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Palladium-mediated organic synthesis using porous polymer monolith formed in situ as a continuous catalyst support structure for application in microfluidic devices

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ABSTRACT

The development and advantages of in situ synthesis of organic polymer monolith supports for metal pre-catalysts in narrow bore fused silica capillary microreactors are described. Catalyst immobilisation involves the covalent attachment of ligand binding sites to the porous polymer monolith, followed by coordination to metal centres. Flow-through microreactors using poly(chloromethylstyrene-*co*-divinylbenzene) monolith in capillaries of internal diameter 250 μm were used successfully for Suzuki–Miyaura and Sonogashira reactions, utilising both 1,10-phenanthroline and imidazole/carbene binding to palladium and with very low palladium leaching, illustrating the potential of flow-through technology at the microscale level using organic monolith support for transition metal catalysed reactions.

1. Introduction

Microreactors have the potential to revolutionise the fields of chemistry and biotechnology by replacing conventional glassware with small flow-through devices.[1–8] Excellent performance can be achieved by taking advantage of microchannel system features such as rapid heat and mass transfer. Reactions can be carried out under isothermal conditions with well-defined residence times, so that undesirable side reactions and fragmentations are limited. The small dimensions of microreactors also allow the use of minimal amounts of reagents and solvents under precisely controlled conditions, which reduces potential hazards and thus reduces environmental impacts.

Major issues encountered in the development of narrow bore flow-through microreactors [typical Internal Diameter (ID)<ca. 1 mm] for heterogeneous or polymer-supported catalysis are the packing and retention of the supported catalyst inside the microreactor, as well as the high back pressure over the capillary caused either by the densely packed small particle bed or swelling.[9]

In chromatography, silica and polymer based monolithic columns have been developed to overcome these difficulties. Monoliths can be synthesised in situ, eliminating the need for packing, and can be designed to have pore sizes in the order of 1 μm ensuring good flow-through properties.[10] A polymer monolith can be formed by polymerisation in the presence of a high proportion of cross-linking monomer and a porogen. The physical properties (pore size and surface area) of the monolith are predominantly determined by the solubility of the forming polymer and the nature of the porogen,[11] whereas its chemical properties are determined predominantly by the monomer.[11,12]

Catalytic reactions in microreactors have been explored,[1–7] including for palladium catalysis with ID<ca. 1 mm for hydrogenation (ID 200–530 μm),[13] Suzuki–Miyaura (ID 200–1500 μm),[14] Stille (ID 75 μm),[15] carbonylative cross-coupling (ID 200 μm),[16] and sequential aryl amination/Heck coupling.[17] We have recently reported results for the Suzuki–Miyaura cross-coupling of *p*-tolylboronic acid with iodobenzene using poly(glycidyl-*co*-ethylene dimethacrylate) monolith (GMA/EDMA),[18,19] but see considerable advantage in developing this system for poly(chloromethylstyrene-*co*-divinylbenzene) monolith as it has a structure similar to widely used conventional chloromethylpolystyrene beads and does not have functional groups present in GMA/EDMA that could potentially interfere with catalysis. The Suzuki–Miyaura and Sonogashira

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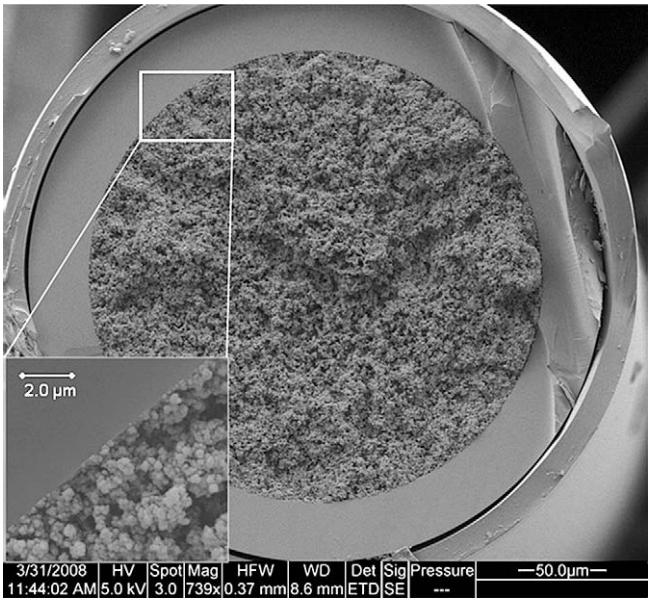
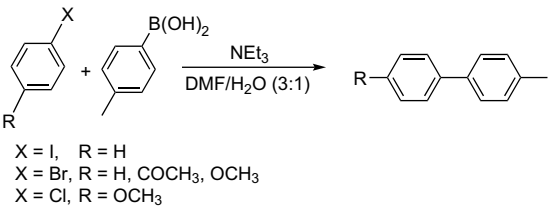


Figure 1. Scanning electron micrographs (magnification of 739× and 15,000×) of a cross-section of a 250 µm capillary completely filled with CMS/DVB monolith.

systems were chosen for the work reported here, as established model reactions for metal complexes anchored onto conventional organic polymers in large scale catalysis.[20] Microreactors were constructed using fused silica capillaries with an internal diameter of 250 µm. Polymeric monoliths were synthesised in situ and used as a pre-catalyst support. The performance of capillary microreactors was compared with that of batch reactions using bulk monolith, and bulk monolith was used to estimate catalyst loadings for capillaries.

2. Results and discussion

The polymer monolith was prepared inside the capillaries after modifying the surface of the inner wall of the capillaries[21] to ensure anchoring of the monolith. A mixture containing 60% porogens (1-dodecanol and toluene), 24% monovinyl monomer and 16% cross-linking monomer was used, in accord with the recommended 6:4 porogen/monomer ratio,[21,22] in order to achieve a suitable porosity and void volume fraction of ca. 60% [23] consistent with good flow-through and high surface area characteristics.[22] The surface modification successfully anchored the formed monolith inside the capillary (Fig. 1), allowing the microreactors to withstand pressures up to at least 500 psi.



Scheme 1. Suzuki–Miyaura cross-coupling of aryl halides and *p*-tolylboronic acid.

The benzyl chloride groups on the monolith were used to covalently attach 5-amino-1,10-phenanthroline or 1-methylimidazole (Fig. 2). In previous work with GMA/EDMA monolith 5-hydroxy-1,10-phenanthroline was used as the reagent,[18] but this compound was successfully replaced by the commercially available amine reagent.[19] Loading with palladium was facilitated by the passage of $PdCl_2(NCMe)_2$ through the modified monolith. For imidazole, present as the imidazolium group when attached to related polymers[24] and a CMS/DVB monolith recently reported,[25] formation of the resulting material may involve the palladium present as an anion to balance the imidazolium group, e.g., $[PdCl_3(NCMe)]^-$,[25] or bonded to the heterocycle present as an *N*-heterocyclic carbene (NHC).[24] If present as NHC an additional donor (L) to complete square-planar coordination is assumed, as illustrated in Figure 2, e.g., MeCN. For the CMS/DVB monolith containing Pd-NHC groups, the void volume fraction was found to be 55%.

With 1-methylimidazole functionalised CMS/DVB, palladium loadings of ca. 0.4 wt % were obtained for bulk material and ca. 0.3 wt % with phenanthroline as the ligand. For comparison, the palladium loadings of polymer-supported catalysts are typically ~0.4–5 wt %.[20] Capillaries that were not functionalised with ligands, but which were subjected to passage of $PdCl_2(NCMe)_2$ as described above, were inactive in catalysis.

2.1. Suzuki–Miyaura reactions

2.1.1. Bulk material

The Suzuki–Miyaura reaction was examined at 80 °C using a range of aryl halides and *p*-tolylboronic acid as indicated in Scheme 1 and Table 1, utilising triethylamine as a homogeneous base. The solvents and bases used were chosen to ensure solubilities of all substrates, and 25% water was a good compromise between reactivity and solubility of the substrates.

In general, the results show lower activity for the less reactive halides, as expected: PhI>PhBr (entries 1, 2 and 6, 7), BrC_6H_4COMe>ClC_6H_4COMe (3, 4 and 8, 9), and PhBr>*p*-$MeOC_6H_4Br$ (2, 5 and 7, 10). Both ligands gave similar results even though the catalyst

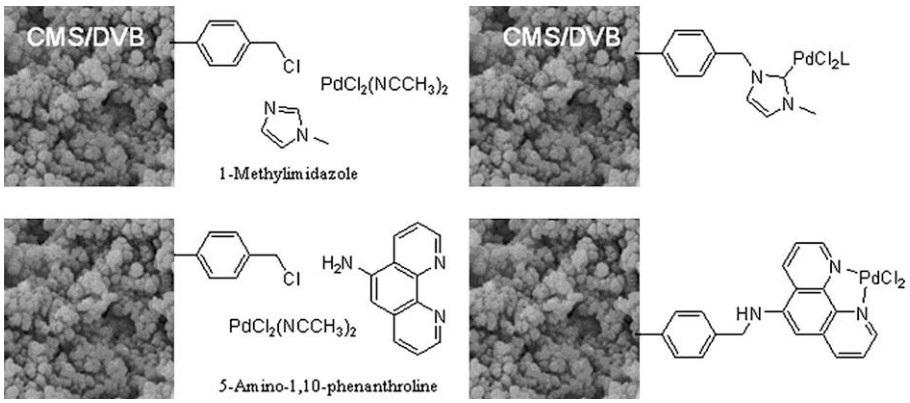


Figure 2. Ligand and $PdCl_2$ attachment to the monolithic support.

Table 1
Suzuki–Miyaura cross-coupling in batch reactions of aryl halide (0.1 mol) with *p*-tolylboronic acid (0.15 mol), utilising triethylamine (0.15 mol/L) as the base in *N*,*N*-dimethylformamide/water (3:1), 20 mg modified bulk monolithic material was reacted in 1.0 mL of reaction solution; phen=1,10-phenanthroline, NHC=*N*-heterocyclic carbene; 80 °C for 60 min

Entry	Ligand	Aryl halide	Yield (%)
1	phen	Iodobenzene	86
2	phen	Bromobenzene	51
3	phen	*p*-Bromoacetophenone	96
4	phen	*p*-Chloroacetophenone	13
5	phen	Bromoanisole	30
6	NHC	Iodobenzene	96
7	NHC	Bromobenzene	52
8	NHC	*p*-Bromoacetophenone	97
9	NHC	*p*-Chloroacetophenone	9
10	NHC	Bromoanisole	44

Table 2
Suzuki–Miyaura cross-coupling in capillaries of aryl halide (0.1 mol) with *p*-tolylboronic acid (0.15 mol), utilising triethylamine (0.15 mol) as the base in *N*,*N*-dimethylformamide (3:1); phen=1,10-phenanthroline, NHC=*N*-heterocyclic carbene; 80 °C; product collected over a 48-h period, contact time of reagents in capillary ca. 45 min.

Entry	Ligand	Aryl halide	Yield (%)
1	phen	Iodobenzene	97
2	phen	*p*-Bromoacetophenone	94
3	NHC	Iodobenzene	95
4	NHC	Bromobenzene	53
5	NHC	*p*-Bromoacetophenone	91
6	NHC	*p*-Chloroacetophenone	11
7	NHC	Bromoanisole	28

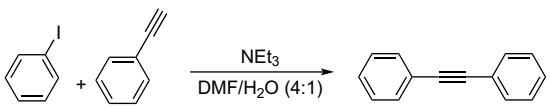
loadings are much lower for phenanthroline. The reaction products were relatively clean with very small amounts of by-products detected only for the coupling of bromobenzene.

2.1.2. Capillaries

Flow-through catalysis in capillaries under similar conditions was studied (Table 2). Flow rates of 0.1 μL min^{-1} in 20 cm capillaries at 80 °C were used throughout. The sampling interval is restricted by the volume required for analysis, and experiments using 12 h sampling intervals over a period of 8 days showed no drop in yield for the conversion of iodobenzene over this period, and with total leaching of palladium at ca. 4%. No other products were detected. Trends in reactivity were identical to bulk samples: PhI>PhBr (entries 3, 4), BrC_6H_4COMe>ClC_6H_4COMe (entries 5, 6) and PhBr>*p*-$MeOC_6H_4Br$ (entries 4, 7).

2.2. Sonogashira reactions

The coupling of iodoacetophenone with phenylacetylene (Scheme 2) employed NEt_3 as a base in DMF/H_2O (4:1) and reaction conditions adapted from a copper-free protocol reported recently.[26] The performance of bulk material in a common batch process using the phen system gave yields of 99% in 3 h at 80 °C (Table 3), compared with 92% with the NHC system. In capillaries, the high catalytic activity of both systems resulted in nearly complete conversion, and no by-products could be detected by GC. Small amounts of by-product were detected in all samples originating



Scheme 2. Sonogashira coupling of iodobenzene with phenylacetylene.

Table 3
Sonogashira cross-coupling of iodobenzene (0.1 mol) with phenylacetylene (0.15 mol), utilising triethylamine (0.15 mol) as the base in *N*,*N*-dimethylformamide/water (4:1). For bulk reactions, 20 mg of modified monolith was reacted in 1.0 mL of reaction solution; phen=1,10-phenanthroline, NHC=*N*-heterocyclic carbene; 80 °C.

Entry	Ligand	Solid support	Contact time/run time	Yield (%)
1	phen	Bulk	3 h	99
2	phen	Capillary	45 min/48 h	96
3	NHC	Bulk	3 h	91
4	NHC	Capillary	45 min/48 h	95

from the bulk experiments. Leaching of palladium from capillaries was minimal, ca. 4% of loading after 8 days of continual operation.

3. Conclusion

Polymer monoliths, present as a continuous phase filling capillaries and bonded to the internal surface, are promising new materials for solid supported catalysis in 250 μm internal diameter narrow bore microreactors. The performance of the flow-through microreactors included quantitative yields for the conversion of iodobenzene in the Suzuki–Miyaura reaction, and quantitative yields for Sonagashira coupling of *p*-iodoacetophenone with phenylacetylene. No significant differences were observed in the performance of the two different ligand systems. The methodology reported here represents a new strategy for the fabrication of capillary flow-through microreactors for cross-coupling reactions, and the application of CMS/DVB monolith is notable owing to the robust and unreactive nature of the polymer.

4. Experimental section

4.1. Materials

Commercially available chloromethylstyrene (CMS), divinylbenzene (DVB), 1-methylimidazole, 5-amino-1,10-phenanthroline and solvents were purchased from Sigma–Aldrich Pty. Ltd (Castle Hill, Australia). Divinylbenzene was purchased as a mixture of different isomers and the wanted isomer (1,4-divinylbenzene) was purified by distillation. 2,2-Azobis-(2-isobutyronitrile) (AIBN) was purchased from MP Biomedicals Australasia Pty. Limited (Seven Hills, Australia) and recrystallised before usage. All solvents and mixtures used in the capillaries were filtered prior to use. Sonogashira bulk reactions were performed under an argon atmosphere using standard Schlenk techniques. Non-commercially available reaction products required for the calibration of the GC instruments were synthesised using conventional techniques.

4.2. General

Controlled solvent pumping was performed using a Harvard Apparatus model PHD 2000 (Holliston, Massachusetts, USA) twin syringe pump and 250 μL Hamilton (Reno, Nevada, USA) Gastight® glass syringes. All capillaries and syringes were connected using Upchurch Scientific (Oak Harbor, Washington, USA) capillary connections. Fused silica capillaries of internal diameter 250 μm with the outer surface coated with polyimide (Polymicro Technologies, Phoenix, Arizona) were heated using a Waters Millipore (Billerica, Massachusetts, USA) 112/WTC-120 temperature controlled column heater. Leading and trailing capillary sections were used to ensure that the whole microreactor was inside the column heater. Figure 3 shows the general experimental setup for flow-through microreactors. Characterisation utilised equipment housed in the Central Science Laboratory, University of Tasmania, including an FEI Quanta 600 MLA ESEM and an ELEMENT high resolution ICP-MS allowing detection down to 0.1 ppb; determination of void volume

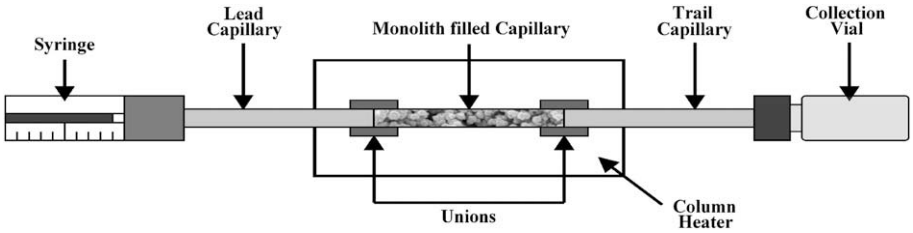


Figure 3. Experimental setup of flow reactions using a porous polymer monolith as a catalyst support structure.

fraction utilised a Sartorius SE2 Ultra-Microbalance (0.1 μg readability).

The palladium content determinations of the bulk monolith were performed by Inductively Coupled Plasma Mass Spectroscopy (ICP-MS). For preparation, samples (50–100 mg) were digested in freshly prepared *aqua regia* (4 mL) for 18 h with sonication, diluted to a final mass of 30 g and indium (100 ppb) was added as an internal standard. The measurements were performed using an ELEMENT high resolution ICP-MS (Finnigan-MAT, Bremen, Germany) on the low resolution setting of 300 $m/(\Delta m)$ at 10% valley definition; palladium was measured as a total of isotopes 105, 106 and 108.

Gas Chromatography–Mass Spectrometry (GC–MS) measurements were performed using a Varian 3800 gas chromatograph coupled with a triple quadrupole mass spectrometer or a Varian Star 3400 CX gas chromatograph coupled with a Varian Saturn 4D mass spectrometer. Gas Chromatography-Flame Ionisation Detection (GC-FID) measurements were performed on a Shimadzu GC-2014AFsc gas chromatograph equipped with a 25 m length (ID 0.32 mm) ID-BPX5 SGE capillary column. Standards were purchased or synthesised using conventional techniques, and mixtures with different concentration ratios were used for calibration.

Polymerisations were performed using a temperature controlled water bath.

4.2.1. Bulk material

The monolith was prepared by thoroughly mixing toluene (0.606 mL) and 1-dodecanol (1.53 mL), to which chloromethylstyrene (0.48 g), divinylbenzene (DVB, 0.72 g) and AIBN (12 mg) were added and the solution purged with nitrogen for 10 min prior to use. The monolith formed after heating at 70 °C for 24 h was crushed and washed with tetrahydrofuran (THF) in a Soxhlet apparatus for 14 h and then dried in vacuo.

4.2.2. Ligand attachment in bulk material

4.2.2.1. 1-Methylimidazole. 1-Methylimidazole (0.30 g) was dissolved in chloroform and added to finely ground monolith (1.0 g). The mixture was stirred for 24 h at 50 °C and the monolith recovered by vacuum filtration, resuspended in chloroform, stirred vigorously for 30 min and recovered again by filtration. The monolith was washed twice with chloroform, and dried in vacuo.

4.2.2.2. 5-Amino-1,10-phenanthroline. Monolith (1.0 g) was finely ground and added to a solution of 5-amino-1,10-phenanthroline (200 mg) in methanol (10 mL). The mixture was stirred for 18 h at 60 °C and the monolith recovered by vacuum filtration, resuspended in methanol, stirred vigorously for 30 min and recovered again by filtration. The monolith was washed twice with methanol, and dried in vacuo.

4.2.3. Palladium attachment in bulk material

Modified monolithic material (100 mg) was added to a solution of $PdCl_2(NCMe)_2$ (10 mg) in acetonitrile (2 mL) and the mixture was stirred for 18 h at room temperature. The monolith was recovered by vacuum filtration, resuspended in acetonitrile, stirred vigorously for 30 min and recovered again by filtration. The monolith was washed twice with acetonitrile, and dried in vacuo.

4.3. General procedure for cross-coupling in bulk material

Modified monolith (20 mg) was placed in a 5 mL *Reacti-Vial* (Thermo Scientific, Rockford, USA) under argon along with 2 mL of the reaction mixture and heated at 80 °C (unless stated otherwise). The catalyst was removed by filtration through a plug of cotton wool and the products analysed by GC.

4.4. Capillaries

Prior to the monolith attachment, the inner surface of capillaries was modified by briefly rinsing the capillary with acetone followed by 0.2 M NaOH (2.0 μL min^{-1}) for 2 h. The capillaries were washed with water, and rinsed with 0.2 M HCl (2.0 μL min^{-1}) for 2 h before being rinsed with water, followed by ethanol (2.0 μL min^{-1}) for 30 min and finally the surface modifying agent (solution of 20 wt % of 3-(trimethoxysilyl)propyl methacrylate in ethanol adjusted to pH 5, 0.25 μL min^{-1}) was passed through the capillaries for 1 h.[22] The capillaries were then washed with acetone and dried by passing air through the capillaries for 24 h.

Toluene (0.606 mL) and 1-dodecanol (1.53 mL) were thoroughly mixed and, to this, chloromethylstyrene (0.48 g), divinylbenzene (DVB, 0.72 g) and AIBN (12 mg) were added and the solution purged with nitrogen for 10 min prior to use. The capillaries were completely filled with the CMS/DVB pre-polymerisation mixture until no air bubbles were apparent, sealed at both ends and placed in a water bath at 70 °C for 20 h. The monolith filled capillary was then flushed with THF (2.0 μL min^{-1}, 1 h).

4.4.1. Ligand attachment in capillaries

4.4.1.1. 1-Methylimidazole. The monolith filled capillary was flushed with chloroform for 30 min at 50 °C (2.0 μL min^{-1}) before the undiluted 1-methylimidazole was pumped through the capillary at 50 °C for 8 h (0.5 μL min^{-1}). The capillaries were then reversed and the solution was pumped for a further 18 h (0.2 μL min^{-1}). The capillary was washed with chloroform for 1 h (2.0 μL min^{-1}) to remove unreacted ligand from the monolith.

4.4.1.2. 5-Amino-1,10-phenanthroline. The monolith filled capillary was flushed with methanol for 30 min at 60 °C (2.0 μL min^{-1}). A solution of 5-amino-1,10-phenanthroline (40 mg) in methanol (2 mL) was pumped through the capillary at 60 °C for 8 h (0.5 μL min^{-1}), then the capillary was reversed and the solution was pumped for a further 18 h (0.2 μL min^{-1}). The capillary was washed with methanol for 1 h (2.0 μL min^{-1}) to remove unreacted ligand from the monolith.

4.4.2. Palladium attachment in capillaries

The monolith filled capillary was flushed with acetonitrile for 30 min at room temperature (2.0 μL min^{-1}). A solution of $PdCl_2(CNMe)_2$ (10 mg) in acetonitrile (2 mL) was filtered to remove

any undissolved solids and passed through the capillary at room temperature for 8 h (0.5 μL min^{-1}), then the capillary was reversed and the solution was pumped for further 18 h (0.2 μL min^{-1}). The capillary was flushed with acetonitrile for 1 h (2.0 μL min^{-1}).

4.5. Determination of void volume fraction for CMS/DVB monolith after Pd/NHC functionalisation

A 5 cm piece of monolith filled capillary was flushed with acetone and dried by flushing with air (2.0 μL min^{-1}) overnight in a column heater at 80 °C, sealed with a septum and weighed prior to filling with ethanol and reweighed. Removal of ethanol (flushing with air overnight at 80 °C) confirmed an identical weight to that prior to addition of ethanol.

4.6. General procedure for cross-coupling reactions in capillaries

To equilibrate the microreactor prior to the reaction the capillary (20 cm) was flushed with the solvent for 1 h at room temperature (2.0 μL min^{-1}), then with a mixture of the solvent with 2 mmol of the base for 2 h at the required reaction temperature (2.0 μL min^{-1}) by placing the microreactor in the pre-heated column heater. The reaction mixtures were passed through the capillary at a flow rate of 0.1 μL min^{-1} (contact time of 45 min) and the product was collected from the opposing end in small glass sample vials. GC–MS or GC-FID analysis was performed to monitor the yields.

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