

Communication

Pd EnCat™ 30 Recycling in Suzuki Cross-Coupling Reactions

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Abstract: Pd EnCat™ 30 is a palladium catalyst broadly used in several hydrogenation and cross-coupling reactions. It is known for its numerous beneficial features, which include high-yielding performance, easy recovery, and reusability. However, the available data regarding its recyclability in Suzuki coupling reactions are limited to a few reaction cycles and, therefore, fail to explore its full potential. Our work focuses on investigating the extent of Pd EnCat™ 30 reusability in Suzuki cross-coupling reactions by measuring its performance according to isolated yields of product. Our findings demonstrate that Pd EnCat™ 30 can be reused over a minimum of 30 reaction cycles, which is advantageous in terms of cost reduction and more sustainable chemical production.

Keywords: Pd EnCat™ 30; catalyst recycling; Suzuki coupling; green chemistry; biaryl synthesis

1. Introduction

Cross-coupling reactions are among the most studied processes within synthetic organic chemistry. Their importance stems from the fact that they allow the formation of new carbon–carbon bonds between two fragments, by use of a metal catalyst and a base [1].

The broad range of products synthesizable via cross-coupling reactions make these reactions fundamental in several academic and industrial fields, such as pharmaceuticals, natural products, and agrochemicals production [2].

Suzuki–Miyaura cross-coupling reactions, also called Suzuki reactions, were invented by Akira Suzuki in 1979, when the first stereospecific coupling of alkenylboranes and alkynylhalides by use of a homogeneous catalyst, namely tetrakis (triphenylphosphine) palladium, was reported [3].

Palladium was and still is the most used metal catalyst of choice in Suzuki coupling processes, due to its higher performance in comparison to more abundant earth metals, such as copper, nickel, and iron, for example [2,4].

However, homogeneous palladium catalysts typically display high sensitivity towards moisture, oxygen, and high temperature, which strictly limits their use to reactions in inert atmosphere, deoxygenated solvents, and ultimately impedes their reusability. Moreover, their use implies high catalytic loading and requires multi-step purification techniques, which cause a significant drop in product yield [5–8].

Consequently, numerous efforts were made to develop novel heterogeneous palladium catalysts that could overcome these limitations and could make Suzuki reactions more efficient and environmentally friendly [2,6,7].

A common downside of the most used heterogeneous palladium catalysts resides in metal leaching [8]. This phenomenon involves the release of metal ions into the reaction mixture, which leads to both a prompt decrease in catalytic activity, and metal contamination of the crude products. Therefore, the recyclability of most heterogeneous palladium catalysts is limited, and removal of the metal particles requires additional purification steps, which has a major impact on chemical production costs [6,8].

In the search of recoverable and reusable palladium catalysts, one of the most successful achievements involved the stabilization of the metal nanoparticles by microencapsulation in polymer beads, which gave rise to the EnCat™ catalysts family [9].



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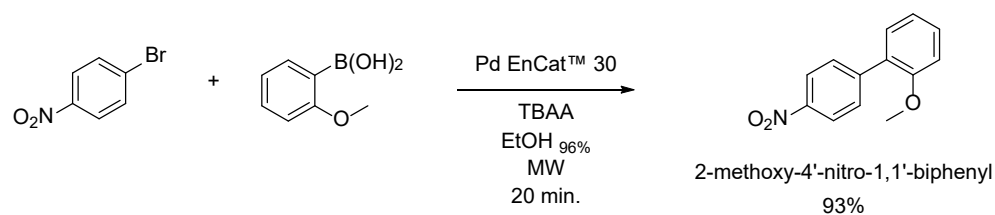
Pd EnCat™ 30 is one of its members, where palladium acetate is microencapsulated in a polyurea matrix. Easy catalyst recovery, high thermal/bench stability, and reusability are only a few of the several beneficial features that Pd EnCat™ 30 displays, which make this catalyst much more efficient and sustainable than its predecessors [9,10].

Nevertheless, only a few reported studies focus on its recyclability properties in Suzuki reactions, and often encompass a limited number of reaction cycles, an increase in reaction time, and single measurements exclusively [11–13]. To bridge these gaps in the literature, we investigated Pd EnCat™ 30 reusability by use of a conventional high-yielding Suzuki reaction to produce a substituted biaryl adduct in constant reaction conditions.

2. Results

Reagents and reaction conditions were selected after evaluating similar procedures reported in the literature [14–16]. The chosen synthetic method stood out for the considerable reduction in reaction time, due to the use of microwave irradiation, and its high yielding outcome [17]. This procedure was employed to prepare 14 different adducts, which consisted of mono/polysubstituted biphenyls, phenylnaphthalene, and a phenylthiophene representative all shown in the Supporting Information. While this procedure was effective in delivering all the desired products, the obtained isolated yields fluctuated between 64% and 95%.

As a result, the synthesis of 2-methoxy-4'-nitrobiphenyl from 4-bromonitrobenzene and 2-methoxyphenyl boronic acid was chosen due to the high yield achieved (93%) in only 20 min, and the prompt isolation of the product by flash column chromatography (Scheme 1).



Scheme 1. Reaction scheme of the Suzuki cross-coupling reaction used for investigating Pd EnCat™ 30 recyclability. TBAA: tetrabutylammonium acetate.

After each reaction cycle, the catalyst was recovered by simple filtration of the crude upon reaching 50 °C, acetone washing, and air-drying for approximately 10 min.

Pd EnCat™ 30 recycling was initially explored by 10-fold repetition of the reaction described in Scheme 1 in triplicate, which led to a 30% drop in yields from 93% to 62%, as shown in Figure 1.

The obtained yields were consistent between the three repetitions for each of the 10 cycles with low standard deviations of the yield ranging from 0.22 (first cycle) to 2.78 (sixth cycle). Mean values of isolated yields and standard deviations for all cycles can be found in Supplementary Materials.

Furthermore, Pd EnCat™ 30 was recycled 30 times to address its full reusability potential, and these results are shown in Figure 2.

The catalytic activity of Pd EnCat™ 30 dropped consistently, with the exception of small increases at the fourth, fourteenth, and fifteenth experiments. The overall average decrease in catalytic activity was circa 2.64%.

Eventually, the catalytic depletion accelerated over the last four runs by dropping quickly from 30% to 14%, which indicated that further recycling of Pd EnCat™ 30 was no longer beneficial if compared to the amounts of reagents and solvents used and was subsequently stopped.

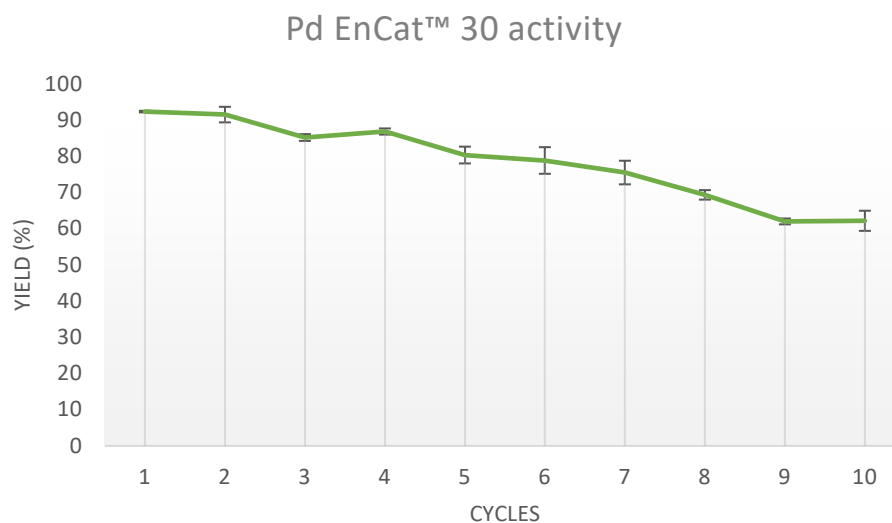


Figure 1. Isolated yields of 2-methoxy-4'-nitrobiphenyl measured across 10 experiments conducted in triplicate.

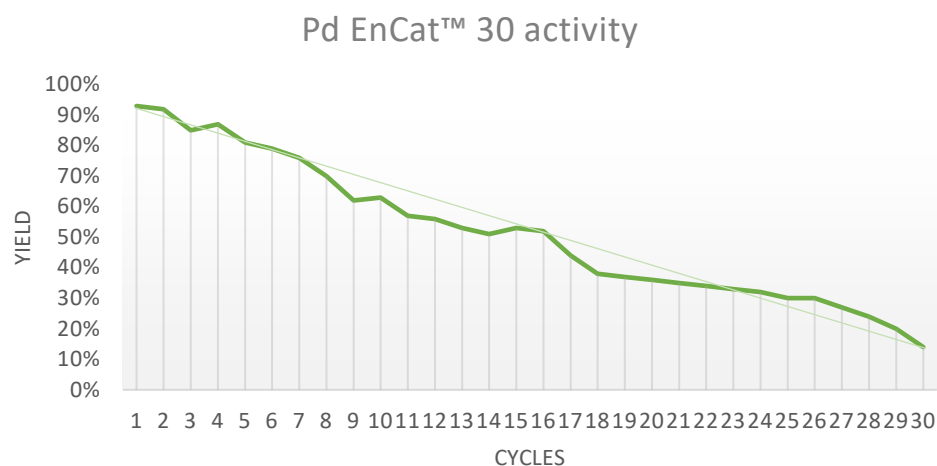


Figure 2. Isolated yields of 2-methoxy-4'-nitrobiphenyl measured across 30 experiments. The overall average decrease in catalytic activity (light green line) amounts to circa 2.64%.

Fourier transform infrared spectroscopy (FT-IR), and X-ray diffraction (XRD) analyses were performed on the catalyst before, during, and after its reuse. Specifically, infrared studies were carried out in triplicate on fresh Pd EnCat™ 30, and after the first, tenth, twentieth, and thirtieth reaction cycles (Supplementary Materials, page 9).

Vibrational peaks at 3336 and 2961/2874 cm^{-1} were attributed to N-H and C-H stretching, while all the main peaks in the 1696–1232 cm^{-1} region result from C=O stretching (1696 cm^{-1}), C=C stretching (1597 cm^{-1}), and other expected vibrational signals which all belong to the polyurea matrix capsules [18,19].

Interestingly, peaks at 2362 and 1507 cm^{-1} were attributed to N=C=O and N=C stretching, which are isocyanate functional groups deriving from unreacted isocyanate molecules used to prepare polyurea matrix microcapsules [18].

The XRD investigation focused on unused Pd EnCat™ 30, recycled catalyst from the first to the tenth reaction cycles, and every other reaction cycle from the twelfth to the thirtieth. The X-ray diffraction pattern deriving from a sample of fresh catalyst showed a main signal at around 20° 2 θ angle, which was attributed to the polyurea matrix [20]. (Figure 3, green line)

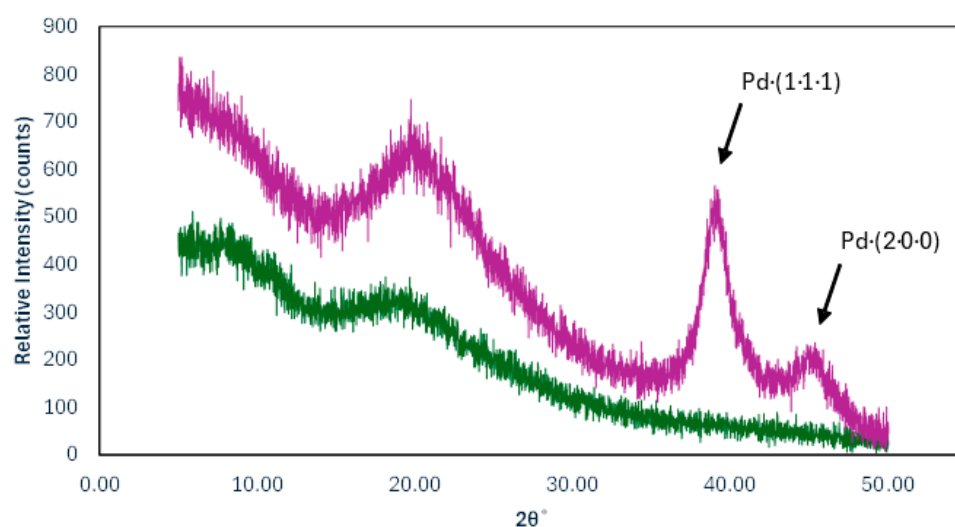


Figure 3. X-ray diffraction patterns of Pd EnCat™ 30 prior to use (green) and after the last reaction cycle (purple). They show its amorphous nature and signals from its main components: the polyurea matrix and two differently sized palladium nanograins.

The XRD spectra generated from the first to the thirtieth reaction cycles displayed a change occurring progressively on the microcapsules surface. The superimposition of the XRD data from unused and 30-fold recycled Pd EnCat™ 30 (purple line) in Figure 3 shows this change: two new peaks at around 40° and 45° 2θ angle emerged. These peaks were attributed to metallic palladium with plane (1 1 1) and (2 0 0), respectively, forming nanograin-sized particles with diameters of 4.40 and 3.60 nm calculated from the Debye Scherrer equation. Similar results have been observed by others [21].

3. Discussion

The reaction was also performed for 30 min but no increase in yield was observed. Moreover, different concentrations of boronic acid were employed, which demonstrated that 1.1 equivalents led to the highest product yields. With equimolar amounts, for example, the yield dropped to 43%. Considering the high rate of conversion with the parameters shown in Scheme 1, no further optimization seemed necessary.

Alternatively, the product can also be isolated by use of crystallization and recrystallization techniques, which allow the recovery of the residual starting organohalide and boronic acid. After concentration of the crude product and solubilization in a minimum volume of acetone, an excess of diethyl ether is slowly added to the vessel under vigorous stirring, which causes tetrabutylammonium acetate/bromide and boron-containing species to precipitate out of the solution. Upon filtration, the filtrate is concentrated. By use of an excess of *n*-pentane, unreacted 2-methoxyboronic acid is crystallized upon heating the vessel, letting it slowly cool down to room temperature, and by isolating the acid crystals via filtration. Unreacted 4-bromonitrobenzene can be recovered by 4-fold recrystallization in a minimum amount of EtOH:H₂O (9:1) solvent system.

Finally, the pure product is obtained by collecting and concentrating the ethanolic filtrates under reduced pressure.

FT-IR spectra from Pd EnCat™ 30 characterization studies did not provide unexpected results. The presence of unreacted isocyanates was previously reported in the literature and, therefore, did not come as a surprise. Palladium acetate signals could not be located considering that they are typically seen within the 1600–1200 cm⁻¹ region, where also strong signals from the polyurea matrix fall [22].

The XRD investigation showed the gradual formation of metallic palladium nanograins across the reaction cycles, which were not present in the unused catalyst sample. Their

presence indicates that palladium acetate is reduced in the presence of ethanol at high temperatures [21,23].

4. Materials and Methods

Experiments were performed by use of CEM Discover[®] 2.0 microwave synthesizer (CEM GmbH, Kamp-Lintfort, Germany) (30 PSI, 250 W), after 1 min. prestirring. Flash column chromatography was performed with a Grace Reveleris[®] Prep Flash Chromatography System (BÜCHI Labortechnik GmbH, Essen, Germany–Reveleris[®] X2 Navigator[™] software) and 55 mL/min. solvent flow rate. Product separation was achieved by use of Claricep[™] CS-series (Phenomenex, Brønshøj, Denmark) screw-on irregular 80 g columns. Pd EnCat[™] 30 was removed by use of a glass fritted filter with 40–60 µm pore size.

NMR analyses of the product were conducted in CDCl₃ using a Bruker AVIII-600 MHz NMR spectrometer (Bruker Corporation, Ettlingen, Germany) equipped with a CPP-TCI cryogenically cooled probe. ¹H and ¹³C spectra were calibrated using the residual TMS signal (0.0 ppm) and CDCl₃ signal (77.16 ppm), respectively, and processed with TopSpin 4.1.4. TLC analyses were performed on ALUGRAM SIL G/UV254 TLC plates (MACHEREY-NAGEL GmbH & Co. KG, Dueren, Germany) with 0.2 mm silica gel and pentane:ethyl acetate (4:1) solvent system. The plates were visualized by use of a Spectroline[®] E-Series UV lamp (Spectronics Corporation, Melville, New York, United States) at 254 nm wavelength. Pd EnCat[™] 30 (0.4 mmol/g Pd loading), Celite[®] 545, 4-bromonitrobenzene (99%) and 2-methoxyphenyl boronic acid (95%) were purchased from Merck (Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany) and used without further purification. Tetrabutylammonium acetate (98%) was purchased from BLD Pharmatech Ltd., Karlsruhe Germany. Solvents were HPLC grade and purchased from VWR Chemicals, VWR International A/S, Søborg, Denmark. Purification of the product was achieved by use of pentane:ethyl acetate as eluent (gradient: 0 B% for 7 min., 0–2 B% over 10 min., 2 B% 5 min.).

IR analyses were conducted by use of a Bruker FT-IR Benchtop TENSOR II spectrometer (Bruker Optics, Billerica, MA, United States) and processed with Bruker Opus v. 7.5 with resolution of 2 cm⁻¹, 64 scans as background and sample scan time. XRD studies were conducted using a PANalytical B.V. Empyrean series 2 X-ray Diffraction System (Malvern Panalytical Ltd., Malvern, Worcestershire, United Kingdom) from 5° to 50° angle, time per step 17.850 s, 0.187575°/s, and 3430 number of steps. XRD spectra were processed using PANalytical B.V. Data Collector software v. 4.1.0.25.

Synthesis of 2-Methoxy-4'-Nitrobiphenyl

In a 35 mL microwave vial, 4-bromobenzene (2 mmol, 1 eq., 408.1 mg), 2-methoxyphenyl boronic acid (2.2 mmol, 1.1 eq., 352 mg), tetrabutylammonium acetate (6 mmol, 3 eq., 1.846 g), and Pd EnCat[™] 30 (0.2 mmol, 0.1 eq., 500 mg) were added to 15 mL of EtOH 96% aqueous solution. The mixture was irradiated in a microwave apparatus at 120 °C for 20 min. Upon cooling to 50 °C, the crude product was filtered, diluted with acetone, adsorbed on 9 g of celite 545, and concentrated under reduced pressure. 2-Methoxy-4'-nitrobiphenyl was purified by flash column chromatography as bright yellow crystals (424.9 mg, 1.85 mmol, 93%, mp 62–63 °C [24]).

¹H NMR (600 MHz, CDCl₃) δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.39 (m, *J* = 4.4 Hz, 1H), 7.31 (q, *J* = 3.0 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 3.82 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 156.47, 146.68, 145.54, 130.72, 130.40, 130.28, 128.28, 123.26, 121.16, 111.51, 55.62.

5. Conclusions

Our investigation assessed the recyclability potential of Pd EnCat[™] 30. To the best of our knowledge, our work is the first study reporting recyclability data over numerous experiments and demonstrates that Pd EnCat[™] 30 can be successfully reused over 30 reaction cycles. Starting from 93%, the isolated product yield dropped to 70% at the

eighth cycle and 51% at the fourteenth, slowly reached 30% at the twenty-sixth, and quickly dropped to 14% at the thirtieth. Characterization studies on Pd EnCat™ 30 at different stages demonstrated depletion of palladium acetate and progressive formation of metallic palladium nanograins. This phenomenon might be the reason behind the gradual loss of activity across the reaction cycles. Catalyst recycling plays a crucial role in advancing towards greener chemical production and can have a major impact on cost reduction. At the same time, the reuse of precious palladium minimizes the necessity for catalyst disposal and diminishes the demand for rare earth metals mining [2,25].

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/org5040023/s1>, ¹H and ¹³C NMR spectra of 2-methoxy-4'-nitrobiphenyl; ¹H NMR spectra of additional products; Figure S1: Combined average FT-IR spectra; Table S1: Isolated yields (%) at each reaction repetition; Table S2: Mean isolated yields (%) ± Standard Deviations; Table S3: Overview of the synthesized additional products.

Author Contributions: Conceptualization, L.D. and C.S.; methodology, L.D.; software, L.D.; validation, L.D.; formal analysis, L.D. and C.S.; investigation, L.D.; resources, L.D.; writing—original draft preparation, L.D.; writing—review and editing, L.D. and C.S.; visualization, L.D.; project administration, L.D. and C.S.; funding acquisition, C.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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