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Electronic Supplementary Information

Aqueous Intramolecular Heck Reaction of (2-iodophenyl)(3-methyl-1H-indol-1-yl)methanone: A Model Reaction for the *in Situ* Performance Evaluation of Pd Catalysts

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Synthetic Procedures and Characterization

(2-iodophenyl)(3-methyl-1H-indol-1-yl)methanone (1) synthesis

To a flask containing pre-distilled $SOCl_2$ (17.55 g, 54.8 mmol), 3.87 g (15.6 mmol) of 2-iodobenzoic acid was added under argon, and the mixture was refluxed for 4 h. The excess of $SOCl_2$ was removed by distillation and the 2-iodobenzoyl chloride was obtained and used in the subsequent step without further purification. To a flask containing a suspension of NaH (0.626 g, 15.6 mmol, 60% in oil) in dry DMF (25 mL) at 0 °C and under argon, a solution of 3-methylindole (1.75 g 13.3 mol) in dry DMF (7 mL) was added dropwise. Next, a solution of 2-iodobenzoyl chloride in dry DMF (7 mL) was added. The reaction was kept at room temperature and stirred for 10 h. The reaction mixture was dissolved in ethyl acetate (EtOAc), washed with water and the organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After purification by flash column chromatography using silica gel (hexane/EtOAc, 95:5) product **1** was obtained as a white solid with a yield of 74%. ^1H NMR (400 MHz, DMSO-d6): δ 8.00 (d, 1H, J = 8.2 Hz), 7.60-7.35 (m, 7H), 6.83 (brs, 1H) and 2.18 (s, 3H).

11-methyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2) synthesis

A 10 mL round-bottom flask equipped with a condenser was loaded with 200 μL of a (2-iodophenyl)(3-methyl-1H-indol-1-yl)methanone solution (38.6 mg, 0.107 mmol) in CH_3CN and NEt_3 (22 μL, 0.3 mmol) and $Pd(OAc)_2$ (4.0 mg, 0.018 mmol) were added. After stirring at 80 ºC for 20 h, further fractions of NEt_3 (7.0 μL, 0.107 mmol) and $Pd(OAc)_2$ (4.0 mg, 0.018 mmol) were added and the system was refluxed again for 20 h. This procedure was repeated twice. After the tenth day of reaction, the mixture was filtered and washed with CH_2Cl_2 for palladium removal. The reaction mixture in CH_2Cl_2 was then washed with water, dried with anhydrous Na_2SO_4 and concentrated over reduced pressure. The product was obtained with 70% of conversion and isolated as a yellow solid with 49% yield after flash chromatography purification (hexane/CH_2Cl_2 1:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.17 (m, 8H), 2.4 (s, 3H).

PS-Me(I) synthesis

The pyridinium salt 1-methyl-2-(propionamidomethyl)pyridinium iodide [PS-Me(I)] is an original compound and it was synthesized in two steps: (i) to a solution of 2-pycolylamine (1.56 g, 14.4 mmol), triethylamine (1.6 g, 15.8 mmol) and CH_2Cl_2 as the solvent at 0 ºC, propionyl chloride (1.43 g, 15.8 mmol) was added dropwise. The reaction was kept in an ice bath and stirred for 30 min. The solvent was evaporated and the crude reaction medium was dissolved in ethyl acetate and washed with water three times. The organic layer was collected and dried with anhydrous $NaSO_4$ and the residue was purified by column chromatography (EtOAc) to obtain the *N*-(pyridin-2-ylmethyl)propionamide as a light yellow oil with a yield of 60%. (ii) The quaternization of the pyridine moiety of the amide obtained in was performed by dissolving the amide (0.94 g, 5.7 mmol) in acetonitrile, mixing with a 5-fold excess of methyl iodide (4 g, 28.5 mmol) and kept under reflux for 5 h. Next, the solvent was evaporated and the crude yellow solid was washed with acetone several times. The PS-Me(I) was obtained as a white solid with a yield of 74%, m.p. 122-125 ºC, elemental analysis calcd (%) for $C_{10}H_{15}N_2O$: C, 39.23; H, 4.94; N, 9.15 found: C, 39.92; H, 6.22; N, 8.98. ^1H NMR (400 MHz, DMSO-d6, Fig. EP1): δ 9.00 (d, J = 5.9 Hz, 1H), 8.69 (Br, NH), 8.55 (t, J = 7.8 Hz, 1H), 8.01 (t, J = 7.0 Hz, 1H), 7.92 (d, J = 8.2, 1H), 4.68 (d, J = 5.5 Hz, 2H), 4.32 (s, 3H), 2.28 (q, J = 7.8 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d6, Fig. EP2): δ 173.9 .(C=O), 155.5 (C), 146.6 (CH), 145.3 (CH); 126.2 (CH); 125.8 (CH), 45.2 (CH_3), 40.0 (CH_2), 28.2 (CH_2), 9.60 (CH_3); IR (KBr, Fig. EP3): ν_{max} = 3228 (N-H), 3050, 3028 (C_{sp2}-H), 2972-2743 (C_{sp3}-H), 1666 (C=O), 1528, 780, 624 (N-H and C-N amide); 1628, 1578, 1467 cm^{-1} (C_{sp2}- C_{sp2} and C_{sp2}-N_{sp2}); ESI-MS (m/z, Fig. EP4): 179.1 (C^+); 485.2 ($C_2^+A^-$); 1097.4 ($C_4^+A_3^-$).

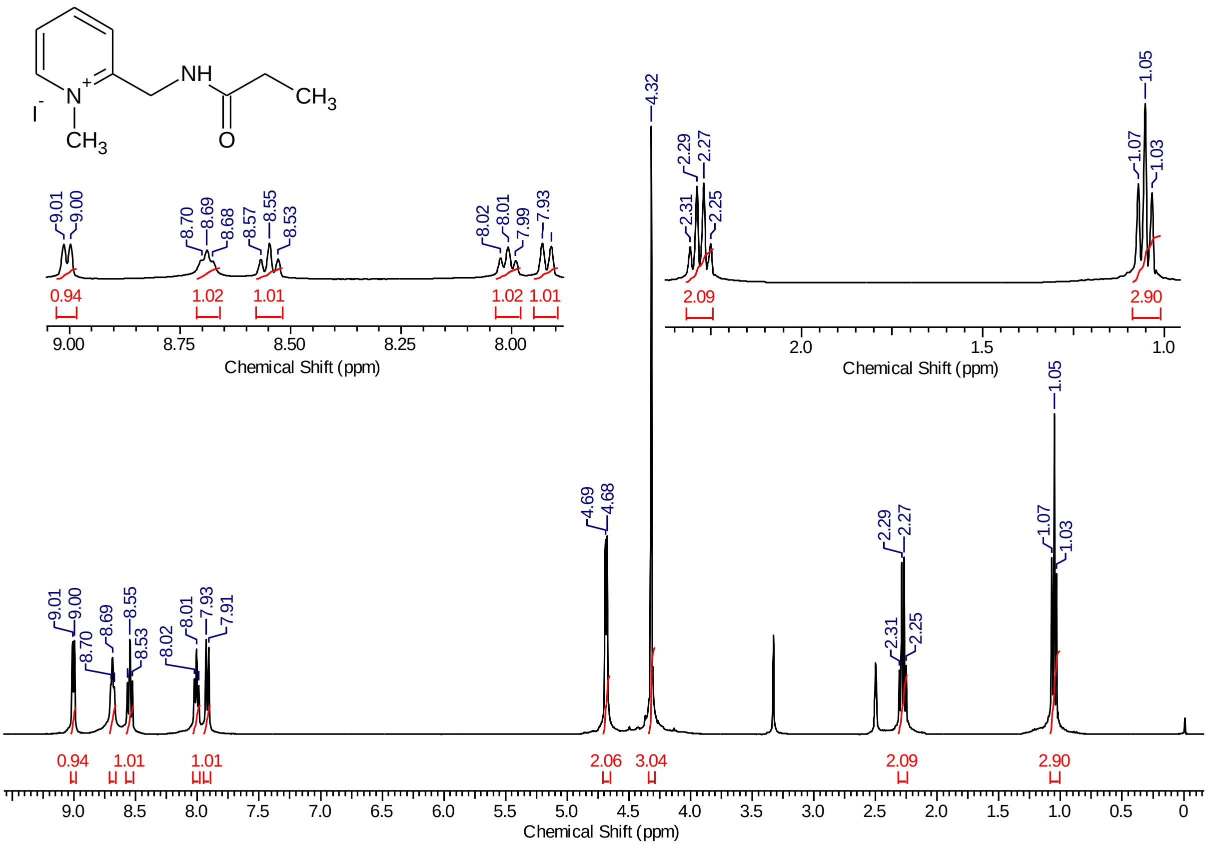

Fig. EP1 ^{1}H NMR (400 MHz, DMSO-d6) for 1-methyl-2-(propionamidomethyl)pyridinium iodide [PS-Me(I)].

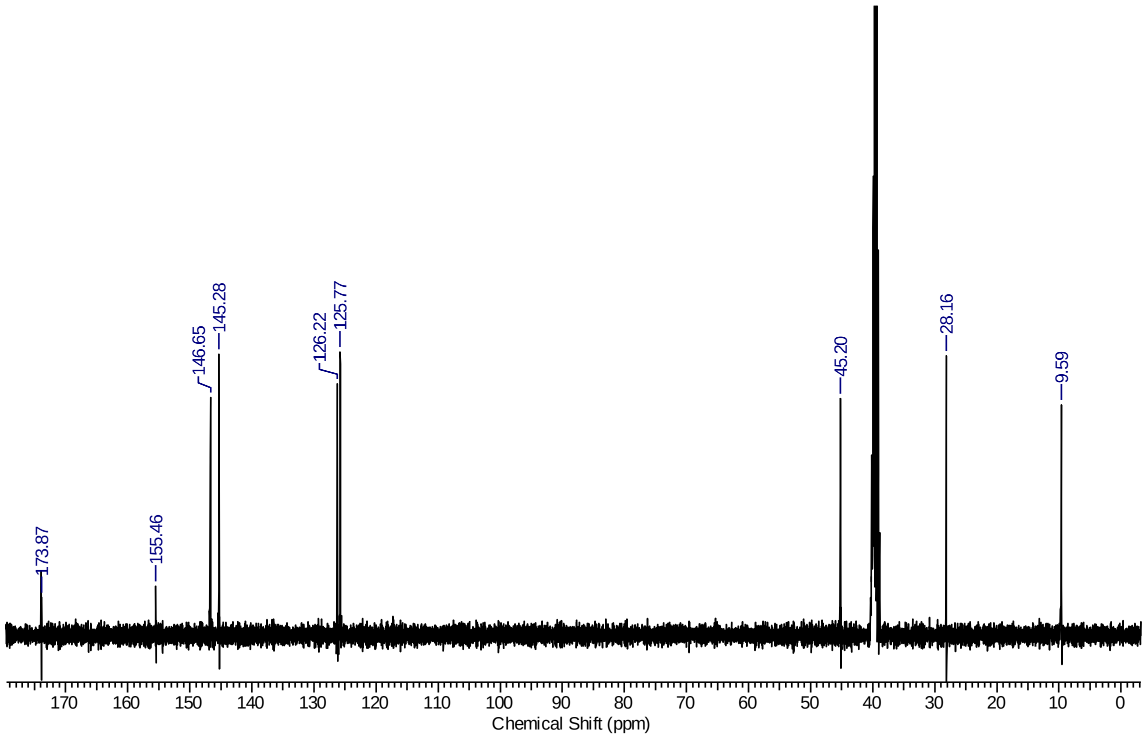

Fig. EP2 ^{13}C NMR (400 MHz, DMSO-d6) for 1-methyl-2-(propionamidomethyl)pyridinium iodide [PS-Me(I)].

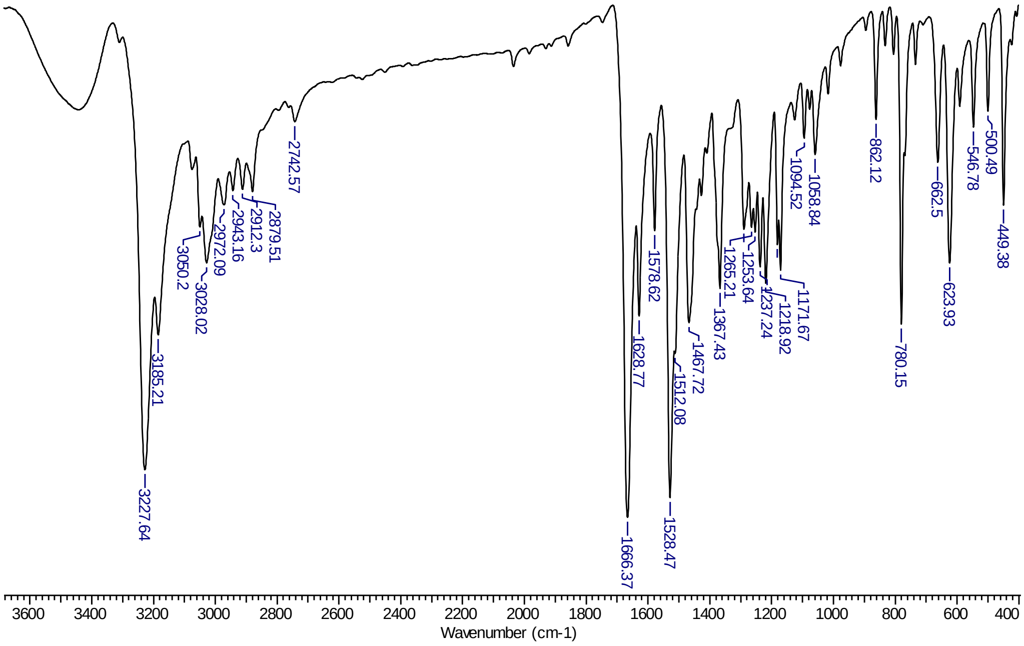

Fig. EP3 FTIR (KBr) for 1-methyl-2-(propionamidomethyl)pyridinium iodide [PS-Me(I)].

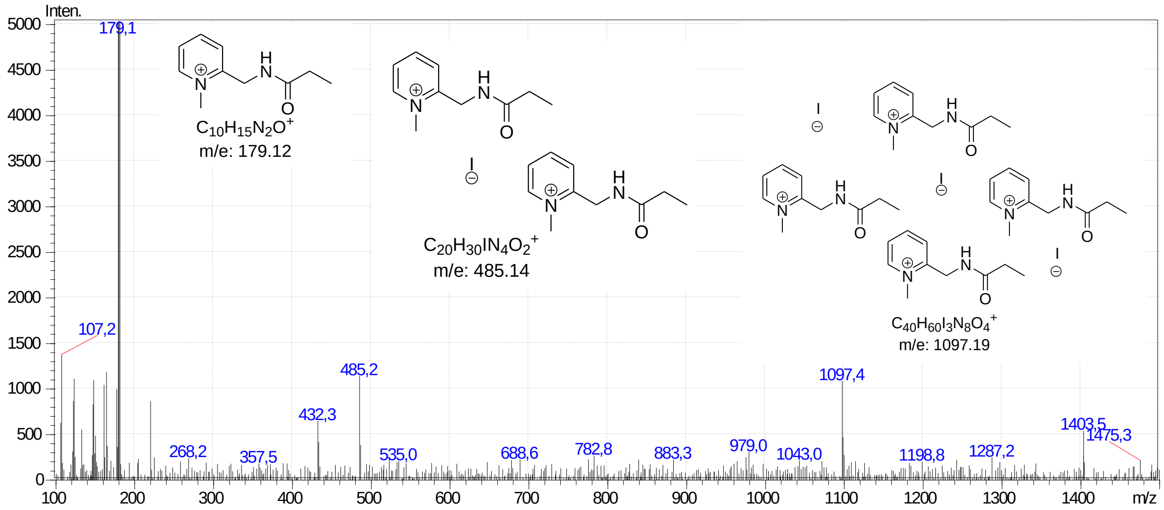

Fig. EP4 ESI-MS (m/z) for 1-methyl-2-(propionamidomethyl)pyridinium iodide [PS-Me(I)].

Kinetic run procedure

All the kinetics experiments were performed at least in triplicate in quartz cuvettes with a volume capacity of 3.5 ml. The progress of the reaction was followed via spectral kinetics in UV-vis spectrophotometer coupled to a thermostatted bath, where the temperature was kept constant at 80 °C throughout the reaction. The experiments were performed in the absence of inert gas, in deionized/degassed water and spectroscopic CH_3CN, in a ratio of 9:1. After the addition of solvent, the base and the catalyst (in that order), the cuvettes were shaken manually and inserted into the spectrophotometer. When the temperature reached 80 °C, the reaction was started by adding the reactant (1) and the spectral changes acquired over time.

Figures (S1-S5)

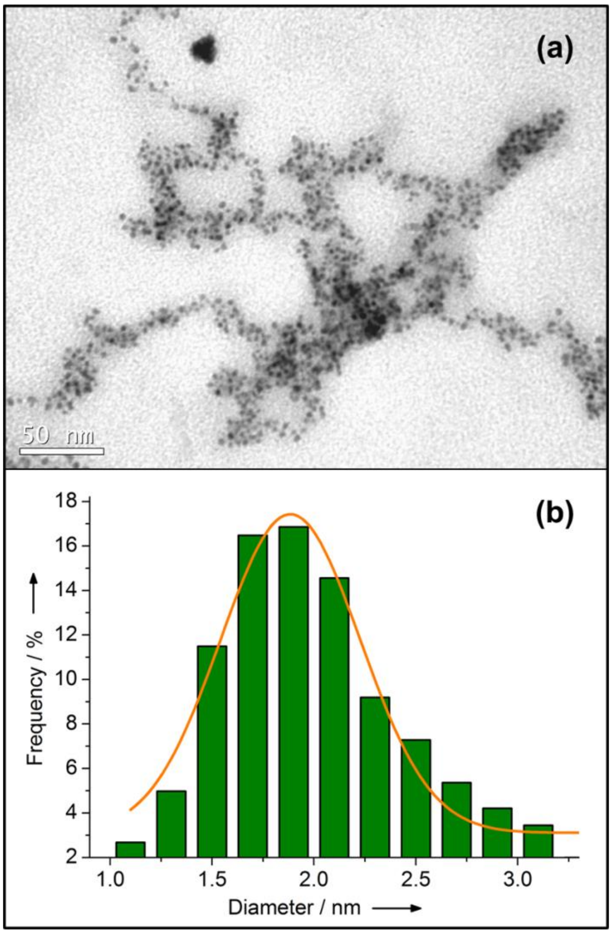

Fig. S1 (a) TEM micrograph and (b) size distribution histogram of the *as*-prepared Pd-NPs.

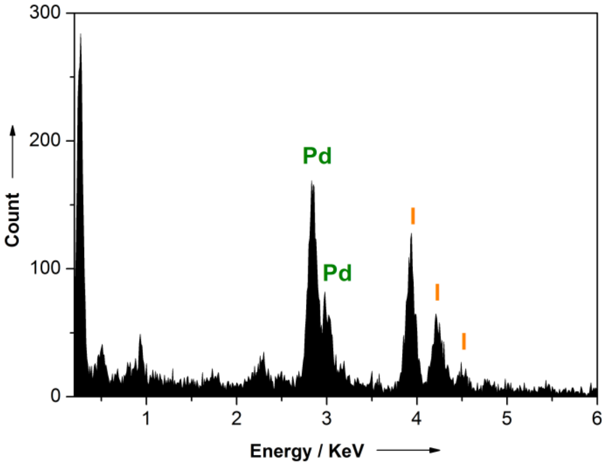

Fig. S2 Energy-dispersive X-ray spectrum of the *as*-prepared Pd-NPs.

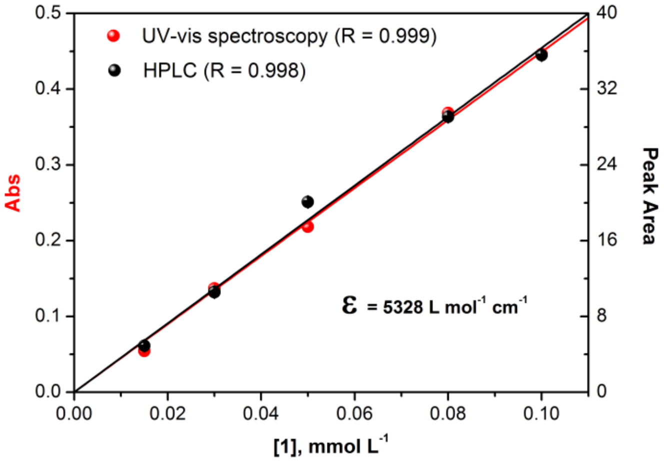

Fig. S3 Determination of the molar absorption coefficient for the product **2** by UV-vis spectroscopy and HPLC.

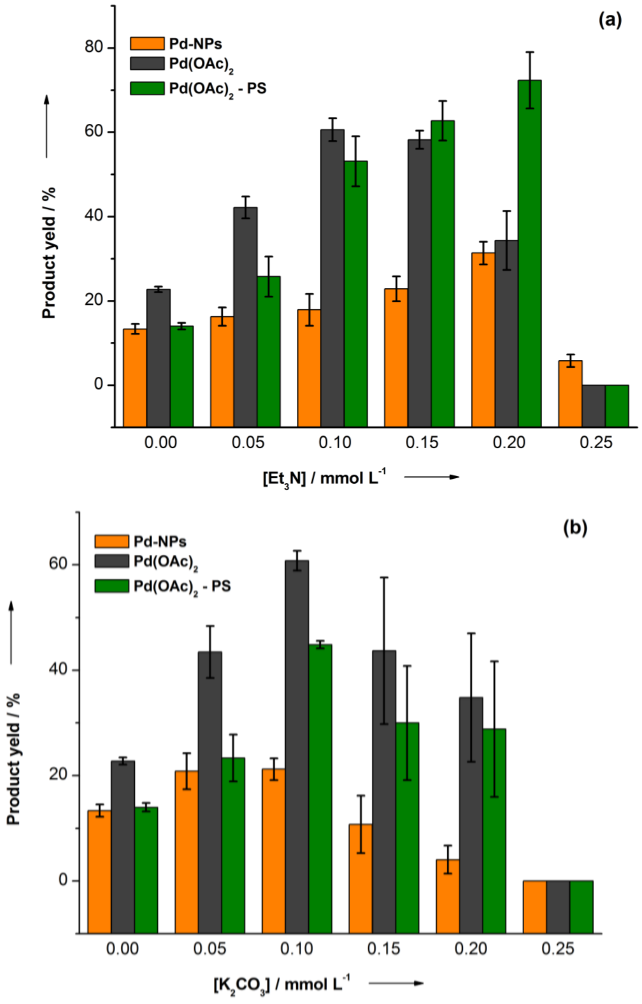

Fig. S4 Product yield as a function of (left) Et_3N and (right) K_2CO_3 concentrations, for the cyclization reaction of **1** catalyzed by Pd-NPs (orange bars), $Pd(OAc)_2$ (grey bars) or $Pd(OAc)_2$-PS (green bars) in H_2O/CH_3CN (9/1, v/v). ([**1**] = 0.1 mmol L^{-1}; [Pd] = 10 mol%; 80 °C).

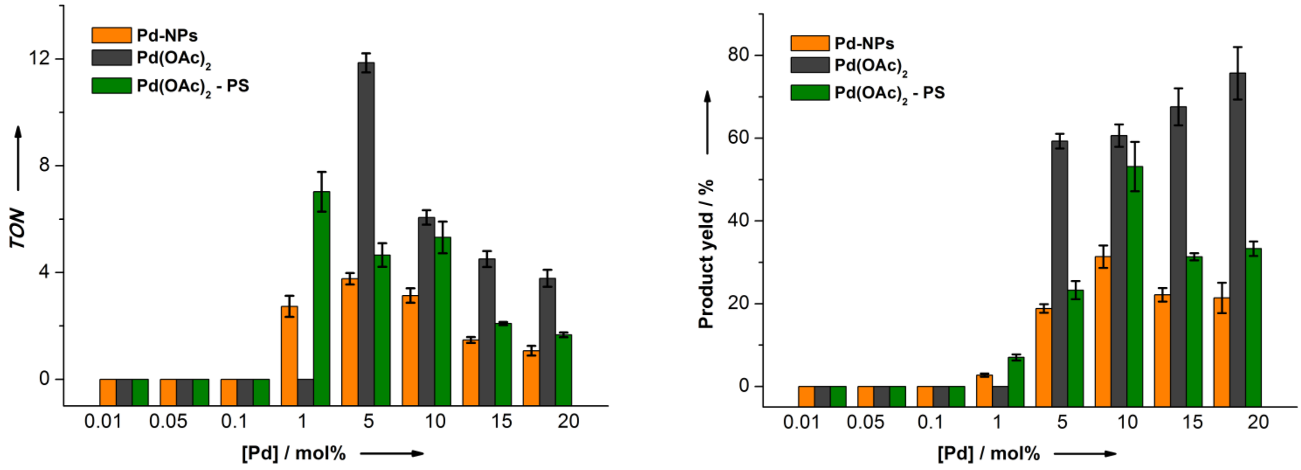

Fig. S5 (Left) TON and (right) product yield as a function of Pd loading (mol%), for the cyclization reaction of **1** catalyzed by Pd-NPs (orange bars), $Pd(OAc)_2$ (grey bars) or $Pd(OAc)_2$-PS (green bars) in H_2O/CH_3CN (9/1, v/v). ([**1**] = 0.1 mmol L^{-1}; [Et_3N] = 0.1 mmol L^{-1}; 80 °C).