Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 9321–9324

Macroporous monolith supports for continuous flow capillary microreactors

Katrina F. Bolton,[a,b] Allan J. Canty,[a] Jeremy A. Deverell,[a,b] Rosanne M. Guijt,[b,*] Emily F. Hilder,[b] Thomas Rodemann[a] and Jason A. Smith[a,*]

[a]*School of Chemistry, University of Tasmania, Private Bag 75, Hobart, Tasmania 7001, Australia*
[b]*Australian Centre for Research on Separation Science, University of Tasmania, Private Bag 75, Hobart, Tasmania 7001, Australia*

Received 4 September 2006; revised 9 October 2006; accepted 19 October 2006
Available online 9 November 2006

Abstract—A solid macroporous monolith is shown to be a suitable substrate for anchoring a palladium complex to obtain a continuous porous material suitable for conducting flow-through catalysis in capillary microreactors.

Chip- and capillary-based microreactor research for organic synthesis is a rapidly growing field following the realisation of the benefits of microfluidic technology over conventional chemical synthesis; including improved temperature control, selectivity, and both environmental and safety issues resulting from the use of small quantities of reagents and solvents.[1] Application of this emerging technology to reactions catalysed by transition metal complexes have included homogeneous and heterogeneous catalysis, and supported catalysis involving ligands covalently bonded to inorganic and organic supports such as silica and Merrifield polystyrene beads.[1] The development of flow-through microreactors is potentially one of the most significant advances to the way organic synthesis is performed. The most recent advances in this area involve the packing of nickel or palladium catalysts supported on polystyrene or silica beads[2] and polyurea[3] into chromatography columns.

A major challenge for flow-through supported catalysis is to utilise more highly intensive surface properties.[4] We have commenced investigations on a new strategy which involves the attachment of transition metal catalysts onto macroporous organic monolith supports. These monolithic materials have been utilised as stationary phases for chromatographic separations[5] and often perform better than the corresponding packed chromatographic materials. They have many potential benefits over traditional catalyst supports as they are essentially an incompressible solid material that fully occupies a channel or capillary space.[6a,b] The material's excellent flow-through properties[6c] make them of interest for catalysis reactions. Initial work[7] has involved capillaries (Fig. 1) in view of their recently demonstrated application in parallel synthesis,[8] although the ultimate aim is incorporation into a chip device. The monolith chosen for this study was GMA-*co*-EDMA[6a] [poly(glycidyl methacrylate-*co*-ethylene dimethacrylate)] due to its extensive use in capillaries for chromatographic separations. The Suzuki–Miyaura reaction was chosen as a model process in view of its wide application in synthesis and microreactor development,[2,3,9] and the classic 1,10-phenanthroline moiety as a donor in polymer supported

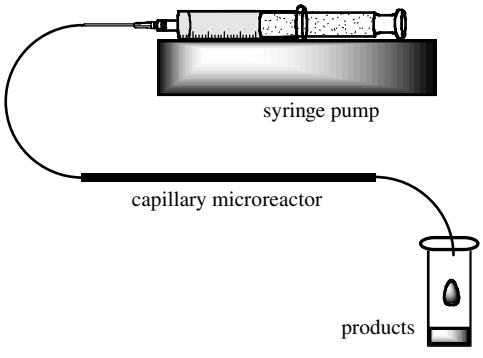


Figure 1. Schematic of the flow-through microreactor comprising a 15 cm length of 250 μm capillary driven by a syringe pump.

* Corresponding authors. Tel.: +61 3 6226 2182; fax: +61 3 6226 2858 (J.A.S.); e-mail addresses: Jason.Smith@utas.edu.au; Rosanne.Guijt@utas.edu.au

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.10.113

catalysis[10] including palladium catalysis.[10a] There is also the potential for facile detection of attached phenanthroline by complexation with iron(II).[11]

The internal surface of fused silica capillaries (250 μm internal diameter, outer surface coated with polyimide; Polymicro Technologies, Phoenix, Arizona) were modified as described[12a] to covalently anchor the GMA-*co*-EDMA monolith to the capillary wall. This avoids the need for frits or other devices to hold the support in place which simplifies the design of the microreactor and hence limits the potential for blockages. The monolith was then synthesised in situ, following the reported method of Preinerstorfer et al.[12b] and characterised by scanning electron microscopy to confirm a complete filling of the capillary (Fig. 2). The median pore diameter of the monolith of the capillary is assumed to be similar to that of the bulk samples of monolith prepared in sample vials which exhibited expected[13] pore sizes of $\sim 1.07 \pm 0.06$ μm as determined by mercury intrusion porosimetry.

Capillaries with a length of 20 cm were flushed with dimethylsulfoxide at 60 °C (2 μL min^{-1} for 30 min) using a syringe pump. The phenanthroline ligand was then covalently attached to the monolith by the ring-opening of the electrophilic epoxide groups as has been reported.[12b,13] Thus, immobilisation of ligand was achieved by passing a solution of 5-hydroxy-1,10-phenanthroline (50 mg)[14] in DMSO (2.5 mL) containing NaOH (10 mg) at 0.5 μL min^{-1} for 8 h at 60 °C, followed by pumping the solution in the reverse direction and washing with DMSO (Scheme 1). DMSO was required as the solvent due to the low solubility of **2** in other solvents, which could lead to blockage of the microreactor. As a test for ligand attachment, the passage of iron(II) sulfate through the capillary gave the capillary the pink appearance expected for Fe(II) coordinated by phenanthroline,[11] being absent for capillaries in which phenanthroline had simply been passed through the capillary and therefore had not been immobilised.[15] To prepare the catalytic microreactor the ligand modified monolith was flushed with acetonitrile followed by a solution of $PdCl_2(NCMe)_2$ (10 mg) in MeCN (2 mL)

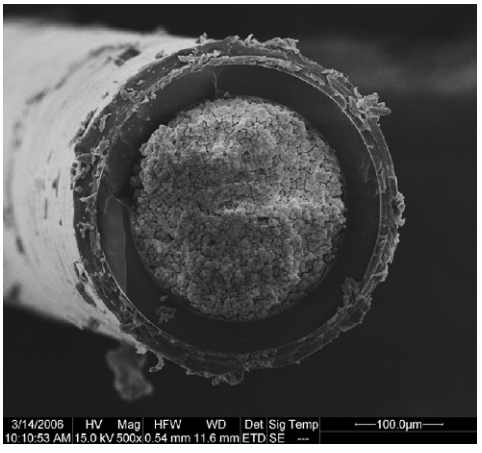
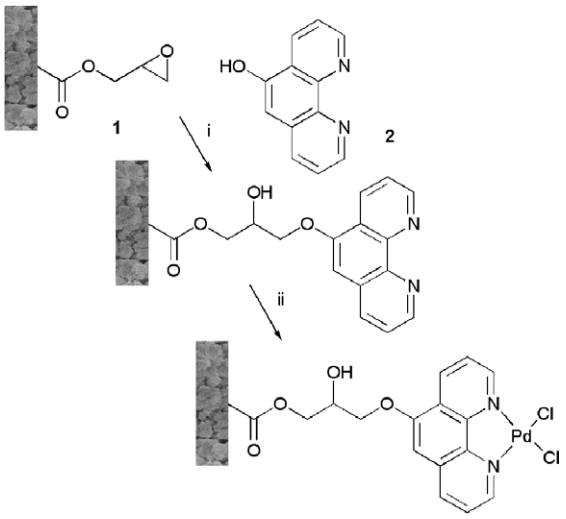


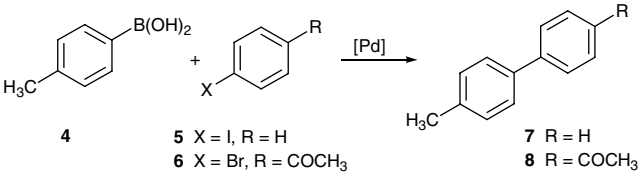
Figure 2. SEM of the monolith completely filling a 250 μm capillary.



Scheme 1. Reagents and conditions: (i) NaOH, DMSO, 60 °C; (ii) $PdCl_2(NCMe)_2$, MeCN 25 °C.

at a rate of 0.5 μL min^{-1} for 8 h at 25 °C. The capillary was then reversed and the process repeated before flushing with MeCN. ICP-MS showed a metal loading of 0.02 mmol g^{-1}, close to typical values for metal loadings on organic polymer supports, ~0.04–0.5 mmol g^{-1}.[16]

The Suzuki–Miyaura reaction was examined using a solution of iodobenzene (50 mM) and *p*-tolylboronic acid (75 mM), and was carried out in 9:1 toluene/methanol (Scheme 2). Due to the potential for blockage of the microreactor and to ensure that there was a homogeneous single liquid phase,[3] $^{n}Bu_4NOMe$ (50 mM) was utilised as a base; diphenyl ether (50 mM) was present as an internal standard for GC–MS analysis. The capillaries of length 15 cm were flushed with the solvent (2 μL min^{-1}) for 1 h at 80 °C, and the reaction solution then passed through at 0.05 μL min^{-1} over 18 h at 80 °C, equivalent to a contact time of ca. 90 min, and the product collected in vials. GC–MS analysis showed a yield of 68% for 4-methylbiphenyl (Table 1). The samples taken at different intervals showed that the yield of product remained consistent over time. The stability of the catalyst was exceptional, thus, when the process was continued uninterrupted for four days, the yield for the eluent collected in the final 4 h remained at 68%, demonstrating the application of this approach for sustainable continuous flow processes. Similar results (59% yield) were obtained for the reaction of the less reactive *p*-bromoacetophenone with *p*-tolylboronic acid. Again, to be sure that the catalyst was covalently attached to the monolith and simply not sequestered in the pores of the structure, 1,10-phenanthroline was



Scheme 2. Suzuki–Miyaura reaction.

Table 1. Yields of product from the Suzuki–Miyaura reaction using a continuous flow microreactor[a]

Entry	Product	Reaction time[b] (h)	Yield[b] (%)	TOF[c]
1	**7**	18	68	2.2
2	**7**	96	68	2.2
3	**8**	96	59	1.8

[a] A solution of aryl halide (50 mmol), *p*-tolylboronic acid (75 mmol) and tetrabutyl ammonium methoxide (50 mmol) in toluene–methanol (9:1) was passed through the capillary heated at 80 °C with a column heater at a flow rate of 0.05 μL per min.

[b] Yields were determined by GC/MS using diphenyl ether as an internal standard.

[c] TOF = [mmol of product/mmol of catalyst] · h^{-1}.

passed through the capillary followed by a solution of palladium. Under these conditions there was only 4% conversion for iodobenzene while *p*-bromoacetophenone was <1%. The conversions from these new microreactors are similar to those reported by Styring and co-workers[2a] although the flow rates are less than both those of Styring and co-workers[2a] and Ley and co-workers,[3] primarily due to the difference in diameter of the devices (⩾3 mm vs 250 μm). The turnover frequencies (TOF's) of ~2 are also within the ranges reported previously. ICP-MS of the residual monolith after four days of operation indicated leaching of 15–20% of Pd. However, analysis of the reaction products after 18 h suggests that the leaching occurs at the early stages of reaction.

To compare the difference between flow-through catalysis and a typical batch reaction, a bulk sample of the functionalised monolith was formed in a similar manner to the monolith in capillaries.[17] Due to the residence time of the flow reactor, the catalysis runs were conducted over 90 min in order to compare results with those obtained for capillaries.[18] Similar yields were obtained (75% for 4-methylbiphenyl, 62% for 4-(*p*-tolyl)acetophenone after 90 min), demonstrating the application of an anchored transition metal on a solid macroporous monolith in conventional batch process mode.

These results establish the methodology for a new approach for constructing flow-through microreactors and future work will focus on increasing palladium loading and different catalysts.

The excellent flow-through properties, firm attachment to capillary walls, and robustness of the capillary systems for catalysis demonstrated after continuous reaction for four days indicate that this approach is suitable for further development of capillary-based microreactors that are suitable for continuous flow processes and parallel synthesis.

Note added in proof

After submission of this manuscript the authors became aware of the related work by Garcia-Verdugo and Luis (*Chem. Commun*. **2006**, 3095) who report that palladium carbene complexes attached to organic monoliths catalyse the Heck reaction in near critical ethanol in a flow-through system.

Acknowledgement

We thank the Australian Research Council and the University of Tasmania for financial support.

References and notes

1. (a) Watts, P.; Haswell, S. J. *Chem. Soc. Rev.* **2005**, *34*, 235; (b) Brivio, M.; Verboom, W.; Reinhoudt, D. N. *Lab. Chip* **2006**, *6*, 329.
2. (a) Phan, N. T. S.; Khan, J.; Styring, P. *Tetrahedron* **2005**, *61*, 12065; (b) Phan, N. T. S.; Brown, D. H.; Styring, P. *Green Chem.* **2004**, *6*, 526.
3. Lee, C. K. Y.; Holmes, A. B.; Ley, S. V.; McConvey, I. F.; Al-Duri, B.; Leeke, G. A.; Santos, R. C. D.; Seville, J. P. K. *Chem. Commun.* **2005**, 2175.
4. He, P.; Haswell, S. J.; Fletcher, P. D. I. *Lab. Chip* **2004**, *4*, 38.
5. Al Bokari, M.; Cherrak, D.; Guiochon, G. *J. Chromatogr., A* **2002**, *975*, 275.
6. (a) Svec, F.; Fréchet, J. M. J. *Anal. Chem.* **1992**, *64*, 820; (b) Svec, F.; Fréchet, J. M. J. *Ind. Eng. Chem. Res.* **1999**, *38*, 34; (c) Svec, F.; Huber, C. G. *Anal. Chem.* **2006**, *78*, 2101; (d) Tallarek, U.; Leinweber, F. C.; Seidel-Morgenstern, A. *Chem. Eng. Technol.* **2002**, *25*, 1177.
7. Bolton, K. F.; Canty, A. J.; Deverell, J. A.; Guijt, R. M; Rodemann, T.; Smith, J. A. Aust. Prov. Pat., 2006901698, 2006.
8. (a) Comer, E.; Organ, M. G. *Chem. Eur. J.* **2005**, *11*, 7223; (b) Shore, G.; Morin, S.; Organ, M. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2761; (c) Shi, G.; Hong, F.; Liang, Q.; Fang, H.; Nelson, S.; Weber, S. G. *Anal. Chem.* **2006**, *78*, 1972.
9. (a) Greenway, G. M.; Haswell, S. J.; Morgan, D. O.; Skelton, V.; Styring, P. *Sens. Actuators, B* **2000**, *63*, 153; (b) Basheer, C.; Hussain, F. S. J.; Lee, H. K.; Valiyaveettil, S. *Tetrahedron Lett.* **2004**, *45*, 7297.
10. (a) Zhuangyu, Z.; Hongwen, H.; Tsi-yu, K. *React. Polym.* **1988**, *9*, 249; (b) Slough, G. A.; Krchňák, V.; Helquist, P.; Canham, S. M. *Org. Lett* **2004**, *6*, 2909; (c) Lenaerts, P.; Driesen, K.; Van Deun, R.; Binnemans, K. *Chem. Mater.* **2005**, *17*, 2148.
11. Bassett, J.; Denney, R. C.; Jeffery, G. H.; Mendham, J. *Vogel's Textbook of Quantitative Inorganic Analysis*; Longman: London, 1983.
12. (a) Rohr, T.; Hilder, E. F.; Donovan, J. J.; Svec, F.; Fréchet, J. M. J. *Macromolecules* **2003**, *36*, 1677; (b) Preinerstorfer, B.; Bicker, W.; Lindner, W.; Lämmerhofer, M. *J. Chromatogr., A* **2004**, *1044*, 187.
13. For a recent example, see: Hutchinson, J. P.; Hilder, E. F.; Shellie, R. A.; Smith, J. A.; Haddad, P. R. *Analyst* **2006**, *131*, 215.
14. Prepared from 5,6-dihydro-5,6-epoxy-1,10-phenanthroline (Sigma–Aldrich) in one step as reported.[10b]
15. The 'blank' experiment involved the passage of a solution of 1,10-phenanthroline and KOH through the capillary which is unable to react with the epoxide groups of the monolith.
16. Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217.
17. Finely ground monolith was added to a solution of 5-hydroxy-1,10-phenanthroline (50 mg) and NaOH (10 mg) in DMSO (2.5 mL), then degassed using nitrogen. The suspension was stirred for 18 h at 60 °C, collected by

filtration (Whatman No. 1), resuspended in MeOH and stirred vigorously for 25 min, recovered by filtration, washed with MeOH and dried in a vacuum. After complexation with $PdCl_2(NCMe)_2$ and washing with MeCN, ICP-MS shows 0.19 wt % palladium.

18. Monolith (100 mg) was placed in a 5 mL *Reacti-Vial* with 2 mL of a reaction mixture identical to that used for the studies of reactions in capillaries. The suspension was stirred vigorously at 80 °C for 90 min, then cooled using an ice bath and filtered through a plug of cotton wool.