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Robust and Reusable Supported Palladium Catalysts for Cross-coupling Reactions in Flow

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Two novel polymer encapsulated silica supported palladium catalysts have been prepared and shown to be highly active, robust and recyclable catalysts for Heck and Suzuki-Miyaura cross coupling reactions under continuous flow conditions. They were demonstrated to give excellent conversions of both electron rich and electron deficient substrates and the catalysts were used for over 50 hours continuous operation without any appreciable decrease in catalytic activity and low levels of Pd leaching measured by ICP-MS.

Introduction

In recent years there has been an increasing amount of interest in the use of continuous flow microreactor technology both within academia and in industry.¹⁻⁵ This is largely driven by the advantages associated with microreactors compared with traditional batch based protocols such as; improved efficiency, heat and mass transfer, use of supported reagents and reduced reaction times.

Palladium catalysed cross-coupling reactions have become a cornerstone of synthetic chemistry since their discovery in the 1960's. Their versatility and functional group tolerance provide simple effective protocols for accessing a huge combination of fused aryl, heteroaryl and alkyl motifs. This versatility has led to the current interest in performing cross-couplings in continuous flow systems.^{6, 7} Recently there has been much work carried out on the use of heterogeneous catalysts in conjunction with microreactor technology to achieve a variety of transformations.⁸ In particular the immobilisation of metal nanoparticles for use in catalysis has been widely studied and shown to be effective in avoiding aggregation and maintaining catalyst activity, selectivity and reuseability.¹⁰

Several examples of supported palladium catalysts have been reported for use in microreactors,^{11, 12} using monoliths,¹³⁻¹⁷ polyurea-encapsulated Pd(OAc)₂ (PdEnCat),¹⁸⁻²⁰ silica^{21, 22} and magnetic nanoparticle^{23, 24} supports. There are also interesting examples of how the activity of supported Pd catalysts can be enhanced using microwave heating.^{20, 25, 26} One of the major issues within this area is the leaching of palladium into the reagent stream, with subsequent loss of activity due to a decrease in the palladium loading. This also requires the use of expensive scavenging reagents at the end of the reaction to remove palladium residues. This is a particular problem for the pharmaceutical industry which requires robust and recyclable catalysts in order to minimise the palladium content within a product, resulting from the use of cross-coupling protocols.^{27,28} Pioneering work by Han *et al.* demonstrated the use of a novel polymer coated palladium nanocatalyst supported on amorphous silica dioxide for conducting hydrogenations in supercritical CO₂.²⁹ The polymer coating restricts access to the active site of the catalyst enhancing the selectivity of hydrogenation reactions, while its insoluble nature significantly improved the catalysts stability. More recently Asefa *et al.* described the preparation of a palladium catalyst that was both supported on ordered silica spheres and encapsulated with a layer of nanoporous silica, which possessed high catalytic activity for hydrogenations and C-C coupling reactions and could be recycled several times with no appreciable loss in activity.³⁰ The use of dendrimer encapsulated electrophilic platinum NP catalysts supported on SBA-15 has also proved effective for a range of σ -bond activation reactions.³¹

Our aim was to use this concept of simultaneously supported and encapsulated metal nanoparticles to develop robust supported palladium catalysts for use in cross-coupling reactions under continuous-flow conditions without a drop in catalytic activity.

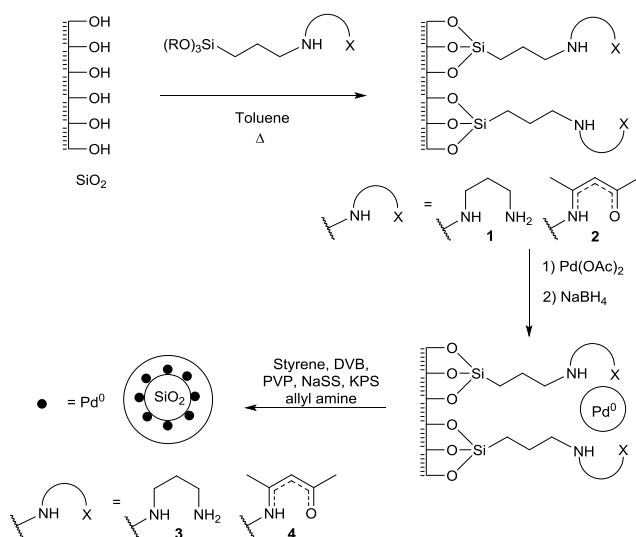
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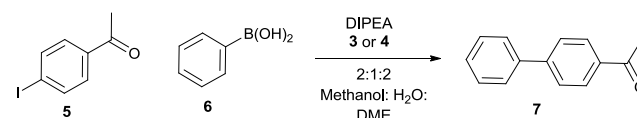
E-mail: c.g.frost@bath.ac.uk

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/



Scheme 1 Synthesis of supported palladium catalysts **3** and **4**

Table 1 Effect of residence time on conversion



Entry ^a	Flow Rate (mL/min)	Residence Time (min) ^b	Conversion (%) ^c	
			3	4
1	0.34	1.6	58	-
2	0.17	3.2	90	70
3	0.08	6.8	> 95, 95 ^d	70
4	0.06	9.1	> 95	> 95
5	0.04	13.7	> 95	> 95, 94 ^d
6	0.03	18.2	-	>95

^a Reaction conditions: 120 °C, 2:1:2 MeOH: H₂O: DME, **5** (2 mmol), **6** (4 mmol) and DIPEA (4 mmol), 200 mg catalyst, 1.5 g sand (column length 4 cm). ^b A voidage of 0.4 was assumed in the calculations of the residence times. ^c Calculated from the ¹H NMR of the crude reaction mixture utilising ferrocene as the internal standard. ^d Isolated yield.

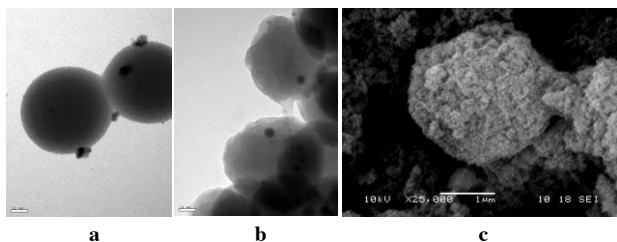


Figure 1 TEM images of pre-catalyst **1** (a) and polymer coated catalyst **3** (b), along with a SEM image of **3** showing the porous polymer coating (c)

10 Results and Discussion

Catalyst preparation

Two polymer encapsulated silica supported Pd⁰ catalysts were developed based on the pre-catalysts **1** and **2** (Scheme 1). The pre-catalyst **1** was synthesised by tethering the ligand precursor *N*-[3-(trimethoxysilyl)propyl]ethyldiamine to the surface of amorphous silica. Palladium ligation was achieved with simple stirring of **1** in an ethanol solution of Pd(OAc)₂, to afford the Pd^{II} species. This was subsequently reduced with NaBH₄ in water to give the Pd⁰ species. To ensure high catalytic reactivity, polymerisation was carried out within 24 h of reduction, according to the method devised by Han,²⁹ to afford the Pd⁰ catalyst **3** (Scheme 1). Using a similar protocol precatalyst **2** firstly involved preparation of the silane *via* a simple imine condensation between 2,4-pentadione and aminopropyltriethoxysilane, which was then tethered to amorphous silica to afford **2**. This was then subjected to palladium ligation, NaBH₄ reduction and polymer encapsulation as before to give catalyst **4**. TEM images of catalyst **1** clearly show the SiO₂ core with a palladium nanoparticle on the surface (a). Upon polymerisation the morphology of the catalyst changes (b) as the Pd nanoparticles are surrounded by the polymer coating

to give **3**. It can be seen that these particles are approximately 100 nm in diameter and a SEM image of **3** (Figure 1c) shows the porous polymer surface of the catalyst.

Suzuki-Miyaura couplings

Both catalysts were then tested for activity in the Suzuki coupling between 4-iodoacetophenone and benzenboronic acid under continuous flow conditions. The microreactor setup is shown in Figure 2. A pre-mixed solution of 4-iodoacetophenone **5**, benzenboronic acid **6** and *N*-diisopropylethylamine (DIPEA) in MeOH:H₂O:DME (2:1:2) was made up, before being pumped around the Vapotec R-Series microreactor, fitted with an Omnifit column³² that contained 200 mg of the required catalyst mixed with 1.5 g sand, to prevent swelling of the nanoparticles, caused by solvent uptake, from blocking the reaction column. A range of flow rates and residence times were explored to find the optimum reaction conditions for each catalyst, which are shown in Table 1. The range of flow rates shown in Table 1 corresponded to laminar flow with the range of Reynolds number (Re), 0.011 > Re > 9 × 10⁻⁴ ($Re = \frac{u_s d \rho}{\mu}$; where: *u_s* = superficial

velocity of the liquid phase, *d* = diameter of sand particles, *d* = 176 ± 10 μm, ρ = density of the liquid phase, μ = dynamic viscosity of the liquid phase). The axial dispersion in the reactor was limited by the molecular diffusion³³ only, due to the low range of the Peclet number (*Pe*) 5.5 > *Pe* > 0.48, ($Pe = \frac{u_s d}{D_m}$;

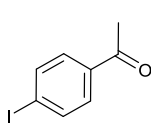
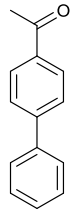
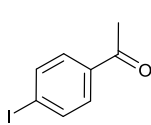

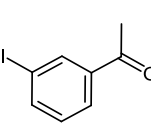
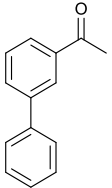
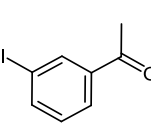

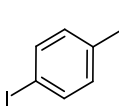
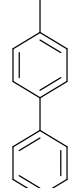
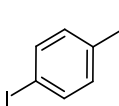

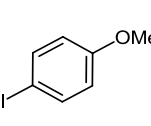
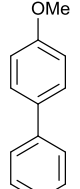
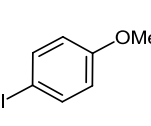

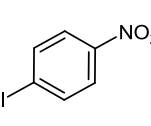
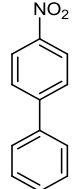
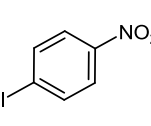

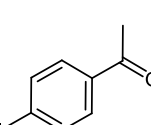
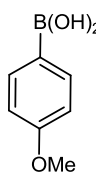
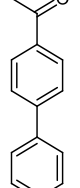
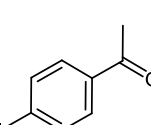
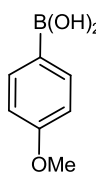

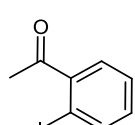
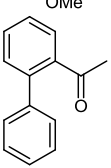
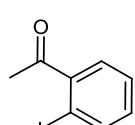

where *D_m* = molecular diffusivity, calculated applying Wilke-Chang correlation³⁴). The analysis of Entries 1 & 2 shows the influence of the external mass transfer (convection) on the overall performance of the reactor. However, detailed analysis of the influence of the external flow rate on this performance cannot be performed without detailed analysis of the reaction kinetics; the application of a differential reactor instead of an integral one.

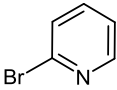
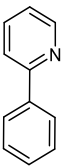
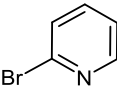
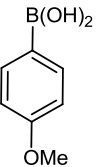
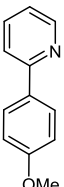
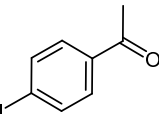
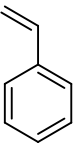
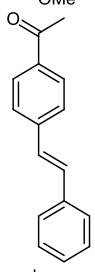
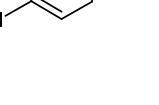
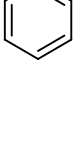
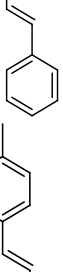
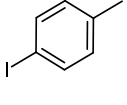
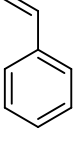
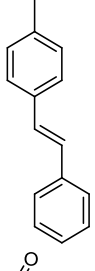


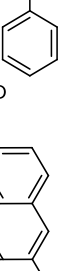
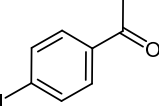
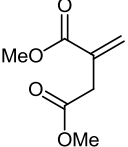
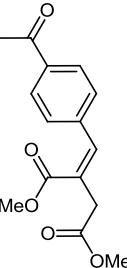

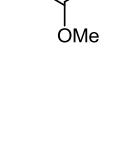
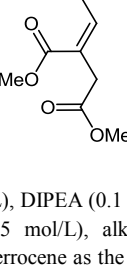
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Paper

Table 2 Suzuki and Heck couplings of aryl iodides and boronic acids/alkenes with supported catalysts **3** and **4**

Entry ^a	Halide	Boronic Acid	Catalyst	Residence time (min)	Product	Conversion (%) ^c
1		PhB(OH) ₂	3	6.8		>95, 95 ^d
2		PhB(OH) ₂	4	9.1		>95, 93 ^d
3		PhB(OH) ₂	3	13.7		93
4		PhB(OH) ₂	4	13.7		92
5		PhB(OH) ₂	3	18.2		86
6		PhB(OH) ₂	4	18.2		43
7		PhB(OH) ₂	3	18.2		56
8		PhB(OH) ₂	4	18.2		19
9		PhB(OH) ₂	3	9.1		>95, 85 ^d
10		PhB(OH) ₂	4	13.7		>95, 76 ^d
11			3	13.7		93
12			4	13.7		68
13		PhB(OH) ₂	3	13.7		trace
14		PhB(OH) ₂	4	13.7		trace

15		PhB(OH) ₂	3	27.4		46
16			3	27.4		50
17 ^b			3	27.4		>95, 51 ^d
18 ^b			4	54.8		>95, 75 ^d
19 ^b			3	54.8		73
20 ^b			4	27.4		30
21 ^b			3	6.8		73
22 ^b			4	54.8		trace

^a Reaction conditions: 120 °C, MeOH: H₂O: DME (2:1:2) (40 mL), iodide (0.05 mol/L), boronic acid (0.1 mol/L), DIPEA (0.1 mol/L), 200 mg of catalyst 1.5 g sand (total column length 4 cm). ^b Reaction conditions: 140 °C, NMP (40 mL) iodide (0.05 mol/L), alkene (0.1 mol/L) and *N*-methylcyclohexylamine (0.1 mol/L). ^c Calculated from the ¹H NMR of the crude reaction mixture utilising ferrocene as the internal standard. ^d Isolated yield.

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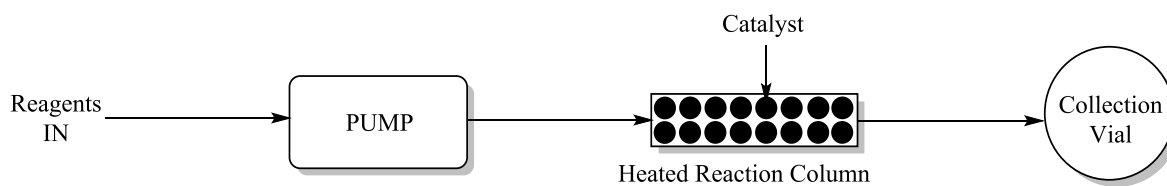


Figure 2 Flow reactor setup using a packed column

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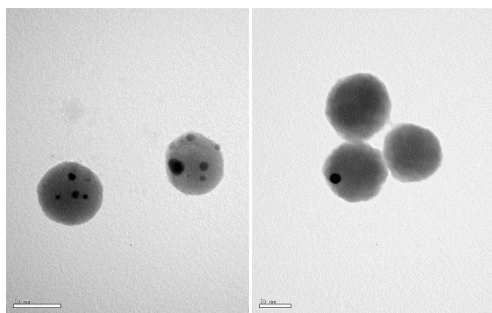


Figure 2 TEM images of post-reaction catalyst **3**

5 This will be the scope of the next paper. Both catalysts displayed excellent activity and gave high conversions, but catalyst **3** was found to be superior due to the shorter residence time required to reach full conversion. A variety of additional substrates were then screened under the optimal conditions and are shown in Table 2. Electron deficient systems such as 4-iodoacetophenone (Table 2, entries 1 and 2) and 4-iodonitrobenzene (Table 2, entries 9 and 10) gave high conversions in reasonable residence times with both catalysts. More electron rich aryl halides 4-iodotoluene (Table 2, entries 5 and 6) and 4-iodomethoxybenzene (Table 2, entries 7 and 8) gave lower conversions in longer residence times and catalyst **3** gave significantly higher conversions than **4**. Attempts to counteract this by lowering the flow rate further and thus increasing residence time resulted in a substantial decrease in conversion. More sterically hindered 2-iodoacetophenone (Table 2, entries 13 and 14) only afforded trace amounts of product, even with longer residence times. The electron rich 4-methoxyphenylboronic acid (Table 2, entries 11 and 12) afforded a decrease in conversion from 93% and 68%, for catalyst **3** and **4** respectively, albeit with a reasonable residence time of 40 minutes. Despite giving lower conversions, electron rich systems may require several passes over the column to increase the conversion. Catalyst **3** also provided a moderate conversion for 2-bromopyridine (Table 2, entries 15 and 16) In all examples it was shown that the catalyst **3** exhibited a greater reactivity often at faster flow rates and hence could give better conversions in shorter residence time.

Heck couplings

Catalysts **3** and **4** were also utilised for Heck couplings in flow. The optimal conditions for the reaction were found to be 140 °C using 1-methyl-2-pyrrolidinone (NMP), with *N*-methylcyclohexylamine as the base. A range of substrates were screened under these conditions (Table 2, entries 17-22), most of which gave moderate to good conversions, but with much longer and residence times of 80-100 min. Increasing residence time further lead to a significant decrease in conversion and an increase in an unidentified bi-product. It was evident that **3** was again the more active catalyst for the Heck couplings.

Catalyst Stability

Throughout the screening of substrates for Suzuki and Heck couplings, the same batch of catalysts **3** and **4** were used for all the reactions discussed previously. 200 mg of each catalyst was used for over 50 hours in continuous operation, with no appreciable decrease in activity. To analyse the effect of this continuous operation on the structure of the catalysts, TEM images of **3** were taken after use (Figure 2) and showed that palladium nanoparticles were still present and there was very little change in the surface structure of the catalyst. ICP-MS analysis of the product residues was used to test for any residual palladium and determine the extent of Pd leaching. The residues were found to contain 1 ppm Pd which corresponds to 0.05% of the total Pd in the catalyst.

Conclusions

Two novel polymer encapsulated silica supported Pd⁰ catalysts have been prepared and shown to be highly active catalysts for Suzuki-Miyaura and Heck cross-coupling reactions on a variety of substrates, in a continuous flow microreactor. In every example examined the catalyst **3** exhibited superior activity to catalyst **4** affording higher conversions in shorter residence times. Both the catalysts were used for >50 hours in continuous operation with no reduction in activity and a level of 1 ppm (0.05%) Pd leaching for catalyst **3** was measured by ICP-MS, which makes it an ideal robust and reusable catalyst for use in the development of continuous-flow processes for palladium catalysed reactions within organic synthesis. Efforts to expand the substrate scope and make further improvements to the reaction conditions are ongoing.

Experimental Section

General Considerations

Unless otherwise noted, all reagents and catalysts were commercially available and purchased from Sigma-Aldrich Ltd, Fischer Scientific Ltd., Johnson Matthey, Strem Chemical, Frontier Scientific chemical companies, and were used without further purification. All solvents were degassed before use. Continuous flow experiments were conducted using a Vapourtec R-Series instrument fitted with 6.6 mm x 100 mm Omnifit columns.³² Silica gel plates (GF₂₅₄) were used for TLC monitoring and silica gel (230-400 mesh) was used for flash column chromatography. ¹H NMR spectra were recorded on Bruker Avance 250 and 300 MHz instruments and ¹³C NMR spectra were recorded on a Bruker Avance 300 MHz instrument, all with TMS as the internal standard. The mass spectra were run on a microTOF electrospray time of flight (ESI-TOF) coupled to an Agilent 1200 LC system (University of Bath). IR spectra were recorded on Perkin-Elmer 1600 FT IR spectrometer with only selected absorbance quoted as ν in cm⁻¹.

Silica dioxide preparation

A solution of triethyl orthosilicate (16 mL, 72 mmol) and ammonium hydroxide (13.1 mL) in ethanol (188 mL) was stirred at room temperature for 24 hours. The product was isolated by

centrifugation followed by washing with methanol (2 × 50 mL). This afforded silica dioxide as a colourless powder (10.4g).

5 Preparation of functionalised silica (1)

A suspension of silica dioxide (1.7 g) in toluene was sonicated for 10 minutes before the addition of *N*-[3-(trimethoxysilyl)propyl]-ethylamine (5.7 mL). The suspension was stirred at reflux for 16 hours. Product was separated by centrifugation, washing with toluene (2 × 30 mL) and ethanol (2 × 30 mL). This afforded **1** as a light yellow powder (1.34 g).

Preparation of functionalised silica (2)

15 A suspension of silica dioxide (2.2 g) in toluene was sonicated for 10 minutes before the addition of 4-[[3-(triethoxysilyl)propyl]amino]-3-penten-2-one (13 g). The suspension was stirred at reflux for 16 hours. Product was separated by centrifugation, washing with toluene (2 × 30 mL) and ethanol (2 × 30 mL). This afforded **2** as a yellow powder (1.74 g).

25 Preparation of 4-[[3-(triethoxysilyl)propyl]amino]-3-penten-2-one

A solution of 2,4-pentadione (10 mL, 100 mmol) and 3-aminopropyltriethoxysilane (21 mL, 90 mmol) in methanol (60 mL) were heated to 80 °C and stirred at this temperature for 16 hours. After volatile removal 4-[[3-(triethoxysilyl)propyl]amino]-3-penten-2-one was isolated (26 g, 87 %) as a yellow oil. ¹H NMR (250 MHz, CDCl₃) δ 10.85 (br s, 1H), 4.94 (s, 1H), 3.81 (q, *J* = 7.0 Hz, 4H), 3.23 (q, *J* = 7.1 Hz, 2H), 1.99 (s, 3H), 1.91 (s, 3H), 1.69 (dt, *J* = 15.7, 8.0 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 6H), 0.66 (dd, *J* = 9.4, 7.1 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 194.6, 163.0, 95.1, 58.5, 45.5, 28.8, 23.9, 18.8, 18.3, 7.6.

General procedure for the preparation of Pd⁰ nanoparticles on functionalised silica

40 A suspension of functionalised silica (1.74 g) in ethanol (40 mL) was sonicated for 10 minutes. Pd(OAc)₂ (174 mg) was added and the mixture was stirred at room temperature for three hours. The dark solid was isolated by filtration and added to water (30 mL). The Pd^{II} species was reduced to Pd⁰ by the stepwise addition of 45 NaBH₄ (1 g) over three hours. After complete addition the product was collected by filtration, washing with water. After drying a grey solid of Pd⁰ ligated to functionalised silica (1.2 g) was isolated.

50 General procedure for the preparation of polymer encapsulated Pd⁰ nanoparticles

A suspension of Pd⁰ functionalised silica (0.15 g) in water (17 mL) was sonicated for 10 minutes. Allylamine (0.12 mL) and 55 PVP (polyvinylpyrrolidone) (250 mg) were added and the mixture was stirred at room temperature for one hour. Sodium styrene sulphonate (0.075 g), potassium peroxydisulfate (75 mg) and water (25 mL) were added and the mixture stirred for 30 minutes. Styrene (1.0 mL) and divinyl benzene (0.1 mL) were 60 added and the mixture stirred at 80 °C for 12 hours. After filtration and washing with water the catalyst was afforded (140 mg) as a grey powder.

65 General procedure for Suzuki-Miyaura coupling under flow conditions

A solution of iodide (0.05 mol/L), boronic acid (0.1 mol/L) and *N*-diisopropylethyl amine (0.1 mol/L mmol) in MeOH: H₂O: DME (2:1:2) (40 mL) was pumped around the Vapourtec R-2+ 70 module in conjunction with the R-4 reactor heater. This was fitted with a 6.6 x 100 mm Omnifit glass column containing a homogeneous mixture of polymer encapsulated catalyst 3 or 4 (200 mg) and sand (1.5 cm), to a total length of 4 cm. The reaction column was purged with MeOH: H₂O: DME (2:1:2) (5 75 mL) and heated to 120 °C before the reagent solution was introduced. The temperature was maintained at 120 °C throughout and an additional portion of MeOH: H₂O: DME (2:1:2) (5 mL) was pumped through the reactor after all of the reagent solution had been used.

80 General procedure for Heck coupling under flow conditions

A solution of iodide (0.05 mol/L), alkene (0.1 mol/L) and 1-methyl-2-dicyclohexylamine (0.1 mol/L) in NMP (40 mL) was pumped around the Vapourtec R-2+ module in conjunction with 85 the R-4 reactor heater. This was fitted with a 6.6 x 100 mm Omnifit glass column containing a homogeneous mixture of polymer encapsulated catalyst **3** or **4** (200 mg) and sand (1.5 cm), to a total length of 4 cm. The reaction column was purged with NMP (5 mL) and heated to 140 °C before the reagent solution 90 was introduced. The temperature was maintained at 140 °C throughout and an additional portion of NMP (5 mL) was pumped through the reactor after all of the reagent solution had been used.

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Notes and references

- 105 1. B. Ahmed-Omer, J. C. Brandt and T. Wirth, *Org. Biomol. Chem.*, 2007, **5**, 733-740.
2. P. H. Seeberger and T. Blume, *New Avenues to Efficient Chemical Synthesis-Emerging Technologies*, Springer-Verlag, 2007.
- 110 3. P. Watts and S. J. Haswell, *Chem. Soc. Rev.*, 2005, **34**, 235-246.
4. D. Barrow, S. Taylor, A. Morgan and L. Giles, in *Microreactors in Organic Chemistry and Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2013, pp. 1-33.
- 115 5. C. Wiles and P. Watts, *Micro Reaction Technology in Organic Synthesis*, CRC Press Inc, 2011.

6. T. Noel and S. L. Buchwald, *Chem. Soc. Rev.*, 2011, **40**, 5010-5029.
7. W. R. Reynolds and C. G. Frost, in *Palladium-Catalyzed Coupling Reactions*, Wiley-VCH Verlag GmbH & Co. KGaA, 2013, pp. 409-443.
8. C. G. Frost and L. Mutton, *Green Chem.*, 2010, **12**, 1687-1703.
9. A. Kirschning, W. Solodenko and K. Mennecke, *Chem. Eur. J.*, 2006, **12**, 5972-5990.
10. V. Polshettiwar, C. Len and A. Fihri, *Coord. Chem. Rev.*, 2009, **253**, 2599-2626.
11. K. Takasu, in *Microreactors in Organic Chemistry and Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2013, pp. 151-196.
12. ThalesNano, Graphisoft Park, Záhony u. 7. H-1031 Budapest.
13. N. Nikbin, M. Ladlow and S. V. Ley, *Org. Process Res. Dev.*, 2007, **11**, 458-462.
14. W. Solodenko, H. Wen, S. Leue, F. Stuhlmann, G. Sourkouni-Argirusi, G. Jas, H. Schönfeld, U. Kunz and A. Kirschning, *Eur. J. Org. Chem.*, 2004, 3601-3610.
15. U. Kunz, A. Kirschning, H. L. Wen, W. Solodenko, R. Cecilia, C. O. Kappe and T. Turek, *Catal. Today*, 2005, **105**, 318-324.
16. A. Michrowska, K. Mennecke, U. Kunz, A. Kirschning and K. Grela, *J. Am. Chem. Soc.*, 2006, **128**, 13261-13267.
17. K. Mennecke, R. Cecilia, T. N. Glasnov, S. Gruhl, C. Vogt, A. Feldhoff, M. A. L. Vargas, C. O. Kappe, U. Kunz and A. Kirschning, *Adv. Synth. Catal.*, 2008, **350**, 717-730.
18. C. Ramarao, S. V. Ley, S. C. Smith, I. M. Shirley and N. DeAlmeida, *Chem. Commun.*, 2002, 1132-1133.
19. C. K. Y. Lee, A. B. Holmes, S. V. Ley, I. F. McConvey, B. Al-Duri, G. A. Leeke, R. C. D. Santos and J. P. K. Seville, *Chem. Commun.*, 2005, 2175-2177.
20. I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley and G. K. Tranmer, *Chem. Eur. J.*, 2006, **12**, 4407-4416.
21. J. Lim, S. N. Riduan, S. S. Lee and J. Y. Ying, *Adv. Synth. Catal.*, 2008, **350**, 1295-1308.
22. N. T. S. Phan, D. H. Brown and P. Styring, *Green Chem.*, 2004, **6**, 526-532.
23. S. Ceylan, C. Friese, C. Lammel, K. Mazac and A. Kirschning, *Angew. Chem. Int. Ed.*, 2008, **47**, 8950-8953.
24. U. Laska, C. G. Frost, G. J. Price and P. K. Plucinski, *J. Catal.*, 2009, **268**, 318-328.
25. G. Shore, S. Morin and M. G. Organ, in *Angew. Chem., Int. Ed.*, 2006, **45**, 2761-2766.
26. P. He, S. J. Haswell and P. D. I. Fletcher, *Appl. Catal., A-Gen.*, 2004, **274**, 111-114.
27. C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889-900.
28. R. C. Wheeler, O. Benali, M. Deal, E. Farrant, S. J. F. MacDonald and B. H. Warrington, *Org. Process Res. Dev.*, 2007, **11**, 704-710.
29. T. Wu, T. Jiang, B. Hu, B. Han, J. He and X. Zhou, *Green Chem.*, 2009, **11**, 798-803.
30. Y. Wang, A. V. Biradar, C. T. Duncan and T. Asefa, *J. Mater. Chem.*, 2010, **20**, 7834-7841.
31. C. A. Witham, W. Huang, C.-K. Tsung, J. N. Kuhn, G. A. Somorjai and F. D. Toste, *Nat. Chem.*, 2010, **2**, 36-41.
32. C. P. Omnifit Ltd., Coldhams Lane, Cambridge, UK. CB1 3HD.
33. O. Levenspiel, *Chemical reaction engineering*, 3rd edn., Wiley, New York, 1999.
34. C. R. Wilke and P. Chang, *AIChEJ*, 1955, **1**, 264-270.