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Continuous Flow Ligand-Free Heck Reactions Using Monolithic Pd [0] Nanoparticles

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Abstract:

An automated reactor has been developed for performing ligand-free Heck reactions in continuous flow mode. The reactor utilises a monolithic reactor cartridge derivatised with Pd(0) nanoparticles in-line with a scavenging cartridge containing Quadrapure-TU to efficiently capture palladium residues and thereby afford Heck products directly in high purity.

Immobilised catalysts and reagents[1] have proven to be very useful in parallel synthesis applications, especially within the pharmaceutical industry. Heterogeneous catalysts are attractive for both laboratory scale and larger industrial processing, and the application of such supported catalysts/reagents in continuous flow mode offers advantages in terms of ease of automation, safety, and reproducibility.[2] Moreover, optimally, no purification steps are needed and flow reactors can be used repeatedly, thus bringing down production costs.

Supported reagents prepared from insoluble gel-type polystyrene-based polymers are most commonly used in conventional batch processes. These materials, usually in the form of beads, can be adapted for use in flow processes by simply packing them into column or tube arrangements. However, these randomly packed columns can be problematic, largely because they suffer from poorly controlled fluid dynamics.[3] These problems typically include mass and heat transfer limitations and less-than-efficient surface area exposure and utilisation. Moreover, compression of these polymers under pressure can tend to block the flow system, and alternatively differential swelling of microporous polystyrene beads upon exposure to different solvents may lead to changes in column dimensions and packing that can result in detrimental "channeling" or bypassing of the particles. Macroporous beads offer a preferential arrangement whereby a high degree of cross-linking ensures that the geometry of the reactor, and thereby porosity, is maintained irrespective of the solvent being used. However, although macroporous reactor columns rarely suffer from blockages attributable to compaction, access to active sites within the beads may be diffusion limited and compromised by convective flow around the beads (even an ideally packed column of monodisperse beads has a void volume of approximately 27%[4]). Moreover the production of uniformly sized beads by a suspension polymerisation process can be difficult, and extensive sieving is often necessary to produce a monodisperse bead size.

Table 1. **Optimal composition of polymerisation mixture (v/v) used to prepare basic macroporous organic monolithic columns**

vinyl benzyl chloride	divinyl benzene	1-dodecanol	AIBN	temp
35%	20%	45%	1%	80 °C

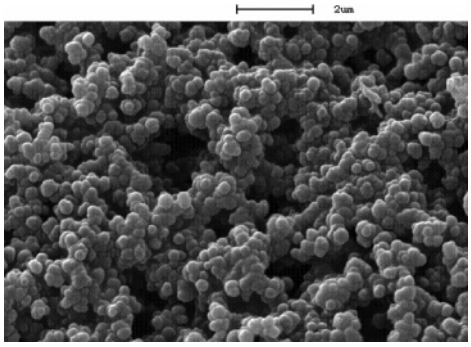

Figure 1. **SEM picture of the macroporous polymer before immobilisation of Pd.**

Many of these drawbacks can be overcome by using functionalised monolithic materials as the basis for continuous flow reactor columns.[5] In this context, monoliths are a single continuous piece of porous material which can be made from either inorganic[6] or organic material.[7] Organic monoliths can be made of a variety of different polymers using different polymerisation methods to induce pores within a controlled range. Optimally, a monolithic material provides a high surface area, short diffusion paths, effective mass transfer under convective flow,[8] and comparatively low back pressures characteristic of high porosity.

Transition metal nanoparticles have attracted a great deal of attention in wide-ranging disciplines, although applications in catalysis remain preeminent.[9] These particles are typically 1−100 nm in diameter and show size-dependent properties. Their interesting catalytic properties can be attributed to a higher percentage of atoms expressed on the reacting surface, and nanoparticular catalysts have shown interesting results

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(1) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1*, **2000**, *23*, 3815−4195.
(2) Jas, G.; Kirschning, A. *Chem. Eur. J.* **2003**, *9*, 5708−5723.
(3) Stankiewicz, A. *Chem. Eng. Sci.* **2001**, *56*, 359−361.
(4) Svec, F.; Frechet, J. M. J. *Science* **1996**, *273*, 205−211.
(5) Svec, F.; Frechet, J. M. J. *Chem. Mater.* **1995**, *7*, 707−715.
(6) Heck, R. M.; Gulati, S.; Farratu, R. J. *Chem. Eng. J.* **2001**, *82*, 149−156.
(7) Barby, D.; Haq, Z. Eur. Pat. 0060138, 1982.
(8) Kunz, U.; Kirschning, A.; Wen, H.-L.; Solodenko, W.; Cecilia, R.; Kappe, C. O.; Turek, T. *Catal. Today* **2005**, *105*, 318−324.
(9) Roucoux, A.; Schulz, J.; Patin, H. *Chem. Rev.* **2002**, *102*, 3757−3778.

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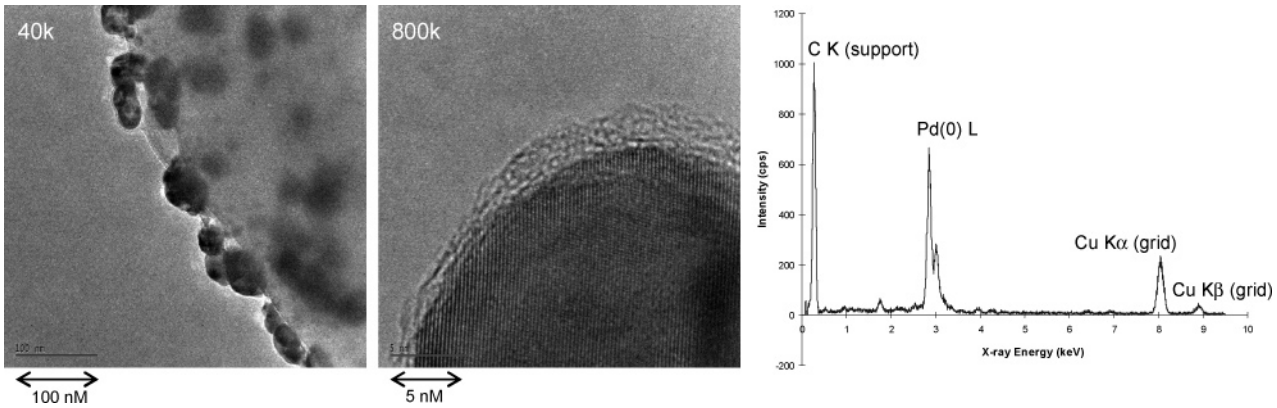

Figure 2. **(a) TEM image of a nanoparticular Pd derivatised monolith (40k). (b) HRTEM image of a Pd nanoparticle showing an ordered lattice structure (800k). (c) EDS spectrum of a nanoparticle showing only Pd(0) to be present.**

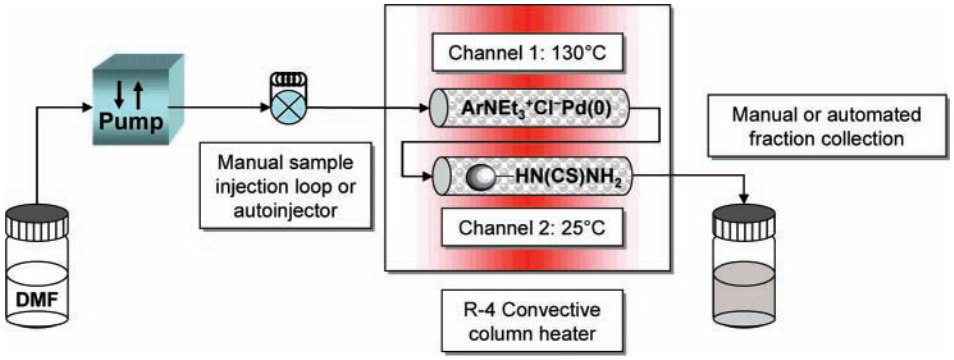

Figure 3. **Flow-through reactor setup.**

in a variety of reactions, in particular C−C coupling processes. One of the most versatile of these metal-catalysed C−C bond forming reactions is the Heck reaction.[10] Several groups have used Pd nanoparticles to perform Heck cross-coupling.[11,12] Recently, Kirschning et al. reported the preparation of Pd nanoparticles dispersed inside a composite glass/polymer monolith.[13] Amongst other useful Pd catalysed reactions, their article described one example of a Heck reaction using this composite reactor.

Herein we report the development of a rigid macroporous organic monolith, of the type first described by Frechet and Svec,[4] which we have derivatised with Pd nanoparticles and used to perform Heck cross-coupling reactions as part of an automated flow-through reactor system. We believe that organic monoliths of this type are well-suited for use in flow-through polymer assisted synthesis. Usually, they benefit from a higher loading than polymers prepared by suspension polymerisation due to the fact that polymerisation happens only in one phase and the problem of partitioning does not arise. Moreover, they can be readily and reproducibly prepared in a wide range of sizes suitable for micro- and mesoflow applications.[14−16]

Results and Discussion

Preparation of Monolithic Supported Pd(0) Nanoparticles. A. Preparation of Macroporous Organic Monolithic Reactor Columns (Quaternary Ammonium Form). The physical characteristics of macroporous organic monoliths are dependent upon composition, the nature of the porogen used, and the conditions used to promote polymerisation. Therefore, considerable preliminary experimentation was performed with the objective of identifying a rigid monolithic polymer that could be reproducibly prepared with both high porosity to reduce backpressure experienced in a flowing system and the ability to be stably derivatised with Pd nanoparticles such that the column reactor could be reused for a range of substrates before regeneration became necessary. All polymerisation experiments were performed under 1 bar of pressure in situ within 6.6 mm id × 70 mm glass columns[17] which were temporarily sealed at one end and located within a multichannel convective heating device[18] to enable polymerisation to be induced thermally in the presence of AIBN as the radical initiator. In this way, polymerisation of the mixture given in Table 1 at 80 °C for 20 h, followed by washing with THF (1.0 mL/min; rt; 2h) to remove the porogen and residual nonpolymeric material,

(10) Heck, R. F.; Nolley, J. *J. Org. Chem.* **1972**, 1133−1136.
(11) Beller, M.; Fischer, H.; Kuhlein, K.; Reisinger, C.-P.; Hermann, W. *J. Organomet. Chem.* **1996**, *520*, 257−260.
(12) Reetz, M. T.; Lohmer, G. *Chem. Commun.* **1996**, 1921−1922.
(13) Solodenko, W.; Wen, H.-L.; Leue, S.; Stuhlmann, F.; Sourkouni-Argirusi, G.; Jas, G.; Schonfeld, H.; Kunz, U.; Kirschning, A. *Eur. J. Org. Chem.* **2004**, 3601−3610.
(14) Baxendale, I. R.; Griffith-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Synlett* **2006**, 427−430.
(15) Baxendale, I. R.; Deely, J.; Griffith-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K. *Chem. Commun.* **2006**, 2566−2568.
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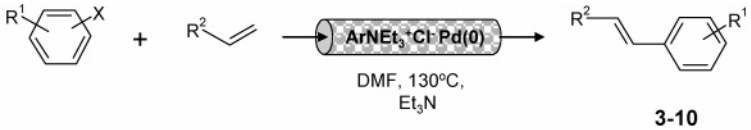
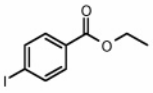
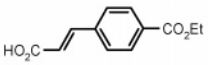
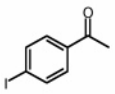
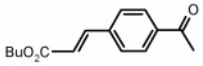
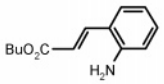
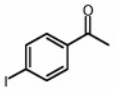
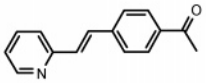
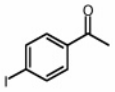
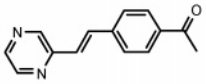
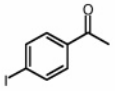
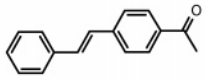
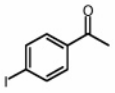
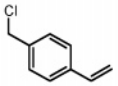
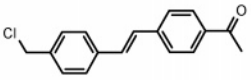
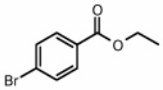
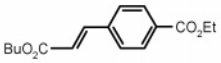
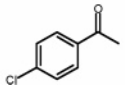
(17) Omnifit Ltd., 2 College Park, Coldhams Lane, Cambridge, UK CB1 3HD. Website: http://www.omnifit.com.
(18) The R-4 Flow Reactor module is available from Vapourtec Ltd., Place Farm, Ingham, Suffolk, UK 1P31 1NQ. http://www.vapourtec.com.

Table 2. **Cross-coupling reactions between selected aryl halides and alkenes**



3-10

entry	aryl halide	alkene	product		conversion (%)	purity (%)	yield (%)
1				**3**	100	>99	82
2				**4**	100	>98	87
3				**5**	100	>95	84
4				**6**	100	>99	87
5				**7**	100	>99	86
6				**8**	100	>99	83
7				**9**	41	<50	<50
8				**10**	51	<50	N/A
9			No Reaction	-	0	N/A	N/A

gave a rigid white monolith that completely filled the glass column (Figure 1). Mercury intrusion analysis established the median pore size to be 3147 nm, and the surface area was determined to be 4.93 m^2/g using nitrogen absorption and BET theory. Other formulations having potentially higher surface areas lacked the physical robustness and overall viability of this combination for the application in hand.

The monolith was converted to the quaternary ammonium form by elution with a solution of triethylamine in toluene (1:4) at 0.04 mL/min and 60 °C for 48 h which was then washed with toluene at 1.0 mL/min for 30 min at 60 °C to afford a loading of 2.0 mmol/g, according to C, H, and N analysis.

B. Preparation of Palladium(0) Derivatised Monolith: A solution of sodium tetrachloropalladate (465 mg, 1.6 mmol) in water (80 mL; dark brown) was pumped through the monolith at 0.3 mL/min. Initially, a clear solution exited from the column which, on removal of water, was found to contain only sodium chloride. After about 3 h (equivalent to pumping through approximately 1.0 mmol of sodium palladate), the outflow turned yellow. This procedure was repeated using a freshly prepared solution of sodium tetrachloropalladate before the monolith was washed with water (20 mL) at 1.0 mL/min. An aqueous solution of sodium borohydride (625 mg in 50 mL water) was pumped through the column at 0.5 mL/min whereupon the previously white monolith immediately turned black. Finally, the column was conditioned by flushing with water (20 mL), then 1.0 M HCl (20 mL), water (30 mL), and ethanol (20 mL), all at 1.0 mL/min. Imaging of a representative monolith by HRTEM

Scheme 1. **Heck coupling in superheated ethanol**

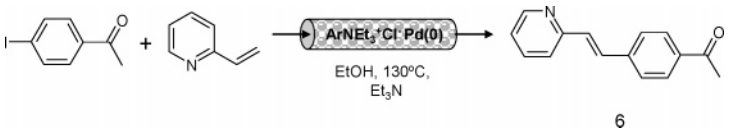
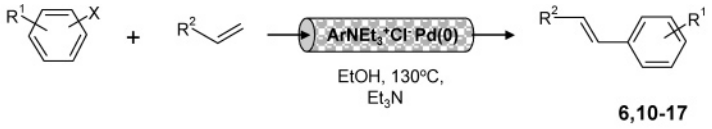


Table 3. **Results of Heck cross-coupling reaction in superheated ethanol**



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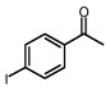
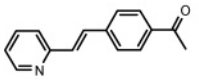
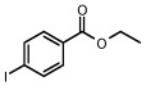
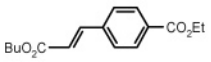
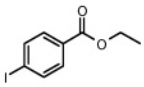
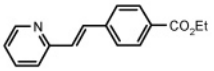
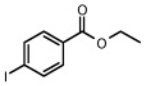
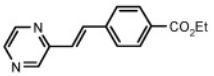
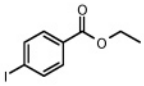
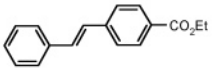
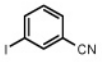
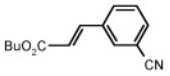
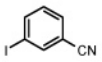
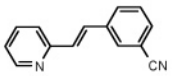
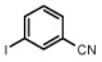
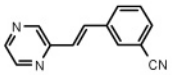
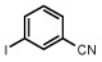
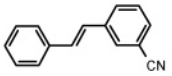
1				**6**	100	>99	86
2				**10**	100	>95	87
3				**11**	100	>95%	88
4				**12**	100	>95	87
5				**13**	100	>95	88
6				**14**	100	>99	79
7				**15**	100	>99	85
8				**16**	100	>99	78
9				**17**	100	>99	73

clearly showed the presence of Pd nanoparticles attached to the polystyrene support in the size range 5−50 nM (Figure 2a). Closer examination of the Pd particles revealed an ordered lattice arrangement (Figure 2b) which remained stable over an extended period of time. EDS analysis confirmed that only Pd(0) was present (Figure 2c).

Pd Catalysed Ligand-Free Heck Reaction. A variety of aryl halides and alkenes were used to examine the effectiveness of the monolithic reactor to promote the Heck cross-coupling reaction in DMF in the presence of triethylamine. In each reaction, an aryl halide (0.2 mmol), an alkene (0.3 mmol), and triethylamine (0.3 mmol) were dissolved in DMF (1.0 mL), and this mixture was introduced onto the monolithic nanoparticular Pd reactor column using either manual loop injection or an automated injection module[19] with DMF as the system solvent pumped at 0.05 mL/min throughout (Figure 3). The reactor column was maintained at 130 °C using a convective heating device. The output from the flow reactor was collected for 2.0 h, either manually or by automated fraction collection, and then the solvent was evaporated under high vacuum and the residue dissolved in dichloromethane and was washed with water. Removal of the dichloromethane afforded the isolated products which were characterised by LC−MS and NMR analysis (Table 2).

An attractive advantage of flow reactors resides in the ability to readily perform chemistries above atmospheric pressure. DMF is both toxic and difficult to remove after synthesis but benefits from a high boiling point that, in this case, allows the Heck coupling to proceed rapidly at 130 °C

(19) Typically a Gilson 233XL XYZ liquid handler was used for both automated injection and fraction collection. Website: http://gilson.com.

within a reasonable residence time (approx 25 min[20]). However, these conditions may be attained in a flow reactor using a more benign but lower boiling solvent by operating under superheated conditions at elevated pressure to prevent boiling. To this effect, we examined the use of ethanol as a more acceptable alternative to DMF and quickly established that using an in-line 100 psi back-pressure regulator, ethanol could be safely heated to 130 °C under continuous flow conditions, and that the Heck cross-coupling reaction between 4′-iodoacetophenone (49 mg, 0.2 mmol) and 2-vinylpyridine (31 mg, 0.3 mmol) in the presence of triethylamine (30 mg, 0.3 mmol) proceeded just as efficiently as when using DMF as the system solvent (Scheme 1).[21] Following workup and evaporation as before, NMR confirmed that the desired product **6** was obtained in high yield (86%) and purity (99%).

This protocol was exploited to prepare a library of cross-coupled Heck products in ethanol (Table 3); again the conversion and purity were determined by LC−MS and NMR in each case.

The reactor was reused at least 25 times without regeneration, and consecutive use of the column does not seem to affect its efficiency. However, if necessary, it could easily be regenerated by repeating the same procedure used initially to prepare Pd(0) nanoparticles.

One of the main disadvantages associated with the use of supported metals is that they typically tend to leach into solution and that their subsequent removal can be problematic. In our early experiments, ICP−MS analysis of the isolated solid products revealed an unacceptable average metal content of approximately 270 ppm Pd. However, this problem could be easily resolved by inserting a second column containing the metal scavenger resin Quadrapure TU[22] directly after the nanoparticular Pd reactor column. This routinely reduced Pd levels in the isolated products to below 5 ppm, according to ICP−MS analysis.

(20) In practise, a range of residence times are observed, but an average value may be obtained empirically by loop injection of a plug of either a visible dye or a UV active substrate and determining the time at which a maximal response is observed at the outflow (allowing for dead volumes in the tubing used at the column inlet and outlet).

(21) Karbass, N.; Sans, V.; Garcia-Verdugo, E.; Burguete, M. I.; Luis, S. V. *Chem. Commun.* **2006**, 3095−3097.

Conclusion

A new organic monolithic Pd(0) reactor has been developed. This reactor can be used in conjugation with a simple flow-through setup which can easily be automated. The reaction can potentially be scaled up, and the monolith is reusable. The problem of separating the catalyst from the product is largely circumvented. Although some degree of Pd leaching was observed in flow mode the problem could be eliminated by the in-line use of Quadrapure TU metal scavenger. When compared to other monolithic systems, the new system has a higher loading capacity, it is easier and cheaper to prepare, and less practical problems are encountered. The reactor can be used with a wide variety of aryl iodides and alkenes, although aryl iodides are more active than bromides. The yields in the Heck reaction are generally very high (>80%), and the reaction time is shorter than its corresponding batch equivalent[23] especially when smaller amounts of product (<0.5 mmol) are required. In every example, 40−50 mg of the product were generated and the catalyst showed good activity and stability during the flow mode reactions. The process does not require the use of an inert atmosphere, and DMF, a solvent commonly used for Heck reactions, can be replaced by ethanol, which both is less toxic and provides easier workup conditions that are suitable for automation.

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(22) Quadrapure TU [655422], a thiourea-based scavenger resin with a high affinity for metal ions. Commercially available from Sigma-Aldrich. Website: http://www.sigmaaldrich.com.

(23) Zhou, L.; Wang, L. *Synthesis* **2006**, 2649−2652.