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Complete List of Authors:	Camp, Jason; University of Huddersfield, Dunsford, Jay; University of Nottingham, Chemistry Dacosta, Oliver; University of Nottingham, Chemistry Blundell, Rebecca; University of Nottingham, School of Chemistry Britton, Joshua; Flinders University, School of Chemical and Physical Scienes Fay, Michael; University of Nottingham, Nottingham Nanotechnology and Nanoscience Centre Smith, Robert; University of Nottingham, Chemistry Bousfield, Thomas; University of Huddersfield Adams, James; University of Nottingham
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Recyclable Glucose-Derived Palladium(0) Nanoparticles as in situ-Formed Catalysts for Cross-Coupling Reactions in Aqueous Media

Jason E. Camp,[*,†,§] Jay J. Dunsford,[†] Oliver S. G. Dacosta,[†] Rebecca K. Blundell,[†] James Adams,[†] Joshua Britton,[†] Robert J. Smith,[†] Thomas W. Bousfield[§] and Michael W. Fay[‡]

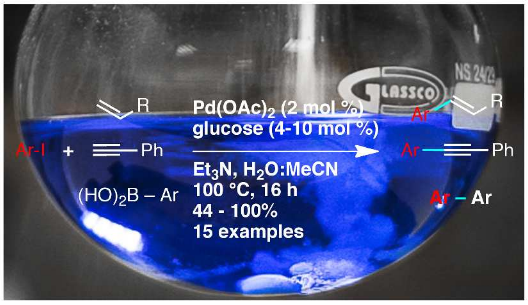
[†] School of Chemistry, University of Nottingham, Nottingham, U.K.

[‡] Nottingham Nanotechnology and Nanoscience Centre, University of Nottingham, Nottingham, U.K.

[§] Department of Chemical Sciences, University of Huddersfield, Queensgate, Huddersfield, U.K.

j.e.camp@hud.ac.uk

ABSTRACT In situ-generated, glucose-derived palladium(0) nanoparticles were shown to be convenient and effective catalysts for aqueous Mizoroki-Heck, Sonogashira and Suzuki-Miyaura cross-coupling reactions. The addition of only 4-10 mol % glucose to the reaction mixture lead to a significant increase in yield of the desired products in comparison to processes that omitted the renewable sugar. Interestingly, the Mizoroki-Heck reaction was observed to proceed in good yield even as the reaction reached acidic pH levels. Extensive analysis of the size and morphology of the in situ-formed palladium nanoparticles using advanced analytical techniques showed that the zero valent metal was surrounded by hydrophilic hydroxyl groups. The increased aqueous phase affinity afford by these groups allowed for facile recycling of the catalyst.



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Palladium-catalysed cross-coupling reactions are some of the most powerful methods for the creation of new carbon-carbon bonds due to their high selectivity, functional group tolerance and regio- / stereoselectivity.[1] Many industries, including the pharmaceutical and agrochemical, have made extensive use of palladium mediated cross-couplings for the synthesis of added-value compounds.[2] In order to work effectively these processes often require toxic and expensive additives, which leads to unnecessary waste, expense and cost to the environment. One area of catalysis that addresses some of the limitations of traditional palladium-mediated bond formation is the use of palladium nanoparticles (PdNPs).[3] The rapid increase in the use of metal nanoparticles for catalysis is due to the fact that they have a good reactivity / selectivity profile,[4] require low catalyst loadings and are recoverable and recyclable.[5] Traditionally, palladium(0) nanoparticle (Pd^0NP) are formed via reduction of a palladium(II) precatalyst in the presence of a nanoparticle support and capping agents.[6] Once isolated, Pd^0NPs can then be used as efficient catalysts for bond formation under standard cross-coupling conditions.[7] Two key drawbacks to the use of nanoparticles in palladium catalysis are the cost associated with the synthesis, isolation and purification of the nanoparticles[8] and the use of toxic additives, capping reagents and excess reagents that lead to a decrease in the activity and recyclability of the catalyst.[9] The in situ formation of catalytically active PdNPs using a renewable reductant without the addition of capping agents would overcome many of these issues. Whilst it has been established that simple monosaccharides such as glucose,[10] fructose,[11] sucrose,[11] other biomass (cellulose/starch/beet juice/lignan)[12,13] and even whole plants[14] can reduce metal salts and form metal nanoparticles (MNPs),[15,16] very little research has been conducted on the ability of in situ formed nanoparticles to catalyse carbon-carbon bond forming reactions (Figure 1).[17,18] Recently Nacci *et al.* showed that the addition of a reducing sugars to palladium-catalysed Ullman couplings in the presence of TBAOH resulted in the formation of the desired symmetric biaryl products.[17a] In addition, we have shown that sugar derived palladium nanoparticles are viable catalysts for Suzuki-Miyaura cross-coupling reactions of aryliodides and boronic acids in isopropanol.[17c] Despite the important role of monosacharaides in transition metal catalysis, where they have been mainly used as ligands,[19] their effect on cross-coupling processes is poorly understood. Herein, we harness renewable sugars for the in situ formation and stabilisation of palladium(0) nanoparticles in aqueous solutions, which allowed for the development of a variety of palladium-mediated cross-coupling reactions as well as facial recycling of the catalyst.

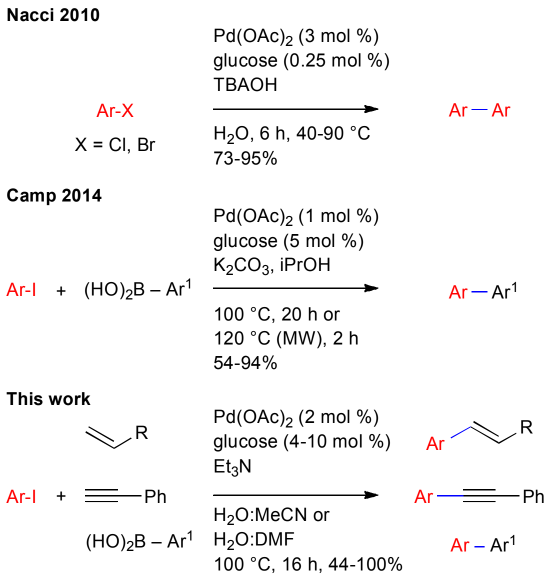
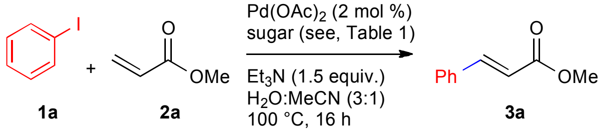


Figure 1. Use of renewable sugars in palladium-catalysed coupling reactions.

RESULTS AND DISCUSSION

Initial investigations were aimed at establishing the catalytic viability of the sugar-derived palladium nanoparticles under aqueous conditions[20] and to gain an increased understanding of the role of the reducing sugar in the overall process. Due to its extensively studied mechanism and synthetic importance, the Mizoroki-Heck reaction was chosen as an archetypal transformation.[21] Importantly, aqueous conditions were investigated that should allow for increased recyclability of the catalysts and overall greener processes (*vide infra*).[22] Two key variables that needed to be examined were the choice of reducing sugar and the ratio of sugar to palladium. Thus, the coupling of iodobenzene (**1a**) with methyl acrylate (**2a**) in the presence of Pd(OAc)$_2$, a reducing sugar and triethylamine in water:acetonitrile (3:1) at 100 °C was used to probe the feasibility of the process (Table 1).[23] Whilst fructose,[24] cellulose,[25] sucrose[26] and glucose[27] all have the ability to reduce palladium(II) precatalysts to palladium(0), the yield of product obtained from the in situ generated nanoparticles varied significantly (Table 1, entries 1-4). Of the four sugars tested, fructose has the highest reduction potential and gives the smallest average particle size when used to form metal nanoparticles.[11] Despite these facts, fructose gave the lowest yield of product and actually inhibited the reaction when compared with control experiments (Table 1, entry 1 vs. 5). The PdNPs formed employing cellulose as the reductant also gave a low yield (Table 1, entry 2). Sucrose, which is hydrolysed under the reaction conditions to form a 1:1 mixture of fructose and glucose,[28] gave a moderate yield of the desired product after stirring for 16 h at 100 °C (Table 1, entry 3). Nearly quantitative yield of (*E*)-methyl cinnamate (**3a**) was obtained when glucose was used as the reducing sugar (Table 1, entry 4). Control experiments in which the sugar, base and palladium were omitted all showed significantly lower product production than the glucose system (Table 1, entry 4 vs. 5-8). The observed benefit of glucose to the process is most likely due to the fact that it allows enough of the palladium surface to be accessible for catalysis whilst preventing catalyst poisoning via aggregation (*vide supra*). Having established the benefits of glucose in the Mizoroki-Heck reaction, the ratio of sugar to palladium was examined (Table 1, entries 9-11). A 1:2 ratio of palladium to sugar was found to give the highest yield of **3a**. Excess sugar may prevent the surface of the catalyst from being solvent exposed, whilst too little results in increased aggregation of the palladium(0) and deactivation of the catalyst. It was also found that a reaction time of 16 h was required for completion of the process at 100 °C.[29] Additionally, experiments showed that the in situ formed palladium nanoparticles gave a significantly better yield of **3a** than ones that were preformed and isolated prior to addition to the reaction (Table 1, entry 4 *vs*. 12).[11,30] This is most likely due to the surface of the nanoparticle being coated with a layer of organic material, which can block many of the catalytic sites.

Table 1. Sugar-derived palladium(0) nanoparticles as catalysts for the Mizoroki-Heck reaction



entry	sugar	Pd / sugar ratio	yield (%)[a]
1	fructose	1:2	2
2	cellulose	1:10[b]	21
3	sucrose	1:2	58
4	glucose	1:2	97
5	-	1:0	18
6[c]	-	1:0	12
7[c]	glucose	1:2	6
8[c,d]	glucose[e]	-	0
9	glucose	1:1	70
10	glucose	1:3.5	50
11	glucose	1:4	42
12[f]	glucose	1:2	20

[a] Isolated yield [b] A 1:10 weight to weight ratio of palladium acetate to cellulose was used [c] No Et$_3$N was added [d] No palladium was added [e] 4 mol % glucose was added [f] PdNPs were preformed and isolated

Next the pH of the reaction was monitored as a function of time (Figure 2). To accomplish this, a series of reaction between iodobenzene (**1a**) and methyl acrylate (**2a**) under the standard condition were run for set amounts of time and the pH was determined. After the pH measurement was made, the crude reaction mixture was worked-up and purified according to the general procedure to obtain the isolated yields. A plot of pH vs. time vs. yield revealed that the reaction proceeds in good yield even at acidic pH (increasing from 30-97% as the pH decrease from 4.52-2.66). Unfortunately, complete removal of base from the system gave only a small amount of the desired product (Table 1, entry 7). These results are in contrast to other pH dependency studies that established a pH range of 9-11.5 to be optimal for palladium-catalysed cross-coupling reactions.[31] It is likely that the role of the sugar at basic pH levels is to act as a ligand for the palladium catalyst, as proposed by Jian *et al.* for the use of mannose,[19g] and that the reaction proceeds through a standard Mizoroki-Heck mechanism.[32] As the solution becomes acid, it is possible that the sugar is then responsible for reducing the palladium(II) species to the catalytically active palladium(0) complex.[27] These observations could have important implications for the development of Pd(0) mediated, base-free carbon-carbon bond forming reactions under acidic conditions.

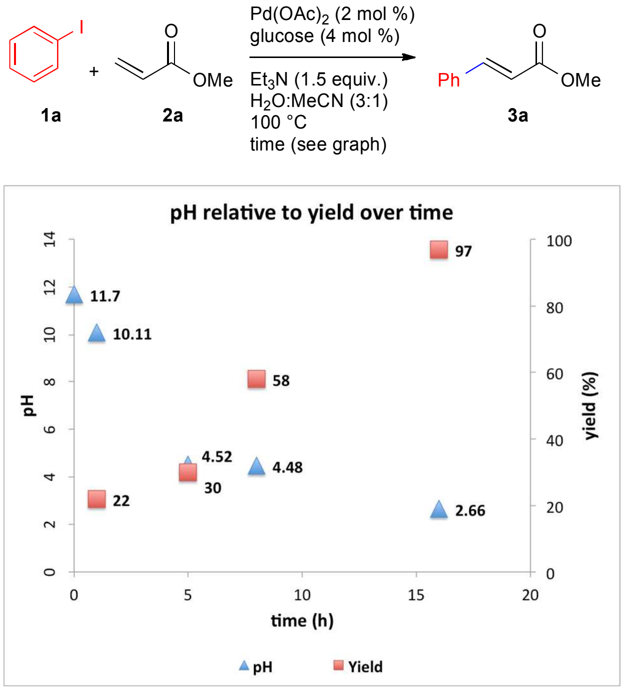
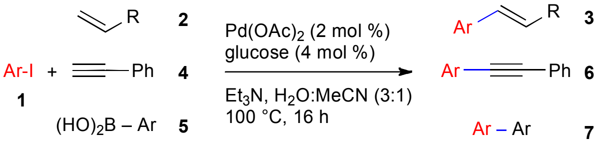


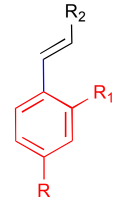
Figure 2. Comparison of pH vs. time vs. yield of the PdNP mediated reaction

In order to assess the catalytic ability of the in situ formed PdNPs with respect to both reaction type and substrate scope a variety of substituted aryl iodides were interrogated. Three palladium mediated carbon-carbon bond forming reactions, the Mizoroki-Heck, Sonogashira and Suzuki-Miyaura were investigated (Table 2). Unprotected arenes with both electron donating and withdrawing substituents were examined in an attempt to mitigate the use of protecting groups.[33] Several features of the sugar derived palladium nanoparticle methodology are noteworthy. It was shown that both electron withdrawing groups, such as carboxylic acid and nitro moieties, as well as basic functionality, such as anilines were well tolerated in the Mizoroki-Heck reaction between aryl iodides **1** and various alkenes **2** to give styrene derivatives **3a-i**. Substitution at both the 2- and 4-positions of the iodobenzene ring was found to be compatible with the cross-coupling procedure. Interestingly, it was also shown that sodium erythorbate, a common food additive, could be used to afford a viable catalytic system for the synthesis of (*E*)-3-phenyl-2(*E*)-propenoic acid (**3b**), though in a slightly reduced yield. The sugar derived palladium nanoparticles were also efficient catalysts for the Sonogashira and Suzuki-Miyaura reactions under aqueous conditions. Coupling of aryliodides **1** and phenyl acetylene (**4**) gave disubstituted alkynes **6a-c** in moderate to good yield. Additionally, the Suzuki-Miyaura reaction between aryl iodides **1** and phenyl boronic acid (**5**) gave biaryls **7a-c** in good to excellent yields under slightly modified conditions. In contrast to our recently reported methods in isopropanol,[17c] arylbromides also coupled efficiently in a DMF:H_2O (10:1) solvent system to afford biphenyl (**7a**) in excellent yield. Unfortunately, the use of arylbromides and arylchlorides in the Mizoroki-Heck and Sonogashira cross-coupling reactions only gave the desired products in 2-8% yield.[29] In contrast to a recent related study, the nitro moiety was not reduced under the reaction conditions and cleanly afford the cross-coupled products **3f**, **6b**, and **7b**.[19g]

Table 2. Substrate and reaction scope

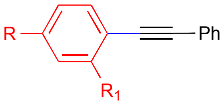


Mizoroki-Heck



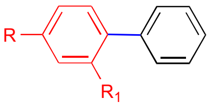
3a, R = R_1 = H, R_2 = CO_2Me, 97%
3b, R = R_1 = H, R_2 = CO_2H, 100% (87%)[a]
3c, R, R_2 = CO_2H, R_1 = H, 100%
3d, R = H, R_1 = NH_2, R_2 = CO_2H, 93%
3e, R = R_1 = H, R_2 = Ph, 90%
3f, R = NO_2, R_1 = H, R_2 = Ph, 94%
3g,R = CN, R_1 = H, R_2 = CO_2Me, 23%
3h,R = CHO, R_1 = H, R_2 = CO_2Me, 47%
3i, R = CN, R_1 = H, R_2 = Ph, 36%

Sonogashira



6a, R = R_1 = H, 95%
6b, R = NO_2, R_1 = H, 60%
6c, R = H, R_1 = NH_2, 44%

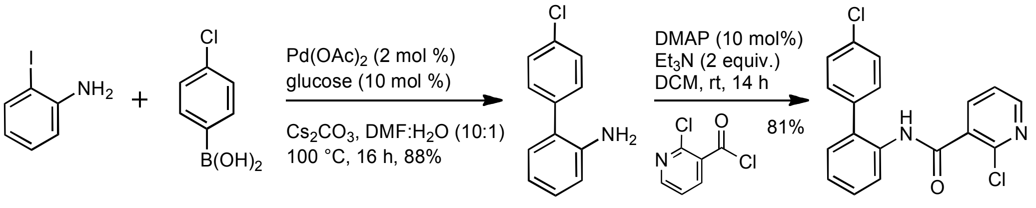
Suzuki-Miyaura[b]



7a, R = R_1 = H, 98% (98%)[c]
7b, R = NO_2, R_1 = H, 94%
7c, R = H, R_1 = NH_2, 65%

[a] sodium erythorbate (4 mol %) was used in place of glucose [b] Ar-I (1.0 equiv.), $(HO)_2B$-Ph (1.5 equiv.), glucose (10 mol %), $Pd(OAc)_2$ (2 mol %), Cs_2CO_3 (2.0 equiv.), DMF:H_2O (10:1), 100 °C, 16 h [c] Ph-Br (1.0 equiv.) was used

Building upon our substrate scope study, we turned our attention to the synthesis of the important agrochemical Boscalid (**8**).[34] Thus, reaction of 4-chlorophenylboronic acid (**5b**) with 2-iodoaniline (**1d**) under the standard conditions gave the desired biaryl **7d**. Amidation of aniline **7d** afforded the fungicide in good overall yield. Boscalid has been the target of a number of synthetic approaches.[35] Due to the fact that unprotected anilines are well tolerated under the reaction conditions, this method provides a nearly two-fold increase in molar efficiency[36,37] compared to a standard protocol.[38]



1d **5b** **7d** Boscalid (**8**)

Scheme 1. Synthesis of Boscalid (**8**) using *in situ* formed palladium nanoparticles

CHARACTERISATION OF IN SITU-FORMED PALLADIUM(0) NANOPARTICLES

A number of analytical techniques were used to confirm the formation of the glucose-derived palladium nanoparticles as well as to establish their size, morphology, surface characteristics and oxidation state. Transmission Electron Microscopy (TEM) analysis indicated that the palladium nanoparticles were semi-crystalline, approximately 5-20 nm in size and exist in a variety of conformations and morphologies, including spheres and prisms (Figure 3a,b).[29] In addition, EDS-TEM was used to determine that the surface of the nanoparticles is decorated with carbon and oxygen molecules (Figure 3c). Thus, the lighter amorphous material at the periphery most likely contains the sugar residues, which served as both the reductant and stabiliser of the palladium nanoparticles. This sugar coating provides a hydrophilic environment around the palladium catalyst. XPS analysis determined that the individual nanoparticles were predominately in the palladium(0) oxidation state. Analysis of the sugar-derived nanoparticles suspended in water at room temperature by nanoparticle tracking analysis (NTA), scanning ion occlusion sensing (SIOS) and dynamic light scattering **(**DLS) analysis showed that the nanoparticles aggregate into larger clusters of around 100 nm. This average particle size in solution is significantly greater than the small particles identifiable by TEM analysis. Similar levels of aggregation have been observed in related sugar-derived palladium nanoparticles.[39]

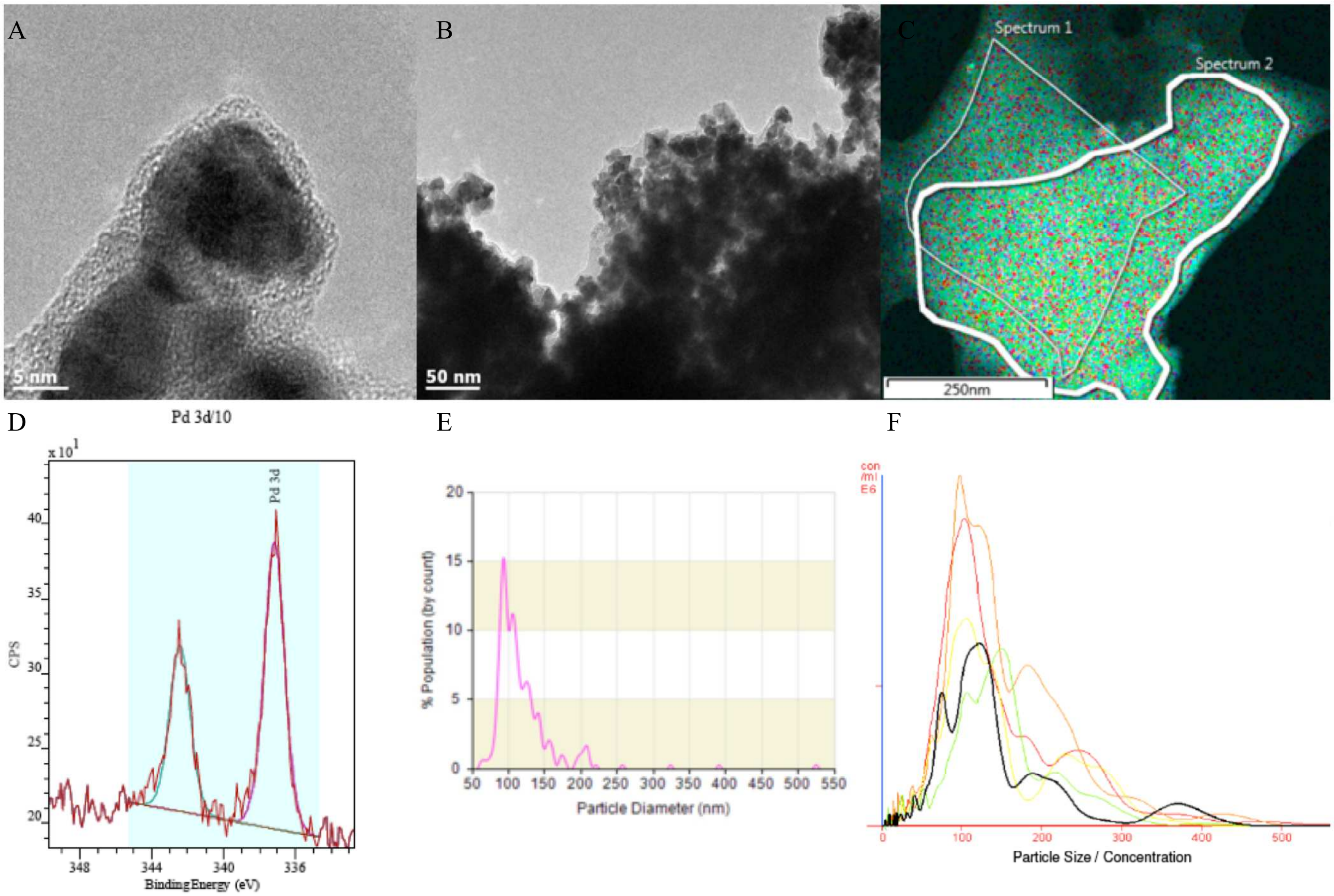
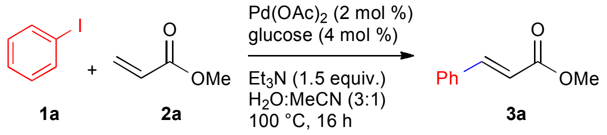


Figure 3. Structural and surface characterisation of the sugar-PdNPs. (a,b) typical TEM image of sugar-derived palladium nanoparticles (c) EDS-TEM map of the nanoparticles showing the nanoparticles surrounded by a hydrophilic hydroxyl shell; palladium (green), oxygen (red), and carbon (blue) (d) XPS analysis (e) scanning ion occlusion sensing analysis (f) nanoparticle tracking analysis

RECYCLING Of THE PALLADIUM NANOPARTICLE CATALYSTS

To exploit the hydrophilic nature of the palladium catalysts we investigated the recyclability of the in situ formed catalyst in an aqueous solvent. Importantly, the hydrophilic surface of the renewable sugar derived PdNP should help keep the catalyst in the aqueous layer during extraction by an organic solvent. To probe this hypothesis the recyclability of the in situ formed palladium nanoparticles was investigated via a series of reactions between iodobenzene (**1a**) and methyl acrylate (**2a**, Table 3). After the initial reaction was performed under the standard conditions, diethylether was added and the solution was subjected to centrifugation. The organic layer was isolated, the solvent was removed under reduced pressure and the residue was purified via flash chromatography. To the aqueous layer were added the substrates (**1a** and **2a**), acetonitrile (1 mL) and triethylamine (1.5 equiv). No additional palladium or glucose was added at this stage. Importantly, it was not necessary to wash the aqueous mixture to remove excess salts or base.[40] This study showed that the in situ formed palladium nanoparticles were recyclable for up to three additional cycles without significant loss of catalytic activity. A fifth reaction catalysed by the same palladium(0) nanoparticles gave the product in 61% yield. A similar, though more substantial, drop-off in reactivity was reported for the recycling of sugar-derived catalysts in the Ullman reaction.[17a] The decrease in yield in our system is most likely caused by the low level of sugar residue on the surface of the nanoparticles at this point in the reaction, which lead to increased aggregation of the palladium(0) and deactivation. Similar results were observed in our initial stoichiometry study (see, Table 1, entries 4 *vs.* 9). Thus, it may be necessary to add glucose at various points of the reaction in order to improve the recyclability of the catalyst. Efforts are currently ongoing in our laboratory to study the effect of continuous glucose addition on the overall yield of the process.

Table 3. Recyclability of the in situ-formed palladium nanoparticle catalysts



entry	Pd / sugar ratio	yield (%)[b]	notes
1	1:2	97	
2[a]	-	92	1st recycle
3[a]	-	92	2nd recycle
4[a]	-	82	3rd recycle
5[a]	-	61	4th recycle

[a] Et_3N (1.5 equiv.) was added after each cycle, but no additional palladium or glucose [b] Isolated yield

CONCLUSION

In summary, the ability of simple sugars to both form and stabilise recyclable, catalytically active palladium(0) nanoparticles was demonstrated for a variety of synthetically important carbon-carbon bond forming reactions. Additionally, the sugar coating on the surface of the palladium not only prevented aggregation and deactivation via palladium black formation, but also allowed for facial recycling of the in situ formed catalyst. Only a catalytic amount of palladium and a small amount of sugar are required in the C-C bond forming reactions, which can be run under aqueous conditions. This in situ catalyst formation method compares favorably to other recyclable bio-derived palladium nanoparticles catalyst as it mitigates the requirement to preform and isolate the palladium nanoparticles.[29] We believe that our study provides the groundwork for a simple technology that opens up exciting opportunities for the development of a variety of catalytic systems in which the reducing potential of renewable sugars is harnessed for the generation, stabilisation and turnover of catalytically active metal nanoparticles – Sugar-Powered Catalysis.

EXPERIMENTAL SECTION

General Procedures. *Mizoroki-Heck*. A 5 mL microwave vial was charged with $Pd(OAc)_2$ (2 mol %) and glucose (4 mol %). Water / acetonitrile (3:1, 0.2 M) was added followed by triethylamine (1.2 equiv.), iodobenzene (1.0 equiv.) and methyl acrylate (1.2 equiv.). The vial was sealed and the resultant mixture was heated at 100 °C for 16 h. The mixture was cooled to rt and water (10 mL) and diethylether (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol / EtOAc, 15:1) to afford the desired cross-coupled product.

Sonogashira. A 5 mL microwave vial was charged with $Pd(OAc)_2$ (2 mol %) and glucose (4 mol %). Water / acetonitrile (3:1, 0.2 M) was added followed by triethylamine (1.2 equiv.), phenyl acetylene (1.0 equiv.) and iodobenzene (1.0 equiv.). The vial was sealed and the mixture was heated to 100 °C for 16 h. The mixture was cooled and water (10 mL) and diethylether (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol / EtOAc, 9:1) to afford the desired cross-coupled product.

Suzuki-Miyaura. A 5 mL microwave vial was charged with $Pd(OAc)_2$ (2 mol %) and glucose (10 mol %). Water / DMF (1:10, 0.2 M) was added followed by cesium carbonate (2.0 equiv.), iodobenzene (1.0 equiv.) and phenylboronic acid (1.5 equiv.). The vial was sealed and the mixture was heated to 100 °C for 16 h. The mixture was cooled and water (10 mL) and diethylether (10 mL) were added. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (petrol / EtOAc, 30:1) to afford the desired cross-coupled product.

ASSOCIATED CONTENT

Supporting Information. Nanoparticle characterisation (TEM, EDS-TEM, XPS, DLS, q-nano and nanosight data), experimental procedures, and 1H/13C{1H} NMR data for all compounds. This material is free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Present Addresses

§ (Jason E. Camp) Department of Chemical Sciences, University of Huddersfield, Huddersfield, HD1 3DH, United Kingdom. Tel.: +44 (0)14 8447 3180.

Notes

The authors declare no competing financial interest.

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Recyclable Glucose-Derived Palladium(0) Nanoparticles as in situ-Formed Catalysts for Cross-Coupling Reactions in Aqueous Media

Jason E. Camp,* Jay J. Dunsford, Oliver S. G. Dacosta, Rebecca K. Blundell, James Adams, Joshua Britton, Robert J. Smith, Thomas W. Bousfield and Michael W. Fay

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Renewable sugar-derived palladium(0) nanoparticles (PdNPs) are effective as *in situ* formed catalysts for cross-coupling reactions in aqueous solutions.