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# The continuous synthesis and application of graphene supported palladium nanoparticles: a highly effective catalyst for Suzuki-Miyaura cross-coupling reactions

DOI 10.1515/gps-2015-0021

Received March 18, 2015; accepted April 30, 2015

**Abstract:** An efficient, sustainable, and continuous method for the preparation of graphene supported palladium nanoparticles (Pd/G) has been developed using microwave irradiation as a heating source for the metal deposition process. The Pd/G produced from this method was effective in Suzuki-Miyaura cross-coupling reactions with a broad range of substrates. When incorporated into a packed bed flow reactor, this ligand free catalyst system continued to demonstrate high reaction conversions with limited catalyst leaching in the reaction mixture (347 ppb palladium).

**Keywords:** flow chemistry; graphene; palladium; solid supported catalysis; Suzuki-Miyaura cross-coupling.

## 1 Introduction

Continuous processing represents a significant element of process intensification by which chemical operations can be carried out in smaller equipment with improved product quality and reduced waste generation [1–4]. One of the most important attributes of continuous processing is in the ability to precisely control critical process parameters

once steady state conditions have been achieved. This approach can dramatically reduce variations in yield and product quality that are normally observed in batch operations. In 2011, continuous processing topped the list of green engineering research priorities set forth by the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable [5] and continues to gain traction in both industrial and academic laboratories [6–8].

One clear opportunity offered by continuous processing lies in the application of solid supported catalysis, whereby reactants can be passed through a cartridge or packed bed filled with an immobilized catalyst [9–12]. The product is collected downstream, often with limited additional work up, providing substantial benefits in terms of product isolation. Furthermore, this approach allows chemists to leverage reaction stoichiometry in a way that would be impractical with analogous batch processes. Solid supported catalysts tend to be easily recovered and recycled, thus providing a more sustainable and cost effective manufacturing platform.

Recently we reported the remarkable catalytic activity of palladium (Pd) nanoparticles supported on graphene (Pd/G) that were prepared by the microwave-assisted reduction of palladium nitrate and dispersed graphite oxide (GO) sheets under batch reaction conditions [13]. This Pd/G demonstrated excellent catalytic activity for cross-coupling reactions with a broad range of utility under ligand-free ambient conditions. Based on the high catalytic activity and low Pd leaching observed with this catalyst system, we hypothesized that the Pd/G may be a good candidate for continuous operations. However, the ability to provide sufficient quantities of Pd/G catalyst for continuous experimentation proved to be problematic due to the low throughput from the batch process and lot to lot variability in catalytic activity.

Aiming to exploit the intrinsic reproducibility and high throughput of a flow regime, we examined a continuous approach for the preparation of Pd/G. Although a

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limited number of examples exist for flow-based syntheses of metal nanoparticles [14–17], the ability to continuously prepare solid supported Pd catalysts is unprecedented in the literature to the best of our knowledge. We now report a reproducible and scalable continuous method for the preparation of Pd/G and the application of this ligand-free catalyst system to Suzuki-Miyaura cross-coupling reactions under both batch and continuous flow conditions.

## 2 Materials and methods

### 2.1 Reagents

Graphite powder (99.999%, 200 mesh) was purchased from Alfa Aesar (Ward Hill, MA, USA). Palladium nitrate (10 wt% in 10 wt% HNO<sub>3</sub>, 99.99%) and hydrazine hydrate were obtained from Sigma Aldrich. Aryl bromides, aryl substituted boronic acids, potassium carbonate, and all other chemicals were also obtained from Sigma Aldrich (St. Louis, MO, USA) and used as received.

### 2.2 Synthesis of graphite oxide

Graphite oxide (GO) was synthesized using Hummer's method [18]. For this procedure, concentrated sulfuric acid (115 ml) was cooled in an ice bath, and ground sodium nitrate (2.5 g) was added to the acid. Graphite powder (4.5 g) and potassium permanganate (15 g) were added to the solution. The temperature was increased to 35°C and held constant for 3 h. Deionized water was then added in two portions (230 ml followed by 700 ml). Finally hydrogen peroxide (20 ml of a 10% solution) was added to the reaction. The reaction mixture was filtered and washed several times with warm deionized water. The resulting powder was dried in an oven at 70°C.

### 2.3 Preparation of Pd/G catalyst

To prepare the graphene supported palladium catalyst (Pd/G), graphite oxide (0.09 g) was sonicated in deionized water (200 ml) until a homogeneous suspension was obtained. Palladium nitrate (194 µl, 0.094 mmol) was then added, and the resulting solution was stirred for 1 h. In a separate vessel, hydrazine hydrate (0.2 M in deionized water) was prepared and agitated with a magnetic stirrer. Using a calibrated peristaltic pump, the two solutions were fed at equal rates into an ArrheniusOne Wavecraft continuous microwave reactor (Wavecraft AB, Uppsala, Sweden) operating at 80°C, with an overall flow rate of 4 ml/min (internal reactor volume=1.4 ml; residence time=0.35 min). The resulting solution was placed in a drying oven at 70°C for several hours to give a fine black powder.

### 2.4 Characterization of Pd/G catalyst

TEM images were obtained using a JEOL JEM-1230 electron microscope (JEOL USA, Inc, Peabody, MA, USA) operated at 120 kV. The microscope is equipped with Gatan UltraScan software and CCD

camera (4000SP 4 K×4 K). TEM samples were prepared by adding one droplet of suspended sample in methanol on a Formvar carbon-carbon, 300 mesh copper grid, obtained from Ted Pella (Redding, CA, USA), and allowed to evaporate in air at room temperature. X-ray photoelectron spectroscopy (XPS) was performed on a Thermo Fisher Scientific Inc (Waltham, MA, USA) ESCALAB 250 using a monochromatic Al KR X-ray. Dry samples were mounted to a sample holder using two way carbon tape and indium foil.

### 2.5 General procedure for traditional batch Suzuki-Miyaura reactions

Batch cross-coupling reactions were performed in a CEM Discover batch microwave reactor (CEM Corporation, Matthews, NC, USA) operating at a maximum output power of 250 W. For initial experiments, diversity studies, and lot-to-lot consistency tests, reactions were performed according to the same procedure, unless noted. A representative example is as follows: bromobenzene (**1a**, 43 mg, 0.27 mmol, 1 eq.) was dissolved in a 4 ml mixture of water and ethanol (H<sub>2</sub>O/EtOH) (1:1) and placed in a 10 ml microwave tube. Phenylboronic acid (**2a**, 40 mg, 0.33 mmol, 1.2 eq.) and potassium carbonate (113.5 mg, 0.82 mmol, 3 eq.) were added to the same tube. Pd/G catalyst (5 mg, 2 mol% based on Pd content) was then added, and the tube was sealed and heated under microwave irradiation (250 W, 2.45 MHz) at 80°C for 10 min. Reaction conversions were determined using an Agilent 6890 gas chromatograph (GC) equipped with an Agilent 5973 mass selective detector (Agilent Technologies, Santa Clara, CA, USA). All compounds were compared to authentic standards.

### 2.6 Procedure for the recycling of Pd/G catalyst in Suzuki-Miyaura reactions

Bromobenzene (**1a**, 50 mg, 0.32 mmol) and phenylboronic acid (**2a**, 47 mg, 0.384 mmol, 1.2 eq.) were dissolved in 4 ml of H<sub>2</sub>O:EtOH (1:1) and placed in a 10 ml microwave tube. To this were added potassium carbonate (133 mg, 0.96 mmol, 3 eq.) and Pd/G catalyst (3 mg, 3.2 µmol, 1 mol%). The tube was sealed and heated at 80°C for 10 min under microwave irradiation (250 W, 2.45 MHz), and the progress of the reaction was monitored by GC-MS analysis. Upon the completion of the reaction period, the mixture was diluted with 10 ml of ethanol and agitated to dissolve the biphenyl reaction product. The entire mixture was then centrifuged, and the solvent above the Pd/G catalyst was completely decanted. The washing and centrifugation were repeated two additional times to ensure the removal of organic products from the surface of the catalyst. The Pd/G catalyst was then reused for the subsequent reaction by adding fresh reagents to the tube. This procedure was applied for every recycling experiment and the percentage conversion to the products was determined by means of GC-MS spectroscopy.

### 2.7 Continuous flow Suzuki-Miyaura reaction procedure

4-Bromobenzaldehyde (**1b**, 625 mg, 3.37 mmol, 1 eq.) was dissolved in 100 ml of H<sub>2</sub>O/EtOH/tetrahydrofuran (THF) (1:1:1) and placed in a flask. Phenylboronic acid (**2b**, 494 mg, 4.05 mmol, 1.2 eq.) and

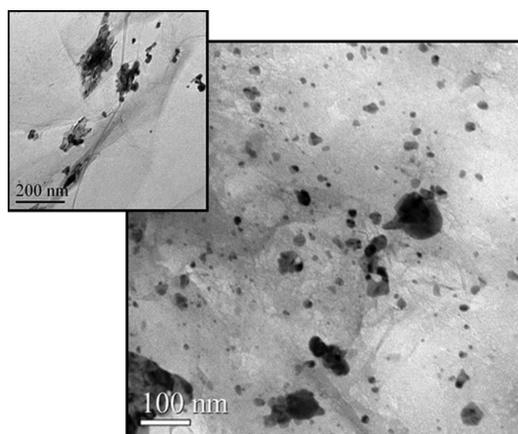
potassium carbonate (1.4 g, 10.1 mmol, 3 eq.) were added to the same flask. For the preparation of the catalyst cartridge, Pd/G (100 mg) was suspended in deionized water and loaded with a syringe into a stainless steel cartridge (70×4 mm) fitted with a porous metal frit and a 8  $\mu\text{m}$  membrane at one end. The catalyst bed was established by applying vacuum to the base of the cartridge to remove the water. The other end of the cartridge was then sealed with a 8  $\mu\text{m}$  membrane, and the entire unit was placed in the cartridge holder of a ThalesNano X-cube flow reactor (ThalesNano Nanotechnology Inc., Budapest, Hungary). Solvent was pumped through the apparatus and the temperature was changed to a set point of 135°C in 5°C increments to equilibrate the system. Once the desired temperature was reached, the reagent solution was fed into the X-cube at a flow rate of 0.2 ml/min. Samples were collected in 30 min increments and analyzed by GC-MS as described above.

## 3 Results and discussion

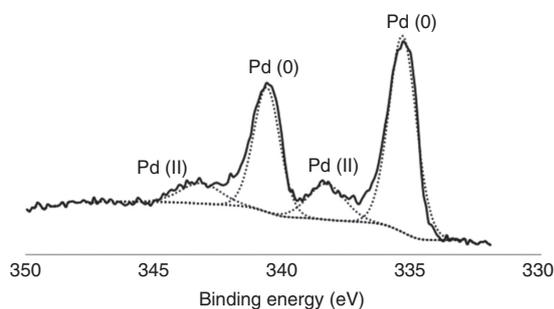
### 3.1 Preparation and characterization of Pd/G catalyst

Using an ArrheniusOne Wavcraft microwave flow reactor, Pd/G was prepared by the reductive deposition of Pd(II) nitrate onto graphite oxide. The resulting Pd/G exhibited a narrow particle size distribution with an average particle diameter of 9.37 nm (Figure 1). Some Pd agglomeration was observed, mainly along the edges and creases of the graphene sheets. This localization is likely due to an increased concentration of defect sites within these areas.

The continuous-flow microwave assisted synthesis of Pd/G produces a catalyst with a high concentration of



**Figure 1:** TEM images of Pd/G catalyst produced using a continuous microwave reactor. Inset shows creases along graphene sheets where Pd agglomerations tend to form.



**Figure 2:** XPS spectra of Pd/G catalyst. \_\_\_\_\_ Raw data; ..... Fitted spectra.

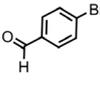
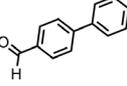
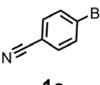
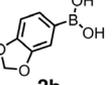
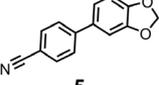
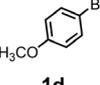
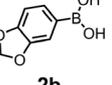
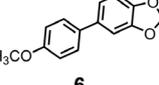
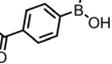
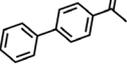
Pd(0), the active redox species required to initiate Pd-catalyzed cross-coupling reactions. Deconvolution of the XPS spectra (Figure 2) indicated a Pd(0) content of 80%, with the remaining 20% as Pd(II). Observed binding energies were 335 eV and 341 eV for Pd(0) and 339 eV and 344 eV for Pd(II).

Several discrete lots of Pd/G were generated and characterized to test the reproducibility of our synthetic approach. All samples exhibited similar size distribution of the Pd nanoparticles and the formation of agglomerations around the creases and edges of the graphene sheets. Moreover, all lots were consistent with respect to Pd(0) content, suggesting that a continuous microwave-assisted approach to the synthesis of Pd/G provides reliable access to this useful ligand-free catalyst system.

### 3.2 Catalytic activity of Pd/G in traditional “batch” Suzuki-Miyaura cross-coupling reactions

The catalytic activity of Pd/G prepared using our continuous synthesis method was initially evaluated for the Suzuki-Miyaura cross-coupling reaction between bromobenzene (**1a**) and phenylboronic acid (**2a**) in microwave-assisted batch reactions. The catalyst loading was varied between 0.5 mol% and 5 mol% to determine the optimum catalyst loading. Full conversion was observed by GC-MS at 1 mol% catalyst loading for this reaction; however, below this level a decrease in conversion was evident.

A variety of functionalized aryl bromides (**1**) and phenylboronic acids (**2**) were then used to evaluate catalyst versatility in Suzuki cross-coupling reactions (Figure 3). For these batch reactions, substrates were combined with Pd/G and potassium carbonate in a  $\text{H}_2\text{O}/\text{EtOH}$  solvent system and heated to 80°C for 10 min in a CEM microwave. The Pd/G catalyst exhibited good to excellent conversion

Entry	Aryl Halide	Boronic acid	Product	Percent conversion
1	 <b>1a</b>	 <b>2a</b>	 <b>3</b>	100
2	 <b>1b</b>	 <b>2a</b>	 <b>4</b>	100
3	 <b>1c</b>	 <b>2b</b>	 <b>5</b>	94
4	 <b>1d</b>	 <b>2b</b>	 <b>6</b>	95
5	 <b>1a</b>	 <b>2c</b>	 <b>7</b>	65

**Figure 3:** Suzuki-Miyaura reactions were completed under traditional batch conditions. Reactions were carried out by combining an aryl halide (0.27 mmol), a substituted boronic acid (0.32 mmol),  $K_2CO_3$  (0.9 mmol), and the Pd/G catalyst (2 mol%) in 4 ml of  $H_2O:EtOH$  (1:1) and irradiating in the microwave at  $80^\circ C$  for 10 min.

in Suzuki reactions with both electron-withdrawing and electron-donating functional groups.

We then tested eight separate lots of continuously-produced Pd/G with two Suzuki-Miyaura cross-coupling reactions in order to determine the lot-to-lot variability in catalytic activity (Table 1). We examined the reaction of two different aryl halide substrates (**1a** and **1b**) with phenylboronic acid (**2a**), and all eight catalyst lots gave essentially equivalent yields under standard reaction conditions. As with the reproducible physical characteristics of Pd/G described above, the lot-to-lot consistency

of catalytic activity may also be attributed to the uniform application of irradiation available from a continuous microwave reactor [19].

The recyclability of continuously produced Pd/G was then evaluated using the Suzuki-Miyaura reaction between bromobenzene and phenylboronic acid. Microwave-assisted batch reactions were set up as before, except that Pd/G catalyst loading was lowered to 1 mol%. After completion, the reaction mixtures were diluted to dissolve the precipitated Suzuki-Miyaura product, biphenyl (**3**). The solid-supported catalyst was then isolated by centrifugation, washed, and re-used in subsequent reactions with fresh substrates and reagents. High conversions were recorded for the first three rounds of reactions (Table 2; calculated turnover number: 372), indicating that Pd/G may be a good candidate for continuous applications.

**Table 1:** Lot-to-lot consistency of Pd/G activity in two Suzuki-Miyaura reactions.

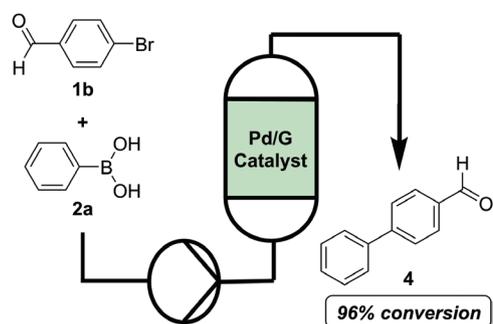
Pd/G	Conversion (%) <sup>a</sup> 1a+2a <sup>b</sup>	Conversion (%) <sup>a</sup> 1b+2a <sup>b</sup>
Lot 1	100	100
Lot 2	100	99
Lot 3	100	100
Lot 4	100	100
Lot 5	100	97
Lot 6	100	97
Lot 7	100	100
Lot 8	100	99

<sup>a</sup>Conversions determined by GC-MS. <sup>b</sup>Aryl halide (0.27 mmol), substituted boronic acid (0.32 mmol),  $K_2CO_3$  (0.9 mmol), and Pd/G catalyst (2 mol%) were combined in 4 ml of  $H_2O:EtOH$  (1:1) and irradiated at  $80^\circ C$  for 10 min.

**Table 2:** Recyclability of Pd/G in Suzuki-Miyaura reactions.

Run	Conversion (%) <sup>a</sup> 1a+2a <sup>b</sup>
1	100
2	100
3	95
4	77

<sup>a</sup>Conversions determined by GC-MS. <sup>b</sup>Reaction conditions as listed in Table 1, except that catalyst loading was lowered to 1 mol%.



**Figure 4:** Process flow diagram for a continuous Suzuki-Miyaura reaction.

### 3.3 Suzuki-Miyaura cross-coupling reactions executed under continuous flow conditions

With a reliable and scalable preparation of Pd/G in hand, we sought to highlight the combined benefits of solid supported catalysts and flow synthesis by applying our catalyst to a continuous Suzuki-Miyaura cross-coupling system. The reaction between 4-bromobenzaldehyde (**1b**) and phenylboronic acid (**2a**) provided the best solubility profile to demonstrate the application of our catalyst in flow (Figure 4). A small amount (100 mg) of the Pd/G catalyst synthesized under continuous flow conditions was loaded into a catalyst cartridge. The catalyst cartridge was then equilibrated to 135°C on a ThalesNano X-Cube flow reactor. Reactants were dissolved in a H<sub>2</sub>O/EtOH/THF (1:1:1) solvent mixture and fed into the packed bed at a flow rate of 0.2 ml/min, resulting in a contact time of <1 min, assuming that the catalyst remains packed as a uniform plug. If the catalyst bed were disrupted, contact times of up to 3.4 min could be possible based on the residence time of the reaction solution within the catalyst cartridge (0.682 ml interior volume). Using these conditions, the Suzuki reaction proceeded with a conversion of 96%. The product was collected in 30 min increments for 2 h without a reduction in product conversion.

One of the major concerns in translating the Pd/G catalyzed Suzuki-Miyaura reaction from batch to continuous operations is the potential for rapid catalyst deactivation due to metal leaching under non-equilibrium (continuous) conditions [20, 21]. Accordingly, the Pd content of the continuous Suzuki-Miyaura reaction product stream was evaluated using inductively coupled plasma mass spectrometry (ICP-MS). This solution contained only 347 ppb of Pd, suggesting that graphene is a reliable and robust support for Pd nanoparticles. Furthermore, the low Pd leaching provides some insight into the strong interaction between the nanoparticles and the graphene support system.

## 4 Conclusions

In conclusion, we have developed a highly efficient method for the preparation of Pd nanoparticles supported on graphene by exploiting a continuous microwave-assisted chemical reduction of an aqueous mixture of palladium nitrate and dispersed graphite oxide sheets. This process serves as a convenient and scalable method for accessing multi-gram quantities of this material. Furthermore, this procedure is capable of delivering a catalyst of consistent and reproducible physical and catalytic properties and serves as the first flow-based method for producing a solid supported Pd catalyst. We were also able to demonstrate that these catalysts can be employed in continuous Suzuki-Miyaura cross-coupling reactions under ligand-free conditions in an environmentally friendly solvent system with minimal catalyst leaching/deactivation over an extended period of time.

**Acknowledgments:** We gratefully acknowledge Dr. Dmitry Pestov and Dr. Carlos Castano Londono for their assistance in obtaining TEM and XPS measurements. We would also like to thank ThalesNano for their generous support in the form of flow reactors for this effort.

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## Bionotes



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Michael Burkholder obtained his undergraduate degree in Chemical Engineering and Chemistry at Virginia Commonwealth University in Richmond, VA, USA, in 2014. As an undergraduate, his research focused on the synthesis of metal nanoparticles and catalysts utilizing microwave technology. He is currently continuing research in catalysis at Virginia Commonwealth University in Richmond, VA, USA.



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