 25% NH$_4$OAc (7.5 mL), washed using the usual wash procedure and dried in vacuo at 50 °C for 48 h, to produce 4-methoxybiphenyl carboxylate supported on PolyHIPE monolith (0.32 g, 133% conversion by weight). IR (KBr disk) v_{max}/cm^{-1} 3447br (OH), 2925m and 2853w (CH), 1718s (C=O), 1605m (aryl C=C), 1272s (CCl),

Scheme 1. PolyHIPE-supported Synthesis of Biphenyl-4-carboxylic Acid Methyl Esters
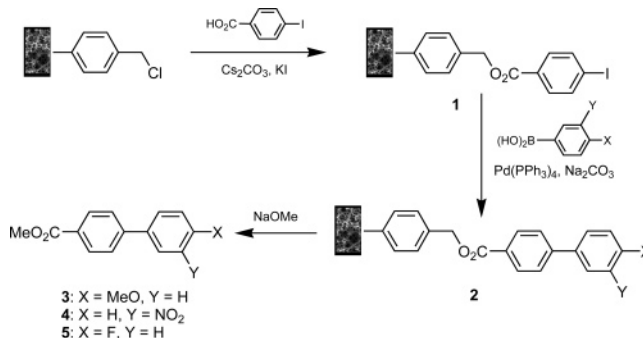
1251m and 1039w (CO) 828m (*p*-disubstituted benzene ring), 551br (CI).

The product was cleaved initially from the monolith (0.32 g, 0.5 mmol) by passing through a solution of 2 M NaOMe (0.07 mL, 0.14 mmol) in dry MeOH/THF (1:4, 5 mL) 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 2 M 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 immer-sion took place over a total of 72 h. To ensure complete cleavage of the product, a third solution of 2 M NaOMe (0.23 g Na in dry MeOH, 5 mL) (0.7 mL, 1.4 mmol) in dry MeOH (5 mL) was flowed through 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%). NMR data of **1** were in accord with those given above.

All other experimental procedures and associated characterization data are found in the Supporting Information.

Results and Discussion

Work began by preparing poly(VBC/DVB) PolyHIPE with monomers in the ratio of 78:22 (VBC:DVB) by weight. Portions of the emulsion were polymerized inside PE bottles and PTFE reactor tubes for use in batch and flow-through reactions, respectively. 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. The VBC PolyHIPE materials in granular and cubic form were used in the synthesis of 4-methoxybiphenylcarboxylic acid methylester (**3**) by Suzuki coupling (Scheme 1). Initially, conditions reported for Suzuki coupling using chloromethyl polystyrene beads[4,5] were replicated (Table 1, conditions A). Despite high loadings of 4-iodobenzoate and (apparent) high conversion to the corresponding supported biaryl compound, yields of isolated 4-meth-oxybiphenyl carboxylic acid methyl ester were disap-pointingly low. Therefore, optimization of the Pd cata-lyzed coupling step was undertaken. Classical conditions

Table 1. Suzuki Cross Coupling Experimental Conditions and Results

support format	conversion to **1** (%)[a]	Suzuki conditions[b]	conversion to **2** (%)[a]	isolated yield of **3** (%)[c]
granular	69	A	96	38
cubes	67	A	86	28
granular	66	B	92	18
cubes	81	B	83	22
granular	78	C	83	70
cubes	76	C	83	93
beads	59	C	70	70

[a] Determined by iodine analysis. [b] A: coupling − commercial Pd(PPh$_3$)$_4$ (0.14 eq.), 4-MeO−Ph-B(OH)$_2$ (5.6 equiv), Na$_2$CO$_3$ (7 equiv), DME, reflux, 24 h.; cleavage − NaOMe (0.6 equiv), MeOH: THF (1:1), 70 °C, 48 h. B: coupling − in-house Pd(PPh$_3$)$_4$ (0.06 equiv), 4-MeO−Ph−B(OH)$_2$ (1.2 equiv.), Na$_2$CO$_3$ (3.6 equiv), DME, reflux, 40 h.; cleavage − NaOMe (0.5 equiv), MeOH:THF (1:1), 70 °C, 48 h. C: coupling − in-house Pd(PPh$_3$)$_4$ (0.17 equiv), 4-MeO−Ph−B(OH)$_2$ (3.5 equiv), Na$_2$CO$_3$ (10 equiv), DME, reflux, 40 h.; cleavage − NaOMe (1.0 equiv), MeOH:THF (1:1), 70 °C, 72 h. [c] Obtained by preparative HPLC.

for solution phase Suzuki reactions[30] were employed, and 'in house' Pd(PPh$_3$)$_4$ was employed.[31] Due to the sensitivity of palladium (0) complexes, the quality of commercially available catalysts can vary substantially.[32] Once again, conversion to supported biaryl was high however the yield of isolated **3** was much lower (Table 1).

The crude products obtained contained significant quantities of impurities, as determined by HPLC. From a thorough analytical investigation into the identity of the other species present, it was concluded that the main impurity in the reactions was unreacted 4-iodobenzoic acid. To increase the purities of the biaryl products, higher concentrations of reagents and catalyst were employed. An optimized version of the classical conditions was developed (Table 1; experimental conditions C). Conversion to the PolyHIPE-immobilized biaryls appeared to take place successfully and preparative HPLC of the crude product obtained from the granular support gave 70% of **3**. The major impurity in the product constituted 18% of the total, which due to the lack of ^{1}H NMR signals appeared to be an inorganic material. Recovery of the major component from the cubic PolyHIPE by preparative HPLC resulted in an isolated yield of **3** of 93% (identity confirmed by NMR spectroscopy). The single impurity (7% of the crude product) was found to have the same structure as the minor impurity obtained from the granular support. From the results of the couplings on both supports, it appeared that the cubic PolyHIPE produced biaryl **3** in a higher overall yield than the corresponding granular form.

The performance of PolyHIPE as a support in batch Suzuki coupling reactions was compared to that of commercial permanently porous chloromethyl polymer beads (ArgoPore-Cl) (1.2 mmol −CH$_2$Cl g^{-1}), which were reacted with 4-iodobenzoic acid under identical conditions to those applied to PolyHIPE. Mass recovery of the beads revealed a 79% yield of 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. The conversion to iodine, however, was calculated to be 59%, which is slightly lower than the average conversion obtained on PolyHIPE (73%).

The optimized conditions developed for PolyHIPE were utilized in the coupling of iodine-loaded beads with

4-methoxybenzeneboronic acid. Conversion to the bead-bound coupled product was calculated to be 70% and subsequent cleavage from the support gave an isolated pure yield of **3** of 70% (following isolation by preparative HPLC). This yield was found to match exactly with the pure yield of **3** synthesized on granular PolyHIPE, however, it was significantly lower than the pure yield obtained with cubic PolyHIPE (93%). The formation of the corresponding biaryl carboxylic acid with the bead-based support 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.

To demonstrate the suitability of PolyHIPE with a wider range of substrates, it was decided to introduce two other boronic acids into the synthesis program. To monitor progress of coupling on the PolyHIPE supports, aryl boronic acids containing functional groups such as −F and −NO$_2$ were chosen, as these could be quantified by elemental analysis. Iodine-loaded PolyHIPEs (granular and cubic forms) were coupled with 3-nitrobenzeneboronic acid according to the optimized conditions outlined above (Scheme 1). Mass recovery and nitrogen analysis indicated that the couplings had proceeded successfully (81% and 96%, respectively for the granular support; 83% and 100% for the cubic form). The biaryl product was cleaved from the support as above, yielding 72% of **4**. The impurity with a retention time of 1.3 min., which constituted the remaining 28% of the product, was isolated and characterized. However, this again was found to be an inorganic residue by ^{1}H NMR spectroscopy. The purity of the crude product from the cubic PolyHIPE was determined by both preparative and analytical HPLC. The yield of pure **4** (confirmed by ^{1}H and ^{13}C NMR) was calculated to be 81%. The inorganic impurity was found to comprise 8% of the crude product. 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.

Iodobenzoate functionalized PolyHIPE in both granular and cubic forms (loadings 1.54 and 1.57 mmol −I g^{-1}, respectively) were then coupled with 4-fluorobenzeneboronic acid according to the improved conditions described (Scheme 1). Frenette and Friesen[3] used this boronic acid in their bead-supported Suzuki couplings and reported a yield of 4′-fluoro-biphenyl-4-carboxylic acid methyl ester **5** of 91%. The conversion to granular PolyHIPE-bound biaryl 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 with the cubic support 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 rather than granular form. The crude yields of product obtained from both forms of support after cleavage were between 100% and 110% indicating the presence of impurities. The crude product synthesized on the granular support was identified as **5** by NMR spectroscopy and the pure yield of **5** was found to be 82% (preparative HPLC). The identity of the pure fraction was confirmed by NMR spectroscopy and MS analysis (m/z (EI) 230). Similar results were observed for the crude product synthesized on the cubic

Table 2. Isolated Yields of Pure Products Obtained from Coupling on Different Support Types

boronic acid substituent	yield of pure biaryl product (%)[a]		
	granular PolyHIPE	cubic PolyHIPE	permanently porous beads
MeO-	70	93	70
NO$_2$-	72	81	
F-	82	73	

[a] Obtained by preparative HPLC.

PolyHIPE. The yield of the pure biaryl **5** was calculated to be 73%. As before an inorganic impurity was present in the crude product in 21% abundance.

From the above, it can be seen that Suzuki coupling conditions have been 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 2).

In the cases involving the methoxy- and nitroboronic acids, slightly higher yields of product were obtained with the cubic form of PolyHIPE than the granular form. This result is rather surprising since diffusion into the interior of the cubes should be slower than into powdered PolyHIPE. In any case the differences are rather small and indicate that there is no detrimental effect of using PolyHIPE supports in cubic form in batch synthetic procedures. 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, suggested an inorganic residue. This could possibly be a byproduct from the catalyst, Pd(PPh$_3$)$_4$, employed in the couplings or from the inorganic base employed.

Strategies for Flow-Through Suzuki Cross-Coupling. Since both granular and cubic PolyHIPE proved to be successful supports for Suzuki coupling in a batch process, the reaction applied to PolyHIPE monoliths under flow-through conditions was investigated. In this study, VBC/DVB (78:22 wt %) HIPE was polymerized inside fritted PTFE tubes for use in a Quest parallel synthesizer. The resultant PolyHIPE monoliths were found by N$_2$ adsorption analysis to have an average BET[33] surface area (two runs) of 11.8 ± 2.1 m^2 g^{-1} and an average pore size of 16.1 ± 0.3 nm (NB nitrogen adsorption analysis only provides information on the size of pores < 300 nm). PTFE tubes were also loaded with permanently porous 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, for the beads the average size of pores of <300 nm was approximately half that of the PolyHIPE material (8.4 ± 0.01 nm).

The flow-through synthesis began by attaching 4-iodobenzoic acid onto the chloromethyl groups of mono-

lithic PolyHIPE (3.7 mmol −CH$_2$Cl groups g^{-1}). This resulted in a conversion to iodine of 74%, which was significantly higher than the average conversions obtained in the batch reactions (65%). The optimized 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. The reaction was run under flow-through conditions 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 was found to be 60% (analytical HPLC). 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** the purity of which was found to be 54% by analytical HPLC. 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%.

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. To allow a fair comparison between the two types of support, identical conditions and procedures were applied to the beads as were employed for monolith derivatization (although it is noted that the support types have very different surface areas). 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$_2$-Cl groups g^{-1}). This resulted in a 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 reaction was occurring on the beads, possibly as a result of the channelling effect. The coupling of 4-methoxybenzene boronic acid to iodobenzoate-loaded beads was carried out in the established flow-through manner, and cleavage was performed in stages as with the PolyHIPE support.

The initial cleavage resulted in a 22% yield of crude product. ^{1}H NMR analysis showed that biaryl ester **1** had been obtained, and analytical HPLC revealed the purity to be 48%. As with the PolyHIPE reaction, the beads were cleaved a further two times to ensure complete removal of the biaryl product. 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). 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.

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 smaller percentage of 4-iodoben-

zoic acid was loaded onto the beads in the first instance. As a consequence of the channelling effect, only the chloromethyl groups on the external 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. 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 synthesized on the beads, than on the Poly-HIPE monolith (76 mg). Therefore, under identical flow-through conditions, PolyHIPE converted a greater amount of chloromethyl groups into biaryl product than permanently porous beads, making it a much more efficient form of support material. Furthermore, the surface area of the PolyHIPE material is relatively low (11.8 ± 2.1 m^{2}g^{-1} as determined by BET[33] treatment of N$_2$ adsorption data) relative to that of the porous beads used in flow-through experiments (785.1 ± 13.9 m^2 g^{-1}). The higher surface area should lead to more efficient coupling, however due to channelling the opposite is in fact observed.

Conclusions

The preparation and subsequent functionalization of PolyHIPE monoliths with high loadings of chloromethyl groups has been described. The monoliths were synthesized by the direct copolymerization of VBC and DVB, and their suitability as supports in the Suzuki cross-coupling reaction was investigated. In batch reactions involving different boronic acids, the classical Suzuki conditions were optimized in order to maximize 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, 4-methoxy-biphenyl-4-carboxylic acid also formed during cleavage with NaOMe. This was not observed in the reactions involving PolyHIPE. In identical flow-through reactions employing monolithic PolyHIPE and permanently porous beads, PolyHIPE was found to be a much more efficient form of support material, converting a greater amount of chloromethyl groups into biaryl product.

Acknowledgment

Supporting Information Available: procedures for the preparation of PolyHIPE monoliths in Quest tubes, all chemical functionalizations of supports (beads and PolyHIPEs) and the preparation of Pd(PPh$_3$)$_4$, plus associated characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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