

Application Note 49: Suzuki Coupling with SiliaCat DPP-Pd Heterogeneous Catalyst

Produced by Vapourtec

Abstract

This report describes a Suzuki coupling with:

- Short residence time of 1 minute, 15 seconds
- With > 95% conversion
- High reaction yield

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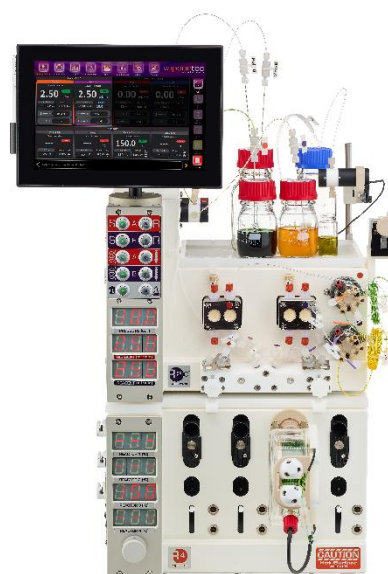
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Background

The Suzuki-Miyaura palladium coupling is used in a wide range of syntheses of biaryl and heterobiaryl products throughout the pharmaceutical and fine chemical industries. Typically, in batch, the Suzuki coupling cannot be performed above the boiling point of the reaction solvent, which can result in long reaction times, however flow chemistry permits higher operating pressures with greatly improved safety, allowing higher reaction temperatures, and faster reaction times.



Catalyst stability is an important consideration when performing heterogeneous reactions at higher temperature, which led to the selection of the SiliCycle SiliaCat DPP-Pd heterogeneous catalyst; a commercially available sol-gel entrapped catalyst. The SiliaCat DPP-Pd is ideal for continuous flow Suzuki couplings, with good thermal stability (max. temperature 125 °C), air-stable and significantly, not susceptible to swelling in the presence of organic solvents.

Setup

Reactions were performed using a Vapourtec R-series R4 and R2C, equipped with a 2 ml Vapourtec standard reactor and a 10 cm, 6.6 mm inner diameter Omnifit glass column, Figure 1. Reagent bottle A contained a 0.395 M solution of 3-bromopyridine in THF, and bottle B held a 0.19 M solution of phenylboronic acid and 0.23 M potassium carbonate in H₂O/EtOH (2.2:1). A system solvent of H₂O/EtOH/THF (1.14:1:1 v/v) was prepared. The Vapourtec standard reactor was included to pre-heat the reaction mixture before it reached the catalyst, and to ensure good mixing prior to reaction. Insulating foam was wrapped along the pre-heater outlet to the column inlet to prevent

excess cooling of the reagent stream. The catalyst (SiliCycle SiliaCat DPP-Pd, 1.1 g 0.25 mmol/g Pd loading) was packed within the Omnifit column. The column outflow was directed through an 8 bar BPR (back pressure regulator). Significantly, this allowed the reaction to be performed above the boiling point of each solvent, and increased reaction throughput. The system was controlled using the Vapourtec flow control software.

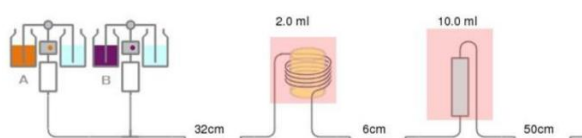


Figure 1: The setup of the Vapourtec R-Series during the Suzuki coupling using the SiliaCat DPP-Pd supported catalyst.

Synthesis of 3-Phenyl Pyridine

It has been demonstrated that SiliaCat DPP-Pd can be used for Suzuki coupling in continuous flow by Pandarus et al.¹ To demonstrate the capability of the Vapourtec system for this coupling, similar conditions were chosen to those examined by Pandarus. A brief investigation demonstrated that at 100 °C it was possible to get comparable results to those obtained by Pandarus but at a much-reduced residence time, Table 1.

Temperature / °C	Residence Time / min	Starting Material % ^a	Product % ^a
70	2.85	1.8	82.9
70	5.00	0.2	93.3
100	1.00	3.2	88.7
100	1.25	3.6	85.7
100	1.50	3.2	89.6

Table 1: Effect of temperature on residence time on conversion of starting material. It is clear that at a higher reaction temperature, it is possible to operate with a shorter residence time.^a percentage area composition of HPLC at 250 nm

A reaction temperature of 100 °C is above the boiling point of the system solvent mixture, however using flow apparatus allows for easy operation at pressure, allowing a higher temperature to be reached. To minimize cooling of the catalyst, a 2 ml Vapourtec standard tube reactor was installed prior to the catalyst, and the connect tubing insulated, resulting in a higher conversion of the product, Table 2.

Temperature / °C	Residence Time / min	Starting Material % ^b	Product % ^b
100	1.00	0.00	87.4
100	1.25	0.38	90.6
100	1.50	0.00	86.2

Table 2: Effect of pre heating the reaction mixture prior to contact with the catalyst. It can be seen that the conversion of starting material is higher than when not pre heated as in Table 1.^b percentage area composition of HPLC at 250 nm

Method

The column reactor and pre-heating reactor were set to the reaction temperature, 100 °C. The experiment was programmed using flow control software, which controlled the flow rates of the two reagent solutions according to the desired stoichiometry, 1:1.25 3-bromopyridine:phenylboronic acid. The potassium carbonate was consistently in excess. The residence time was maintained at 1 min, 15

seconds and the flow rates were calculated by flow control software accordingly. Samples were collected using the sample collection valve once the reactor had reached steady state, as determined by the flow control software distribution modelling calculations. The system was programmed to collect 2 g of product, determined by theoretical yield calculations. The synthesis was monitored using offline HPLC samples taken every 10 minutes, Figure 2, to ensure conversion and yield remained high.

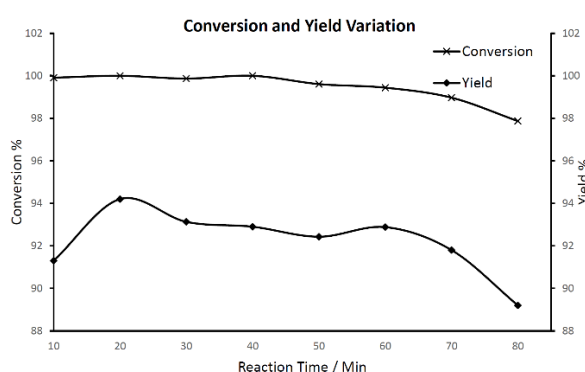


Figure 2: Offline HPLC analysis at 10 min intervals during a 2 g flow synthesis of 3-phenylpyridine. It is clear that conversion and yield remained high throughout the duration of the reaction. Data shown are percentage area by HPLC integration.

Separation and Purification

The product was extracted from the aqueous reaction solvent using three washes of diethyl ether, which was then removed by vacuum. The remaining oil was dissolved in a small volume of ethyl acetate, and purified using dry-column flash chromatography (heptane/ethyl acetate). The product was isolated by this method to a crude yield of 81%, and purity of > 95% was achievable.

Analysis

Analysis was performed during the reaction using offline HPLC and TLC to determine catalyst activity and product conversion. HPLC analysis, Figure 3, of the 1 g synthesis product shows minimal impurity following simple chromatographic purification. This was confirmed via proton NMR, Figure 4.

Suzuki Coupling HPLC

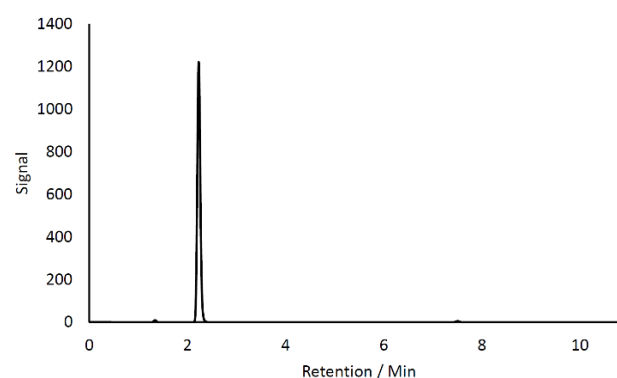


Figure 3: HPLC of the reaction mixture at 250 nm following chromatographic purification. The peaks are assigned as follows: 1.3 min – phenylboronic acid; 2.2 min – 3-phenylpyridine; 7.5 min – unknown.

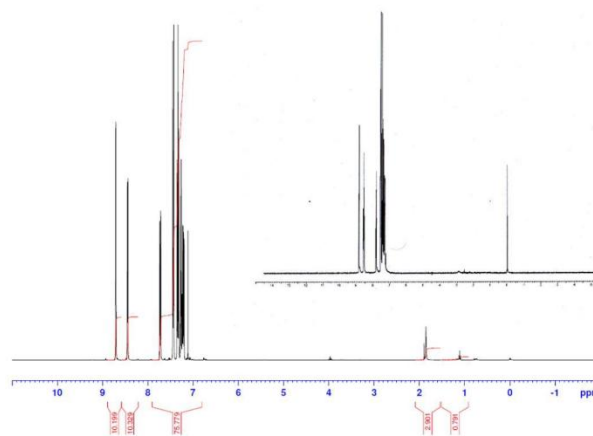


Figure 4: ^1H NMR (CDCl_3 , 400 MHz) of purified reaction product, 3-phenylpyridine. Inset, ^1H NMR (CDCl_3 , 300 MHz) of 3-phenylpyridine obtained from the Sigma-Aldrich spectral database via Scifinder@.

References

1. V. Pandarus, G. Gingras, F. Béland, R. Ciriminna, and M. Pagliaro *Organic Process Research & Development* **2014** *18* (11), 1550-1555