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ARTICLE

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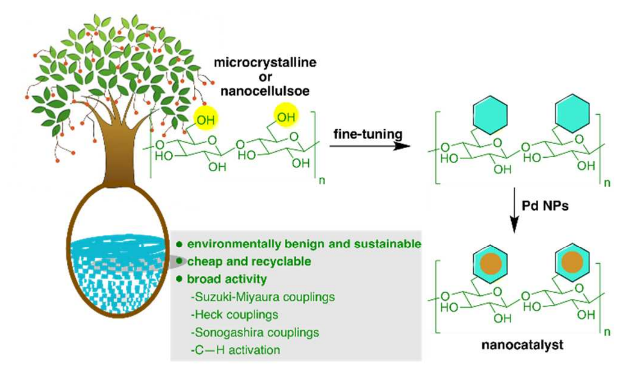
Cheap, recyclable, and robust cellulose-palladium nanoparticles were developed and fully characterized by FTIR, TEM, XPS, TGA, and NMR. The nanoparticles enabled cross-coupling chemistry in a truly general fashion i.e., Suzuki–Miyaura, Heck, Sonogashira, and C-H activation. Notably, all types of transformations were achieved with a single type of nanocatalyst. Complete recyclability of the catalyst and low traces of palladium in the product demonstrates the greenness of the protocol.

Introduction

After peptide bond forming reactions,[1-3] palladium-catalyzed cross-couplings, such as Suzuki–Miyaura, Sonogashira, and Heck reactions have played a significant role in the construction of challenging carbon-carbon bonds,[4-6] and in the recent developments in material chemistry.[7, 8] However, because an economical access to palladium supplies is limited, this element is regarded as an endangered element.[9] Significant efforts have been devoted by the scientific community to finding better catalysts that can assist in prolonging the palladium reserve, either by moving away from palladium or by developing alternative technologies.[5, 10] Nonetheless, the high costs associated with ligands, the difficulty in recycling the catalysts, and, notably, their lack of generality toward all types of cross-coupling reactions are major unsolved pitfalls. In addition, catalyst residues inevitably contaminate the product during these reactions.[11] Thus, it is important to develop a catalyst that exhibits broader activity, that is designed from environmentally benign materials, that is easy to recycle without additional effort and without adversely affecting activity, and that will not cause trace metal contamination of the product.[12]

To address the above issues, cellulose, as a sustainable, cost-effective, environmentally benign, and most abundant natural biopolymer,[13, 14] is potentially a suitable scaffold. Its surface can interact with metal nanoparticles to display the desired catalytic activity. Cellulose possesses an extra handle to fine-tune its physiochemical behavior, i.e., solubility, dispersity, and ligation properties. Cellulose and its derivatives have been also used as efficient, cheap, renewable, and biodegradable supports in catalysis.[15-21] Among the numerous methods that have been used to prepare cellulose-supported catalysts, deposited Pd particles on cellulose are one of the most widely studied.[22-24] This approach though may cause problems like catalyst deactivation and metal leaching. Li and other groups have introduced diphenylphosphinite-anchored cellulose to coordinate with palladium. But this methodology required a tediously long-time for preparation and showed a narrow range of applications.[25, 26] Herein, we report a cellulose-Pd nanocatalyst with wide catalytic activity. The efficiency and recyclability of this environmentally friendly cellulose–palladium catalyst was examined using common palladium-catalyzed cross coupling reactions (Scheme 1).



Scheme 1 Cellulose-Pd nanoparticles for general cross-coupling chemistry.

Results and discussion

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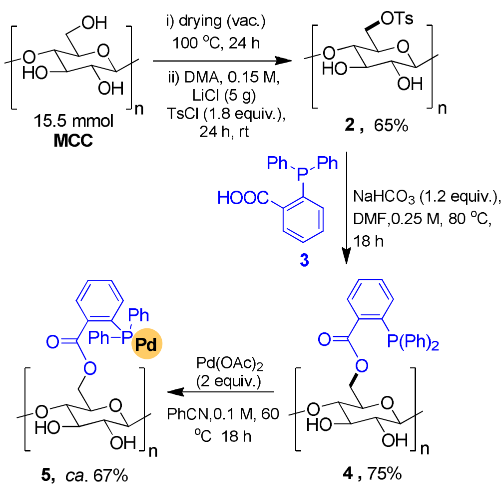
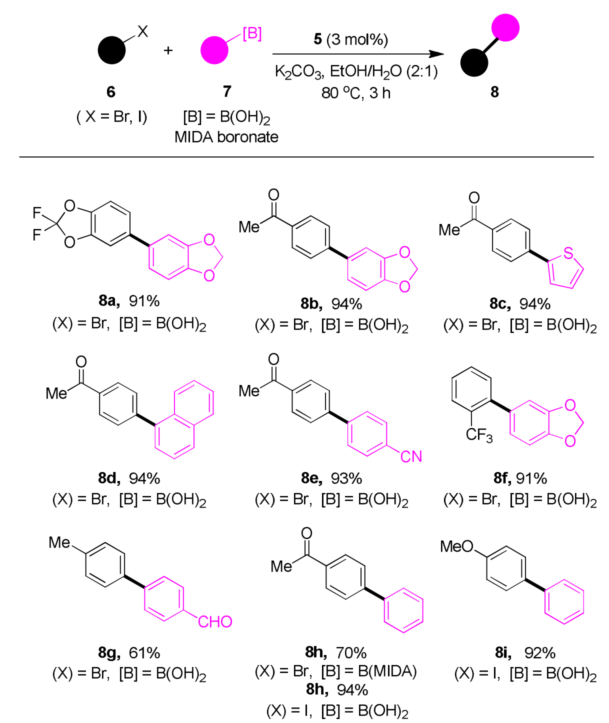
We began our study using an inexpensive 2-(diphenylphosphino) benzoic acid that acted as a linker to the microcrystalline cellulose (Cell) and which was then coordinated with palladium nanoparticles (NPs). It was anticipated that the position of the phosphine and ester linkages was going to be crucial for imparting stability and efficacy to the resulting catalyst. The steric bulk from the diphenylphosphine motif was thought to protect the ester linkage from hydrolysis under basic conditions. At the same time, the ester group was thought to coordinate with the Pd center to stabilize the catalyst. The synthetic protocol began with the nucleophilic substitution of Cell-OTs with 2-(diphenylphosphino) benzoic acid (Scheme 2). The resulting microcrystalline cellulose-phosphinite was then doped with palladium nanoparticles to complete the preparation of **5**; this catalyst was fully characterized by FTIR and NMR. (see Supporting Information)



Scheme 2. Synthetic protocol of Cellulose-Pd NPs.

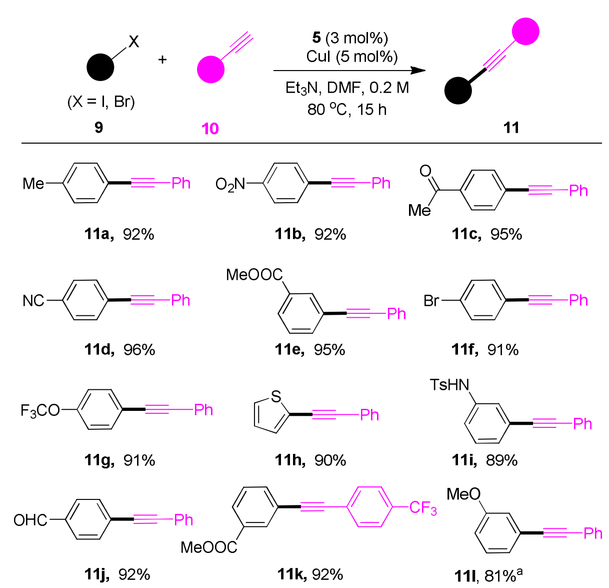
After obtaining **5**, its catalytic activity was surveyed. At first, it was used in Suzuki-Miyaura (SM) cross-couplings (Table 1). Aryl bromides and iodides displayed very good reactivity. MIDA boronate and boronic acid were also tolerated. Fluoro (**8a**), cyclic ether (**8a**, **b**, **f**), acetyl (**8b**-**e**, **h**), nitrile (**8e**), trifluoromethyl (**8f**), and aldehyde (**8h**) functionalities displayed good-to-excellent reactivity. The activity of this nanocatalyst was next tested in Sonogashira couplings (Table 2). Aryl iodides and bromides showed good reactivity. Excellent yields were obtained in all cases. Nitro (**11b**), acetyl (**11c**), nitrile (**11d**), ester (**11e**, **k**), trifluoromethylether (**11g**), sulfonamide (**11i**), aldehyde (**11j**), and trifluoromethyl (**11k**) residues tolerated the reaction conditions without decrease in reaction yields. Notably, esters **11e**, **k** did not hydrolyze.

Table 1. Catalytic activity of **5** for Suzuki–Miyaura couplings



Reaction conditions: Aryl halide (0.2 mmol), aryl boronic acid (1.1 equiv), **5** (3 mol %), K_2CO_3 (2.0 equiv.), 2 mL EtOH, 1 mL H_2O, 80 °C, 3 h.

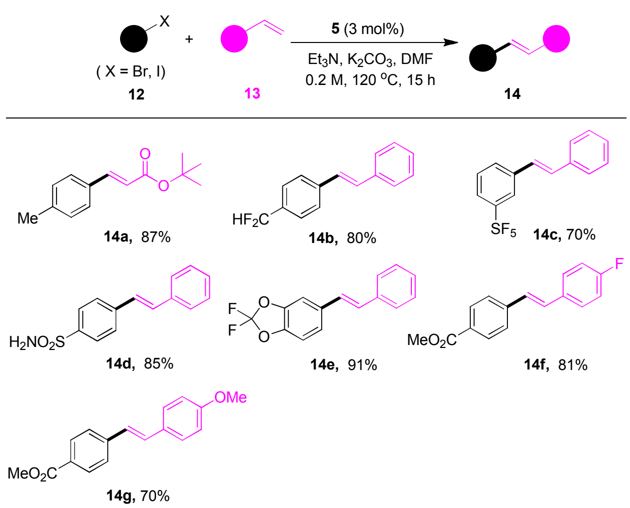
Table 2. Sonogashira couplings with **5**



Reaction conditions: Aryl halide (0.2 mmol), alkyne (1.1 equiv.), **5** (3 mol %), CuI (5 mol %), Et_3N (2.0 equiv.), 1 mL DMF, 80 °C, 15 h. [a] X = Br

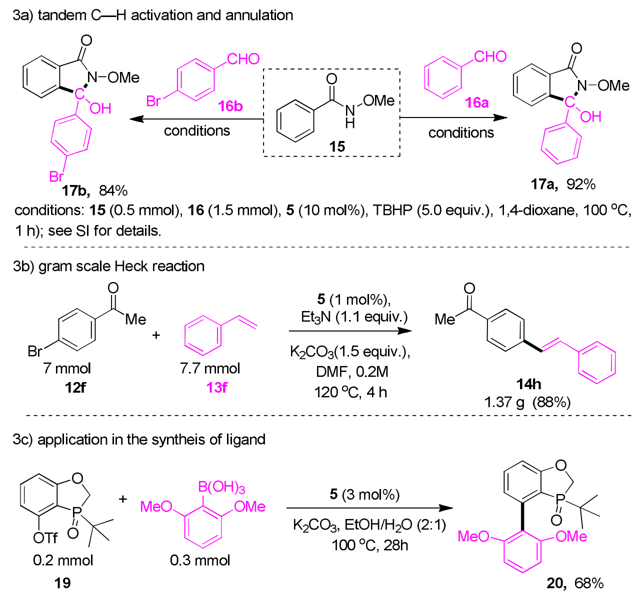
The catalytic activity was also examined in Heck cross-couplings. (Table 3). Both aryl iodide (**14a**) and bromides (**14b**-**g**) were suitable substrates. Electron-rich and electrondeficient (**14a**, **g**) residues displayed similar behaviours. Different functionalities such as ether (**14e**), ester (**14a, f**, **g**), ketal (**14e**), and sulfonamide (**14d**) were tolerated. Notably, substrates possessing the difluoromethyl (**14b**, **14e**) and pentafluorosulfur (**14c**) motifs remained intact and no side reactions were observed. Furthermore, no ester hydrolysis was observed in cases where coupling partners had ester residues (**14f**, **g**).

Table 3. Catalytic activity for heck couplings



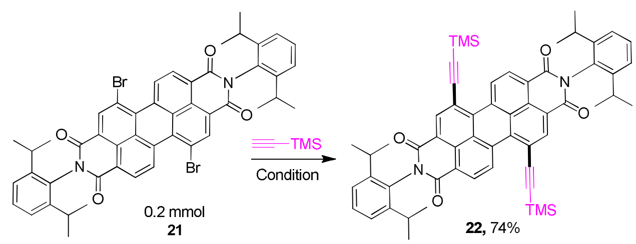
Reaction conditions: Aryl halide (0.2 mmol), alkene (1.1 equiv.), **5** (3 mol %), Et_3N (1.1 equiv.), K_2CO_3 (1.5 equiv.), 1 mL DMF, 120 °C, 15 h.

The catalyst activity was further tested in a tandem reaction, namely C—H activation followed by annulation, to prepare a hydroxylisoindolone derivative.[27] As shown in Scheme 3a, the reaction was completed in one hour, furnishing **17b** in excellent isolated yield. Surprisingly, the bromo functionality on the aryl residue did not show any reactivity. This nanocatalyst was then employed on a gram scale intermolecular Heck reaction: within 4 h the product **14h** was obtained in 88% yield, employing only 1 mol% catalyst. Another application of this protocol was the synthesis of a ligand precursor. Upon reaction of aryl triflate **19** with a sterically congested 2,6-dimethylphenylboronic acid, the product **20** was obtained in 68% isolated yield, along with catalyst recovery and re-use.[28, 29]



Scheme 3. Synthetic value of protocol.

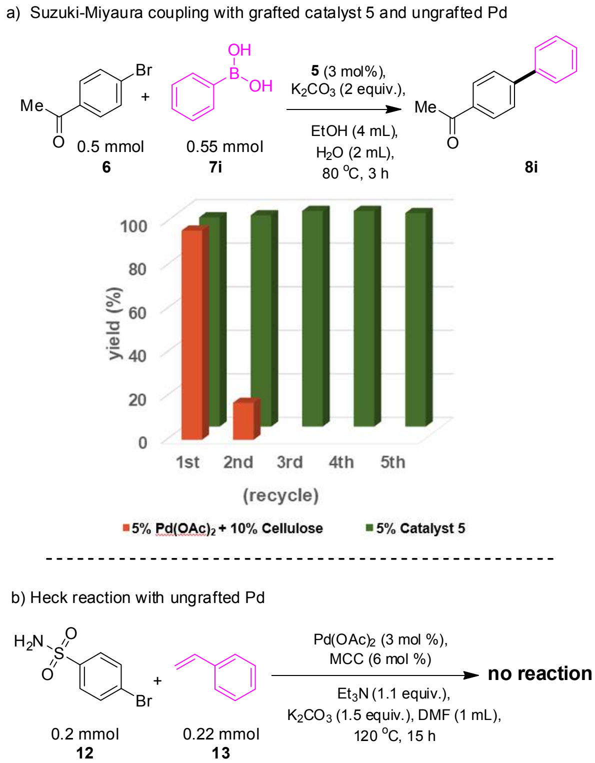
Another demonstration of the value of our catalyst was in the synthesis of organic materials; as shown in Scheme 4, dibromoperylene diimide (PDIs) **21** underwent simultaneous double substitution to afford **22** in good yield.[30]



Condition: **21** (0.2 mmol), **5** (2 mol%), ethynyltrimethylsilane (3 mmol), CuI (1 mol%), Et_3N (3 equiv), 1,4-dioxane, 0.2 M, 80 °C, 27 h

Scheme 4. Synthesis of PDI.

Our catalyst was recycled by simple filtration, without any additional manipulation, and without losing its catalytic activity. A recycling study revealed that the effectiveness of the catalyst held for up to five cycles. To recycle this catalyst, the liquid phase was removed after reaction completion by centrifugation, followed by washing with water to remove the salt. The catalyst was re-used without adding more palladium nanoparticles (see SI for details). A control experiment was also conducted using $Pd(OAc)_2$ and cellulose particles; in it we observed a 80% reduction in yield in the second recycle event (Scheme 5a, for details, See SI). In a separate control experiment, a Heck reaction was conducted with cellulose and $Pd(OAc)_2$ and none of the desired product was detected, underscoring the importance of our catalyst grafting process (Scheme 5b).



Scheme 5. Catalyst recycling with control experiment.

In order to gain insights into the nature of catalyst **5**, transmission electron microscopic (TEM) images of the fresh as well as the five-times recycled catalyst were recorded in Figure 1. In both samples, a high concentration of Pd nanoparticles (appearing as bright spots) was observed on the surface of carbon support particles (Figure 1 a,c). There is a clear difference in the Pd nanoparticle size distribution between these two samples.

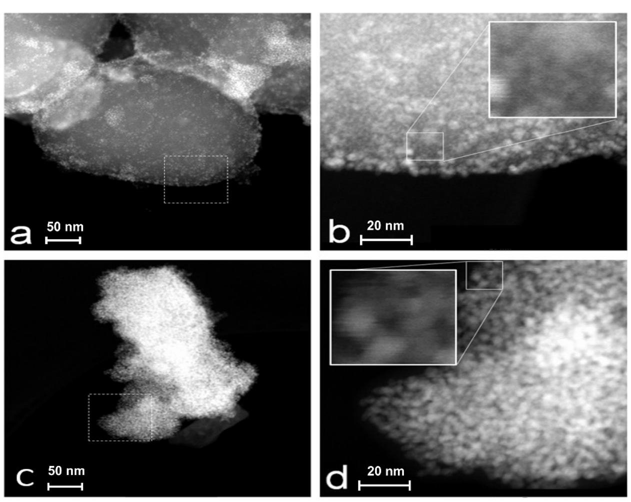


Figure 1. (a). Low-magnification STEM data from fresh catalyst, (b) Higher-magnification STEM images of regions marked in panel (a); (c). Low-magnification STEM data from five-times recycled catalyst; (d) Higher-magnification STEM images of regions marked in panels (c).

For the fresh catalyst, a bimodal size distribution is evident with many nanoparticles having ~1 nm diameter and with the remaining nanoparticles in a size range of about 3-4 nm (Figure 1b). On the other hand, the recycled catalyst shows almost all particles in the 3-4 nm range (Figure 1d). XPS analysis of these two catalysts shows the change in the Pd valence state. As indicated by the analysis of the Pd3d line, both catalysts show Pd(II) and Pd(0) states. The relative concentration of these valence states changed slightly, from 0.44 in the fresh catalyst (Figure 2a) to 0.39 in the recycled catalyst (Figure 2b), which helped to explain why the catalyst maintained its catalytic efficiency. Thermogravimetric analysis was performed to evaluate the stability of the catalyst at high temperature. As shown in Figure S2 in the SI, the catalyst system showed high thermal stability with decomposition occurring around 225 °C.

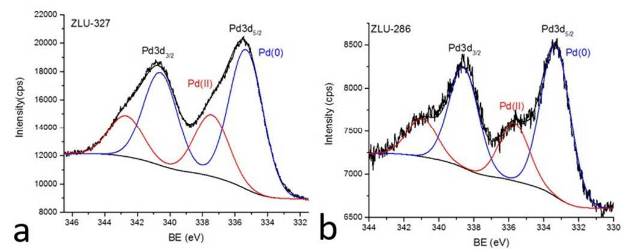


Figure 2. Deconvoluted high-resolution Pd3d XPS spectra. (a) XPS data of fresh catalyst; (b) XPS data of five-times recycled catalyst.

The residual palladium in the product was also assayed with inductively coupled plasma mass spectrometry (ICP-MS). Two products, **8a** and **14b**, from different types of coupling reactions were tested and both fell within the normal limits set by the FDA (**8a**: 2ppm, **14b**: 0.3ppm). The low Pd content further underscored the usefulness of this cellulose-bound nanocatalyst.

Conclusions

In summary, we have developed a new cellulose-palladium nanocatalyst (Cell-OOCPhPPh$_2$-Pd) using simple starting materials and a convenient synthesis. This catalyst shows good activity in C-H activation and three other types of cross-coupling reactions. The products from those reactions contain low Pd residues. This catalyst was also easily recycled without obvious loss in the catalytic activity even after several runs. Considering the importance of the above features, we believe that this catalyst could be an excellent choice for the pharmaceutical industry.

Experimental

General procedure for Suzuki-Miyaura coupling reactions:
An 8-mL vial fitted with a stirring bar was charged with aryl halide (0.2 mmol), K_2CO_3 (0.4 mmol), boronic acid (0.22mmol), 3% catalyst **5** (4 mg). 3 mL of a mixed solvent (ethanol: water = 2:1) was added and the mixture was flushed with argon for 1 min. The reaction was heated to 80 °C and stirred at 500 r/min for 2 hours while monitored by GC-MS. After the reaction was

completed, the mixture was poured into 30 mL EtOAc that was then washed with 10 mL water, and brine. The organic layer was dried over Na_2SO_4. filtered and the filtrate was concentrated. The resulting crude product was purified with flash chromatography.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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