Supporting Information

"Water Soluble" Palladium Nanoparticles Engineering for C-C Coupling, Reduction and Cyclization Catalysis

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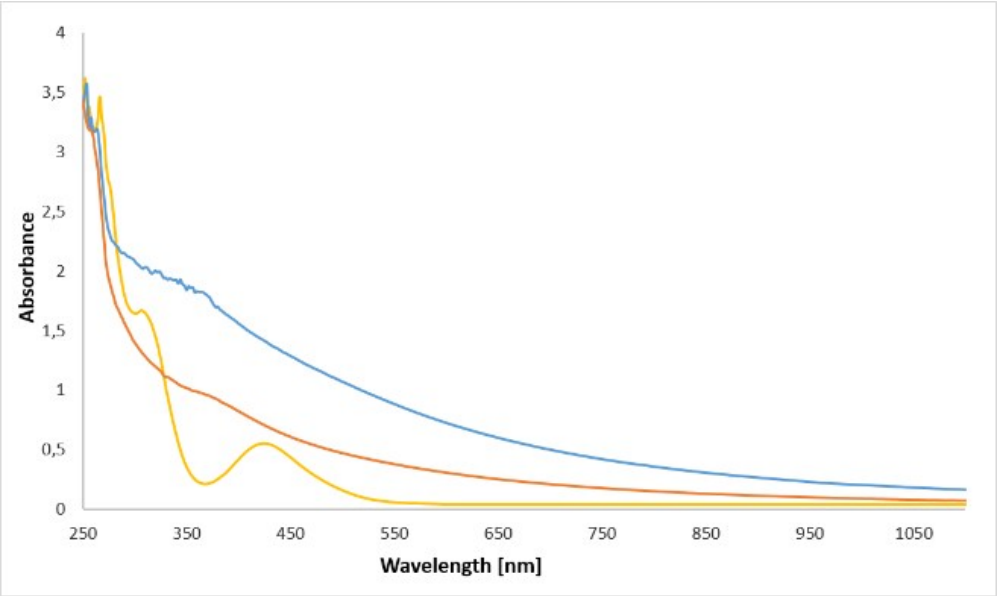
Contains;

UV-vis spectra comparison of the Pd-NPs vs Na_2PdCl_4 Protocols for the synthesis of HMBPs **1-5**. NMR Spectra for compound **1**, **3**, **4**. NMR Spectra for products of Suzuki Miayura (reacting 4-Iodonitrobenzene and tolylboronic acid), Sonogashira (reacting 4-Iodonitrobenzene and phenylactylene), Heck (reacting 4-Iodonitrobenzene and ethyl acrylate) pentynoic cycloaddition catalyzed by Pd NPs.

UV-vis spectra of Na_2PdCl_4 solution (orange), Pd_NPs obtained from basic solution of compound 3 (red) and Pd_NPs obtained from acidic solution of compound 3 (blue).



General protocol for the synthesis of HMBP 1, 3, 4 and 5

These compounds were synthesized following the protocol described in Aufaure et al. (R. Aufaure, Y. Lalatonne, O. Heintz, N. Liévre, L. Motte, E. Guénin, RSC Adv. 2014, 4 (103), 59315 - 59322). Briefly, 5 mmol of the corresponding acid chloride were frozen in a round bottom flask of 25 mL with liquid nitrogen, then 5 mL of tris-(trimethylsilyl phosphite) were added. A white slurry was obtained and stirred over night. Unreacted material was evaporated under vacuum at 70 °C (0.1 Torr) for 20 minutes and hydrolyzed 4 h in 20 mL of MeOH. The solvent was removed under reduced pressure, and the remaining yellow oil was crystallized at pH 2.3 in a MeOH–H_2O 9 : 1 system. The white solid was filltered on Buchner yielding the desired HMBP.

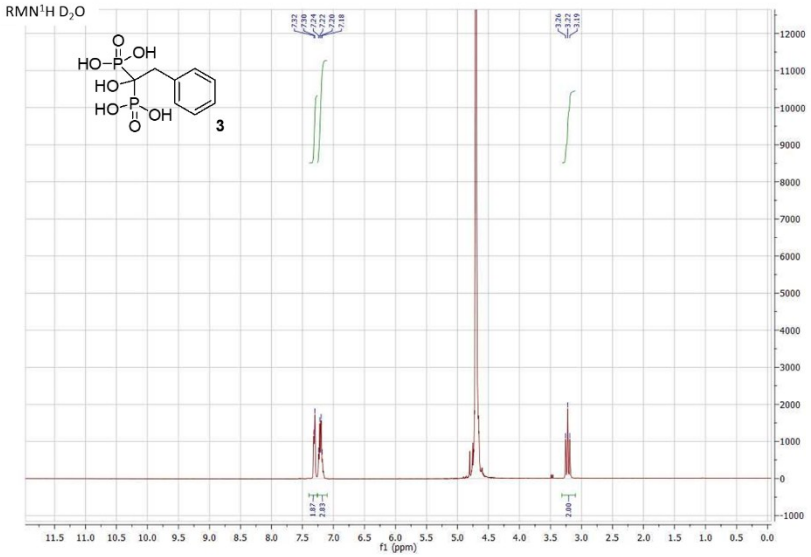
For compound **1**: NMR data could be found in the article cited before.

Compound **4** ^{1}H NMR (400 MHz, D_2O) δ 8.10 – 7.01 (m, 9H), 3.32 (t, *J* = 13.3 Hz, 2H). ^{13}C NMR (101 MHz, D_2O) δ 140.5 (s), 138.2 (s), 137.6 – 137.3 (m), 132.1 (s), 129.1 (s), 127.4 (s), 126. 8 (s), 126.1 (s), 74.0 (t, *J* = 130.0 Hz), 38.39 (s).^{31}P NMR (162 MHz, D_2O) δ 18.67.

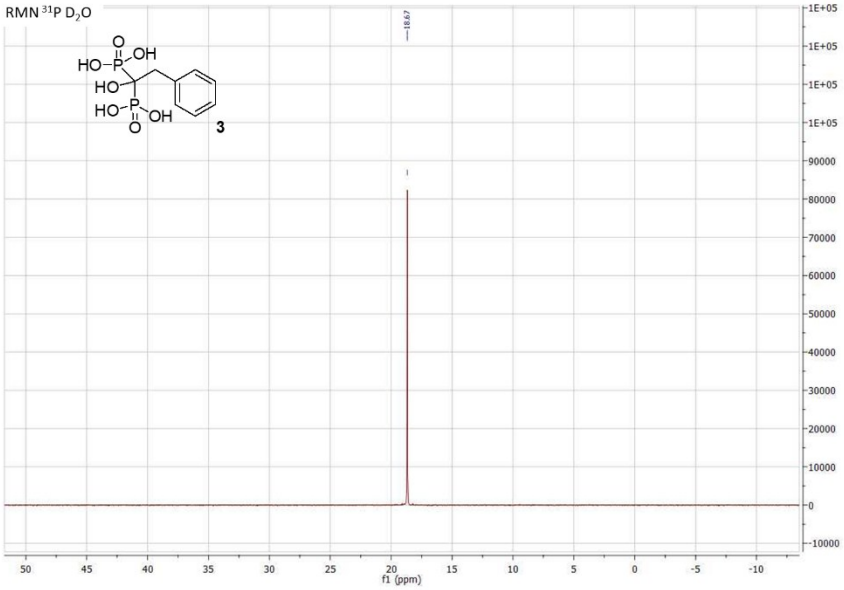
Compound **3** ^{1}H NMR (400 MHz, D_2O) δ 7.31 (d, *J* = 6.5 Hz, 1H), 7.23 – 7.11 (m, 1H), 3.22 (t, *J* = 13.5 Hz, 1H). ^{13}C NMR (101 MHz, D_2O) δ 135.7 (s), 131.1 (s), 127.9 (s), 126.8 (s), 73.8 (t, *J* = 140.6 Hz), 38.2 (s). ^{31}P NMR (162 MHz, D_2O) δ 18.67.

Compound **5** ^{1}H NMR (400 MHz, D_2O) δ 1.53-1.43 (m, 3H). ^{13}C NMR (101 MHz, D_2O) δ 70.0 (t, *J* = 150.2 Hz), 19.0 (s). ^{31}P NMR (162 MHz, D_2O) δ 19.89.

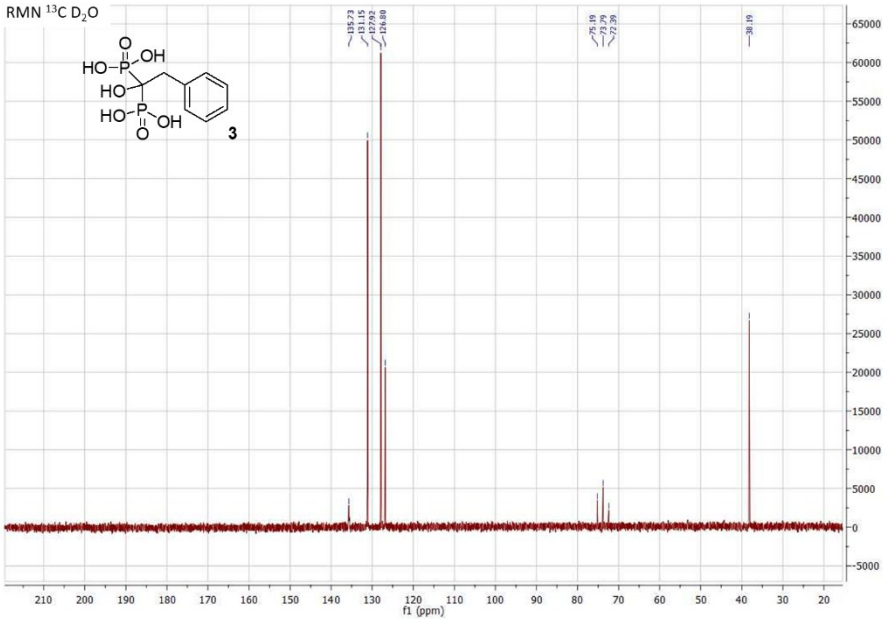
RMN ^{1}H D_2O



RMN ^{31}P D_2O



RMN ^{13}C D_2O



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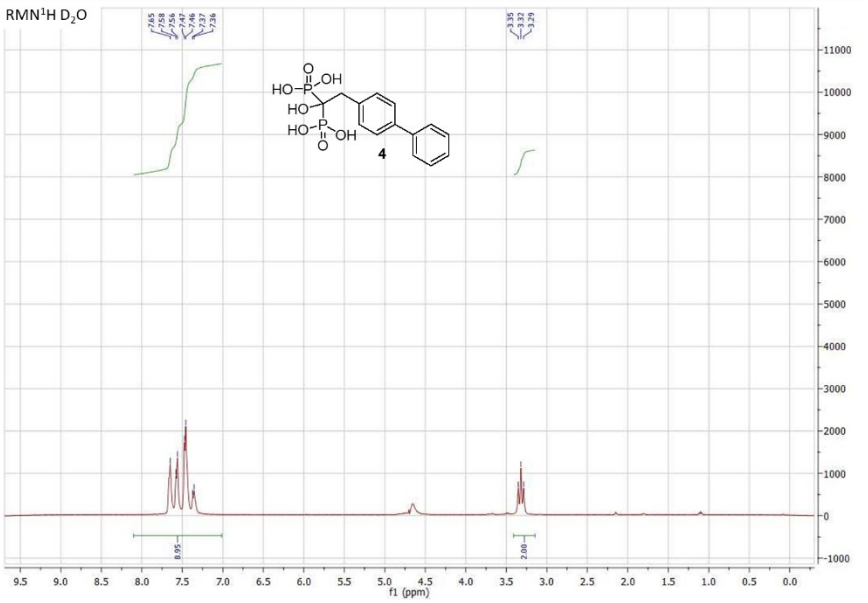
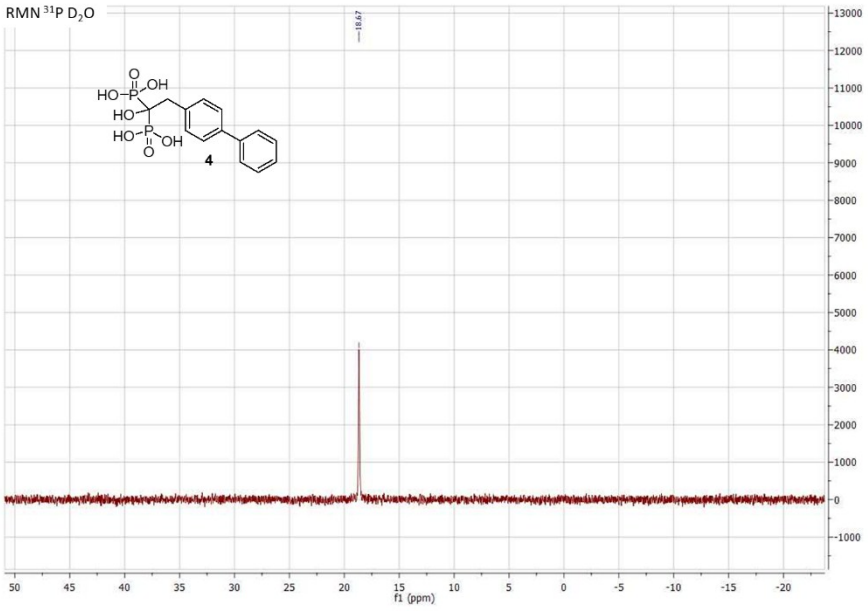


RMN ^{31}P D_2O



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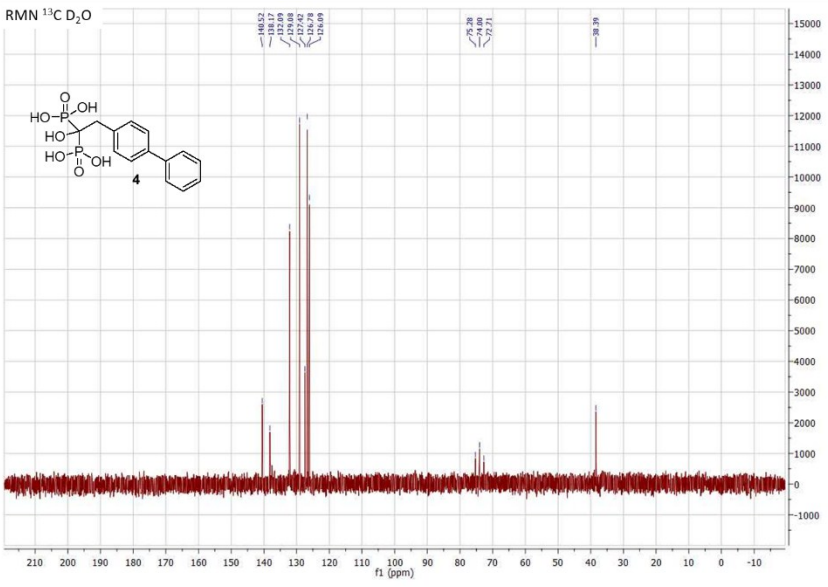
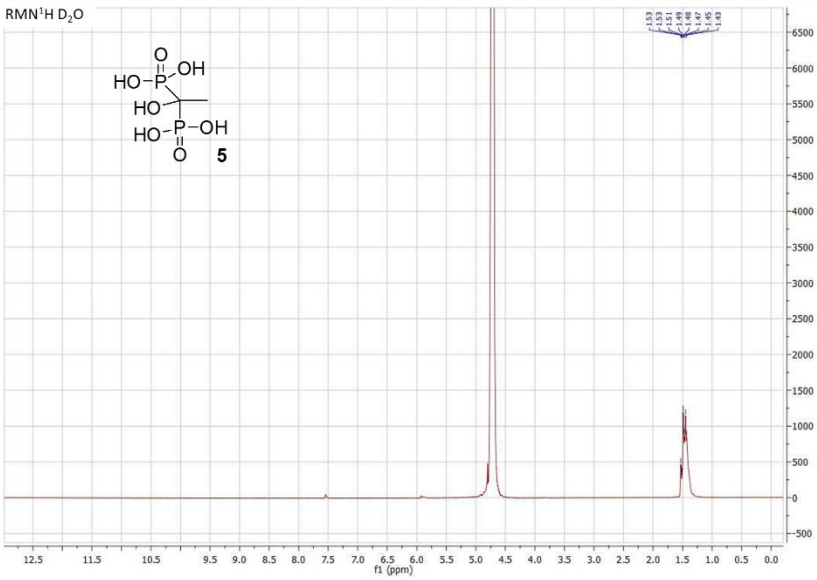


RMN ^{1}H D_2O



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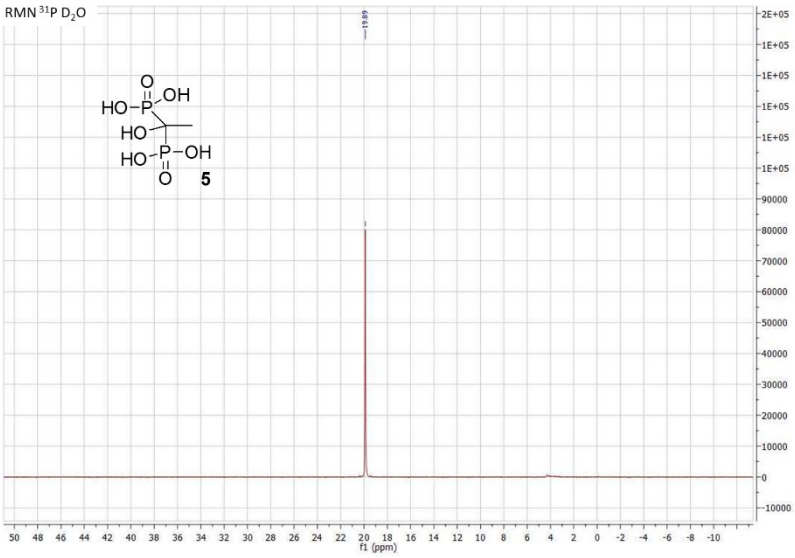
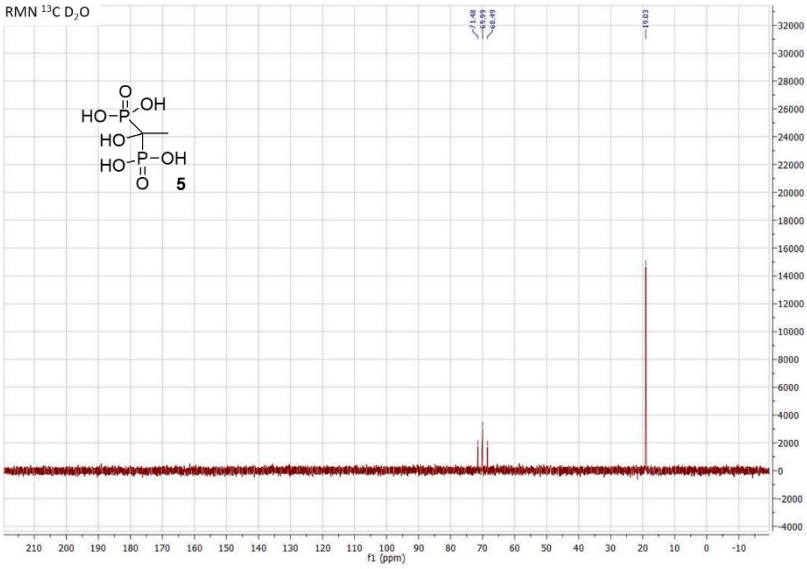
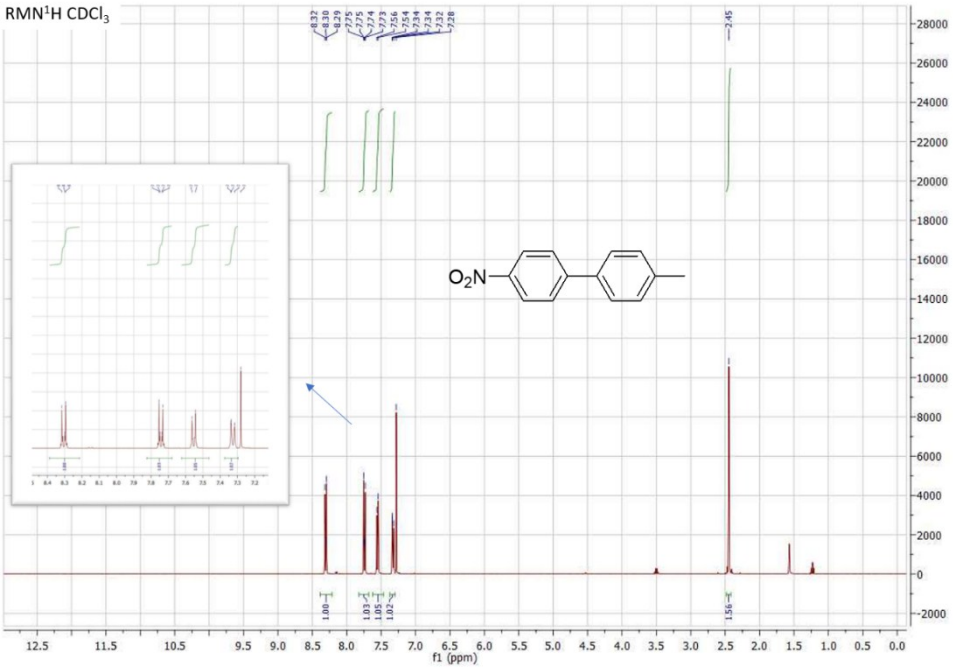


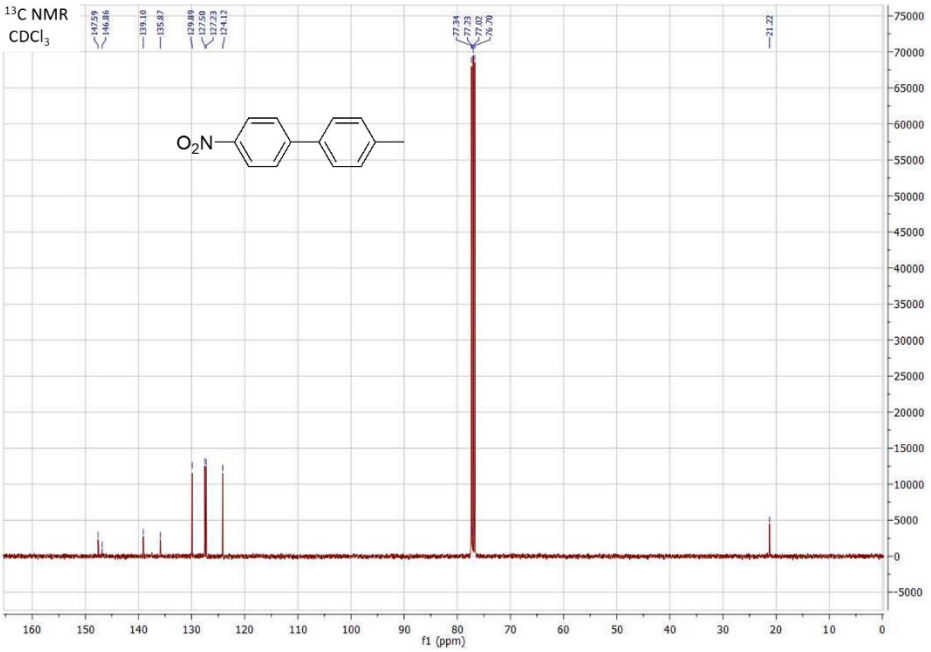
RMN ^{13}C D_2O



Compound 2 (Alendronate) was synthesized according to the general procedure described by Kieczykowski et al. (Kieczykowski GR, Jobson RB, Melillo DG, Reinhold DF, Grenda VJ, Shinkai I. J. Org. Chem. 1995;60:8310-2) and characterized by ^{1}H and ^{31}P NMR. BPs was prepared from the corresponding carboxylic acid precursor according to the following reaction carboxylic acid (150 mmol) and H3PO3 (150 mmol) were introduced in a three-necked round-bottom flask under inert atmosphere followed by 30 mL of methanesulfonic acid. After heating at 65 °C for 1 h, PCl3 (40 mmol) was added slowly and the reaction allowed to proceed overnight at 65 °C. The resulting yellow viscous reaction mixture was cooled to room temperature, quenched with 500 mL of ice-cold water. The pH was adjusted to 4.3 with a NaOH aqueous solution (0.5 M) and the obtained white precipitate was collected by filtration. This solid was washed five times with a mixture of methanol/water (95:5), dialyzed for 3 days and freeze-dried to finally obtain Alendronate (82%). NMR data could be found in the following article E. Guénin, M. Monteil, N. Bouchemal, T. Prangé, M. Lecouvey. Eur. J. Org. Chem., 2007, 20, 3380-3391.

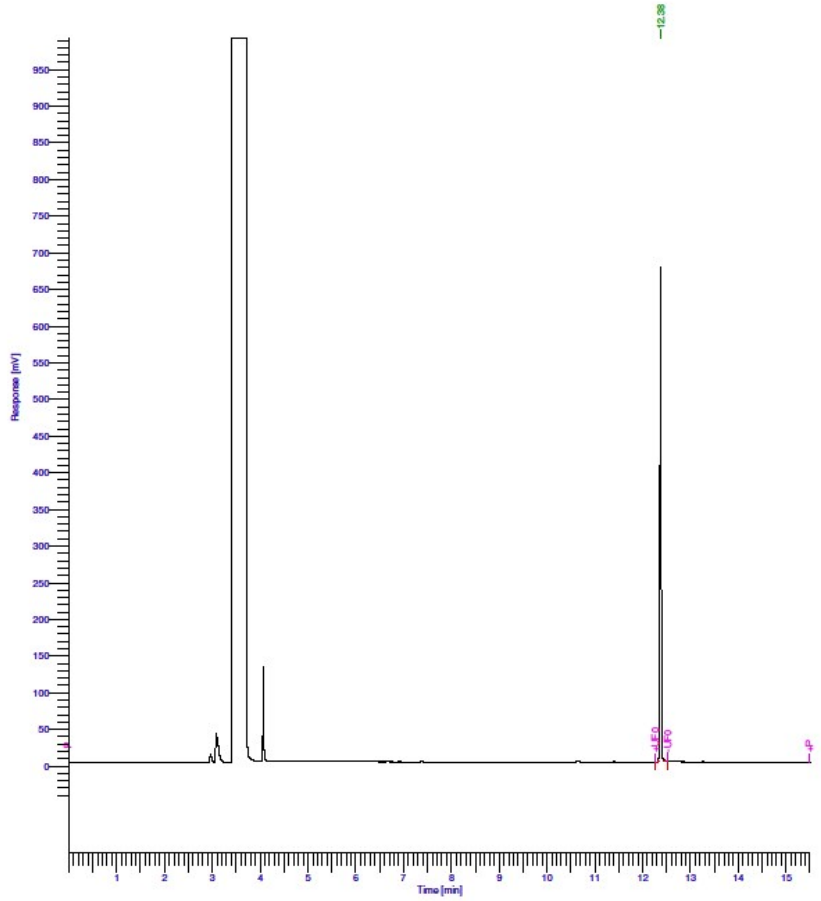
General procedure for Suzuki-Miyaura cross coupling reaction of 4-tolylboronic acid with 4-iodonitrobenzene with Pd-NPs: in a 10 mL MW vial, 23 µL of an aqueous solution of Pd-NPs ([Pd] = 0.02 µM) was added to 1 mL of water. 49.8 mg of 4-iodonitrobenzene (0.20 mmole) and 30 mg of 4-tolylboronic acid (0.22 mmole) and 400 µL of a 0.1 M K_2CO_3 solution (0.4 mmole) were then added. The glass walls of the vial were rinsed with 1 mL ethanol and a cap was fixed on the top of the vial. The vial was heated in a microwave apparatus (Monowave 300, Anton Paar GmbH) for 30 min. at 80°C using ruby thermometer (step 1: heat in 2 min. to 80°C, step 2 hold at 80°C for 28 min. Stirrer speed 1200 rpm for both steps). After cooling of the solution, 1 mL of diethyl ether or ethyl acetate was added and the organic layer was extracted 5 times. The product was then isolated by evaporation and purified by simple filtration over silica when conversion was total or purified by silica gel column chromatography using ethyl acetate hexane mixtures when starting halogenated reactants remained un-reacted. ^{1}H NMR ($CDCl_3$, 25°C): δ = 8.28 (d, J = 8.8 Hz, 2H); 7.72 (d, J = 8.8 Hz, 2H); 7.53 (d, J = 8.8 Hz, 2H); 7.30 (d, J = 8.8 Hz, 2H); 2.42 (s, 3H) ppm. $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 25°C): δ = 147.8; 147.0; 139.3; 136.0; 130.0; 127.7; 127.4; 124.3; 21.4 ppm.



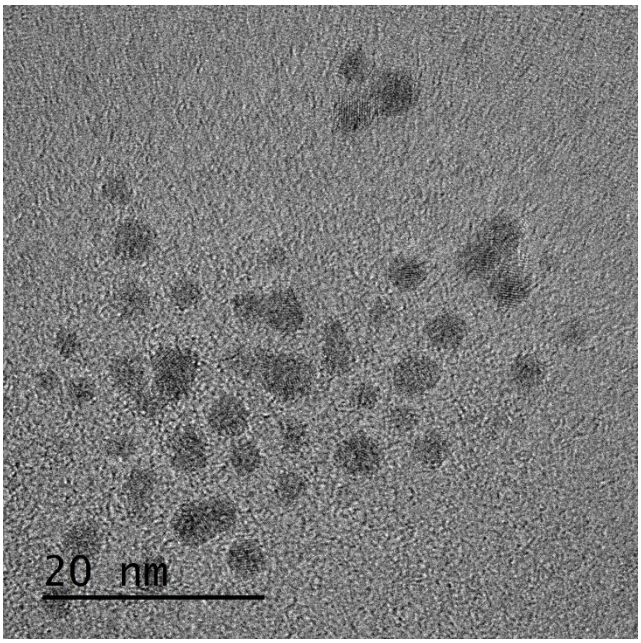


Chromatogram

Sample Name : aib-EG70A Sample # : 1 Page 1 of 1
FileName : c:\data_utc\results\anas\aib-EG70A.raw
Date : 4/24/2019 10:09:45 AM
Method :
Time of Injection: 4/12/2019 6:33:06 PM
Start Time : 0.00 min End Time : 15.50 min Low Point : -47.60 mV High Point : 993.88 mV
Plot Offset: -47.60 mV Plot Scale: 1041.5 mV

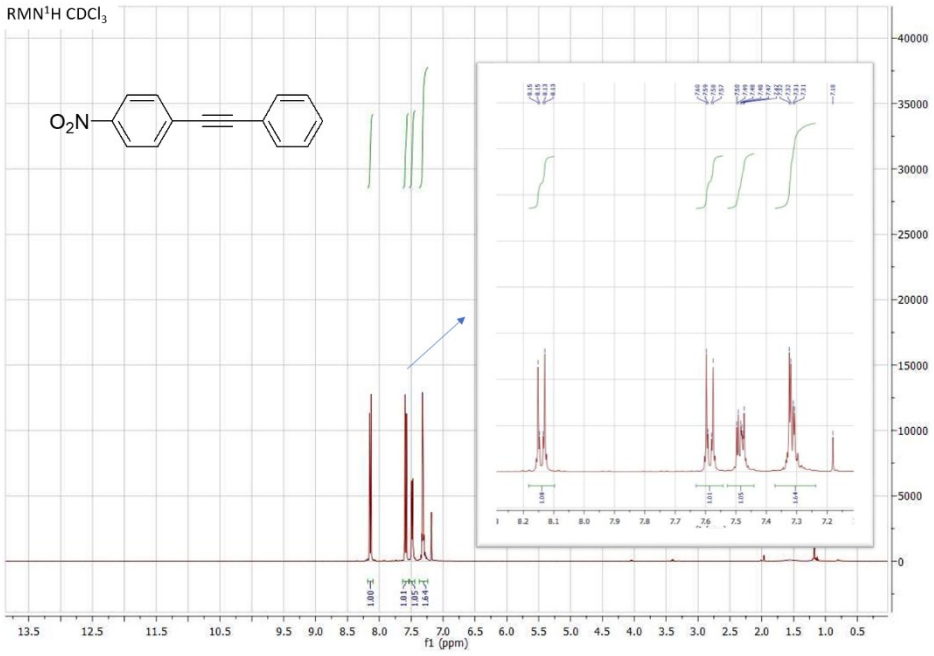


TEM images of Pd-NPs after Suzuki reaction

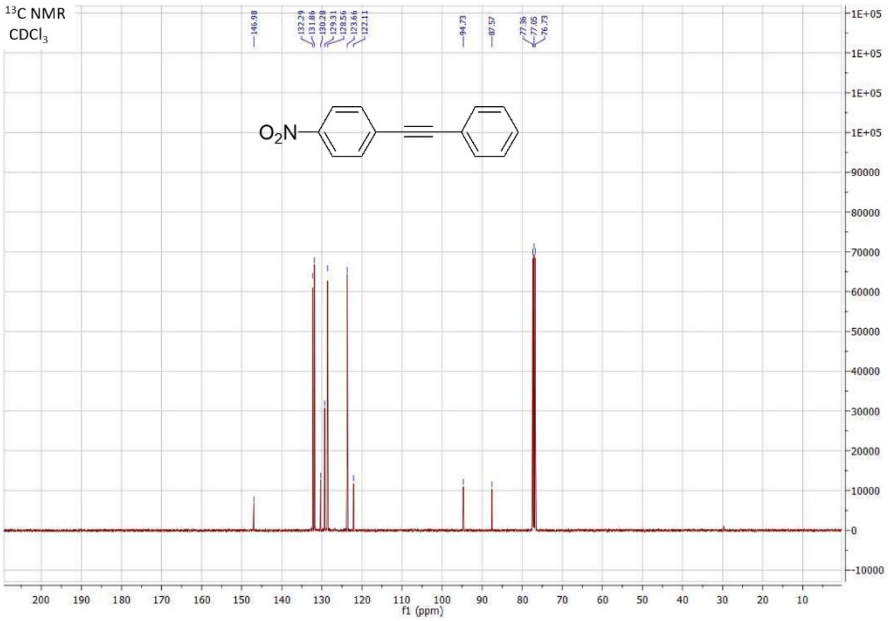


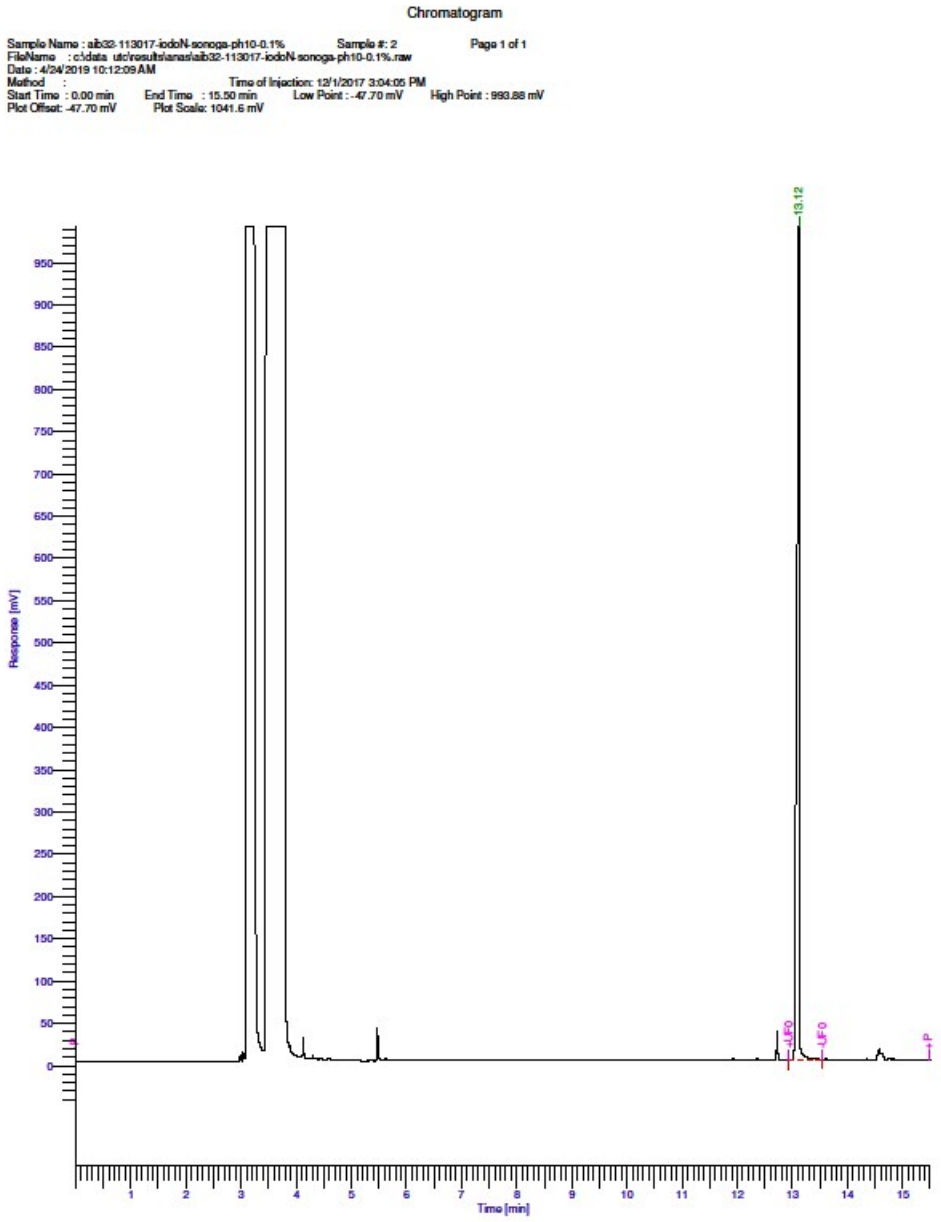
General procedure for Sonogashira reaction of phenylacetylene with 4-iodonitrobenzene with Pd-NPs: in a 10 mL MW vial, 43.5 µL of an aqueous solution of Pd-NPs ([Pd] = 0.695 mM) was added to 600 µL of water. 49.8 mg of 4-iodonitrobenzene (0.20 mmole) and 24 µL of phenylacetylene (0.22 mmole) and 400 µL of a 1 M K_2CO_3 solution were then added. The glass walls of the vial were rinsed with 1 mL ethanol and a cap was fixed on the top of the vial. The vial was heated with an oil bath or in a microwave apparatus for 30 min at 80°C using ruby thermometer (step 1: heat in 2 min. to 80°C, step 2 hold at 80°C for 30 min. Stirrer speed 1200 rpm for both steps). After cooling of the solution 1 mL of diethyl ether or ethyl acetate was added and the organic layer was extracted 5 times. The product was then isolated by evaporation and purified by simple filtration over silica when conversion was total or purified by silica gel column chromatography using ethyl acetate hexane mixtures when starting halogenated reactants remained un-reacted. ^{1}H NMR ($CDCl_3$, 25°C): δ = 8.23 (d, J = 9 Hz, 2H); 7.67 (d, J = 8.8 Hz, 2H); 7.56 (m, 2H); 7.39 (m, 3H) ppm. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 25°C): δ = 146.9; 132.3; 131.9; 130.3; 129.3; 128.6; 123.7; 122.1; 94.7; 87.5 ppm.

RMN^{1}H $CDCl_3$



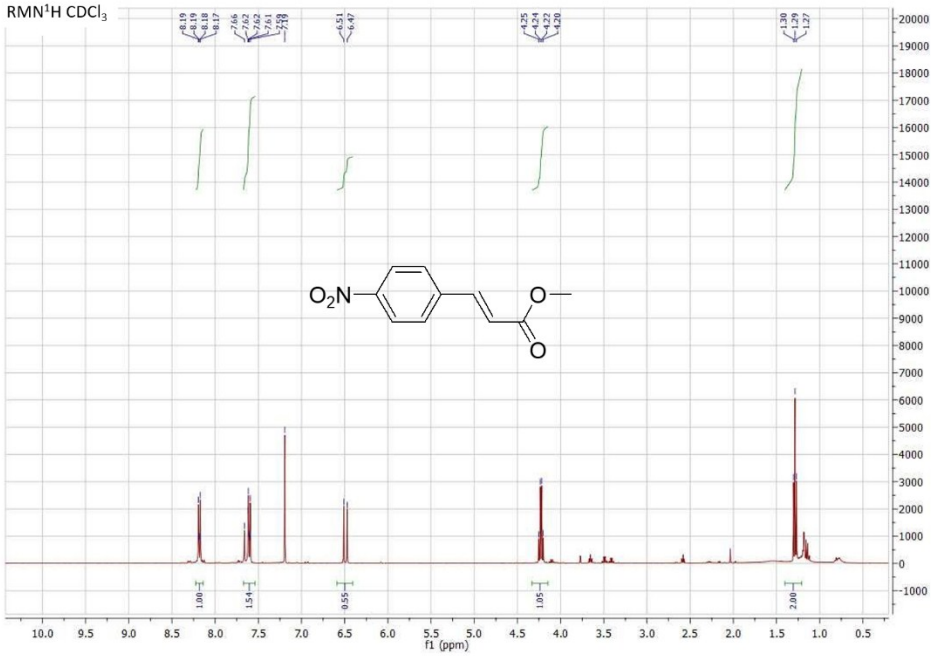
^{13}C NMR
$CDCl_3$



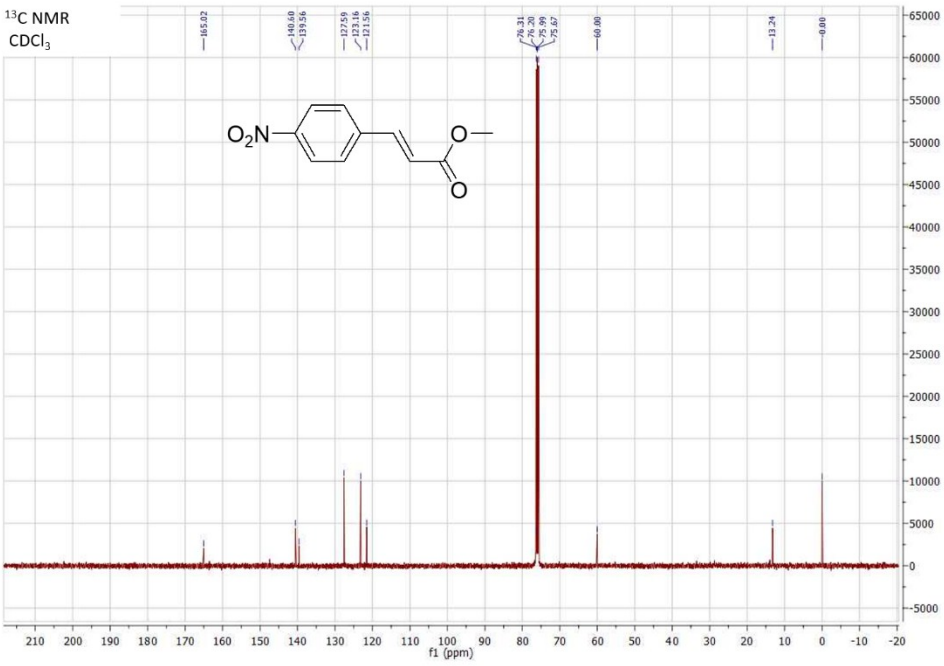


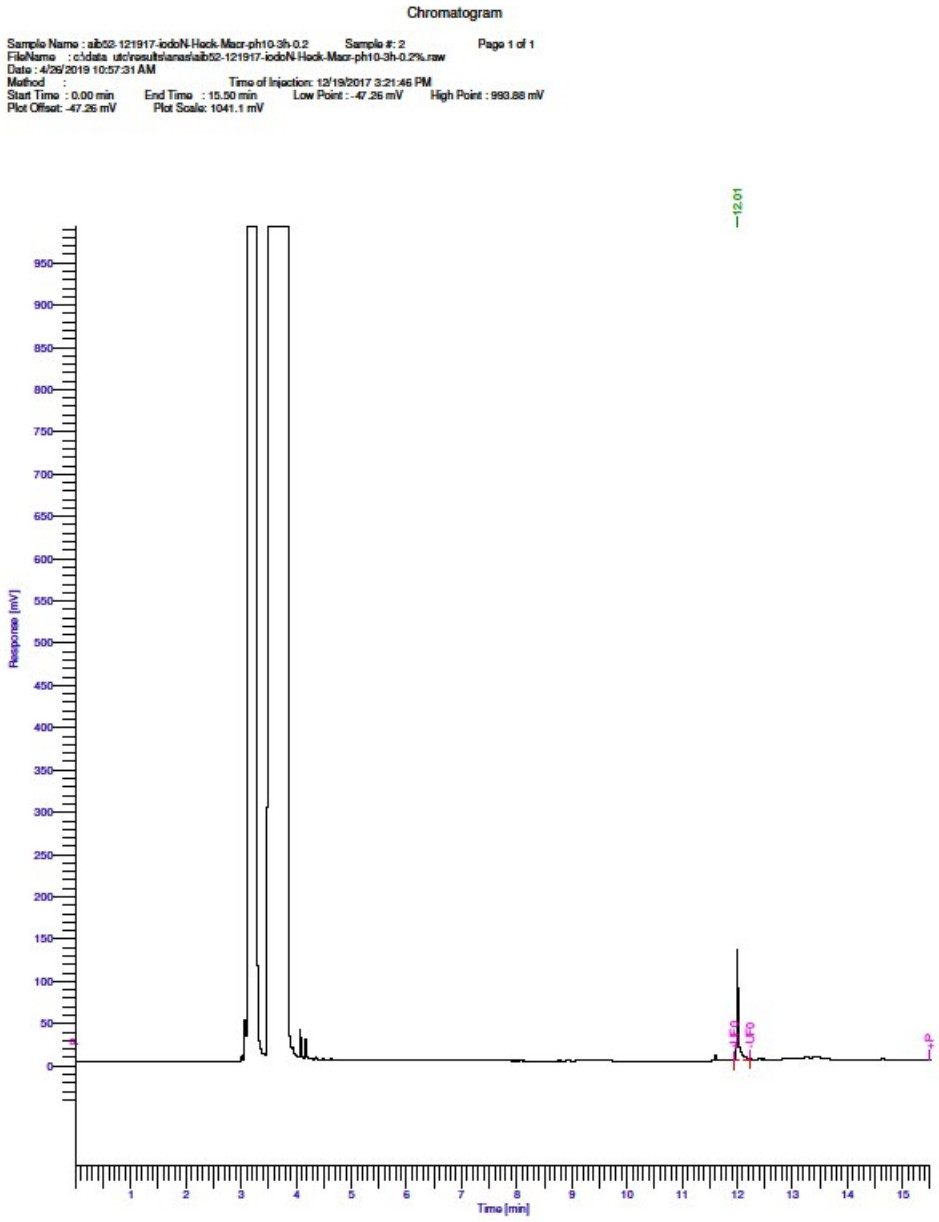
General procedure for Heck reaction of methyl metacrylate with 4-iodonitrobenzene with Pd@-NPs: in a 10 mL MW vial, 287.7 µL of an aqueous solution of Pd-NPs ([Pd] = 0.695 mM) was added to 400 µL of water. 49.8 mg of 4-iodonitrobenzene (0.20 mmole) and 27 µL of methyl metacrylate (0.2 mmole) and 400 µL of a 1 M K_2CO_3 solution were then added. The glass walls of the vial were rinsed with 1 mL ethanol and a cap was fixed on the top of the vial. The vial was heated in a microwave apparatus for 2h at 80°C using ruby thermometer (step 1: heat in 2 min. to 80°C, step 2 hold at 80°C for 2h. Stirrer speed 1200 rpm for both steps). After cooling of the solution 1 mL of diethyl ether or ethyl acetate was added and the organic layer was extracted 5 times. The product was then isolated by evaporation and purified by simple filtration over silica when conversion was total or purified by silica gel column chromatography using ethyl acetate hexane mixtures when starting halogenated reactants remained un-reacted. NMR ^{1}H ($CDCl_3$, 25°C): δ = 8.24 (d, J = 8.8 Hz, 2H); 7.71 (d, J = 16.2 Hz, 1H) ; 7.66 (d, J=8.8 Hz, 2H) ; 6.56 (d, J = 16.2 Hz, 2H); 3.83 (s, 3H) ppm. NMR $^{13}C\{^{1}H\}$ ($CDCl_3$, 25°C): δ = 166.7; 148.5; 142.0; 140.5; 128.6; 124.5; 122.1; 52.1 ppm.

RMN^{1}H $CDCl_3$



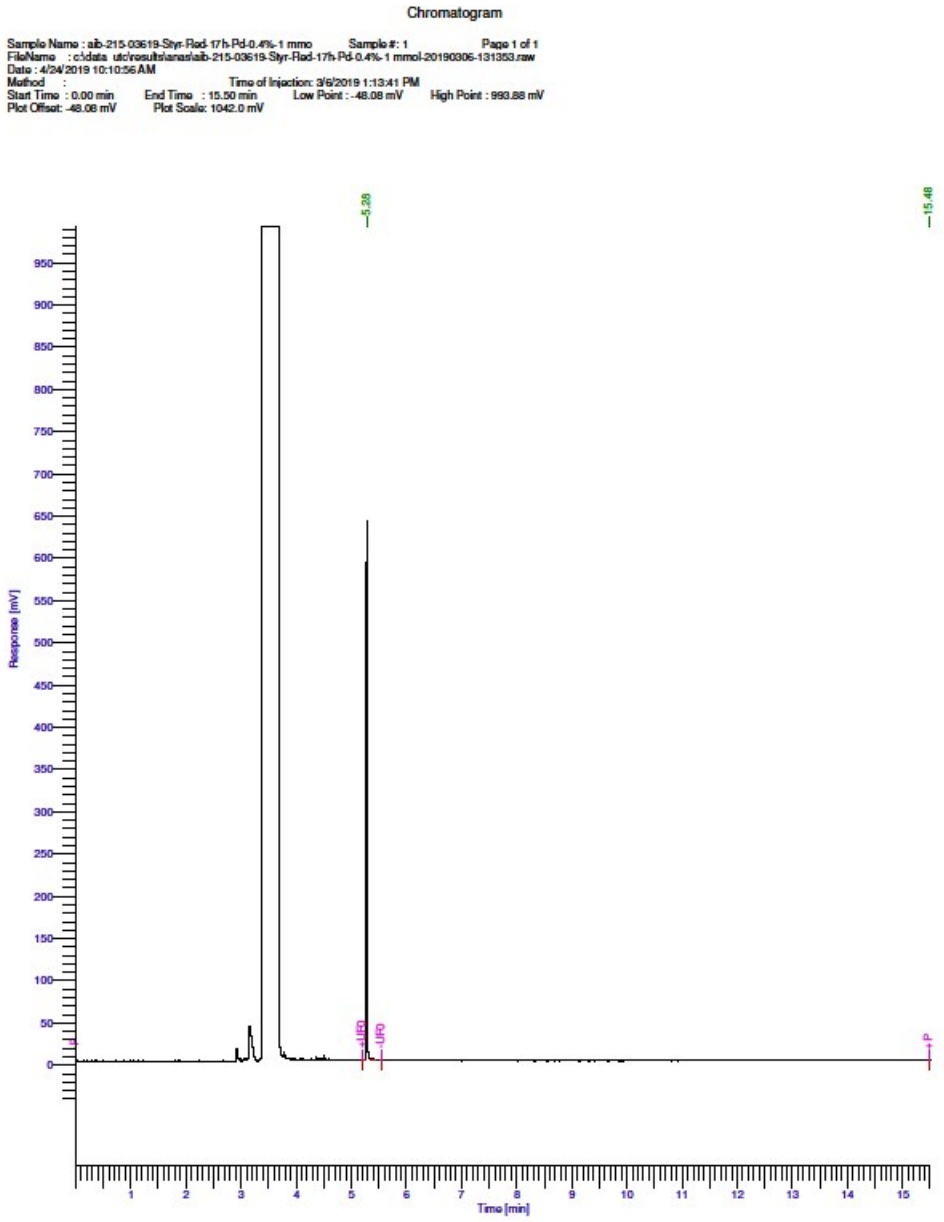
^{13}C NMR
$CDCl_3$





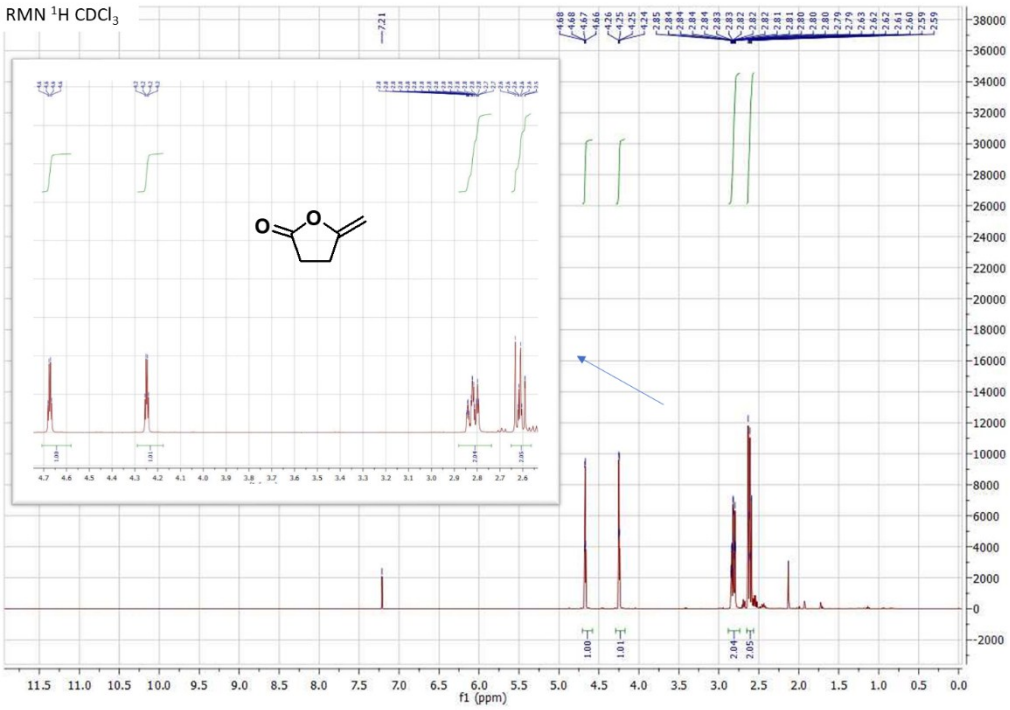
General procedure for reduction of styrene with Pd-NPs: 5.75 mL of the solution of Pd-NP-B3 ([Pd] = 0.68 mM) were added in a 50 mL boiling flask and purged with H_2 for 3 min, 57 µL of styrene (0.5 mmol) was added to the reaction medium, and purged a second time with H_2 for 4 min. Then, immediately the flask is closed to perform the reduction reaction at room temperature and 1200 rpm for 3h. The reaction evolution was followed by Gaz Chromatography using ethyl acetate as solvent.

In the case of use of $NaBH_4$ as reductants, 114 mg of sodium borohydride (6 eq) were added in a 50 mL boiling flask with 5.75 mL of Pd-NP-B3 ([Pd] = 0.68 mM). The solution was stirred at 1200 rpm for one minute, after which 57 µL of styrene (0.5 mmol) was added to the reaction medium. The reaction performed at room temperature for 3h. The reaction evolution was followed by Gaz Chromatography using ethyl acetate as solvent.

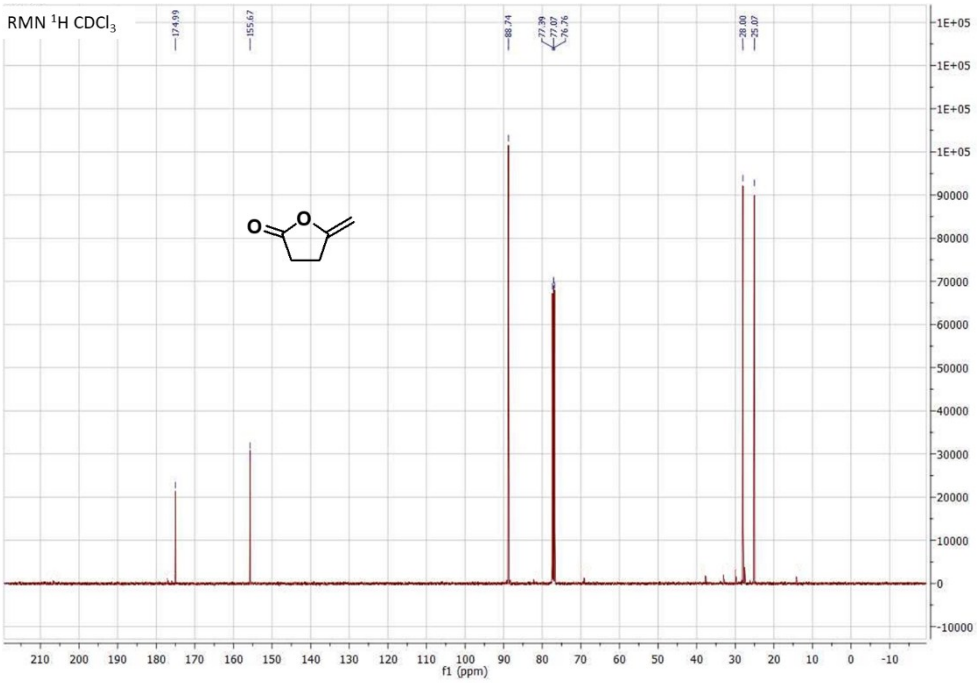


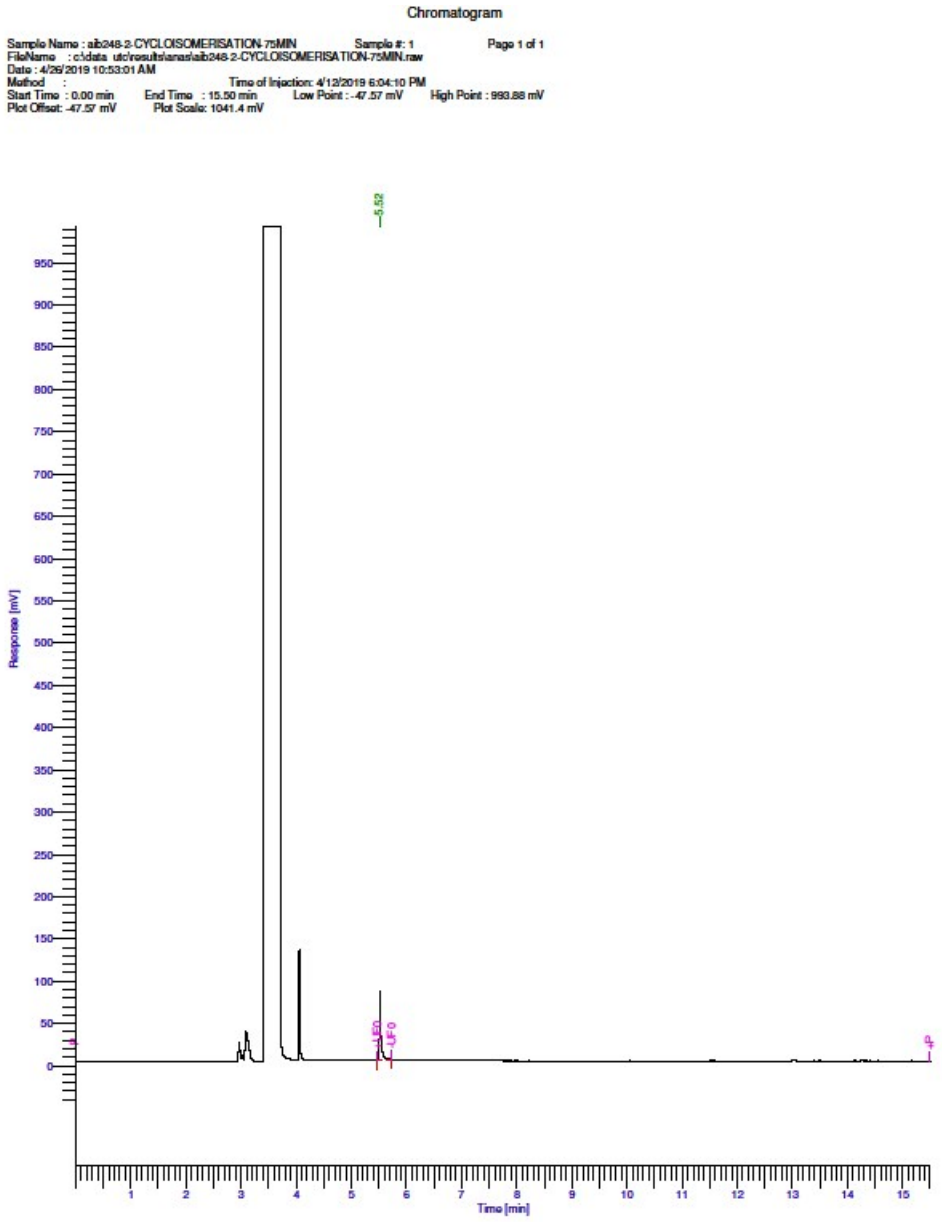
General procedure for Cycloisomerization reaction with Pd-NPs: Cycloisomerization product (5-Methylenedihydrofuran-2(3H)-one): in a 10 mL MW vial, 115 µL of an aqueous solution of Pd-NPs ([Pd] = 0.695 mM) was added to 500 µL of water. 19.6 mg of pentynoic acid (0.20 mmole) was then added and a cap was fixed on the top of the vial. The vial was heated in a microwave apparatus for 60 min at 40°C using a ruby thermometer (step 1: heat in 2 min. to 40°C, step 2 hold at 40°C for 60 min. Stirrer speed 1200 rpm for both steps). After cooling of the solution, 1 mL of diethyl ether or ethyl acetate was added and the organic layer was extracted 5 times. The high volatility of the compound prevented accurate determination of the isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (dd, J = 4.5, 2.2 Hz, 1H), 4.30 (dd, J = 4.3, 1.8 Hz, 1H), 2.91 – 2.81 (m, 2H), 2.70 – 2.63 (m, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 175.0, 155. 7, 88.7, 28.0, 25.1. Colourless oil.

RMN ^{1}H $CDCl_3$



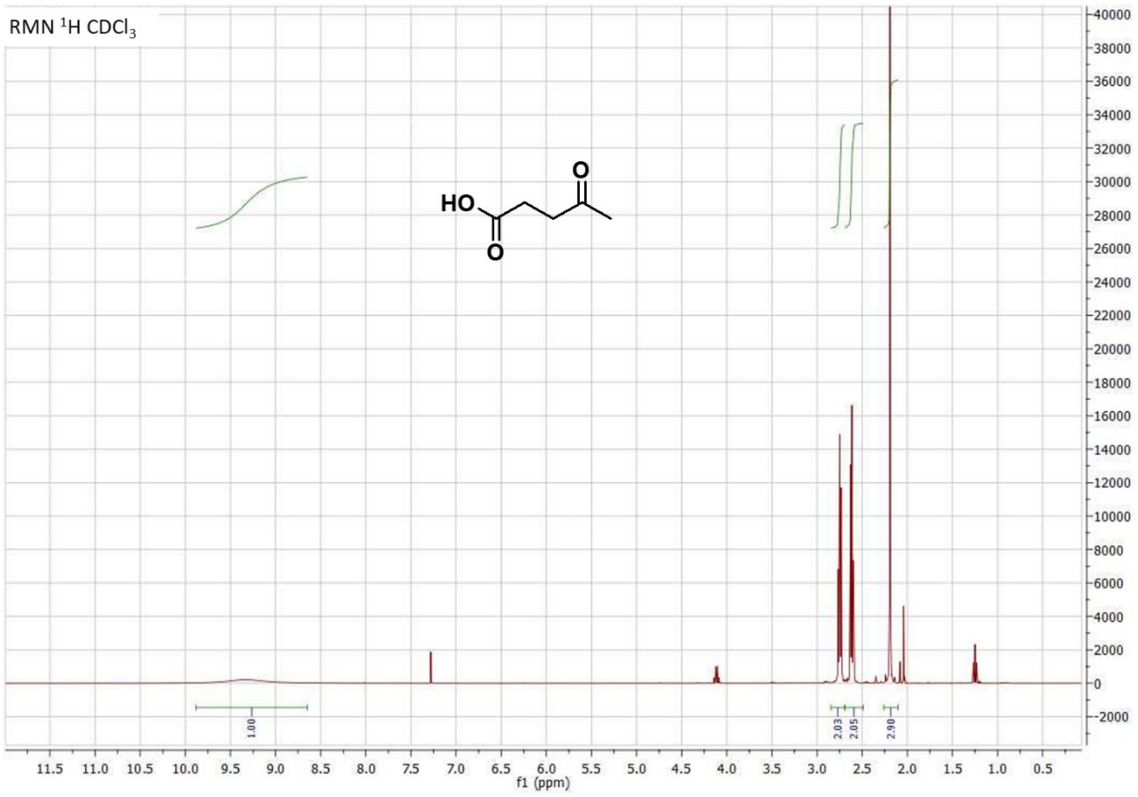
RMN ^{1}H $CDCl_3$





Ketoacid by-product (4-Oxopentanoic acid): 19.6 mg of pentynoic acid (0.20 mmole) was added in a 10 mL MW vial with 500 µL of water, and 143 µL of an aqueous solution of Pd-NPs (0.695 mM). Subsequently, the vial was sealed with a cap and heated in a microwave apparatus for 180 min at 90°C using a ruby thermometer (step 1: heat in 2 min. to 90°C, step 2 hold at 90°C for 180 min. Stirrer speed 1200 rpm for both steps). After cooling of the solution, 1 mL of diethyl ether or ethyl acetate was added and the organic layer was extracted 5 times. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 2.73 (t, J = 6.5 Hz, 1H), 2.59 (t, J = 6.5 Hz, 1H), 2.17 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 178.6, 37.7, 29.8, 27.8. Colourless oil.

RMN ^{1}H $CDCl_3$



RMN ^{13}C $CDCl_3$