

Highly Recoverable Pd(II) Catalysts for the Mizoroki–Heck Reaction based on N-Heterocyclic Carbenes and Poly(Benzyl Ether) Dendrons

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1. General Procedures

All reactions were performed under an argon atmosphere using standard Schlenk or dry-box techniques. Unless otherwise stated, reagents were obtained from commercial sources and used as received. Solvents were previously dried prior to use and distilled under argon as described elsewhere.¹ Dichloromethane, diethyl ether, *n*-hexane, tetrahydrofuran, and toluene (HPLC grade) were purified by flash column chromatography and collected under argon, using a MBraun MB SPS solvent purification device. Ethyl acetate (synthesis grade) was used as received. ¹H and ¹³C NMR spectra were recorded with a Varian Mercury 300, Unity 300, or Unity 500 Plus spectrometer. Chemical shifts (δ parts per million) are quoted relative to SiMe₄ (¹H, ¹³C). They were measured by internal referencing to the ¹³C or residual ¹H resonances of the deuterated solvents. Coupling constants (*J*) are given in hertz. When required, two-dimensional ¹H-¹³C HSQC and HMBC experiments were carried out for the unequivocal assignment of ¹H and ¹³C resonances. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum-2000 spectrophotometer. The Analytical Services of the Universidad de Alcalá performed the C, H, and N analyses using a LECO CHNS-932 microanalyzer, and the mass spectra using an Agilent G3250AA LC/MSD TOF Multi (MALDI and ESI) mass spectrometer. Palladium analyses were performed by the Centre for Applied Chemistry and Biotechnology of the Universidad de Alcalá in an Agilent 7700x ICP-MS instrument. TEM images were obtained at the Instituto de Catálisis y Petroquímica (ICP-CSIC)

using a JEOL 2100Fm microscope operating at an accelerating voltage of 200 kV. Samples were prepared by placing five drops of the aqueous solutions on a holey carbon film copper grid (200 mesh) and allowing the solvent to evaporate in air. The metal content of the nanoparticles or conglomerates was analyzed by EDS (Energy Dispersive X-ray Spectroscopy). Dynamic light scattering (DLS) measurements were performed on Malvern Zetasizer Nano ZEN3600 Instrument, fitted with a He-Ne Laser ($\lambda = 632,8 \text{ nm}$).

2. Synthesis of 1,2-Di(1*H*-imidazol-1-yl)ethane

This compound was prepared by a modification of the procedure previously reported.² Replacement of dibromoethane by dichloroethane reduced significantly the amount of by-products and increased the yields. A mixture of 1*H*-imidazole (7.00 g, 103 mmol), powdered potassium hydroxide (6.92 g, 123 mmol), and tetrabutylammonium bromide (0.994 g, 3.10 mmol) was stirred for 1 h at room temperature. 1,2-Dichloroethane (4.08 mL, 51.5 mmol) was then added, and the mixture was stirred for 24 h at 55 °C. Subsequently, additional portions of potassium hydroxide (3.46 g, 61.5 mmol) and 1,2-dichloroethane (4.08 mL, 51.5 mmol) were added to the reaction mixture to ensure complete consumption of the imidazole reagent. Stirring was continued for 24 h at 55 °C. The mixture was extracted with ethanol (4 × 50 mL) and the ethanol phase was filtered and evaporated to dryness under vacuum. The residue consisted on a mixture of the desired product and 1-vinylimidazole. This mixture was separated by column chromatography using chloroform/ethanol (17:3) as eluent. 1,2-Di(1*H*-imidazol-1-yl)ethane was obtained as a white solid (10.9 g, 65%). ¹H NMR (CDCl₃, 293 K): δ 4.21 (s, 4H), 6.63 (d, 2H, $J = 1.3$), 6.97 (d, 2H, $J = 1.3$), 7.17 (s, 2H). ¹H NMR data for 1-vinylimidazole (CDCl₃, 293 K): δ 4.88 (dd, 1H, $J = 1.6$ and 8.6), 5.28 (dd, 1H, $J = 1.6$ and 15.6), 6.88 (dd, 1H, $J = 8.6$ and 15.6), 7.08 (s, 1H), 7.16 (s, 1H), 7.63 (s, 1H).

3. Crystallographic Data for Complexes 1, 2, and 10

Table S1. Crystallographic data for complexes 1, 2, and 12.

	1	2·CH₂Cl₂	10·dmf
empirical formula	C ₃₄ H ₃₂ Br ₂ N ₄ Pd	C ₉₁ H ₈₂ Br ₂ Cl ₂ N ₄ O ₈ Pd	C ₅₃ H ₅₃ Br ₂ N ₅ O ₅ Pd
formula weight	762.85	1696.72	1106.22
crystal size (mm)	0.3 × 0.2 × 0.1	0.5 × 0.25 × 0.14	0.4 × 0.3 × 0.1
temperature (K)	200(2)	200(2)	200(2)
wavelength (Å)	0.71073	0.71073	0.71073
crystal system	monoclinic	triclinic	monoclinic
space group	P2 ₁ /n	P-1	P2 ₁ /c
<i>a</i> (Å)	10.9263(13)	12.798(2)	8.3084(10)
<i>b</i> (Å)	12.6594(5)	17.5370(6)	13.475(2)
<i>c</i> (Å)	11.4378(10)	19.875(3)	42.490(6)
α (deg)	90	114.524(6)	90
β (deg)	106.136(8)	91.344(12)	93.147(10)
γ (deg)	90	90.963(3)	90
volume (Å ³)	1519.8(2)	4055.5(9)	4749.7(11)
<i>Z</i>	2	2	4
calcd density (g/cm ³)	1.667	1.389	1.547
μ (mm ⁻¹)	3.270	1.339	2.128
<i>F</i> (000)	760.0	1740.0	2248
θ range (deg)	3.034 to 27.501	3.05 to 25.997	3.023 to 27.511
limiting indices (<i>h</i> , <i>k</i> , <i>l</i>)	±14, -16 to 15, ±14	±15, -21 to 20, -23 to 24	±10, -15 to 17, -54 to 55
no. of reflns collected	12683	15729	9828
no. of reflns unique / <i>R</i> _{int}	3490 / 0.0724	15729 / 0.169	9828 / 0.058
no. of reflns observed [<i>I</i> > 2σ(<i>I</i>)]	2573	6099	5062
completeness to θ	99.9%	98.7%	89.9%
absorption correction	multi-scan	multi-scan	multi-scan
min. and max. transmission	0.509 and 0.548	0.770 and 0.905	0.960 and 0.999
refinement method		full-matrix least-squares on <i>F</i> ²	
no. of data / restraints / param.	3490 / 0 / 187	15729 / 0 / 939	9828 / 0 / 595
goodness of fit on <i>F</i> ²	1.042	0.934	0.950
<i>R</i> ₁ / <i>wR</i> ₂ [<i>I</i> > 2σ(<i>I</i>)] ^a	0.0779 / 0.2364	0.0959 / 0.1981	0.0450 / 0.0819
<i>R</i> ₁ / <i>wR</i> ₂ (all data)	0.1061 / 0.2517	0.2367 / 0.2493	0.1274 / 0.0998
largest diff. peak and hole (e/Å ³)	2.80 and 3.53	0.72 and -1.08	0.90 and -0.59

^a $R_1 = \Sigma(|F_o| - |F_c|) / \Sigma|F_o|$; $wR_2 = \{[\Sigma\omega(F_o^2 - F_c^2)] / [\Sigma\omega(F_o^2)]\}^{1/2}$.

4. Catalytic Studies

General Conditions. All the catalytic tests were performed at least in duplicate. The reaction solvent (dimethylformamide, dmf) was distilled under argon prior to use. The glassware and magnetic stirrers used for the preparation of solutions or for running the catalytic reactions were washed with aqua regia to remove any trace of metal deposit. The possibility of artefacts due to Pd contamination of the starting materials was discarded performing periodic tests in the absence of the Pd catalyst. Gas chromatograms were recorded on an HP-5890 Series II Instrument fitted with a flame ionization detector and a fused silica Agilent DB-1 capillary column (15 m length, 0.25 mm internal diameter, 0.10 μm film thickness) under the following conditions: injector temperature, 250 $^{\circ}\text{C}$; detector temperature, 260 $^{\circ}\text{C}$; oven temperature program: 120 $^{\circ}\text{C}$ isotherm.

Scheme S1. Heck-Mizoroki Reaction of Methyl Acrylate with *para*-Iodotoluene

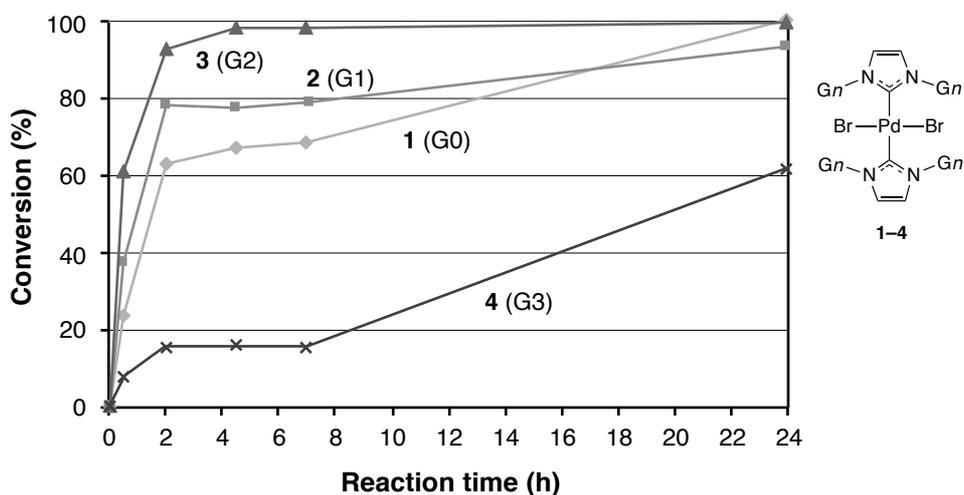
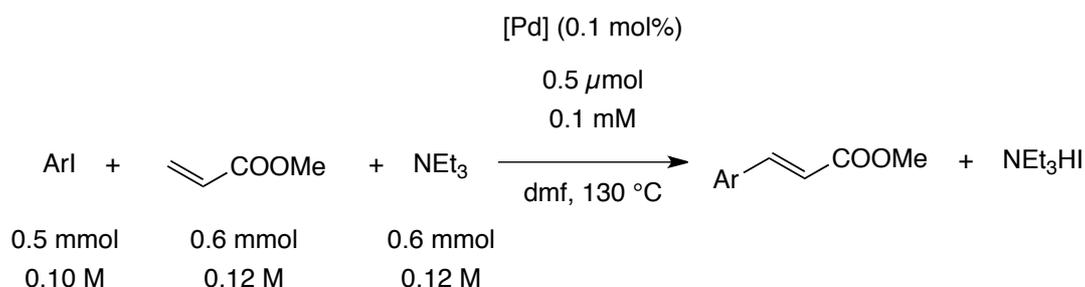


Figure S1. Kinetic profiles for monodentate complexes **1-4** at the initial reaction cycle under the conditions specified in Scheme S1.

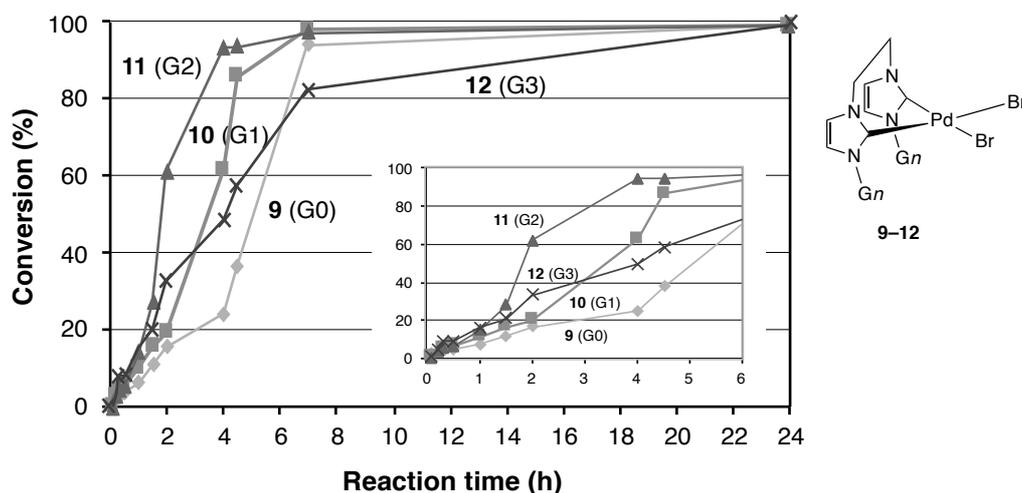


Figure S2. Kinetic profiles for chelate complexes **9-12** at the initial reaction cycle under the conditions specified in Scheme S1. The catalysts were not preactivated in these experiments.

Test with a Pd(II) Scavenger (PVPy). Catalyst **9** (2.5 μmol) and poly(4-vinylpyridine) (2% cross-linked with divinylbenzene; 31.6 mg, 300 μmol of pyridine groups) were stirred in dmf (5 mL) for 5 h. The PVPy polymer was separated by filtration and an aliquot of the resulting solution (1 mL) was transferred to a glass ampoule. Methyl acrylate (0.6 mmol), *para*-iodotoluene (0.5 mmol), triethylamine (0.6 mmol) and naphthalene (0.5 mmol) were subsequently added and the reaction was monitored as described in the Catalytic studies section.

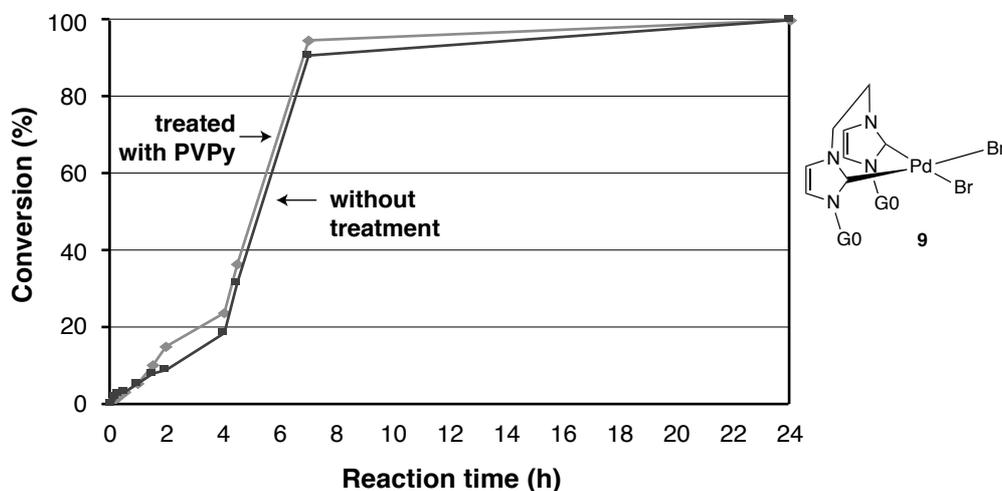


Figure S3. Comparison of the kinetic profiles obtained with and without pretreatment of the catalyst with PVPy in the case of complex **9**.

Incubation Experiments. These experiments were performed as described above with the following modification. The glass ampoule was initially filled with the solvent, catalyst and the next reactants: methyl acrylate and triethylamine (test **A**), triethylamine (test **B**), or methyl acrylate (test **C**). The mixture was heated at 130 $^{\circ}\text{C}$ for 3.5 h before the addition of the remaining reactants (*para*-iodotoluene in test **A**, *para*-iodotoluene and methyl acrylate in test **B**, and *para*-iodotoluene and triethylamine in test **C**).

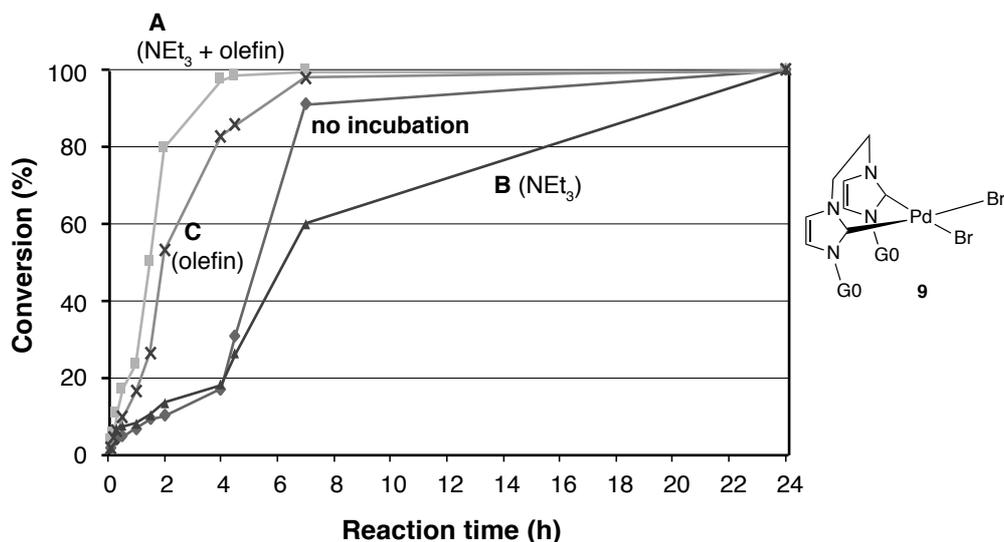


Figure S4. Comparison of the kinetic profiles obtained for **9** under different preincubation conditions. Profiles A-C were obtained after preincubation of the catalysts during 3 h in the presence of the indicated reagents.

Incubation Experiments: ^1H NMR Monitoring. Complex **9** (10 mg, 0.016 mmol), methyl acrylate (2.90 μL , 0.032 mmol), triethylamine (4.60 μL , 0.032 mmol), and $\text{dmf-}d_7$ (5 mL) were introduced into a valved NMR tube (spectrum in Figure S5a). The tube was inserted into a silicone bath and heated at 130 $^\circ\text{C}$ for 3 h (spectrum in Figure S5b). Then, *para*-iodotoluene (3.5 mg, 0.016 mmol) was added to the solution and the NMR spectrum recorded again after 6 h of reaction (Figure S5c).

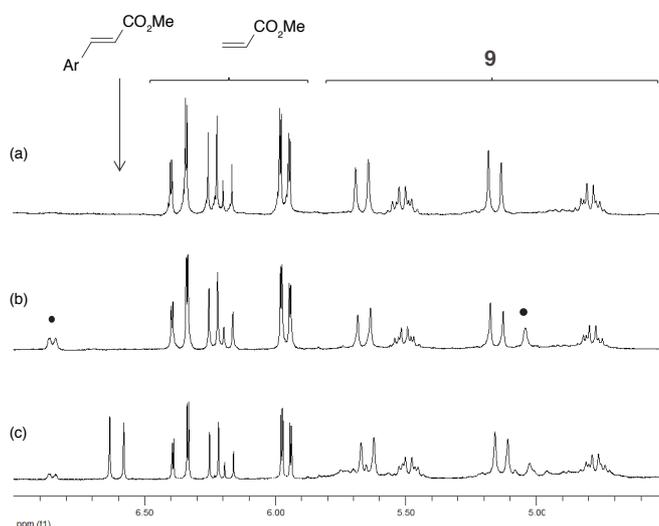


Figure S5. ^1H NMR spectra of a solution containing a mixture of complex **9**, 2 equiv of methyl acrylate, and 2 equiv of triethylamine (a) after dissolution at room temperature and (b) after 3 h at 130 C. (c) ^1H NMR spectrum of the same solution after addition of 1 equiv of *para*-iodotoluene. The resonances marked with a black circle (●) at 6.85 ppm (doublet) and 5.02 ppm correspond to a new NHC complex that could not be identified.

Reloading Experiments. Methyl acrylate (0.54 mL, 6 mmol), *para*-iodotoluene (1.10 g, 5.0 mmol), and triethylamine (0.84 mL, 6.0 mmol) were dissolved in dmf (1.80 mL). An aliquot of this solution (0.180 mL) was added to the reaction medium at the end of every reloading cycle to

recover the initial amounts of reagents. Subsequently, the solution was heated at 130 °C for a new catalytic cycle.

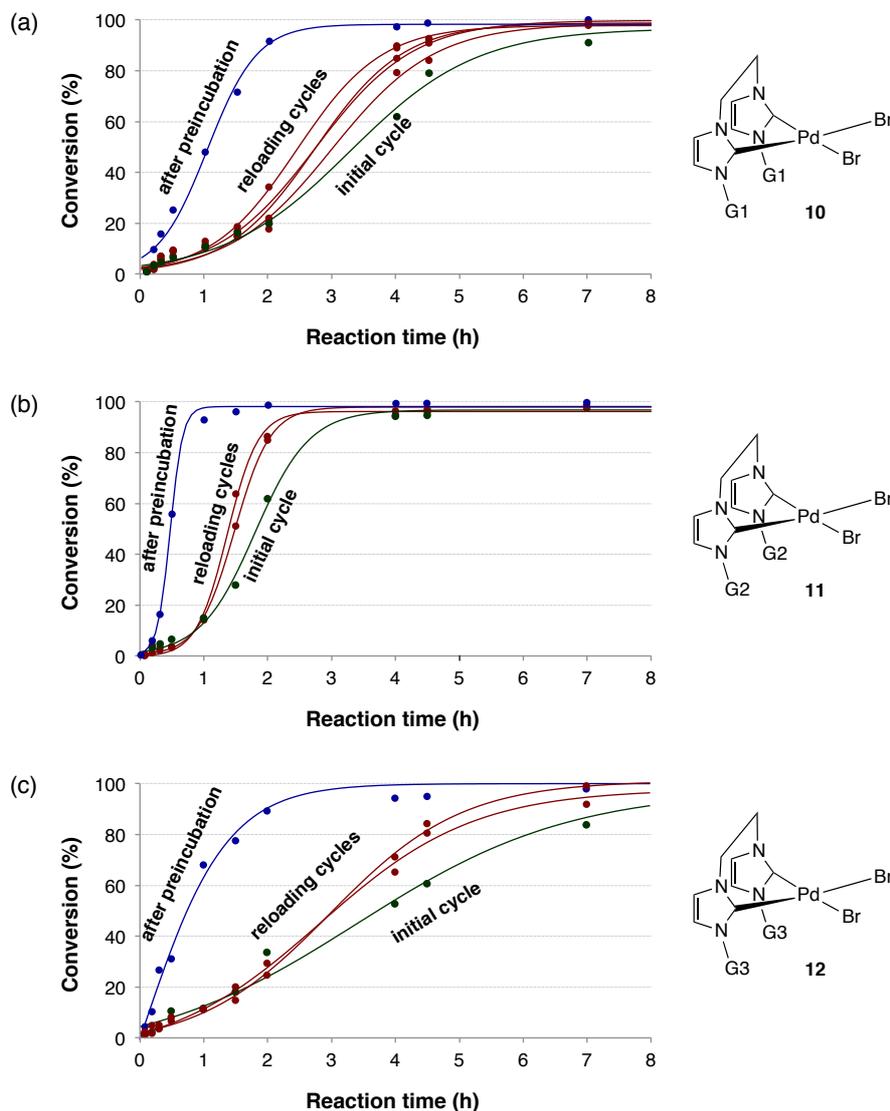


Figure S6. Kinetic profiles for chelate complexes (a) **10** (G0), (b) **10** (G1), and (c) **12** (G2) at the initial cycle and four (for **10**) or two (for **11** and **12**) consecutive reloading cycles. Conversions were measured by GC and are referred to the amount of aryl iodide added in each reaction cycle.

Table S2. Conversions (%) measured for monodentate complexes **1** and **3** in the initial reaction cycle and in three consecutive reloading experiments

reaction time	1 (G0)				3 (G2)			
	initial cycle	1st reloading cycle	2nd reloading cycle	3rd reloading cycle	1st reloading cycle	2nd reloading cycle	3rd reloading cycle	1st reloading cycle
2 h	63%	70%	69%	72%	92%	93%	94%	91%
24 h	100%	100%	100%	100%	100%	100%	100%	100%

^a Conversions are referred to the amount of *para*-iodotoluene added for the corresponding reaction cycle.

5. Catalyst Recovery Studies

Nanofiltration Cell. Recovery experiments were performed on a high-pressure stirred cell built with 316 stainless steel (METcell, Membrane Extraction Technology, Ltd.; Figure S6).³ This cell has a processable volume of 300 mL, a hold-up volume of ca. 5 mL, and a maximum operating pressure of 69 bar (1000 psig). The sintered disk (f in Figure S6) was removed when using ceramic membranes. Ceramic DisRAM™ membranes of 90 mm of diameter and molecular weight cut-off (MWCO) of 1 kDa were furnished by TAMI industries (reference MPD90000N001).⁴ The active layer of these membranes is composed by zirconia/titania and it is supported over titania. The membranes are compatible with organic solvents and with aqueous solutions in the pH range between 0 and 14. The maximum working pressure is nominally 4 bar but we occasionally observed the formation of small cracks in the active layer at pressures above 3 bar when using these membranes in a METcell system. The membrane was washed with dimethylformamide at the end of every recovery cycle, but membrane regeneration can be also performed with acids, bases or oxidants.

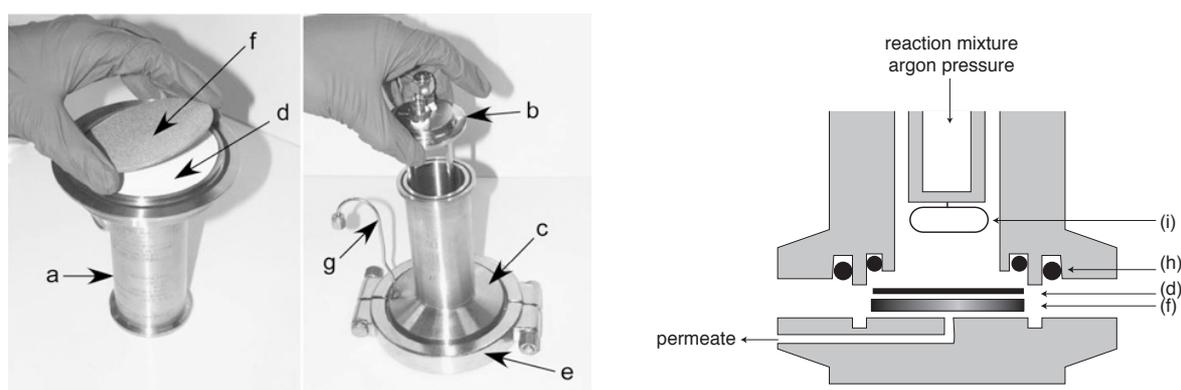


Figure S7. METcell nanofiltration system. (a) METcell body (300 mL), (b) METcell lid with stirring bar, (c) METcell base, (d) membrane, (e) high pressure clamp, (f) sintered disk, (g) permeate line, (h) o-ring, (i) stirring bar.

Table S3. Conversions (%) attained in the successive recovery cycles.^a

cycle	1	2	3	4	5	6	7	8	9	10	11	12	13
10 (G1)	100	50											^c
11 (G2)	100	93.3	92	91.3	84.5	94.1	80.1						^c
12 (G3)	100	100	100	98.2	99.8	100	100	100	99.9	99.8	99.7	99.7	99.6

^a Determined by Gas Chromatography using naphthalene as internal standard.

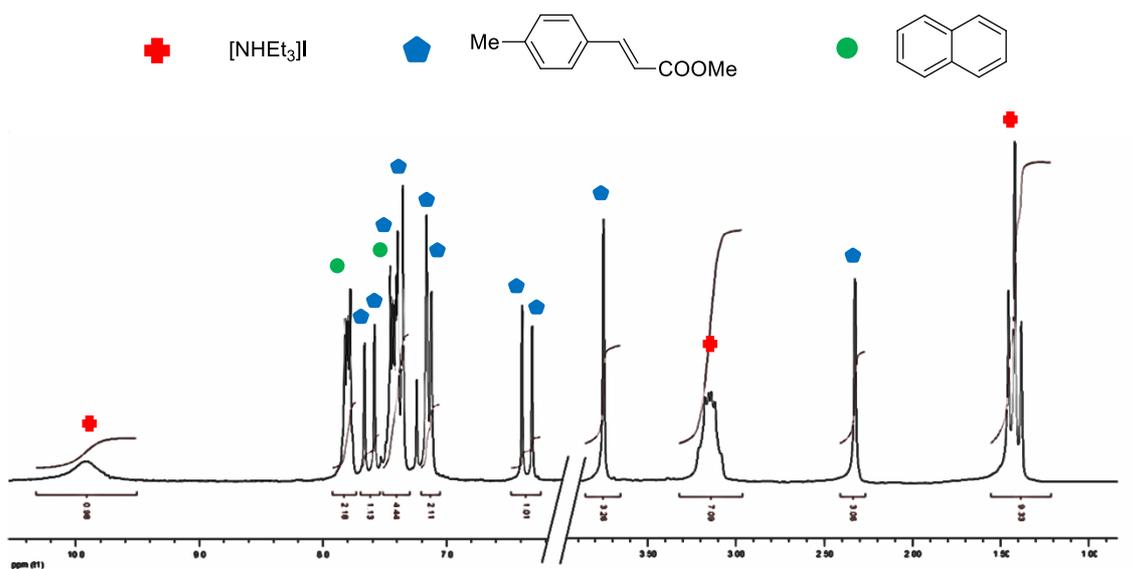


Figure S8. ^1H NMR in CDCl_3 of the permeate obtained after the first cycle of nanofiltration with complex **11**. The sample contains equimolar amounts of the coupling product (methyl *para*-methylcinnamate) and ammonium iodide (together with naphthalene, which was used as internal standard). This test was performed to assure that the nanofiltration membrane does not retain the salt which would result in their precipitation by accumulation over the cycles in the retentate.⁵

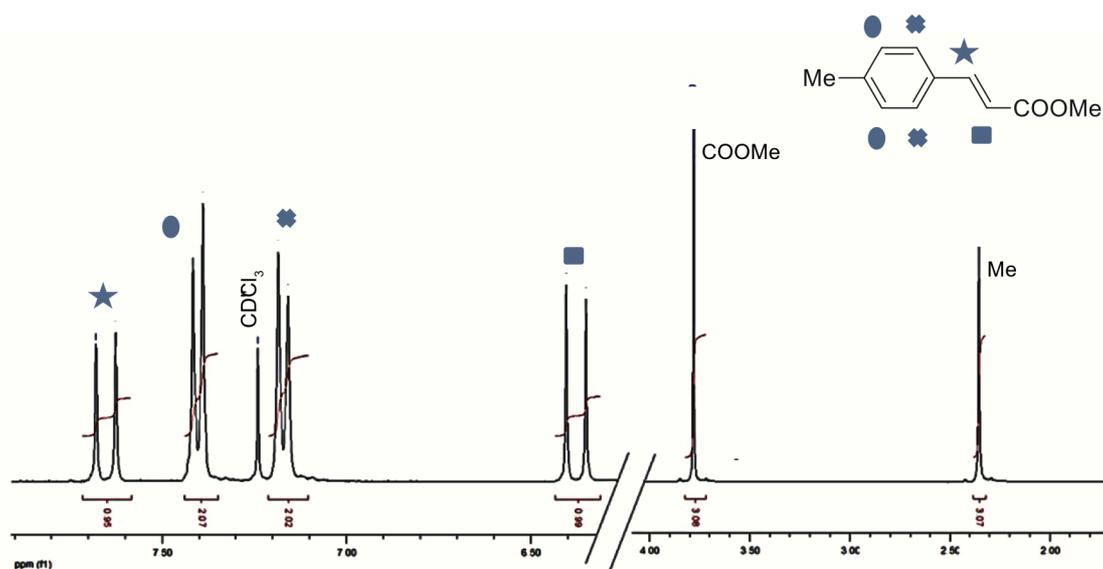


Figure S9. ^1H NMR in CDCl_3 of the coupling product (methyl *para*-methylcinnamate) after extraction from the crude of reaction.

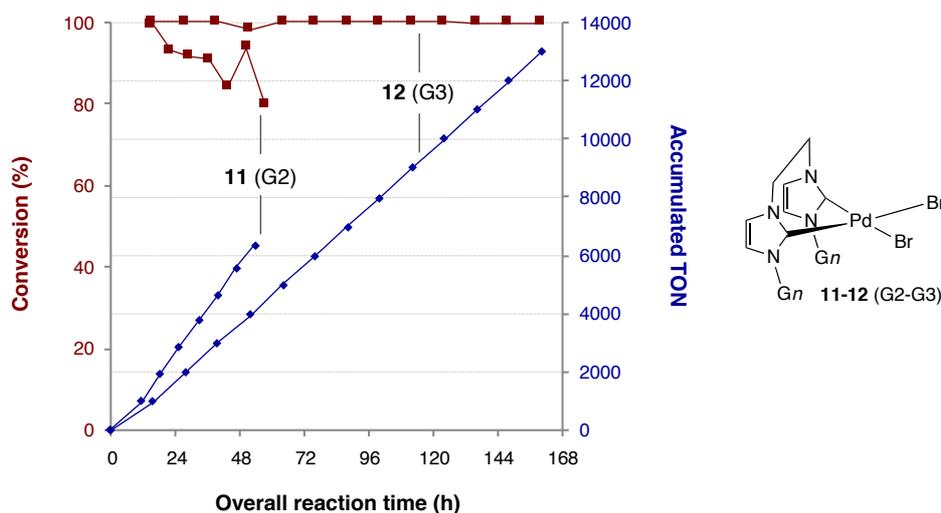


Figure S10. Conversions per cycle (in red) and accumulated turnover numbers (TON, in blue) over the overall reaction time for **11** and **12**.

Palladium analyses. After separation by nanofiltration, the palladium content was analyzed in the permeate (for the intermediate recovery cycle) or the retentate (for the last recovery cycle). The samples were prepared for analysis as follows: the corresponding solutions were evaporated to dryness. The solid thus obtained was weighted and a portion of this solid was separated and sent to analysis. The samples were analyzed by duplicate by ICP-MS spectrometry. The content of Pd in the permeates (for the intermediate cycles) or retentate (for the last cycle) is shown in Table S4 as a percentage of the total amount of Pd (in mole).

The evolution of Pd content over the successive recovery cycles shown in Figure 6b was calculated by subtracting the Pd content determined in the permeates (Table S4) from the Pd content in the initial reaction mixture.

Table S4. Pd content (%) in permeates (for the intermediate recovery cycles) or retentate (for the last cycle).^a

cycle	1	2	3	4	5	6	7	8	9	10	11	12	13
11 (G2)	17.3			2.0 ^b			1.0	71.7^c					
12 (G3)	5.14	0.60	0.32	0.76	0.48	0.23	0.51	0.15	0.39	0.87	0.29	0.32	89.9^c

^a Pd content determined by ICP-MS spectrometry. Values are given as percentage of Pd in the permeate or retentate in respect to the total amount of Pd present in the initial reaction mixture (in mole). ^b Permeates 2-6 were combined before analysis. This value represents the average Pd lost per cycle. ^c Pd content in the retentate.

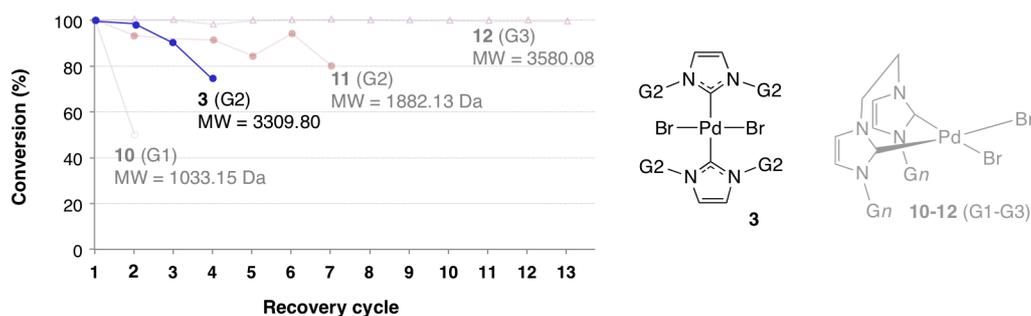


Figure S11. Conversions obtained in the recovery experiments for complex **3** after 7 h of reaction [12 h in the initial cycle], compared with those observed for **10-12**.

Retention Factors. The retention of the dendritic complexes by the DisRAMTM membrane was determined as follows. A solution of the complex (100 mL, 0.025 μ M) was transferred to the nanofiltration cell that was pressurized at 1.5 bar. Under continuous stirring, the permeate was collected in a graduate test tube up to reach a volume of 50 mL. Concentrations of Pd in the permeate and retentate solutions were determined by ICP-MS (9.67 and 4600 pg/mL, respectively, for the G3 complex **4**; retention factor = 99.8%).

Table S5. Palladium content (%) calculated from the retention factor measured for **12** (99.8%).^a

cycle	1	2	3	4	5	6	7	8	9	10	11	12	13
reaction	100	99.72	99.44	99.16	98.89	98.61	98.33	98.06	97.78	97.51	97.24	96.96	96.69
permeate ^b	0.280	0.279	0.278	0.277	0.277	0.276	0.275	0.274	0.274	0.273	0.272	0.271	0.271

^a Values are given in percentage of the Pd present in the initial reaction mixture. The value was calculated considering the two nanofiltration steps performed for each recovery cycle: the 100 mL of the initial solution were reduced to 30 mL in the first step, refilled with dmf to 100 mL and reduced again to 30 mL in the second step. The next equation was used for determining the Pd content in the permeate (P) from the Pd content in the reaction mixture (R): $P = R \times (1 - 0.998) \times (70/100) \times (2 - (1 - 0.998) \times (70/100))$.

6. Other Studies

Evaluation of the catalytic activity of the permeate solutions: The potential presence of active species in the permeate solutions was evaluated as follows: The first 5 mL of the permeate solution were carefully collected under an inert atmosphere and transferred to a glass ampoule together with methyl acrylate (0.054 mL, 0.60 mmol), *para*-iodotoluene (0.110 g, 0.50 mmol) and triethylamine (0.084 mL, 0.60 mmol). The mixture was heated at 130 °C and conversions were determined by CG. This study was performed with the permeates obtained from **10** (1st cycle), **11** (1st, 3rd, and 6th cycles), and **12** (1st, 3rd, 6th and 10th cycles). Complete conversion of substrates was observed for complex **10** after 36 h of reaction in agreement with the low recoverability of the catalyst. For complexes **11** and **12**, no conversion was observable.

Mercury Poisoning Test. Two glass ampoules were loaded with catalyst **9** and reagents as described in the Catalytic studies Section and heated at 130 °C. After 90 min of reaction, Hg (0.002 mL, 300 equiv with respect the amount of Pd catalyst) was added to one of the ampoules. The procedure was continued as described in the Catalytic Studies Section. The kinetic profiles of both experiments are compared in Figure S12.

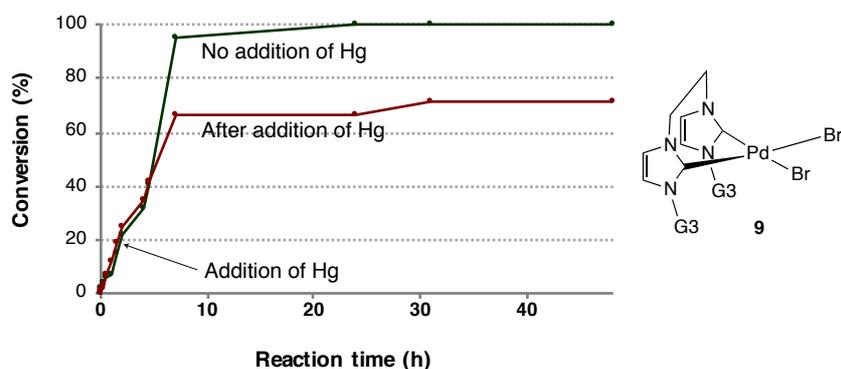
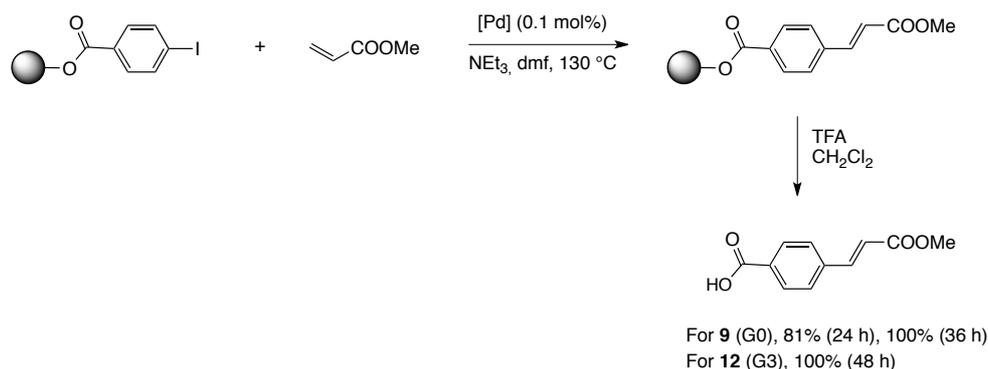


Figure S12. Kinetic profiles for the G0 chelate complex **9** in two parallel experiments. In one of them, Hg was added after 90 min of reaction.

Collman Test. A Wang resin was modified by attaching 4-iodobenzoate groups and the iodine loading ($0.636 \text{ mmol g}^{-1}$) was determined as described elsewhere.⁶ A Schlenk flask was charged under an argon atmosphere with the modified Wang resin (786 mg, 0.5 mmol of iodine), methyl acrylate (0.6 mmol), triethylamine (0.6 mmol), the corresponding catalyst (0.5 μmol) and dmf (5 mL). The reaction mixture was stirred at 130 °C for 24 h (for complex **9**) or 48 h (for complex **12**). The Wang resin was collected on a filter funnel, washed with dmf ($3 \times 5 \text{ mL}$), water ($3 \times 5 \text{ mL}$), dmf ($3 \times 5 \text{ mL}$), dichloromethane ($3 \times 5 \text{ mL}$), and methanol ($3 \times 5 \text{ mL}$), and dried under vacuum. The Wang resin was suspended in a mixture of trifluoroacetic acid (TFA):dichloromethane 1:1 (v/v) (3 mL) and stirred for 2 h to cleave the linking of the benzoate group to the Wang resin (Scheme S2). The cleavage solution was dried under vacuum and the Heck product quantified by $^1\text{H NMR}$ using 1,3,5-tri-hydroxybenzene as internal standard. Complete conversions were obtained after 36 h (for **10**) or 48 h (for **12**) of reaction.

Scheme S2. Collman Test



7. References

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