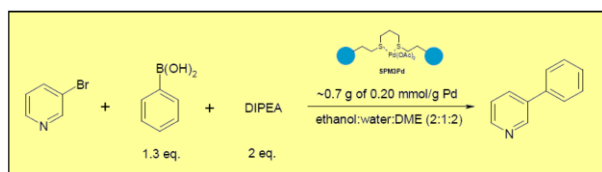


Application Note 13: Supported Palladium Suzuki

Produced by Vapourtec

Abstract

This example illustrates use of a heterogeneous catalyst to perform a Suzuki coupling with high conversion and short residence times.



For more details, please contact:

Vapourtec Application Support

application.support@vapourtec.com or call:

+44 (0) 1284 728659

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 optimization of residence time and concentration and investigates useful working life of the catalyst.

Setup:

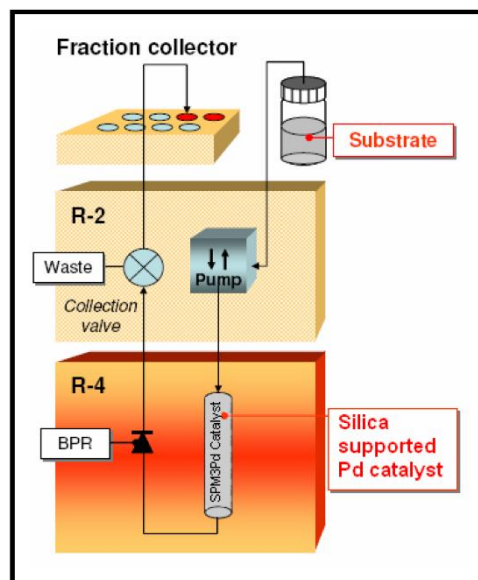
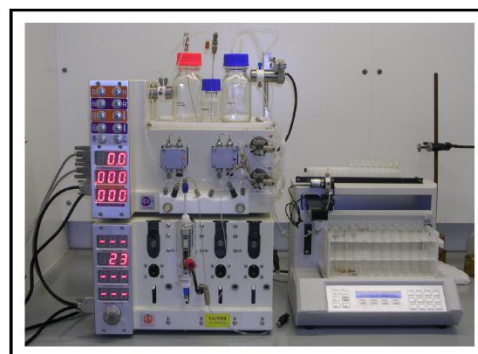


Figure 1. Representative flow reactor setup for Suzuki Coupling

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. Functionalized 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 immobilized heterogeneous palladium catalysts (**Appendix A**) that have been successfully utilized in cross-coupling reactions including Suzuki and Heck reactions under batch slurry conditions.¹⁻³ The catalysts feature either immobilized 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.

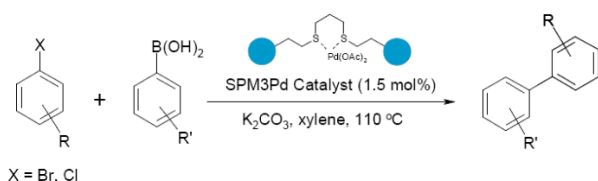


Figure 2. Suzuki coupling in slurry batch mode using SPM3Pd catalyst

Due to the successful performance of these heterogeneous catalysts under traditional slurry reaction conditions and the potential benefits offered, PhosphonicS™ in collaboration with Vapourtec has now 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.

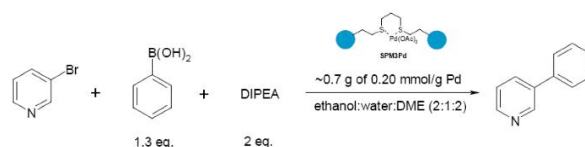


Figure 3. Suzuki coupling in flow mode using SPM3Pd catalyst to synthesize 3-phenylpyridine

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 2**) was replaced by *N,N'*-diisopropylethylamine in the flow reactor. Although DIPEA is generally less effective than K_2CO_3 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 3**, was formed with 99% conversion in slurry batch mode using the SPM3Pd catalyst when employing K_2CO_3 as base in xylene at 110 °C over 2 hours, under analogous batch slurry conditions, using DIPEA as base, in toluene at 110 °C, 3-phenylpyridine was formed in 60% conversion after 3 hours.

Setup:

The flow reactor was configured as shown in **Figure 1**. 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 functionalized 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 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 analyzed by LCMS.

Method:

Key parameters considered to be highly important for performing chemistry under flow chemistry conditions were optimized in turn. In general, heterogeneous palladium-catalyzed flow processes reported in the literature have tended to suffer from requirements for relatively long residence times to effect high conversion to coupling products; reduced throughput due to the need to use dilute solutions of the substrates to prevent solubility issues (molarities of just 0.1 M have been employed with other catalysts) and capacities of the catalysts themselves.

(a). Determining 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 4**). 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.

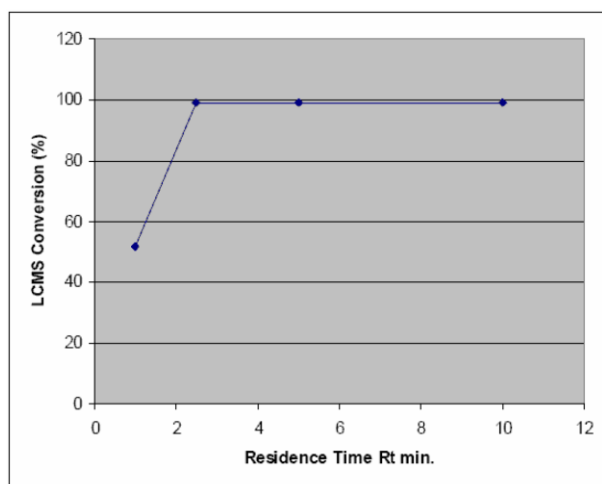


Figure 4. Conversion dependence on residence time in the Suzuki reaction between 3-bromopyridine (0.5 M) and phenylboronic acid (0.65 M) at 150 °C

(b). 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 5**, suggesting that at this higher concentration a slightly longer residence time may be required for complete conversion.

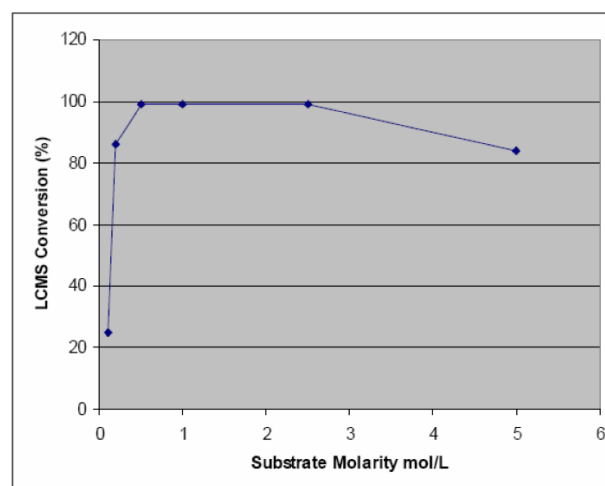


Figure 5. Conversion dependence on substrate concentration in Suzuki reaction between 3-bromopyridine phenylboronic acid at 150 °C and with R_t 2.5 mins (Flow Rate = 0.400 mL/min.)

(c). Catalyst Capacity

i) Continuous Reaction

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_s were investigated, corresponding to flow rates of 0.100 mL/min. and 0.400 mL/min. Product samples were analyzed by LCMS. The results of this study are shown in **Figure 6**.

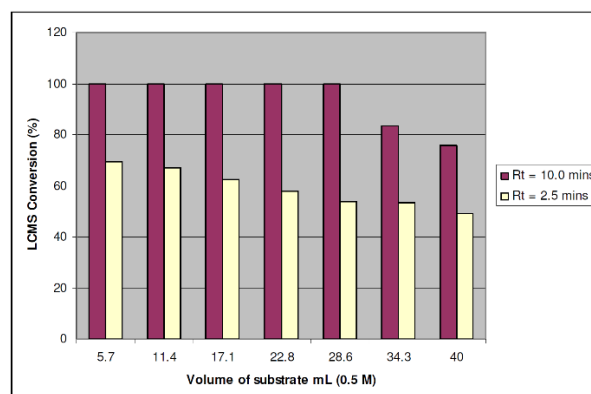


Figure 6. Study of conversion dependence on continuous Suzuki Reaction of 3-bromopyridine with phenylboronic acid at 130 °C with R_t 10.0 mins and R_t 2.5 mins

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 optimization study, in which the effect of variation of both residence time and reaction temperature upon conversion and throughput is assessed further, is ongoing.

ii). Column size

Note that in the study shown above, the column size was small, 6.6 x 75 mm. By substituting a 15 mm x 150 mm column, it would be possible to use 10x the volume of catalyst, thereby increasing the throughput and the overall capacity accordingly. This would allow almost 30 g of product to be synthesized in a single continuous run, at a rate of 4 g per hour.

iii) Discrete reactions with intermediate washing

A further study was also performed in which a fixed volume of the substrate mixture was introduced to the catalyst column in a start-stop manner, with an intermediate wash stage between cycles. Very high conversion was observed over many cycles. This study suggests the catalyst would also be highly-appropriate for the synthesis of small arrays of cross-coupling-derived compounds under flow conditions.

d). Purity

A typical LCMS trace for the crude reaction product formed under flow conditions is shown in

Figure 7. The 3-phenylpyridine product of the flow synthesis was generally as clean as the corresponding sample prepared similarly under batch conditions.

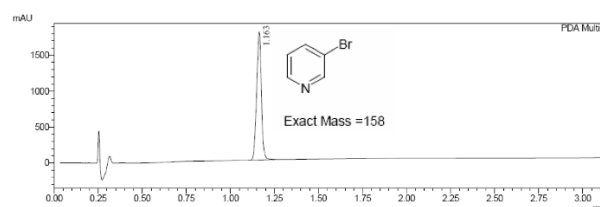


Fig 7 a) HPLC chromatograph (UV₂₁₅ nm) of the 3-bromopyridine starting material

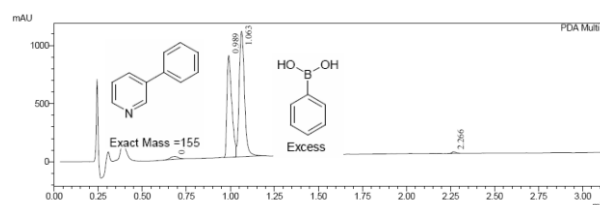


Fig 7 b) HPLC chromatograph (UV₂₁₅ nm) of 3-phenylpyridine crude reaction product

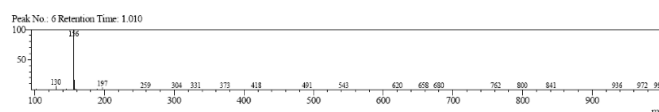
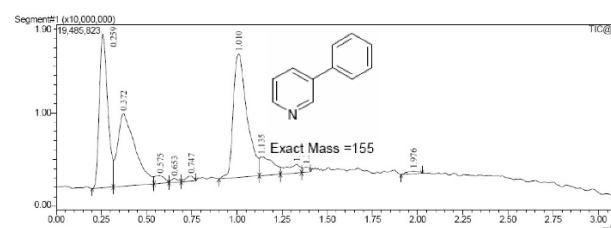


Fig 7 c) MS chromatograph of the crude mixture from flow synthesis at 150 °C, R_t 2.5 mins

e). Varying the Boronic Acid: Array of 3-Substituted Pyridines

A small set of substituted pyridines (**Table 1**) were synthesized 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.

f). 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 unoptimized 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 Table 1, Entry 5. For this reaction, lower conversions were noted in the ethanol/water/DME solvent system successfully employed for substituted pyridine synthesis. As might be expected, 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.

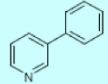
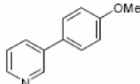
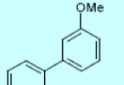
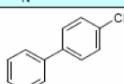
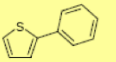
Entry	Suzuki Product	Conversion % by HPLC (UV _{215 nm})
1		> 99
2		> 99
3		> 99
4		60
5*		96

Table 1. Suzuki reaction products from 3-bromopyridine and boronic acids under flow conditions with SPM3Pd catalyst

g). 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 2° and 3° 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 unoptimized yield of 70% and in 95% purity.

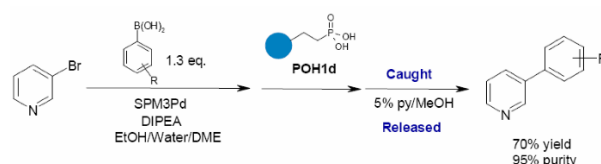


Figure 8. 'Catch and release' SPE purification of 3-phenylpyridine using POH1d

Catalysts – further information:

Palladium Content of Reaction Products

Under the relatively harsh reaction conditions employed in the flow reactor, the potential for Pd loss from the catalyst is increased, especially as residence times are shortened and temperatures increased to increase throughput. Under slurry conditions, Pd leaching from the catalyst has not been observed, as indicated by both hot filtration tests and ICP measurements.

Under flow conditions initial analysis indicates some palladium contamination of the reaction products and there may be a relationship between any metal content of the products and the higher temperatures employed in flow. Further investigation of this is ongoing. In order to ensure Suzuki reaction products are delivered with very low Pd content, a cartridge of a PhosphonicS™ palladium scavenger such as SPM32 or SPM36f should be employed in series with the reactor cartridge.

Heterogeneous Palladium Catalyst and Metal Scavenger Properties

The SPM3Pd catalyst employed in this study has particle size 60-200 microns and pore size 60 Å. Particle size and pore diameter are important parameters of functionalized silicas, both as catalysts and metal scavengers, that can be easily varied in order to optimize particular processes and applications. Optimization of these important material parameters in flow environments is ongoing.

Summary:

This study demonstrates the effective use of a cartridge of PhosphonicS™ heterogeneous palladium catalyst SPM3Pd in the Vapourtec R2+/R4 flow reactor system for Suzuki coupling reactions. Potential throughput capacity for the system developed is high, as under challenging constraints of short column residence times, high temperatures and high substrate concentrations, conversions to product remained very high and the catalyst can also be subjected to multiple cycles without any noticeable loss in activity. For the examples investigated no precipitation problems were noted.

Acknowledgements:

Vapourtec would like to thank PhosphonicS™ for contributing this application note.

References and Notes:

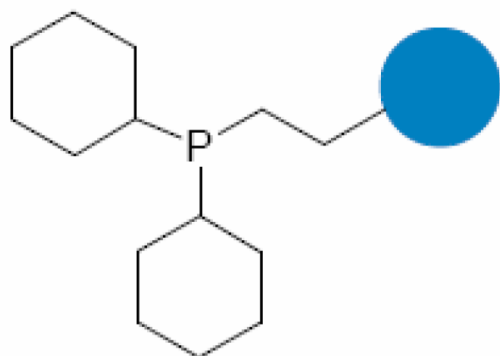
- ¹ Al-Hashimi, M.; Qazi, A.; Sullivan, A. C. Wilson, J. R. *H. J. Mol. Catal. A: Chem.* **2007**, 278, 160.
- ² Al-Hashimi, M.; Sullivan, A. C.; Wilson, J. R. H. J. *Mol. Catal. A: Chem.* **2007**, 273, 298.
- ³ Guino, M.; Sullivan, A. C.; Wilson, J. R. H. *J. Mol. Catal. A: Chem.* **2008**, in press.
- 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, in press.

Appendix A:

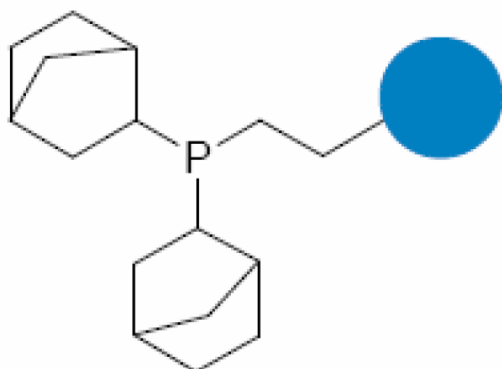
The range of heterogeneous palladium catalysts currently available from PhosphonicS™ is shown below:-

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 phosphadamantane ethyl Silica ³	PAPd1r
	Dibenzylideneacetone palladium(0) phosphadamantane ethyl Silica ³	PAPd2r

Additional specialized phosphine ligands found to demonstrate enhanced performance in crosscoupling reactions have also been immobilized onto silica. Both of these phosphines and their palladium complexes are also available from PhosphonicS™.



Dicyclohexylphosphine ethyl Silica (DCP)



Dinorbornylphosphine ethyl Silica (NP)