Heterogenization of Pd-NHC complexes onto a silica support and their application in the Suzuki-Miyaura coupling under batch and continuous flow conditions

Alberto Martinez-Lombardia,[a] Jamin Krinsky,[a] Itziar Peñafiel,[a] Sergio Castillón,[b] Konstantin Loponov,[c] Alexei Lapkin,[c] Cyril Godard,[a]* and Carmen Claver[a]*

[a] *Department of Physical and Inorganic Chemistry, Universitat Rovira i Virgili, C/ Marcel·li Domingo s/n, 43007 Tarragona, Spain. E-mail: carmen.claver@urv.cat*

[b] *Department of Analytical and Organic Chemistry, Universitat Rovira i Virgili, C/ Marcel·li Domingo s/n, 43007 Tarragona, Spain. E-mail: sergio.castillon@urv.cat*

[c] *Department of Chemical Engineering and Biotechnology, University of Cambridge, New Museum Site, Cambridge CB2 3RA, UK.*

Supporting Information

Table of Contents

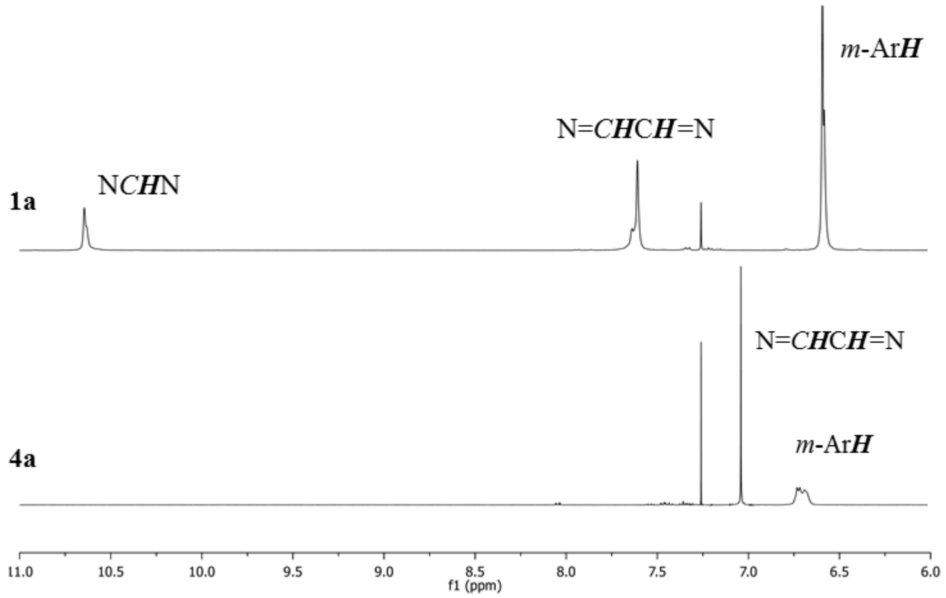
General Procedures

Reactions were carried out using standard bench-top techniques unless the use of a Schlenk flask is specified, in which case Schlenk-line inert atmosphere techniques were used. Where stirring of the reaction mixture is indicated, magnetic stirring using a Teflon-coated stir bar was employed throughout. Commercially supplied compounds were used without further purification. Dry solvents were prepared by distillation from Na/benzophenone, CaH_2 or P_2O_5, or collected from a Braun SPS800 solvent purification system. Photochemical reactions were performed using a Philips HPL-N 125 W high-pressure mercury lamp, which can be purchased at most commercial lighting stores. Solution-state (and $^{29}Si\{^1H\}$ MAS) NMR spectra were obtained at the Servei de Recursos Científics i Tècnics (SRCT), URV, with Varian (Agilent) Mercury VX400 or NMR System400 400 MHz spectrometers and calibrated to residual solvent peaks. CP-MAS spectra were recorded at the Servei de Ressonància Magnètica Nuclear (SeRMN), Universitat Autònoma de Barcelona on a 400 MHz spectrometer with a 12 kHz rotation speed (and calibrated to an external adamantane standard). Chemical and shifts for ^1H, $^{13}C\{^1H\}$ and $^{29}Si\{^1H\}$ NMR spectra are reported relative to TMS. ICP analyses were conducted at the SCRT using an ICP-OES Spectro Arcos instrument. Samples were digested in concentrated HNO_3 under microwave irradiation before being diluted for analysis. HR-MS (ESI-TOF) analyses were also performed at the SCRT, on an Agilent Time-of-Flight 6210 spectrometer. GC-MS and GS-FID analyses were conducted on Shimadzu GC-MS-QP2010 and Agilent 6850 instruments, respectively, fitted with HP-5 capillary columns. Elemental analyses were performed at the Centro de Microanálisis Elemental de la Universidad Complutense de Madrid or at the Unitat d'Anàlisi Química i Estructural-Serveis Tècnics de Recerca, Universitat de Girona. Other than solvents, reagents obtained from commercial sources were used without further purification. Silica used for catalyst immobilization was 60 mesh chromatography-grade (purchased from SDS), dried for 1 h at 80 °C, 10^{-3} bar prior to use. $Pd(acac)_2$,[1] was prepared according to literature procedures.

Synthesis and Characterization of Compounds

*One-pot procedure for preparation of[Pd(**2a**)(acac)Cl@SiO2]* ***4a@SiO$_2$***. A flame-dried Schlenk flask was charged with **1a** (200 mg, 0.441 mmol, 1.0 equiv.), 3-mercaptopropyl(triethoxy)silane (225 µL, 0.887 mmol, 2.0 equiv.) and DMPA (22 mg, 0.09 mmol, 0.20 equiv.), followed by freshly-dried EtOH (1.5 mL). The reaction mixture was then stirred and irradiated with a 125 W high-pressure mercury lamp (8 cm of separation between the bulb and flask) for 24 h. The solvent was removed under reduced pressure, and the residue was re-dissolved in CH_2Cl_2 and evaporated again in order to fully remove the EtOH. Next, Pd(acac)$_2$ (134 mg, 0.441 mmol, 1.0 equiv.) was added along with 1,2-DCE (5 mL). After the reaction mixture was heated at 75 °C with stirring for 2 days and then allowed to cool, it was slowly transferred *via* cannula to another Schlenk flask containing a stirred (400 rpm) suspension of previously dried 60 mesh silica (2.0 g) in 1,2-DCE (5 mL). This suspension was stirred at 250 rpm for 30 min at ambient temperature, then the temperature was increased to 75 °C and stirring was continued for 24 h. During this time all of the yellow color in the supernatant was transferred to the silica. Finally, the material was hot-filtered and washed with copious amounts of CH_2Cl_2. The recovered yield of **4a@SiO$_2$** was 2.36 g. Pd content by ICP: 2.65 wt% (0.249 mmol / g). Anal. Calcd. for $C_{42}H_{64}ClN_2O_6PdS_2Si_2$@$SiO_2$ based on Pd loading: C, 12.5; H, 1.61; N, 0.70; S, 1.60. Found: C, 9.55; H, 1.93; N, 0.67; S, 1.18.

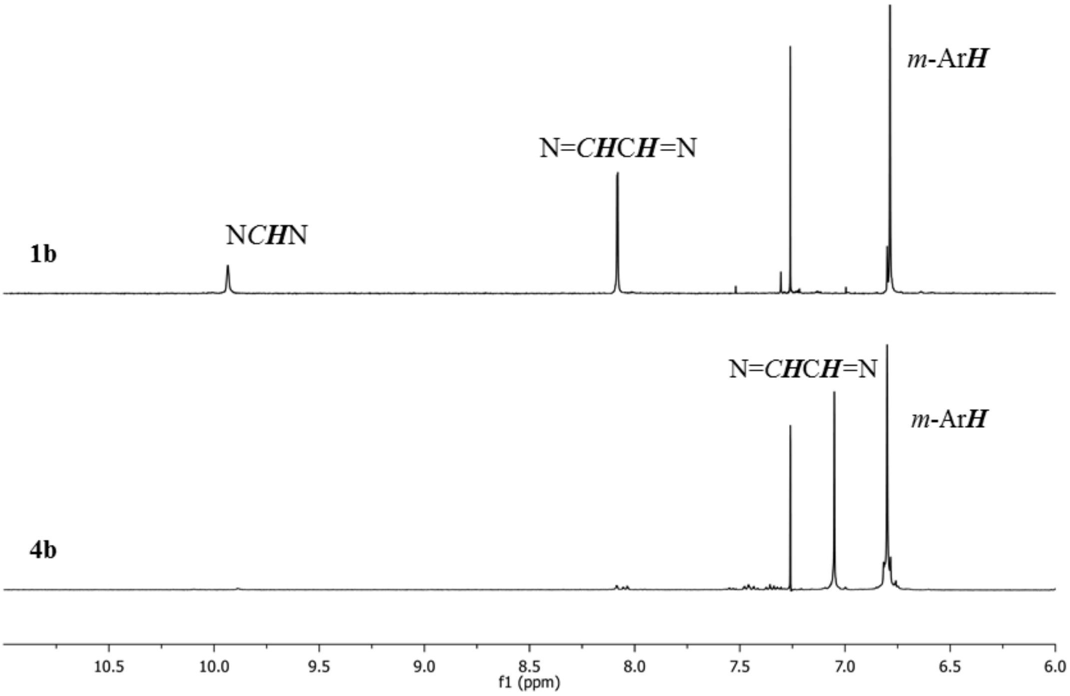
Although **4a** was not isolated, ^{1}H NMR spectroscopy of an aliquot taken at the end of the Pd complex-forming reaction showed that all of the ligand was converted to a carbene as shown in the figure below:



*One-pot procedure for preparation of [Pd(**2b**)(acac)Cl@SiO2]* ***4b@SiO$_2$***. A flame-dried Schlenk flask was charged with **1b** (213 mg, 0.377 mmol, 1.0 equiv.), 3-mercaptopropyl(triethoxy)silane (190 µL, 0.754 mmol, 2.0 equiv.) and DMPA (19 mg, 0.08 mmol, 0.20 equiv.), followed by freshly-dried EtOH (1.5 mL). The reaction mixture was then stirred and irradiated with a 125 W high-pressure mercury lamp (8 cm of separation between the bulb and flask) for 24 h. The solvent was removed under reduced pressure, and the residue was re-dissolved in CH_2Cl_2 and evaporated again in order to fully remove the EtOH. Next, Pd(acac)$_2$ (115 mg, 0.377 mmol, 1.0 equiv.) was added along with 1,2-DCE (5 mL). After the reaction mixture was heated at 75 °C with stirring for 2 days and then allowed to cool, it was slowly transferred *via* cannula to another Schlenk flask containing a stirred (400 rpm) suspension of previously dried 60 mesh silica (1.71 g) in 1,2-DCE (3 mL). This suspension was stirred at 250 rpm for 30 min at ambient temperature, then the temperature was increased to 75 °C and stirring was continued for 24 h. During this time all of the yellow color in the supernatant was transferred to the silica. Finally, the material was hot-filtered and washed with copious amounts of

CH_2Cl_2. The recovered yield of **4b@SiO₂** was 2.5 g. Pd content by ICP: 1.76 wt% (0.165 mmol / g). Anal. Calcd. for $C_{50}H_{80}ClN_2O_6PdS_2Si_2$@$SiO_2$ based on Pd loading: C, 9.91; H, 1.33; N, 0.46; S, 1.06. Found: C, 8.87; H, 1.94; N, 0.58; S, 0.97.

Although **4b** was not isolated, ^{1}H NMR spectroscopy of an aliquot taken at the end of the Pd complex-forming reaction showed that all of the ligand was converted to a carbene complex as shown in the figure below:



One-pot procedure for preparation of [Pd(3a)(acac)Cl@SiO2] ***(5a@SiO₂)***. A flame-dried Schlenk flask was charged with **1a** (1.00 g, 2.21 mmol, 1.0 equiv.), 3-mercaptopropyl(triethoxy)silane (560 µL, 2.21 mmol, 1.0 equiv.) and DMPA (56 mg, 0.221 mmol, 0.10 equiv.), followed by freshly-dried EtOH (40 mL). The reaction mixture was then stirred and irradiated with a 125 W high-pressure mercury lamp (8 cm of separation between the bulb and flask) for 2 days. The solvent was removed under reduced pressure, and the residue was re-dissolved in CH_2Cl_2 and evaporated again in order to fully remove the EtOH. Next, $Pd(acac)_2$ (673 mg, 2.21 mmol, 1.0 equiv.) was added along with 1,2-DCE (15 mL). After the reaction mixture was heated at 75 °C with stirring for 2 days and then allowed to cool, it was slowly transferred *via* cannula to another Schlenk flask containing a stirred (400 rpm) suspension of previously dried 60 mesh silica (7.30 g) in 1,2-DCE (20 mL). This suspension was stirred at 250 rpm for 30 min, then the temperature was increased to 75 °C and stirring was continued for 24 h. Finally, the material was hot-filtered and washed with copious amounts of CH_2Cl_2. The recovered yield of **5a@SiO₂** was 8.66 g. Pd content by ICP: 2.53 wt% (0.238 mmol / g).

One-pot procedure for preparation of [Pd(3b)(acac)Cl@SiO2] ***(5b@SiO₂)***. A flame-dried Schlenk flask was charged with **1b** (875 mg, 1.54 mmol, 1.0 equiv.), 3-mercaptopropyl(triethoxy)silane (390 µL, 1.54 mmol, 1.0 equiv.) and DMPA (50 mg, 0.20 mmol, 0.13 equiv.), followed by freshly-dried EtOH (40 mL). The reaction mixture was then stirred and irradiated with a 125 W high-pressure mercury lamp (8 cm of separation between the bulb and flask) for 2 days. The solvent was removed under reduced pressure, and the residue was re-dissolved in CH_2Cl_2 and evaporated again in order to fully remove the EtOH. Next, $Pd(acac)_2$ (469 mg, 1.54 mmol, 1.0 equiv.) was added along with 1,2-DCE (20 mL). After the reaction mixture was heated at 75 °C with stirring for 2 days and then allowed to cool, it was slowly transferred *via* cannula to another Schlenk flask containing a stirred (400 rpm) suspension of previously dried 60 mesh silica (5.10 g) in 1,2-DCE (10 mL). This suspension was stirred at 250 rpm for 30 min, then the temperature was increased to 75 °C and stirring was continued for 24 h. Finally, the material was hot-filtered and washed with copious amounts of CH_2Cl_2. The recovered yield of **5b@SiO$_2$** was 6.14 g. Pd content by ICP: 2.50 wt% (0.237 mmol / g). $^{13}C\{^1H\}$ CP-MAS and $^{29}Si\{^1H\}$ MAS NMR spectra of a C2 ^{13}C-labeled sample of **5b@SiO$_2$** are included in the NMR spectra section.

End-capping treatment of silica-supported materials for the obtaining of ***4b,5a,5b@SiO$_2$+TMS***. A Schlenk flask was charged with the appropriate supported Pd complex (1.00 g) and flushed with N_2. The solid was suspended in toluene (3 mL) and then stirred at 400 rpm while $MeOSiMe_3$ (1.5 mL) was added dropwise *via* syringe. After fastening the flask's stopper securely and closing the N_2 inlet, the reaction mixture was heated at 60 °C with stirring (150 rpm) overnight. Upon cooling, the product material was collected by filtration and washed with copious amounts of CH_2Cl_2. Note: the synthesis of **5b@SiO$_2$+TMS** was also carried out at a 3 g scale. **4b@SiO$_2$+TMS**: yield = 980 mg. Pd content by ICP: 1.67 wt% (0.157 mmol / g). **5a@SiO$_2$+TMS**: yield = 990 mg. Pd content by ICP: 1.97 wt% (0.185 mmol / g). **5b@SiO$_2$+TMS**: yield = 1.00 g. Pd content by ICP: 1.73 wt% (0.163 mmol / g). $^{13}C\{^1H\}$ CP-MAS and $^{29}Si\{^1H\}$ MAS NMR spectra of a C2 ^{13}C-labeled sample of **5b@SiO$_2$+TMS** are included in the NMR spectra section.

Performance of the silica supported catalysts in Suzuki-Miyaura reactions.

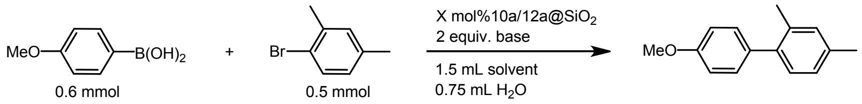
General procedure for catalytic Suzuki-Miyaura reaction runs. A small Schlenk flask or 5 mL screw topped vial was charged with the catalyst, base, boronic acid and the aryl halide (if solid). The flask or vial was capped with a septum or septum cap and flushed with N_2, and then the aryl halide was added *via* microsyringe if liquid. Solvent was added *via* syringe (2 mL organic solvent or 1.5 mL organic solvent and 0.75 mL water) and, in the case of the Schlenk flask runs, the septum was replaced by a glass stopper. The reaction mixture was then stirred at 400 rpm and heated at the indicated temperature. After the indicated reaction time, the vessel was cooled in an ice bath. Next, the organic fraction was filtered through a small plug of silica. In the case of the biphasic aqueous runs, the aqueous layer was then extracted with toluene (2×0.5 mL) and the extracts were filtered through the same silica plug. The silica plug was when washed with toluene (1 mL). The product mixture was analyzed by GC-FID at this stage, and then it was evaporated under reduced pressure and purified by silica gel chromatography using hexane/EtOAc as eluent.

Optimization of reaction conditions for supported catalysts in the Suzuki-Miyaura reaction

The substrate pair 4-bromo-*m*-xylene and 4-methoxyphenylboronic acid were chosen for the optimization runs because they represent a moderately difficult coupling with regard to both sterics and electronics, and because they were shown to give moderate yield of biaryl during preliminary substrate screening. Additionally, all plausible reaction products from these two substrates (the desired biaryl, anisole from deboronation, *m*-xylene from debromination and the two possible homocoupling products) as well as the aryl bromide substrate can be detected by GC-FID as well-separated peaks. Upon analysis of the product mixtures from the optimization runs, no by-products except anisole were detected in measurable quantities unless indicated otherwise (trace quantities of both homocoupling products were observed in some cases).

Reactions were carried out as above, except that undecane (106 µL, 0.5 mmol, 1.0 equiv.) was added as a GC-FID internal standard prior to extraction of the product mixture. GC-FID yields were obtained by comparing peak areas with that of the undecane internal standard. Multipoint calibrations were carried out with known quantities of 4-bromo-*m*-xylene, anisole and the reaction product with at least four different relative undecane concentrations in order to obtain accurate FID yields. The identities of eluted species were confirmed by GC-MS (EI) and by comparison with retention times of authentic samples. The GC-FID method used consisted of: Column; Agilent HP-5, 30 m × 250 µm. Inlet; temp. = 250 °C, pressure = 100.0 kPa, 16:1 split, total flow = 25.0 mL/min, helium carrier. Detector; temp. = 275 °C, hydrogen flow = 40.0 mL/min, air flow 450.0 mL/min, makeup flow (helium) = 45.0 mL/min. Oven; initial temp. = 45 °C (5 min), ramp = 10 °C/min to 250 °C, hold at 250 °C for 5 min. Retention times: anisole, 9.4 min; undecane, 13.0 min; 4-bromo-*m*-xylene, 14.1 min; product; 22.8 min.

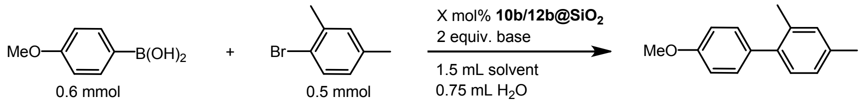
Table S1. Optimization of reaction conditions for the coupling of 4-bromo-*m*-xylene with 4-methoxyphenylboronic acid using **2a@SiO$_2$** and **3a@SiO$_2$** catalytic systems.



entry	ligand	solvent	base	temp (°C)	time (h)	% yield[a] (% deboronation[b])
1	**2a@SiO$_2$** 2.5 mol% Pd	toluene/ H_2O	Na_2CO_3	60	20	69(1)
2	**2a@SiO$_2$** 1.5 mol% Pd	toluene/ H_2O	Cs_2CO_3	60	20	40(0)
3	**3a@SiO$_2$** 4.8 mol% Pd	toluene/ H_2O	Na_2CO_3	60	16	28(49)
4	**3a@SiO$_2$** 2.4 mol% Pd	toluene/ H_2O	Na_2CO_3	60	16	46(36)
5	**3a@SiO$_2$** 1.2 mol% Pd	toluene/ H_2O	Na_2CO_3	60	20	16(90)
6	**3a@SiO$_2$** 1.5 mol% Pd	toluene/ H_2O	Cs_2CO_3	60	20	35(1)
7	**3a@SiO$_2$** 2.4 mol% Pd	dioxane	KO^{t}Bu	60	20	21(16)
8	**3a@SiO$_2$** 2.4 mol% Pd	dioxane	NaOMe	60	20	8(trace)
9	**3a@SiO$_2$** 2.4 mol% Pd	MeCN/ H_2O	Na_2CO_3	60	20	49(44)
10	**3a@SiO2+TMS** 1.8 mol% Pd	toluene/ H_2O	Na_2CO_3	60	20	35(56)

[a] Determined by GC-FID, yield based on ArBr, average of two runs. [b] Percent of 0.5 mmol ArB(OH)$_2$ needed for C–C coupling converted to deboronation product.

Table S2. Optimization of reaction conditions for the coupling of 4-bromo-m-xylene with 4-methoxyphenylboronic acid using **2b@SiO$_2$** and **3b@SiO$_2$** catalytic systems.



entry	catalyst	solvent	base	temp (°C)	time (h)	% yield[a] (% deboronation[b])
1	**2b@SiO$_2$** 1.8 mol% Pd	toluene/ H$_2$O	Na$_2$CO$_3$	60	20	52(0)
2	**2b@SiO$_2$** 1.0 mol% Pd	toluene/ H$_2$O	Cs$_2$CO$_3$	60	5 20	34(0) 58(0)
3	**2b@SiO$_2$** 2.0 mol% Pd	toluene/ H$_2$O	Cs$_2$CO$_3$	60	20	85(0)
4	**2b@SiO$_2$+TMS** 2.0 mol% Pd	toluene/ H$_2$O	Cs$_2$CO$_3$	60	5	87(0)
5	**3b@SiO$_2$** 2.8 mol% Pd	toluene/ H$_2$O	Na$_2$CO$_3$	60	20	**77**(8)
6	**3b@SiO$_2$** 2.8 mol% Pd	toluene/ H$_2$O	Na$_2$CO$_3$	90	16	73(33)
7	**3b@SiO$_2$** 2.8 mol% Pd	MeCN/ H$_2$O	Na$_2$CO$_3$	60	20	74(26)
8	**3b@SiO$_2$** 2.8 mol% Pd	dioxane/ H$_2$O	Na$_2$CO$_3$	60	20	76(0)
9	**3b@SiO$_2$** 2.8 mol% Pd	toluene/ H$_2$O	Na$_2$CO$_3$	60	20	**>95**(0)[c]
10	**3b@SiO$_2$** 2.8 mol% Pd	toluene/ H$_2$O	Cs$_2$CO$_3$	60	20	**>95(0)**
11	**3b@SiO$_2$** 1.5 mol% Pd	toluene/ H$_2$O	Cs$_2$CO$_3$	60	20	**85**(0)
12	**3b@SiO$_2$** 2.8 mol% Pd	toluene/ H$_2$O	Na$_2$CO$_3$	60	20	16(0)[d]
13	**3b@SiO$_2$+TMS** 2.0 mol% Pd	toluene/ H$_2$O	Na$_2$CO$_3$	60	5 20	**81**(0) **95**(8)

14	**3b@SiO$_2$+TMS** 2.2 mol% Pd	toluene/ H_2O	Na_2CO_3	60	5	42(0)[e]
15	**3b@SiO$_2$+TMS** 2.0 mol% Pd	toluene/ H_2O	K_2CO_3	60	5	81(0)
16	**3b@SiO$_2$+TMS** 2.0 mol% Pd	toluene/ H_2O	K_3PO_4	60	5	>**95**(0)
17	**3b@SiO$_2$+TMS** 2.0 mol% Pd	toluene/ H_2O	Cs_2CO_3	60	5	>**95**(0)
18	**3b@SiO$_2$+TMS** 2.0 mol% Pd	toluene/ H_2O	Cs_2CO_3	60	5	>**95**(0)[c]
19	**3b@SiO$_2$+TMS** 2.0 mol% Pd	toluene/ H_2O	Cs_2CO_3 (1.2 eq)	60	5	77(0)
20	**3b@SiO$_2$+TMS** 1.0 mol% Pd	toluene/ H_2O	Cs_2CO_3	60	5	88(0)
21	**13@SiO$_2$+TMS** 1.0 mol% Pd	toluene/ H_2O	Cs_2CO_3 (1.2 eq)	60	5	68(0)

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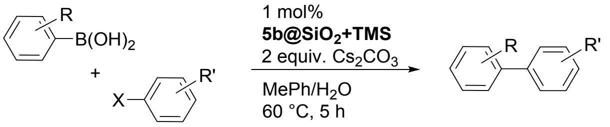
[a] Determined by GC-FID, yield based on ArBr, average of two runs. [b] Percent of 0.5 mmol ArB(OH)$_2$ needed for C-C coupling converted to deboronation product. [c] Used 1.5 equiv. ArB(OH)$_2$. [d] Reaction run under aerobic conditions, significant ArB(OH)$_2$ homocoupling observed. [e] TMS capping treatment repeated, at 75 °C.

Substrate Scope under batch conditions in the presence of water.



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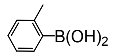
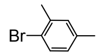
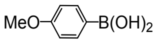
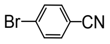
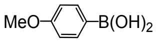
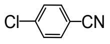
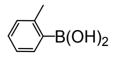
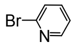
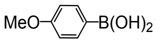
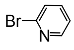
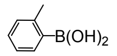
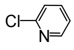
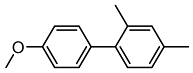
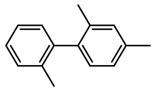
1			79
2			94[b]
3			84
4			92
5			50
6			45

[a] Conditions: 0.5 mmol ArX, 0.6 mmol ArB(OH)$_2$, 1.0 mmol Cs$_2$CO$_3$, 1.5 mL MePh, 0.75 mL H$_2$O, 60 °C, 5 h. [b] No starting material or by-products observed by GC-FID, yield indicates loss during workup.

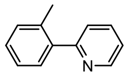
Coupling products from S.M. catalytic runs:



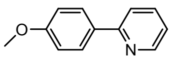
4-methoxy-2′,4′-dimethylbiphenyl. 4-bromo-*m*-xylene (68 µL, 0.5 mmol, 1.0 equiv.), 4-methoxyphenylboronic acid (91 mg, 0.6 mmol, 1.2 equiv.), Cs$_2$CO$_3$ (326 mg, 1.0 mmol, 2.0 equiv.), **5b@SiO$_2$+TMS** (30 mg, 0.01 equiv.). Chromatographed with 25:1 *n*-hexane/EtOAc. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.24 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 7.09 (s, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.36 (s, 3H), 2.25 (s, 3H), NMR peaks match literature values.[2] MS (EI): m/z = 212 (H$^+$), 197, 181.



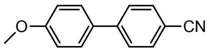
2,4-dimethyl-2′-methylbiphenyl. 4-bromo-*m*-xylene (68 µL, 0.5 mmol, 1.0 equiv.), 2-methylphenylboronic acid (82 mg, 0.6 mmol, 1.2 equiv.), Cs$_2$CO$_3$ (326 mg, 1.0 mmol, 2.0 equiv.), **5b@SiO$_2$+TMS** (30 mg, 0.01 equiv.). Chromatographed with *n*-hexane. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.26-7.19 (m, 3H), 7.11-7.09 (m, 2H), 7.04 (br d, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 2.37 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H). MS (EI): m/z = 196 (M$^+$), 181, 165, 152. NMR and MS peaks match literature values.[3]



2-(2-methylphenyl)pyridine. 2-bromopyridine (48 µL, 0.5 mmol, 1.0 equiv.), 2-methylphenylboronic acid (82 mg, 0.6 mmol, 1.2 equiv.), Cs$_2$CO$_3$ (326 mg, 1.0 mmol, 2.0 equiv.), **5b@SiO$_2$+TMS** (30 mg, 0.01 equiv.). Chromatographed with 10:1 *n*-hexane/EtOAc. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.71 (d d d, J_1 = 4.9 Hz, J_2 = 1.8 Hz, J_3 = 0.9 Hz, 1H), 7.78 (d d d, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 1.8 Hz, 1H), 7.43 (d d d, J_1 = 7.8 Hz, J_2 = 1.1 Hz, J_3 = 1.0 Hz, 1H), 7.41-7.39 (m, 1H), 7.32-7.26 (m, 4H), 2.03 (s, 3H). HR-MS: m/z = 170.1000, calcd. for C$_{12}$H$_{12}$N [M-H$^+$]: 170.0966.



2-(4-methoxyphenyl)pyridine. 2-bromopyridine (48 µL, 0.5 mmol, 1.0 equiv.), 4-methoxyphenylboronic acid (91 mg, 0.6 mmol, 1.2 equiv.), Cs_2CO_3 (326 mg, 1.0 mmol, 2.0 equiv.), **5b@SiO$_2$+TMS** (30 mg, 0.01 equiv.). Chromatographed with 10:1 *n*-hexane/EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d d d, J_1 = 4.9 Hz, J_2 = 1.8 Hz, J_3 = 1.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.75-7.66 (m, 2H), 7.18 (d d d, J_1 = 7.2 Hz, J_2 = 4.9 Hz, J_3 = 1.3 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H). HR-MS: *m*/*z* = 186.0889, calcd. for $C_{12}H_{12}NO$ [M-H$^+$]: 186.0915.



4-(4-methoxyphenyl)benzonitrile. 4-bromobenzonitrile (91 mg, 0.5 mmol, 1.0 equiv.), 4-methoxyphenylboronic acid (91 mg, 0.6 mmol, 1.2 equiv.), Cs_2CO_3 (326 mg, 1.0 mmol, 2.0 equiv.), **5b@SiO$_2$+TMS** (30 mg, 0.01 equiv.). Chromatographed with 5:1 *n*-hexane/EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.9 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H). HR-MS: *m*/*z* = 232.0712, calcd. for $C_{14}H_{11}NNaO$ [M-Na$^+$]: 232.0735.

General procedure for recycling of the silica-supported catalysts. In the cases where catalyst recycling was performed, an internal standard (undecane) was added after cooling the reaction mixture in an ice bath; the supported catalyst was separated from the organic phase by decantation, filtration and washed with toluene (2 × 1 mL), which was combined with the organic phase. The supported catalyst was then successively washed with water, EtOH and Et2O, then dried under vacuum and directly reused in the next cycle.

Recyclability test under batch conditions in the presence of water

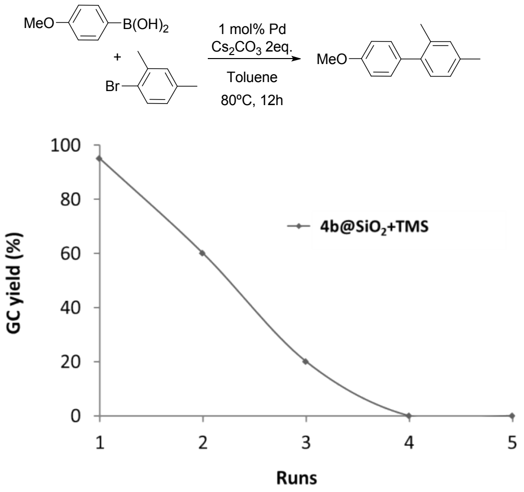


Figure S1. Performance of the supported catalyst (**4b@SiO2+TMS**) in the presence of water

Analysis on leached Pd after anhydrous recycling in batch

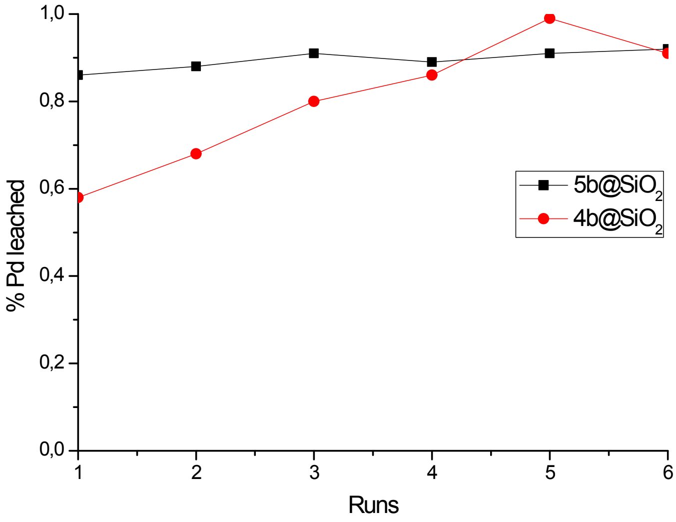


Figure S2. Measurement of the amount of Pd leached after each catalytic run

Experimental procedure for continuous flow tests.

Catalytic activity and stability of the catalysts (4b@SiO2) and (5b@SiO2) were studied under flow conditions using a Vapourtec system with a R2 pump module and a R4 reactor module. The rig is shown schematically in Figure 4.

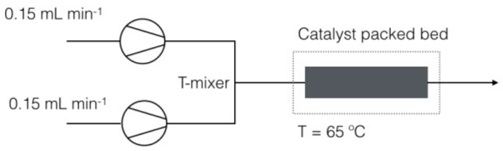


Figure 4. Scheme of a Vapourtec reactor.

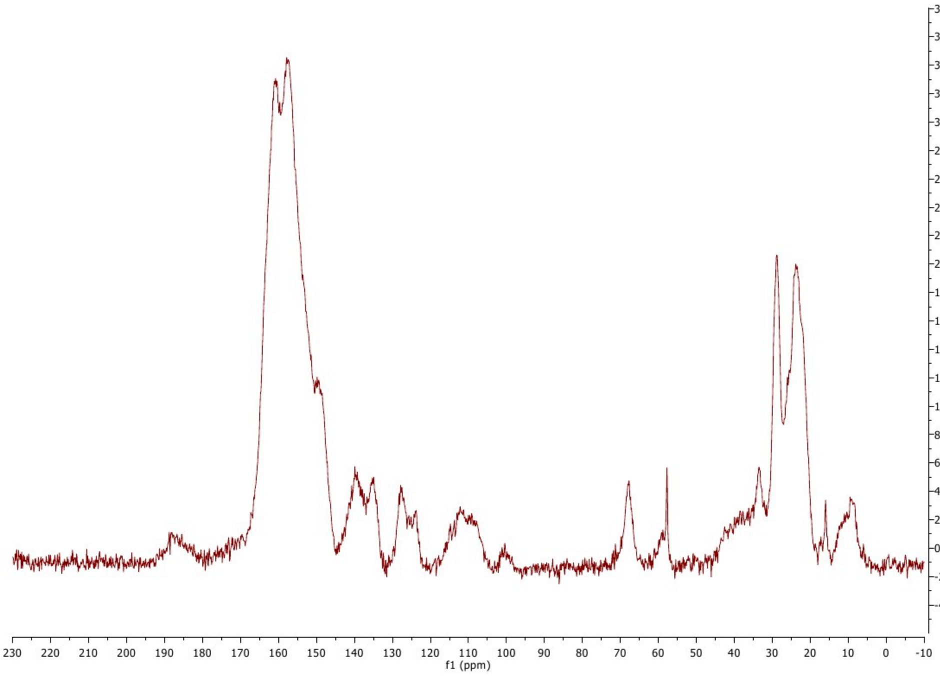
Two feed solutions were deoxygenated by bubbling N_2 for 1 h prior to reactions and then were pumped by two HPLC pumps into the T-connection (PTFE, 0.5 mm through holes, Upchurch Scientific) via PFA tubing (1.6 mm OD, 1.2 mm ID) at equal flow rates ($u_1 = u_2 = 0.15$ mL min^{-1}). The merged flow was then introduced into the inlet of the packed-bed column assembly (borosilicate glass with PTFE end pieces, 6.6 mm ID x 100 mm length, OmniFit). The column was packed with a catalyst providing the length of the catalytic bed of 2.3 cm, which corresponds to the packed bed volume of 0.787 mL. The measured amount of the catalyst was diluted with QuadraSil-AP (Johnson Matthey) spherical silica beads. The void volume in the catalytic bed in the approximation of close random packing of ideal spheres is 0.295 mL (void fraction is about 0.375, neglecting porosity of the support). Mean residence times in the packed bed were found to be 3.5 and 1.9 minutes for the cases of the single phase and the biphasic aqueous-organic flows correspondingly (calculated from residence time distribution curves measured for the QuadraSil-AP using a standard tracer technique). For the loadings of the catalysts used in this study this void corresponds to the initial molar ratio of Ar-Br:Pd≈2.1 in the reactor in the case of the biphasic aqueous-organic flow, or 0.4 in the case of the single phase conditions. The catalytic loadings in the reactor are still quite high even if we assume porosity of the support of about 60 % (Ar-Br:Pd≈4.2 or 0.9 for biphasic and single phase conditions correspondingly).

Table S3. Experiments for the coupling of 4-bromo-m-xylene with 4-methoxyphenylboronic acid using **4b@SiO$_2$** and **5b@SiO$_2$** catalytic systems under flow conditions.

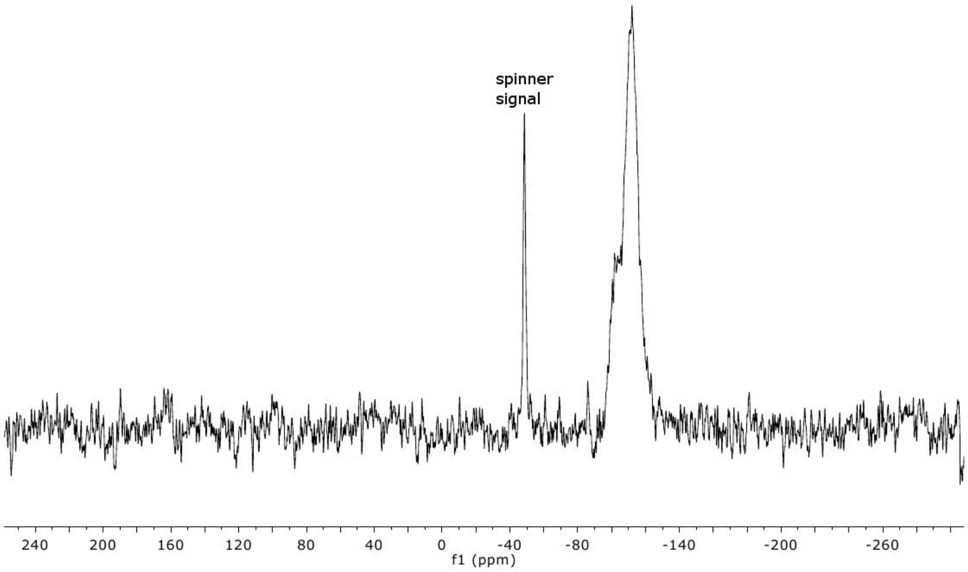
Exp.	**Solution I**		**Solution II**			**Catalyst**	
	Solv.	[ArBr], M	Solvent	Base/C, M	[Boronic Acid], M	Title	Pd, mmol
1[b]	CH_3OH	0.2	CH_3OH	Cs_2CO_3 /0.4	0.2	**5b@SiO2+TMS**	0.07
2[b]	CH_3OH	0.2	CH_3OH	Cs_2CO_3 /0.4	0.2	**4b@SiO2+TMS**	0.07
3	CH_3CN	1	H_2O	K_3PO_4/2	1	**5b@SiO2+TMS**	0.07

NMR spectra of synthesized compounds

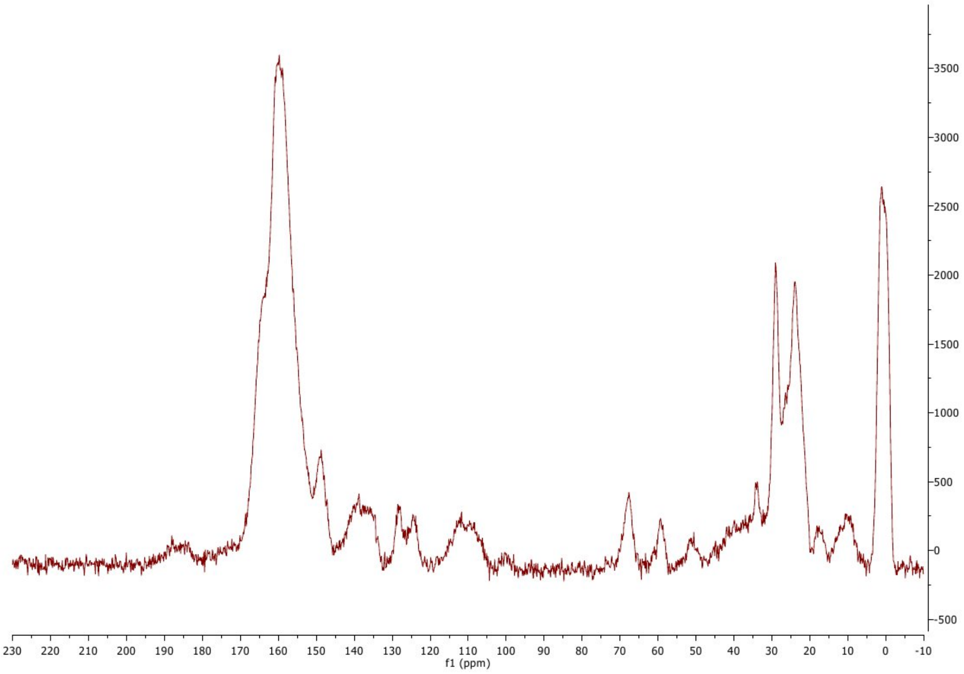
$^{13}C\{^1H\}$ CP-MAS NMR spectrum of **5b@SiO$_2$** at 12 kHz:



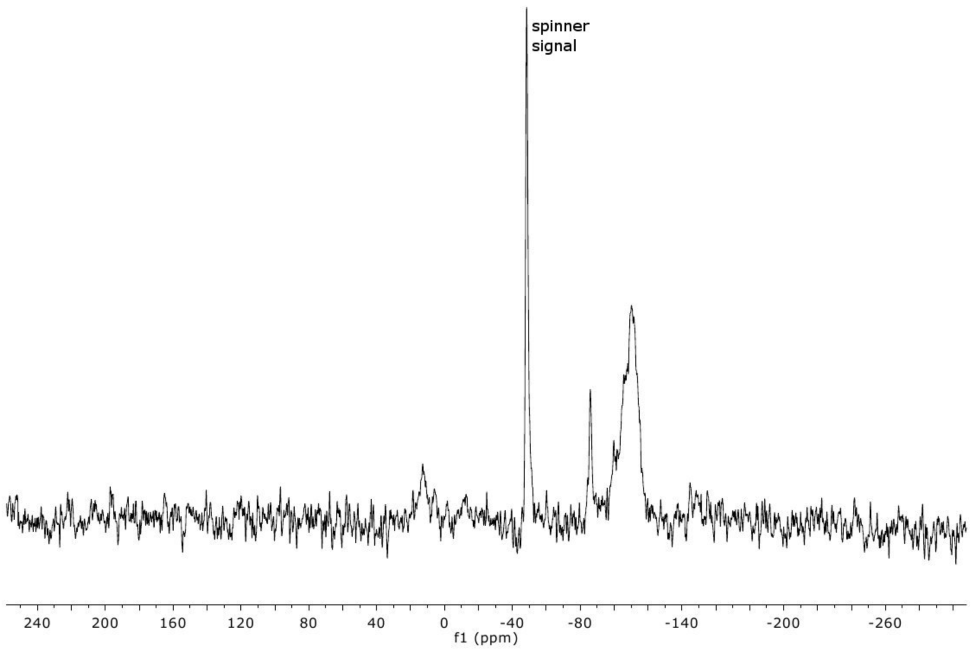
$^{29}Si\{^1H\}$ MAS NMR spectrum of **5b@SiO$_2$** at 3 kHz:



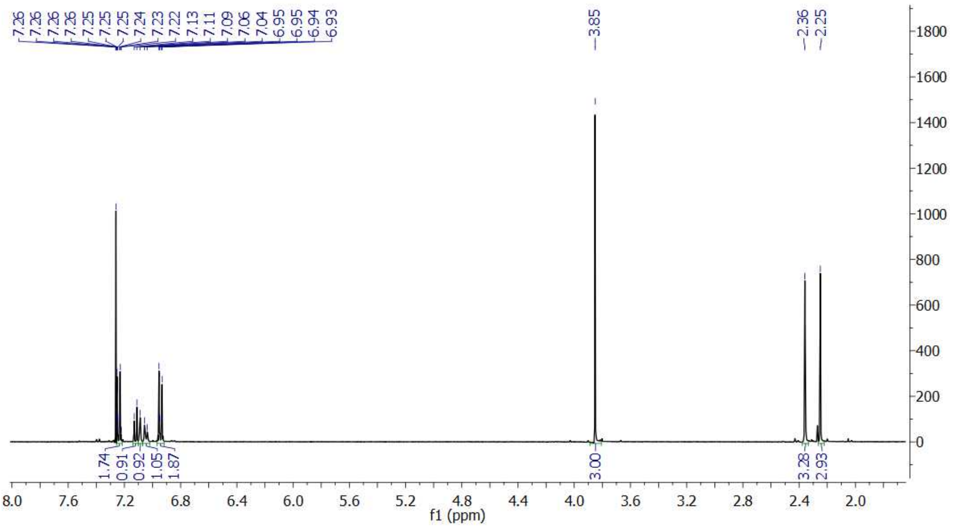
$^{13}C\{^1H\}$ CP-MAS NMR spectrum of **5b@SiO$_2$+TMS** at 12 kHz:



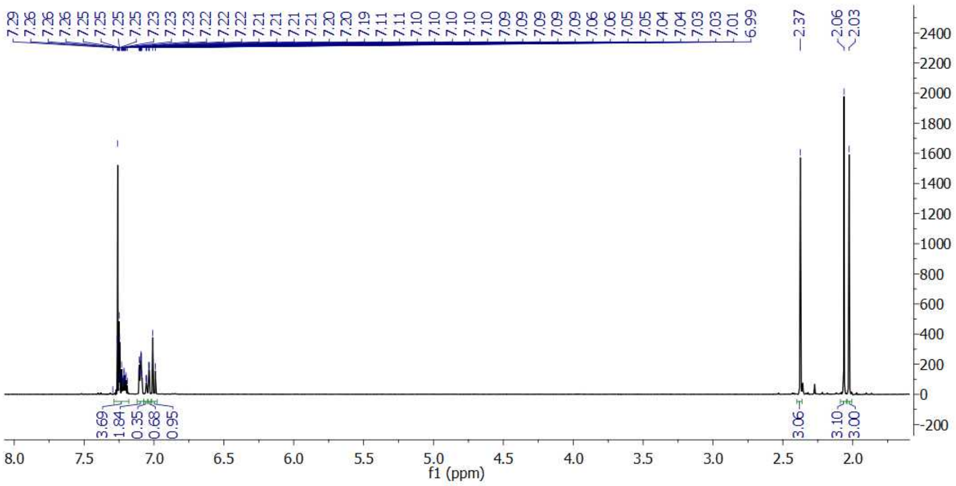
$^{29}Si\{^1H\}$ MAS NMR spectrum of **5b@SiO$_2$+TMS** at 3 kHz:



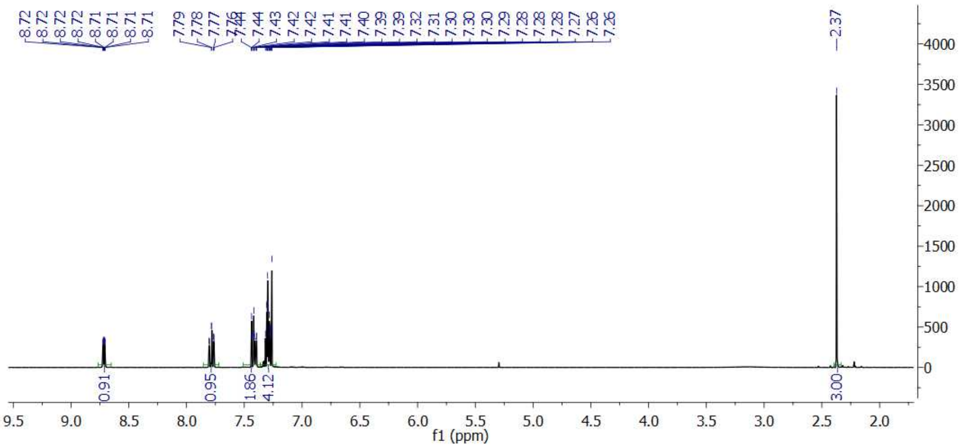
^{1}H NMR spectrum of purified **4-methoxy-2′,4′-dimethylbiphenyl** in $CDCl_3$:



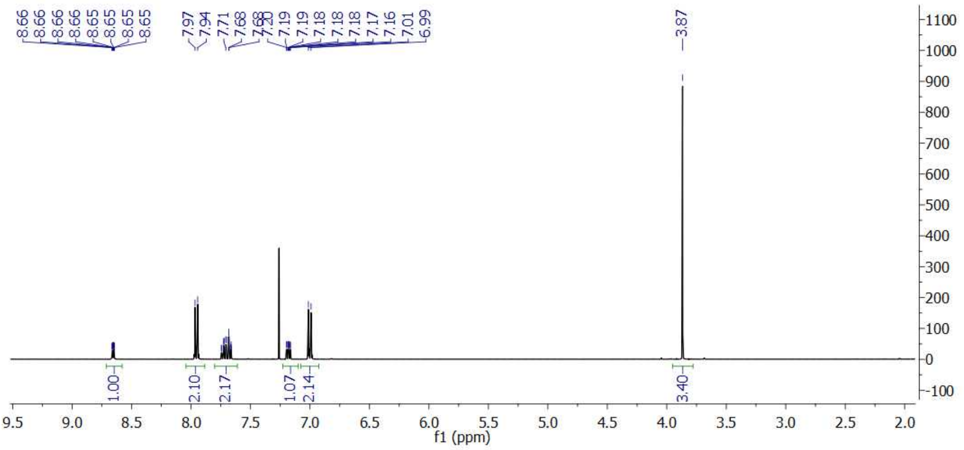
^{1}H NMR spectrum of purified **2,4-dimethyl-2′-methylbiphenyl** in $CDCl_3$:



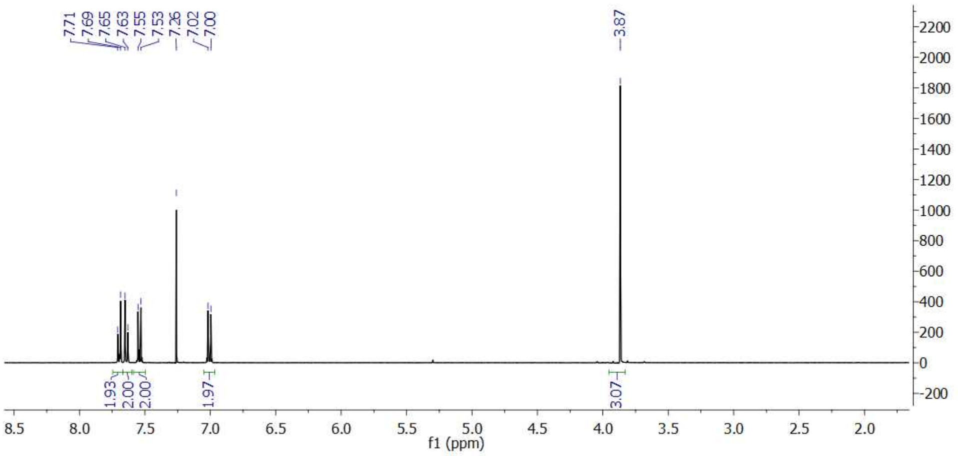
^{1}H NMR spectrum of purified **2-(2-methylphenyl)pyridine** in $CDCl_3$:



^{1}H NMR spectrum of purified **2-(4-methoxyphenyl)pyridine** in $CDCl_3$:



^{1}H NMR spectrum of purified **4-(4-methoxyphenyl)benzonitrile** in $CDCl_3$:



References

[1] G. Künstle, H. Siegl (Wacker-Chemie GmbH), *US Patent* 3,960,909, 1976; *Chem. Abstr.* 1975, **83**, 208102.

[2] K. Pati and R. S. Liu, *Chem. Commun.*, 2012, **48**, 6049-6051.

[3] W.K. Chow, C. M. So, C. P. Lau, F. Y Kwong, *J. Org. Chem.*, 2010, **75**, 5109-5112.