Continuous Flow Suzuki Coupling with a Heterogeneous Pd Catalyst

Robin Wilkes, Alessandra Chighine (PhosphonicS Ltd)

www.phosphonics.com

www.vapourtec.co.uk

INTRODUCTION

This study demonstrates the use of a continuous flow approach with a heterogeneous silica-based Pd catalyst to carry out a Suzuki coupling reaction.

It demonstrates optimisation of residence time and concentration, and investigates useful working life of the catalyst.

BACKGROUND

On large scale, heterogeneous catalysts offer improved efficiency and cost benefits over homogeneous systems by allowing desirable processing aspects such as catalyst recycling; easier product isolation, where the removal of toxic metal residues and phosphine ligands is no longer required; and reduced waste costs. Functionalised silica catalysts possess additional benefits over polymer-based catalysts including no requirements for material swelling, excellent stability at higher temperatures and highly suitable flow properties, limiting potential pressure build-ups.

PhosphonicS™ has developed a range of immobilised heterogeneous palladium catalysts that have been successfully utilised in cross-coupling reactions including Suzuki and Heck reactions under batch slurry conditions.[1-3] The catalysts feature either immobilised sulfide or bulky phosphine ligands and are very effective for a wide range of different substrates, giving the coupled products in high yields and excellent purities. At the end of the reaction these heterogeneous catalysts can simply be filtered off from the reaction mixture. The catalysts can be reused and no apparent loss of activity has been seen over many recycles.

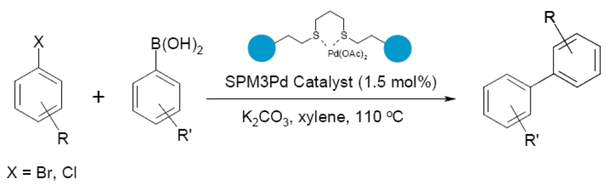


Fig 1 - Suzuki coupling in slurry batch mode using SPM3Pd catalyst

Due to the successful performance of these heterogeneous catalysts under traditional slurry reaction conditions and the potential benefits offered, PhosphonicS™ in collaboration with Vapourtec assessed the suitability of these catalysts for flow chemistry applications.

Synthesis of Aryl Pyridines

Substituted pyridines are attractive pharmaceutical targets because of their potential biological activities. The Suzuki coupling can be very useful for the synthesis of aryl pyridines, but whereas simple aryl halides and aryl boronic acids are successfully coupled using standard Suzuki protocols, reactions involving their heteroaryl analogues can often be less straightforward. [4]

3-Bromopyridine was highly soluble in the solvent system described below and was chosen as the aryl halide substrate for this flow chemistry Suzuki coupling study, where key flow reaction parameters such as residence time and concentration of the substrate were investigated.

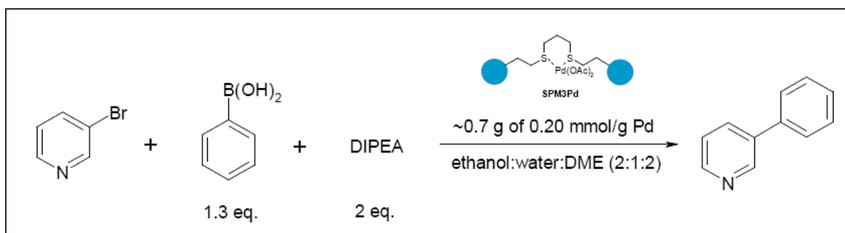


Fig 2 - Suzuki coupling in flow mode using SPM3Pd catalyst to synthesise 3-phenylpyridine

CATALYST, SOLVENT AND BASE SELECTION

Initial testing indicated palladium acetate 3-mercaptopropyl ethyl sulfide *Silica*1 SPM3Pd as the preferred catalyst under the flow conditions outlined, providing the additional advantage over homogeneous conditions of a phosphine-free system for the Suzuki coupling reactions.

It was found that the selection of the solvent system was critical to the success of the flow chemistry process and a combination of ethanol/water/DME was chosen for use in this study. Whilst it would have potentially increased the range of reaction substrates which could be employed in terms of solubility, the use of DMF as a solvent was avoided for both toxicity and product work-up considerations.

The potassium carbonate base used in slurry mode (**Figure 1**) was replaced by *N,N'*-diisopropylethylamine in the flow reactor. Although DIPEA is generally less effective than K2CO3 for Suzuki reactions in batch mode, its use in the continuous flow reactor work described ensured reaction components and products remained in solution throughout the process, avoiding blockages in the reactor and minimising reactor downtime.

It should however be noted that whilst 3-phenylpyridine, as shown in **Figure 2**, was formed with 99% conversion in slurry batch mode using the SPM3Pd catalyst when employing K2CO3 as base in xylene at 110ºC over 2 hours, under analogous batch slurry conditions, using DIPEA as base, in toluene at 110ºC, 3-phenylpyridine was formed in 60% conversion after 3 hours.

PURITY

A typical LCMS trace for the crude reaction product formed under flow conditions is shown in **Figure 9** The 3-phenylpyridine product of the flow synthesis was generally as clean as the corresponding sample prepared similarly under batch conditions.

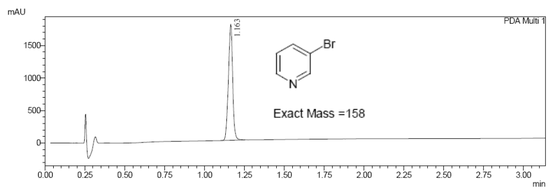


Figure 10. a) HPLC chromatograph ($UV_{215\ nm}$) of the 3- bromopyridine starting material

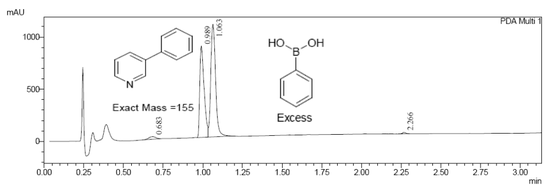


Figure 10. b) HPLC chromatograph ($UV_{215\ nm}$) of 3-phenylpyridine crude reaction product

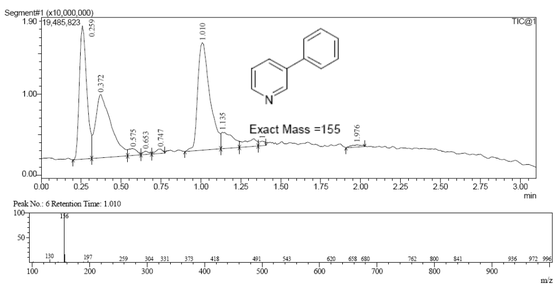


Figure 10.

SPE PURIFICATION OF THE SUZUKI REACTION PRODUCTS

Arylpyridines formed by Suzuki reactions are typically isolated by aqueous work-up procedures followed by often tedious chromatography in order to remove any accompanying pyridyl starting materials. With such basic reaction products, an alternative is the use of solid phase extraction (SPE).[5] Ethyl/butyl phosphonic acid Silica POH1d has been used for 'catch and release' cation exchange purifications for the separation of basic reaction components such as 2º and 3º amines and saturated and unsaturated nitrogen heterocycles.[6] A cartridge filled with 3 g of POH1d was used to separate 3-phenylpyridine from excess starting materials and their salts. The desired 3-phenylpyridine product was retained by POH1d and eluted cleanly with a solution of 5% v/v pyridine in methanol, being isolated in an unoptimised yield of 70% and in 95% purity

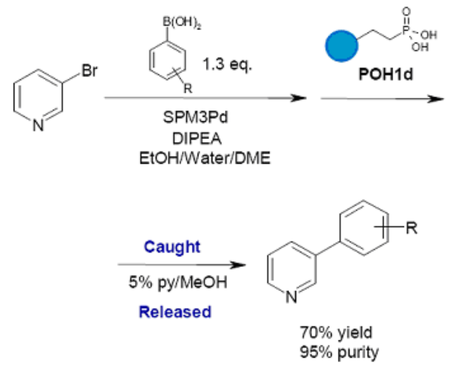
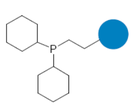


Figure 11. 'Catch and release' SPE purification of 3-phenylpyridine using POH1d

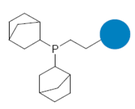
AVAILABLE CATALYSTS

The range of heterogeneous palladium catalysts currently available from PhosphonicS™ is shown in the table in Fig 12

Additional specialised phosphine ligands found to demonstrate enhanced performance in cross-coupling reactions have also been immobilised onto silica. (below). Both of these phosphines and their palladium complexes are also available from PhosphonicS™.



Dicyclohexylphosphine ethyl Silica (DCP)



Dinorbornylphosphine ethyl Silica (NP)

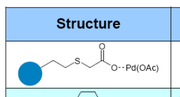
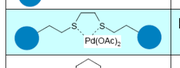
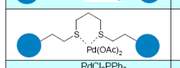
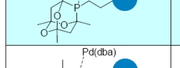
Structure	Product Name	Product Code
	Palladium acetate ethanoate ethyl sulfide *Silica*[2]	SCRPd
	Palladium acetate 2-mercaptoethyl ethyl sulfide *Silica*[1]	SEM2Pd
	Palladium acetate 3-mercaptopropyl ethyl sulfide *Silica*[1]	SPM3Pd
	Triphenylphosphine palladium dichloride phosphaadamantane ethyl *Silica*[3]	PAPd1r
	Dibenzylideneacetone palladium(0) phosphaadamantane ethyl *Silica*[3]	PAPd2r

Fig 12. Range of Palladium Catalysts from PhosphonicS

REFERENCES

[1] Al-Hashimi, M.; Qazi, A.; Sullivan, A. C. Wilson, J. R. H. J. Mol. Catal. A: Chem., 2007, 278, 160.

[2] Al-Hashimi, M.; Sullivan, A. C.; Wilson, J. R. H. J. Mol. Catal. A: Chem., 2007, 273, 298.

[3] Guino, M.; Sullivan, A. C.; Wilson, J. R. H. J. Mol. Catal. A: Chem., 2008, 293, 25

[4] Barder, T. E.; Buchwald, S. L. Org. Lett. 2004, 6, 2649-2652.

[5] Cork, D.; Hird, N. Drug Discovery Today 2002, 7, 56.

[6] Brown, J.; Chighine, A.; Colucci, M. A.; Galaffu, N.; Hirst, S. C.; Seymour, H. M.; Shiers, J. J.; Wilkes, R. D.; Williams, J. G.; Wilson, J. R. H. Tetrahedron Lett. 2008, 49, 4968.

EXPERIMENTAL SETUP

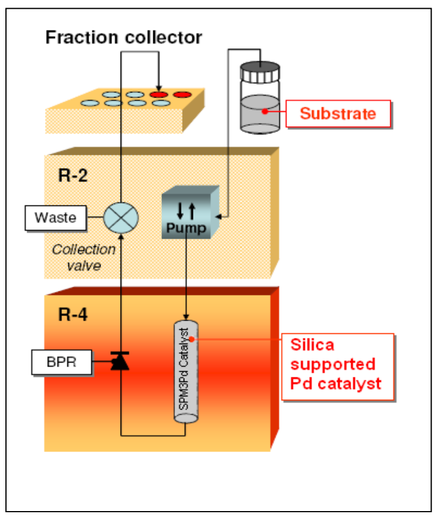


Fig 3 Flow System Setup

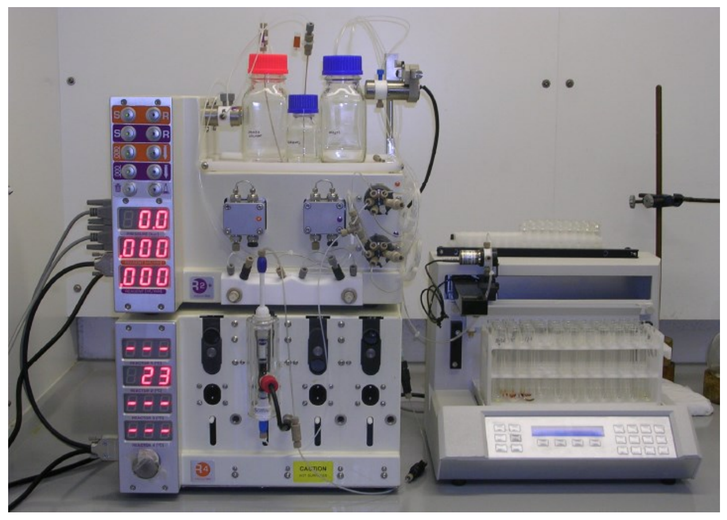


Fig 4 Vapourtec R Series System with fraction collector

The flow reactor was configured as shown in Figure 3. A single flow channel was used to deliver either the system solvent or the reaction mixture via a selection valve directly to the reactor column. The outflow from the valve was connected to a 10 cm × 6.6 mm id glass Omnifit reactor column containing SPM3Pd catalyst (~0.7 g; Pd loading 0.2 mmol/g). Due to the intrinsic properties of functionalised silicas, glass Omnifit reactor columns could be easily and efficiently packed with PhosphonicS™ palladium catalysts. The reactor was connected to a fraction collector. A 100 psi and 40 psi Back Pressure Regulator (BPR) were connected in-line between the Omnifit column reactor and the fraction collector. Fractions were collected in 4 ml sample vials. The solvent bottle was filled with ethanol/water/DME (2:1:2). The reagent stock bottle was filled with a pre-mixed solution of the aryl boronic acid (0.65 M), aryl bromide (0.5 M), DIPEA (1.0 M) and the system solvent.

The experiment was controlled using the Vapourtec Flow Commander software. The system was programmed to collect 0.5 mL "steady state" fractions for each experiment (meaning that the software automatically calculated how much product to discard due to dispersion at the leading and trailing ends of the reaction, and controlled the fraction collector and all other valves to collect exactly 0.5 mL of clean product).

The fractions were individually analysed by LCMS

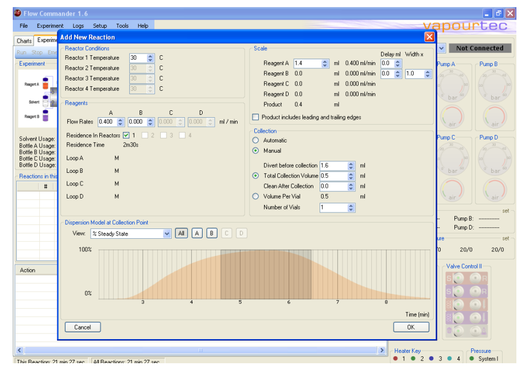


Fig 5 Setup and control of reaction parameters using Vapourtec Flow Command™ software

OPTIMAL RESIDENCE TIME

The reaction was carried out in the reactor at different flow rates to investigate the effect of the residence time of the reagents with the SPM3Pd catalyst upon substrate conversion (**Figure 6**). Using a concentration of 0.5 M of 3-bromopyridine, it was found that 3-phenylpyridine was formed in 52% conversion within 1 min. of residence time. This indicates that the residence time at this flow was too short for complete reaction. Decreasing the flow rate slightly led to better conversions and complete conversion was observed when 2.5 minutes residence time (Flow Rate = 0.400 mL/min.) was employed.

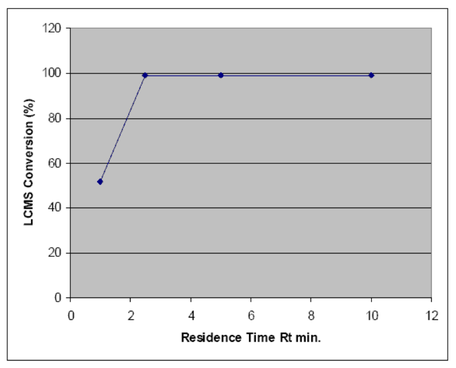


Fig 6. (Right) Conversion dependence on residence time in the Suzuki reactionbetween 3-bromopyridine (0.5 M) and phenylboronic acid (0.65 M) at 150 °C

OPTIMAL CONCENTRATION

Different concentrations of the 3-bromopyridine substrate were tested, ranging from 0.5 M to 2.5 M, at 2.5 minutes residence time. In all cases 99% conversion was observed. The catalyst was also highly active using a 5 M solution of the 3-bromopyridine, affording the product with 84% conversion, **Figure 7**, suggesting that at this higher concentration a slightly longer residence time may be required for complete conversion.

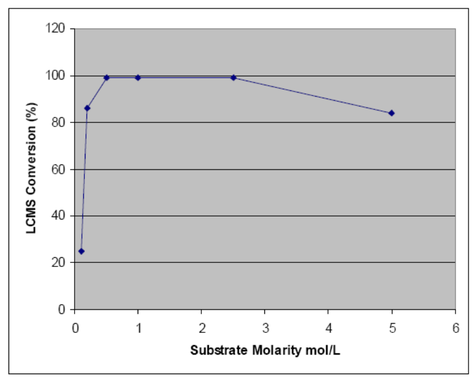


Fig 7. (right) Conversion dependence on substrate concentration in Suzuki reaction between 3- Bromopyridine phenylboronic acid at 150 °C and with R_t 2.5 mins

(Flow Rate = 0.400 mL/min.)

CATALYST CAPACITY

In this study, the reactor using the heterogeneous palladium catalyst SPM3Pd was run continuously with a constant temperature of 130 °C, collecting consecutive fractions of 5.7 mL of steady-state product. Two different R_ts were investigated, corresponding to flow rates of 0.100 mL/min. and 0.400 mL/min. Product samples were analysed by LCMS. The results of this study are shown in **Figure 8**.

At a flow rate of 0.400 mL/min (R_t = 2.5 mins) the reaction progressed relatively constantly for 2 hours, however the product was formed only in an average conversion of ~60%. At a flow rate of 0.100 mL/min (R_t = 10.0 mins), the reaction also progressed constantly over the 7.4 hours, in this case the single 0.7 g catalyst column retaining activity for > 94% conversion for 40 mL of 0.5 M solution of the substrate (equating to 18.8 mmol or 2.92 g of product, produced at a rate of ~ 0.4 g/h). To fine-tune the deliverable from this reaction, an optimisation study, in which the effect of variation of both residence time and reaction temperature upon conversion and throughput is assessed further, is ongoing.

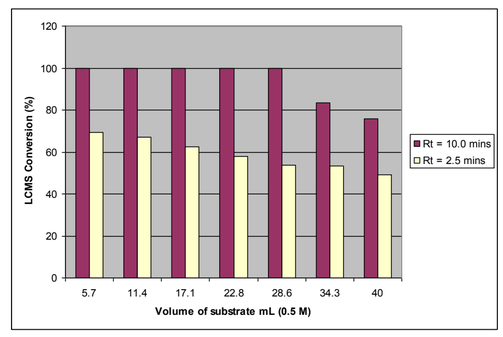


Figure 8. Study of conversion dependence on continuous Suzuki Reaction of 3-bromopyridine with phenylboronic acid at 130 °C with R_t 10.0 mins and R_t 2.5 mins

VARYING THE BORONIC ACID:

A small set of 3-substituted pyridines (**Fig 8**) were synthesised using 0.5 M solution of 3-bromopyridine, a slight excess of the boronic acid component, which was varied for this array, and DIPEA as base at 150 °C. The residence time employed was 2.5 minutes (Flow Rate = 0.400 mL/min.) and the reactions were performed on 0.25 mmol scale. In all cases, no homocoupled products were observed.

VARYING THE ARYL/HETEROARYL HALIDE

This aspect of the study has only been investigated briefly to date. 2-Bromothiophene(at 0.1M concentration) was employed in place of 3-bromopyridine in one instance, and in this case an unoptimised reaction in ethanol/water (1 : 1) at 130 °C and with an extended residence time of 20 minutes gave the resultant product with 96% conversion, as shown in Fig 9, Entry 5. Lower conversions were noted in the ethanol/water/DME solvent system successfully employed for substituted pyridine synthesis. The use of aryl halides will probably require a change in solvent system to that employed for the bromopyridine to ensure complete solubility of all the reaction components.

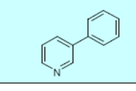
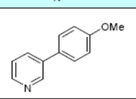
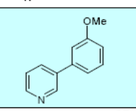
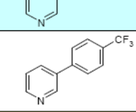
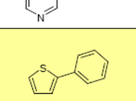
Entry	Suzuki Product	Conversion % by HPLC ($UV_{215\ nm}$)
1		> 99
2		> 99
3		> 99
4		60
5*		96

Fig 9. Suzuki reaction products from 3-bromopyridine and boronic acids under flow conditions with SPM3Pd catalyst