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Glucose-Derived Palladium(0) Nanoparticles as in Situ-Formed Catalysts for Suzuki–Miyaura Cross-Coupling Reactions in Isopropanol

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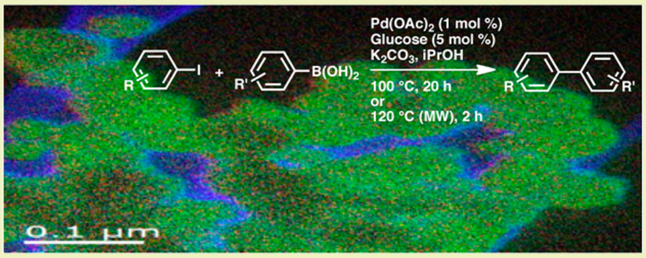
Supporting Information



ABSTRACT: Effective and convenient protocols using renewable sugar-derived palladium(0) nanoparticles (PdNPs) as in situ-formed catalysts for Suzuki–Miyaura cross-coupling reactions in isopropanol under thermal and microwave heating conditions have been developed. The addition of a small amount of glucose (5 mol %) to the reaction mixture lead to an increase in yield of the cross-coupled products compared to control experiments that omitted glucose. The size and morphology of the in situ-formed PdNPs were determined by TEM, and further EF-TEM analysis showed a hydrophilic hydroxylated shell around the individual palladium particles. The polar/hydrophilic nature of the nanoparticles allowed for their facile removal from the cross-coupled product, and a significant decrease in the amount of palladium incorporated into the final product was observed, as measured by ICP-MS analysis.

KEYWORDS: *Renewable sugars, Metal nanoparticles, Palladium catalysis, Alcoholic solvent, Energy-filtered transmission electron microscopy*

INTRODUCTION

Palladium-catalyzed cross-coupling transformations are some of the most widely utilized methods for the generation of C–C, C–N, and C–S bonds in both industry and academia.[1−3] A key palladium(0)-catalyzed transformation is the reaction between an arylhalide and a boronic acid, the Suzuki–Miyaura reaction.[4,5] Palladium catalysis is currently used in spite of the fact that in order to work effectively it can require toxic and expensive additives, which result in unnecessary waste, expense, and hazard to the environment. A variety of approaches have been developed to combat some of these issues, including the employment of ancillary ligands,[6−8] solid supports,[9,10] molten salts,[11] and additives for catalyst turnover.[12] While homogeneous systems have lead the way in this area of research, another line of investigation has centered around the use of heterogeneous palladium nanoparticles (PdNPs).[13−20] These catalysts are particularly attractive due to their good reactivity/selectivity, recoverability/recyclability, and low catalyst loadings.[21−27] Traditionally, PdNPs are synthesized via the reduction of a palladium(II) species in the presence of stabilizing agents, capping agents, or solid supports, which can control both their size and morphology.[28−32] Despite these advances, novel methods of nanoparticle formation, modes of reactivity, and removal/recyclability are important for the advancement of this integral sector.

Recently, the use of simple sugars[33−36] and other biomass[37−48] that both reduce palladium(II) precatalysts and stabilize the resulting palladium(0) nanoparticle have been reported, though little research has investigated their ability to catalyze cross-coupling reactions.[49,50] This method for generating PdNPs represents a simple, effective, and increasingly green method toward PdNP generation as the necessity for potentially harmful stabilizers or capping agents and solid supports is negated. Additionally, the surface of the PdNPs are decorated with sugar residues (vide infra). This hydrophilic shell should allow for the facile removal of the catalyst from the cross-coupled products. Herein, we report the use of in situ-generated glucose-derived PdNPs in the Suzuki–Miyaura cross-coupling reaction of aryl iodides and phenylboronic acid derivatives using isopropanol as a solvent under both thermal and microwave conditions. Importantly, the addition of a renewable sugar glucose to this simple system resulted in both increased yields of cross-coupled products and a significant decrease in the amount of palladium incorporated into the final product as determined by ICP-MS analysis.

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■ EXPERIMENTAL SECTION

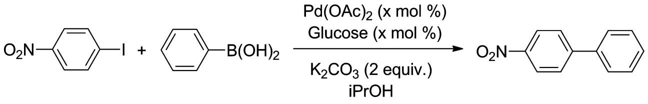
General Procedures. *Thermal Protocol.* A 5 mL microwave vial was loaded with $Pd(OAc)_2$ (1 mol %) and glucose (5 mol %). Technical grade isopropanol (3.0 mL) was added followed by boronic acid (1.5 equiv), aryl halide (1.0 equiv), and K_2CO_3 (2.0 equiv). The vial was sealed and heated to 100 °C with stirring for 20 h. After cooling, the reaction mixture was taken up in water (20 mL) and extracted with ethyl acetate (3 mL × 30 mL); the combined organic fractions were dried over anhydrous Na_2SO_4. All volatiles were removed in vacuo to afford the crude reaction mixture that was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether) to afford the desired biphenyls (Table 2).

Microwave-Assisted Protocol. A 5 mL microwave vial was loaded with $Pd(OAc)_2$ (1 mol %) and glucose (5 mol %). Technical grade isopropanol (1.5 mL) was added followed by boronic acid (1.5 equiv), aryl halide (1.0 equiv), and K_2CO_3 (2.0 equiv). The vial was sealed and was rapidly heated to 120 °C in a microwave. This temperature was maintained for 2 h. Microwave reactions were run in a Biotage Initiator 2.0 microwave, and the temperature of the reaction was monitored by IR. After cooling, the reaction mixture was taken up in water (20 mL) and extracted with ethyl acetate (3 mL × 30 mL); the combined organic fractions were dried over anhydrous Na_2SO_4. All volatiles were removed in vacuo to afford the crude reaction mixture that was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether) to afford the desired biphenyls (Table 3).

■ RESULTS AND DISCUSSION

Initially, the palladium-catalyzed cross-coupling of 1-iodo-4-nitrobenzene and phenylboronic acid was chosen in order to ascertain the effect of glucose on the transformation and develop appropriate reaction conditions (Table 1). Several features of this study are noteworthy. An initial solvent screen showed that the green solvent isopropanol gave the desired biaryl in as good a yield as more traditional solvents such as DMF or acetonitrile, which have increased levels of toxicity.[51] Because of its high yield of product as well as increased workers/process safety and decreased environmental impact,[52−54] the green solvent isopropanol was chosen for this transformation.[55−59] Importantly, isopropanol is a preferred industrial solvent and has significant advantages over the use of pure water in these transformations.[60] A series of bases were also screened, and it was found that the choice of base had little effect on the overall yield of the corresponding biaryl.[51] Because of the lower molecular weight, cost, and toxicity of the potassium carbonate base, it was used to further examine this process. The temperature employed was however found to have a substantial impact upon isolated yields with a distinct decrease arising as a consequence of lowering the reaction temperature (Table 1, entries 1−4). Interestingly, analysis of the $Pd(OAc)_2$ precatalyst and glucose loading (Pd/glucose ratio of 1:5) was noted to demonstrate a minor decrease in yield from 2 to 1 mol % $Pd(OAc)_2$ (80% and 78%, respectively), while a further decrease in catalyst loading to 0.2 mol % afforded a significant decrease in yield to 40% (Table 1, entries 1, 5−6). The highest yield of biaryl was obtained when the reaction was run for 20 h at 100 °C in the presence of 1 mol % $Pd(OAc)_2$ and 5 mol % glucose for 20 h (Table 1, entry 7). It was found that the background reaction, in which glucose was not added, gave the desired biaryl of 73% (Table 1, entry 8). Therefore, an 11% increase in yield was observed by simply adding the cheap renewable sugar glucose to the reaction mixture, which also led to a decrease in residual palladium in the isolated product (vide infra). This increase in yield could possibly be due to the protective properties of the sugar coating (Figure 1).[61−19] Control experiments that omitted both $Pd(OAc)_2$ and glucose only afford the starting materials (Table 1, entry 9).

Table 1. Development of Sugar-Derived PdNP-Catalyzed Cross-Coupling of 1-Iodo-4-nitrobenzene and Phenylboronic Acid[a]



entry	Pd(OAc)2 (mol %)	glucose (mol %)	temp. (°C)	time (h)	yield[b] (%)
1	2	10	100	16	80
2	2	10	80	16	72
3	2	10	60	16	48
4	2	10	rt	16	0
5	1	5	100	16	78
6	0.2	1	100	16	40
7	1	5	100	20	84
8	1	–	100	20	73
9	–	–	100	20	0

[a]Reaction conditions: 1-iodo-4-nitrobenzene (0.78 mmol, 1 equiv), phenylboronic acid (1.16 mmol, 1.5 equiv), and base (1.56 mmol, 2 equiv). [b]Isolated yields.

With high yielding conditions in hand, the substrate scope and functional group tolerance of the sugar-derived PdNP protocol was investigated (Table 2). Neutral, activated, and deactivated substrates were effectively coupled with phenylboronic acid in good yields under the standard conditions (Table 2, entries 1−3). Substrates bearing synthetically relevant functionality that can be further elaborated and that did not contain protecting groups[63] were also investigated. Fortunately, substrates bearing nitrile and hydroxyl functional groups coupled with phenylboronic acid in good yield (Table 2, entries 4, 5). Compounds containing amine, amide, ester, and carboxylic acid functionality were also tolerated (Table 2, entries 6−9). It was noted that when the PdNP system was run in isopropanol that it was selective toward aryl iodides, a result which has been previously reported by other researchers using preformed palladium nanoparticles as catalysts in alcohol solvents.[64,65] In contrast, using DMF as solvent allowed for the facile coupling of bromobenzene with phenyl boronic acid in quantitative yield under similar conditions. Thus, subjection of 4-chlorophenylboronic acid to the standard conditions in the presence of iodobenzene afforded 4-chlorobiphenyl exclusively (Table 2, entry 10). We envisage this result to be of particular relevance for selective cross-coupling reactions at specific positions of polyhalogenated substrates.[66] This study therefore provides insights into the functional group compatibility of palladium-catalyzed cross-coupling reactions in alcoholic solvents.

Having explored the substrate scope and functional group tolerance of the sugar-derived PdNP-catalyzed cross-coupling protocol, research into reducing the overall reaction time via microwave heating was conducted.[67−72] After a brief investigation into the use of microwaves in our in situ palladium nanoparticle protocol,[51] it was found that 1-iodo-4-nitrobenzene and phenylboronic acid could be coupled in 86% yield in 2 h at 120 °C (Table 3, entry 1). 4-Nitrobiphenyl was formed in 74% yield under the microwave conditions when no glucose was added. In addition to an increase in yield versus the control experiments, this procedure also represents a significant

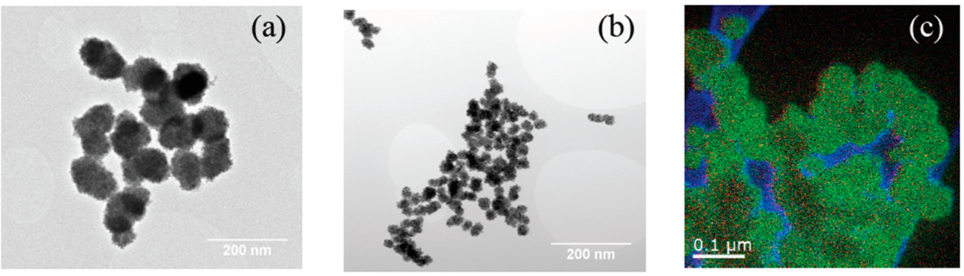
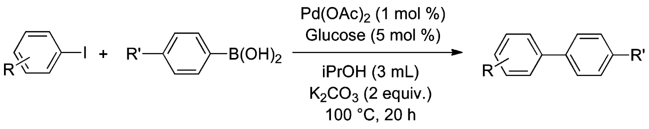


Figure 1. Representative TEM images of sugar-derived palladium nanoparticles generated under (a) thermal and (b) microwave irradiation. (c) EF-TEM map of palladium (green), oxygen (red), and carbon (blue) for PdNPs showing the nanoparticles surrounded by a hydrophilic hydroxyl shell.

Table 2. Substrate Scope of the Sugar-Derived PdNP Catalyst System in the Suzuki−Miyaura Cross-Coupling Reaction[a]



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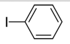
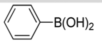
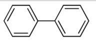
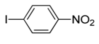
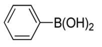
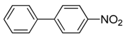
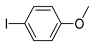
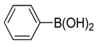
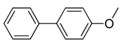
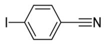
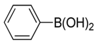
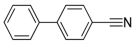
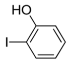
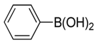
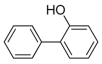
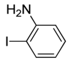
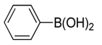
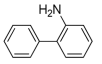
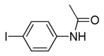
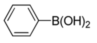
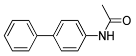
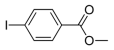
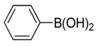
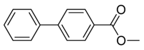
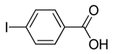
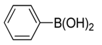
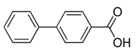
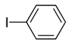
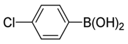
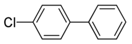
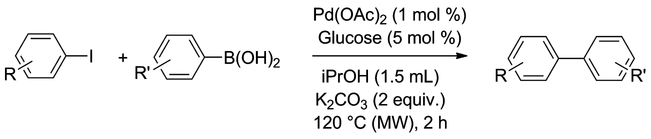
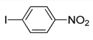
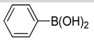
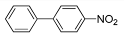
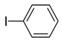
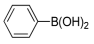
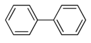
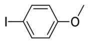
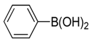
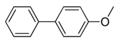
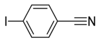
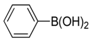
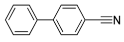
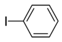
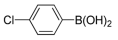
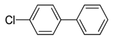
1				88
2				84 (73)^{c}
3				94
4				80
5				89
6				64
7				92
8				54
9				66
10				82

[a] Reaction conditions: aryl halide (0.78 mmol, 1 equiv), boronic acid (1.2 mmol, 1.5 equiv), K_2CO_3 (1.6 mmol, 2 equiv), iPrOH (3.0 mL), $Pd(OAc)_2$ (1 mol %), glucose (5 mol %), 100 °C, and 20 h. [b] Isolated yields. [c] No glucose was added.

rate enhancement over the thermal protocol with a reduction of 18 h in reaction time.[68−73] Neutral, activated, and deactivated substrates all afforded the desired cross-coupled products in good yield (Table 3, entries 2−4). Additionally, 4-chloroboronic acid was found to couple efficiently with iodobenzene under the reaction conditions to give the desired biaryl in good yield (Table 3, entry 5). In comparing the representative yields of the biaryl products, comparable isolated yields were observed under both the thermal and microwave conditions. While a direct comparison of the energy used in the two methods was not practical for this study,[73] it should be noted that an 18 h decrease in time was observed between the thermal and microwave protocols.

Table 3. Sugar-Derived PdNPs in Microwave-Assisted Suzuki−Miyaura Cross-Coupling Reaction[a]



entry	aryl halide	boronic acid	product	yield^{b} (%)
1				86 (74)^{c}
2				73
3				94
4				80
5				92

[a] Reaction conditions: aryl halide (0.39 mmol, 1 equiv), phenylboronic acid (0.58 mmol, 1.5 equiv), K_2CO_3 (0.78 mmol, 2 equiv), iPrOH (1.5 mL), $Pd(OAc)_2$ (1 mol %), glucose (5 mol %), 120 °C, and 2 h. [b] Isolated yields. [c] No glucose was added.

■ TEM ANALYSIS OF IN SITU-FORMED PALLADIUM(0) NANOPARTICLES

Given the rate enhancement demonstrated by the microwave-assisted protocol, we became interested in both the size and morphology of the sugar-derived PdNPs and the influence that the heat source has on these features. Transmission electron microscopy (TEM) of the palladium(0) nanoparticles generated under both thermal heating and microwave irradiation showed that while they both formed circular aggregate structures the microwave generated nanoparticles were smaller and more uniform in size (Figure 1a,b).[51] This increase in monodispersity is most likely due to the uniform heating[74,75] and rapid cooling in the microwave reactor, as the individual nanoparticles exhibit a similar size distribution. Our hypothesis, that the surface of the PdNPs are decorated with sugar residues, was supported via the use of energy filtered transmission electron microscopy (EF-TEM) analysis, which gave a spatially resolved composite image showing a hydrophilic shell of oxygen atoms (red) surrounding the palladium nanoparticle (green, Figure 1c). The layer of oxygen (red) and carbon (blue), presumably sugar residues, surrounding the palladium nanoparticles should increase their polarity as well as solubility in polar media.[51]

ICP-MS ANALYSIS OF THE RESIDUAL PALLADIUM

The removal of toxic heavy metals from active pharmaceutical ingredients needs to be efficient in order to meet regulatory standards, and significant research has been undertaken to facilitate the removal of palladium.[76−78] The degree of palladium incorporation into the biaryl cross-coupled products after both the workup and purification stages was investigated using ICP-MS analysis. The organic extracts from an aqueous workup and silica gel-purified products of the thermal reaction of 1-iodo-4-nitrobenzene and phenylboronic acid both with and without the addition of glucose were subjected to IPS-MS analysis (Table 4).[51] It was found that reactions conducted in the presence of the cheap additive glucose gave a 36% difference in palladium content after simple aqueous workup verses the sample not containing glucose (Table 4, compare entries 1 vs 2).[51] Additionally, a 48% difference in palladium was observed after flash column chromatography in comparison to reactions conducted without glucose (Table 4, compare entries 3 vs 4).[51] These results support our hypothesis that the increased hydrophilicity of the sugar-derived nanoparticles as well as their enlarged polarity and size when compared to the nonglucose system allows for a more facile removal of the palladium.

Table 4. ICP-MS Analysis of Palladium Content Found in 4-Nitrostilbene Product Formed under Thermal Conditions Both with and without Glucose[51]

entry	average (ppb/mg)	glucose (5 mol %)
1[a]	26.98	no
2[a]	17.19	yes
3[b]	1.06	no
4[b]	0.55	yes

[a] Aqueous extraction. [b] Silica gel chromatography.

CONCLUSION

In summary, a simple and effective method for the employment of in situ-generated, renewable, sugar-derived PdNPs in the Suzuki−Miyaura cross-coupling reaction of aryl iodides and phenylboronic acid derivatives conducted in isopropanol was developed. It is noteworthy that a wide range of functional groups were compatible with the reaction conditions and that the use of a microwave influenced both the rate of the reaction and size distribution of the resultant palladium nanoparticles. Moreover, these protocols led to a significant decrease in residual palladium found in both the crude and purified products. Therefore, the addition of a cheap renewable sugar glucose to the system resulted in both increased yields of cross-coupled products and a significant decrease in the amount of palladium incorporated into the final product. Investigations into the nature and role of the reducing sugar as well as further applications of this system into other reaction manifolds are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Nanoparticle characterization (TEM and EF-TEM data), ICP-MS data, experimental procedures, and $^1H/^{13}C\{^1H\}$ data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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