Continuous Flow Synthesis in Monolithic Reactors

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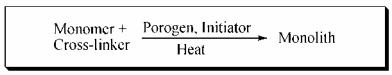
Introduction

Our group has pioneered the use of supported reagents for the synthesis of natural products and other biologically interesting molecules in flow.[1] The most common support systems used in organic synthesis are gel-type and macroporous resins. However there are practical problems when these beads are used in flow. For example, gel-type beads are solvent dependant and suffer from uncontrolled flow dynamics. The large void volume in a column packed with macroporous beads usually leads to poor reaction kinetics and causes the solvent to pass around the bead instead of through them. To overcome some of these problems, monoliths have been proposed and developed for use in solid-supported continuous flow synthesis. Monoliths are a single continuous piece of porous material which can be made of different materials.[2] The monoliths used in our labs are made of organic polymers which can be produced in any shape or size, making them ideal for use in micro- and meso- flow systems. The readily tailored morphologies of these materials make them ideal constructs for use in continuous flow synthesis due to easier control of pore dimensions, tuneable microchannel construction and their greater scope for chemical functionalisation.[2]

Preparation of Monoliths[2]

Rigid macroporous monoliths are prepared by precipitation polymerisation (Scheme 1). Extensive experimentation led to the optimised polymerisation mixture (Table 1) which offers acceptable surface to volume ratios and good flow characteristics for the heterogeneous support (Fig. 1). The monoliths are prepared within glass cartridges (Fig. 2) and can be made and used in the R2/R4 Vapourtec flow units (Fig. 3).



Scheme 1 Precipitation polymerisation for monolith preparation.

VBC	DVB	Dodecanol	AIBN	Temperature
35%	20%	45%	1%	80ºC

Table 1 Polymerisation mixture for a Merrifield-type monolith.

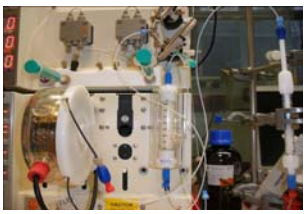


Fig. 3 R2/R4 Vapourtec Flow system.

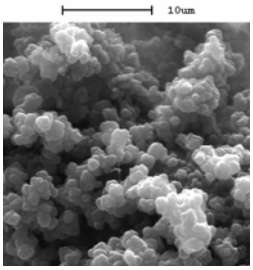
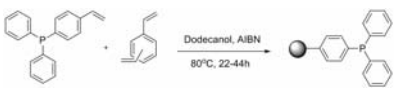


Fig. 1 SEM picture of a monolith.

Fig. 2 Monolithic cartridges.

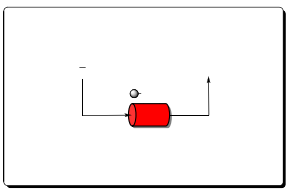
Staudinger/Aza-Wittig Reactions

A monolithic triphenylphosphine system has also been prepared using our standard precipitation polymerisation procedure (Scheme 7).

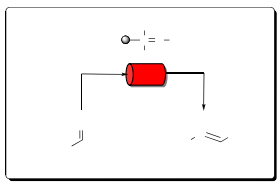


Scheme 7 Preparation of triphenylphosphine monolith.

This monolith can be used to perform Staudinger/Aza-Wittig reactions in combination with the R2/R4 Vapourtec flow system in an automated manner. In the first step an azide is reacted with the monolith to obtain immobilised iminophosphorane (Scheme 8). In the next step this iminophosphorane is reacted with an aldehyde or ketone to give the corresponding imine (Scheme 9). This monolithic reactor has been used to prepare 12 different imines in high yields and purity (Fig. 6).



Scheme 8 Staudinger reaction in flow.



Scheme 9 Aza-Wittig reaction in flow.

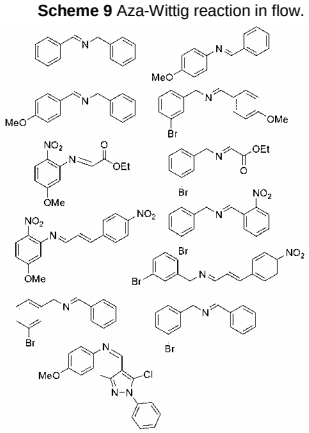
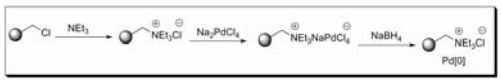


Fig. 6 Staudinger/Aza-Wittig products.

Monolithic Pd Nanoparticles[3]

The Merrifield-type monolith can be easily converted to an ion-exchange type resin by reacting it with triethylamine. A palladium salt can then be immobilised on the monolith which is subsequently reduced to Pd[0] nanoclusters (Scheme 2).



Scheme 2 Preparation of monolithic Pd nanoclusters.

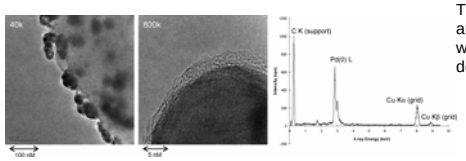
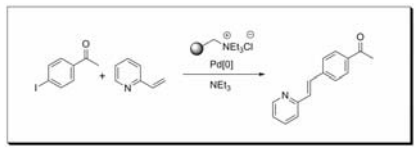


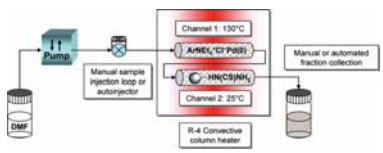
Fig. 4 TEM picture of Pd nanoparticles.

The TEM picture shows Pd clusters are less than 100 nm wide (Fig. 4) which gives these nanoparticles size-depandant characteristics.

An automated monolithic reactor was developed for performing ligand-free Heck reactions in continuous flow mode. The reactor utilised a monolithic cartridge derivatised with Pd[0] nanoclusters and an in-line scavenging column containing Quadrapure-TU to capture Pd residues, thereby affording the Heck products in high yield and purity (Schemes 3 and 4). Initially the reactions were performed in DMF. By using a back-pressure regulator we were able to use super-heated ethanol as a more environmentally accepted solvent. Around 20 cross-coupling products in high yield and purity were prepared.



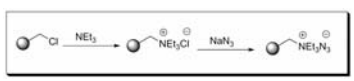
Scheme 3 An example of a Heck reaction.



Scheme 4 Flow set-up to perform Heck reactions.

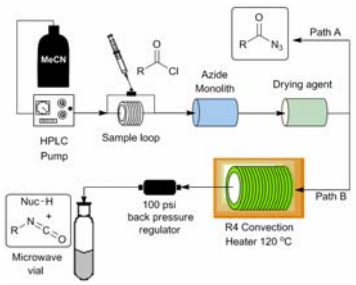
Curtius Rearrangement[4]

The ion-exchange monolith could also be converted to an immobilised azide by reacting it with sodium azide (Scheme 5). The loading of the monolith was 2.0 mmol azide per gram of polymer. A typical cartridge contained approximately 7.0 g of monolith equating to 14.0 mmol of azide. Mercury Intrusion Analysis established the median pore size to be 3147 nm and the surface area to be 4.93 m^2g^{-1} as determined by nitrogen absorption and BET measurements.



Scheme 5 Preparation of monolithic azide.

The monolithic azide reactor was used in combination with R2/R4 flow unit to convert acyl chlorides to their corresponding isocyanates *via* their acyl azide intermediates. The rearranged isocyanates were also further reacted with various nucleophiles using microwave heating to obtain secondary carbamates and urea products in high yield and purity (Scheme 6). The monolith was used to prepare 10 different rearrangement products at various scales (Fig. 5). In addition, the reactor could easily be regenerated by pumping an aqueous solution of sodium azide through it.



Scheme 6 Flow set-up for Curtius rearrangement.

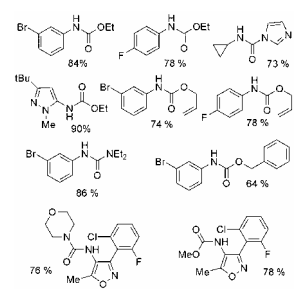


Fig. 5 Curtius products.

References and Acknowledgements

References: (1) S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer and S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3815-4195. **(2)** F. Svec and J. M. J Frechet, *Anal. Chem.*, 1992, **62**, 820-822. **(3)** N. Nikbin, M. Ladlow and S. V . Ley, *Org. Process Res. Dev.*, 2007, **11,** 458-462. **(4)** M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin and C. D. Smith, *Org. Biomol. Chem.*, 2008, **6**, 1587-1593.

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