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ARTICLE TYPE

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

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The heterogenisation of a new family of Pd-NHC complexes is reported via a straightforward and efficient synthetic procedure. These silica-immobilised materials were successfully applied as catalysts in the Suzuki-Miyaura coupling of aryl chlorides and bromides under mild conditions. The materials exhibited improved stability when the catalytic reaction was run under anhydrous conditions and could be recycled up to five times without significant loss of activity. When the reaction was run within a continuous flow microreactor, these catalysts showed good activity during at least two hours on stream.

Introduction

In the last decade, continuous flow operation has emerged as a powerful tool for chemical synthesis, enabling more efficient transformations in the fine chemicals industrial sector.[1] Indeed, continuous flow systems were shown to provide efficient mass transport and mixing,[2] and to improve heat transfer compared to batch systems, resulting in faster and safer reactions with enhanced product yields.[3,4] Furthermore, the combination of improved dynamics and kinetic characteristics of flow chemistry with the use of recyclable catalytic materials represents an innovative synthetic methodology that perfectly fits the current need for more environmentally-friendly procedures for transformations catalysed by precious metals such as the Pd-catalysed Suzuki-Miyaura coupling.

A desirable strategy would be to fully exploit the features of a specifically designed catalyst in conjunction with modern flow techniques to define useful and practical procedures for the recovery and reuse of the catalysts, while obtaining the desired product with minimal cost in terms of time and waste.[5] Among the reported catalysts designed for this purpose, many supported molecular[6] or particulate[7] catalysts have shown high activity and long-term reusability. In these systems, the use of silica supports has proven effective due to their thermal and chemical stability, as well as a rigid yet porous structure devoid of swelling properties, a characteristic that makes them compatible with a wide range of solvents.

Pd-catalysed cross-coupling reactions are currently regarded as one of the most important methods for the construction of carbon-carbon bonds.[8,9,10] The application of flow chemistry for these transformations is particularly challenging due to the formation of salts during the reactions, which often leads to rapid clogging of tubular reactors. However, recently several examples of successful metal-catalysed C-C cross coupling reactions under flow conditions were reported,[11] employing a broad range of solid supports such as monolithic systems,7[12,13,14,15,16,17,18] thin films of palladium nanoparticles,[19] Pd/C[20] and ionic liquids.[21]

In the Suzuki-Miyaura process, several methodologies have been reported for the preparation of catalysts for the flow conditions. These include immobilisation of the catalyst on a membrane at the centre of a microchannel,[22,23,24] the use of a fluorous-tagged palladium complex[25] or the immobilisation of palladium particles on the surface of unfunctionalised and functionalised silica-coated magnetic nanoparticles.[26,27] Alternatively, microwave-assisted continuous-flow processes have been described for this reaction.[28,29] Organ used capillaries coated with a thin film of palladium,19[,30] and Ley and co-workers filled a U-shaped glass tube with the encapsulated catalyst PdEnCat™.[31,32] Kirschning and co-workers also reported the use of a homogenous Pd catalyst attached directly through coordination of the metal centre to a polymeric support, namely polyvinylpyridine.[12] This system was found to operate via a so-called "release and catch" pathway where the active Pd species is initially released from the support and re-deposited onto the support after the reaction. Excellent results were obtained with this system using a 0.2 mol% catalyst, employing isopropyl alcohol as solvent and potassium *tert*-pentoxide as the base. Under flow conditions up to 94% yield

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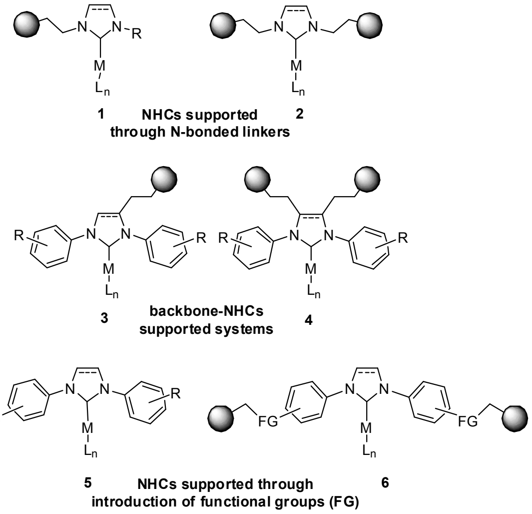
could be achieved for 20 hours on stream using aryl chlorides as substrates.

Under batch conditions, soluble Pd catalysts bearing bulky *N*-heterocyclic carbene (NHC) ligands have proven to be extremely effective for the Suzuki-Miyaura reaction.[33,34] Sterically congested NHC ligands are electronically and sterically stabilised and their electron-rich character makes them attractive ligands for a wide range of catalytic transformations. Furthermore, they are resistant to air oxidation and bind very strongly with soft metal centres, which is essential if one is to avoid metal leaching during the catalytic process. Over the last decade, the immobilisation of NHC-based systems has been reported for various types of support such as polymers, dendrimers, clays and silica.[35,36,37,38,39,40] Various strategies were reported for the anchoring of *N*-heterocyclic carbenes. In most cases, NHC moieties are covalently attached to the support using alkylic linkers bonded to one or both nitrogen atoms of the imidazolylidene ring, see Scheme 1, complexes **1** and **2**.[41,42,43,44,45,46,47] These methods usually exhibit advantages in terms of synthetic procedures, but reduce the steric profile of the ligands and hence the performance of the corresponding catalysts. Alternatively, linkers have been attached to the carbon backbone of the NHC ligands, thus avoiding such alteration but resulting in the need for complex synthetic methods, see Scheme 1, complexes **3** and **4**.[48,49,50,51]

An interesting alternative for the heterogenisation of such systems involves the introduction of functionality at the *N*-aryl moieties, as shown in Scheme 1, complexes **5** and **6**. Following this approach, the anchoring can be performed via substitution at the *para* position of one or both aryl rings of the ligand. Lu and co-workers reported the introduction of an allyl moiety in this position which was subsequently functionalised via thiol-ene methodology and anchored onto an MCM-41 support.[52] This supported carbene system was successfully applied in the chemical fixation of carbon dioxide to form cyclic carbonates.

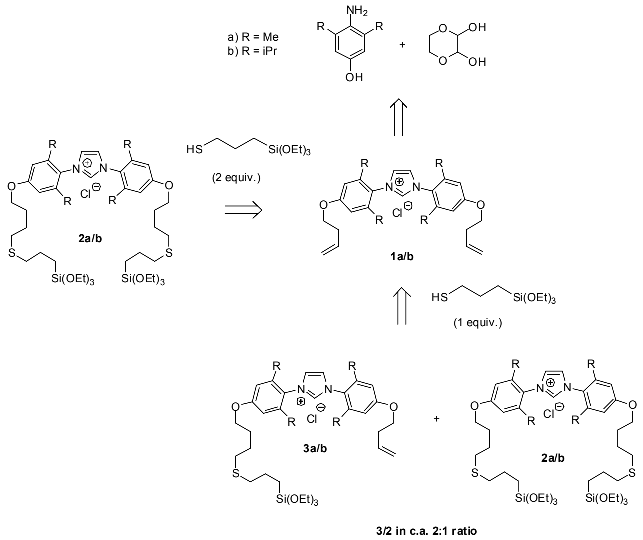


Scheme 1. Reported strategies for anchoring of NHC-based catalysts onto solid supports.

Inspired by the work of Nolan and co-workers, who recently described that *para*-alkoxy functionalized NHCs provide more active Pd catalysts than their unfunctionalised counterparts in the Buchwald-Hartwig C-N coupling,[53] we reported a synthetic strategy for the anchoring of Pd-NHC catalysts via an alkoxy-functionalized ligand.[54] Here, we report the synthesis and characterisation of heterogenized Pd-NHC complexes onto amorphous silica via covalent attachment and their application in the Suzuki-Miyaura coupling reaction of aryl chlorides and bromides under batch and continuous flow conditions.

Results and discussion

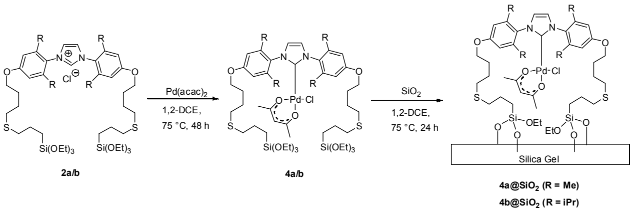
The synthetic procedure for the preparation of the imidazolium pre-ligands **2a/b** was recently reported by our group and is summarised in Scheme 2.[54] This methodology includes the introduction of alkenyl groups through etherification and a subsequent photoinitiated thiol-ene addition of mercaptopropyl(triethoxy)silane for the incorporation of triethoxysilyl groups. Using this synthetic route, the two-tethered imidazolium salts **2a/b** were obtained selectively using two equivalents of the thiol. A mixture of one and two-tethered imidazolium salts **3a/b** and **2a/b** in a *ca*. 2:1 ratio was also obtained when one equivalent of the thiol was used (Scheme 2). While such a mixture of products is not ideal, the preparation of this material afforded a facile method for testing the effect of the ligand's anchoring mode on the resulting catalyst's activity.



Scheme 2. Retrosynthetic scheme for the preparation of the imidazolium pre-ligands **2a/b** and **3a/b**.[54]

These ligand precursors were then used in the synthesis of the corresponding heterogenised catalysts. The species **2a/b** bearing triethoxysilyl groups were first coordinated to Pd to form complexes **4a/b** by reaction with [Pd(acac)$_2$] in 1,2-DCE at 75 °C during 48 h prior to their immobilization onto silica, see Scheme 3.

During the synthesis, the complexes **4** were not isolated and the crude reaction mixtures containing **4a/b** were used directly for immobilisation onto silica gel, yielding **4a/b@SiO$_2$** after heating the Pd-NHC/silica mixtures at 75 °C for 24 h. To confirm that formation of complexes **4** was completed the reaction was monitored by ^{1}H NMR spectroscopy, proving clean, near-quantitative formation of the desired Pd complex under these conditions, see details in Supp. Info.



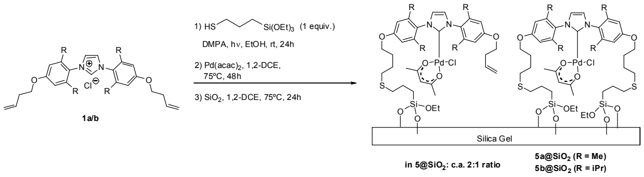
Scheme 3. Two-tethered silica gel-bound Pd-NHC complexes **4a/b@SiO$_2$**.

Further optimisation showed that the entire synthetic sequence, from the thiol addition to alkenyloxy-imidazolium chlorides **1** through the immobilization of Pd-NHC complexes **4** onto silica (3 steps), could be performed as a sequential one-pot reaction as shown in Scheme 4.

This methodology was also used for the preparation of the materials **5a/b@SiO$_2$** by reacting **1a/b** with a single equivalent of the thiol reagent. This procedure afforded a mixture of one and two-tethered imidazolium pre-ligands in a *ca.* 2:1 ratio, estimated by quantifying the amount of unreacted **[**Pd(**1**)(acac)Cl] remaining in solution after the immobilisation procedure.

Finally, the samples of the immobilised catalysts **4@SiO$_2$** and **5@SiO$_2$** were treated with excess MeOSiMe$_3$ in order to cap the remaining accessible hydroxyl groups of the silica surface. The materials obtained are herein labeled (**4,5@SiO$_2$+TMS)**.

The Pd content of these materials was found to range between 1.7 and 2.6 wt % according to ICP analysis and the results of elemental analysis for **4a/b@SiO$_2$** indicated that the immobilised species are 1:1 NHC-Pd complexes.



Scheme 4. Three-step one-pot sequence used for the synthesis of the one-tethered enriched mixture **5a/b@SiO$_2$**.

To further probe the composition of these materials, a sample of **1b** was prepared incorporating a ^{13}C label at the C2 position by using the ^{13}C-enriched paraformaldehyde during the imidazolium-forming step. This modification enabled the electronic environment of the ligand C2 (carbene donor) position to be easily tracked by ^{13}C NMR spectroscopy during the immobilisation and post-immobilisation modification steps. Figure 1 depicts the ^{13}C{^{1}H} NMR spectra of **1b, 4b, 5b** and of the silica-immobilised **5b@SiO$_2$** and post-immobilisation modified (**5b@SiO$_2$+TMS)** (CP-MAS).

No significant difference in chemical shift for C2 was observed between the spectrum of the precursor **1b** (Fig. 1, i) and that of the product of the thiol-ene reaction **2b** (Fig. 1, ii), indicating that the imidazolium C2 carbon's electronic environment is not affected by the introduction of the silyl groups. Upon treatment with Pd, the carbon signal shifts downfield to 160 ppm with the formation of Pd-coordinated imidazol-ylidene species **5b** (Fig. 1, iii). The CP-MAS NMR spectra of the silica-immobilised **5b@SiO$_2$** (Fig. 1, iv) showed a strong, broad signal at similar chemical shift, confirming that most of the immobilised ligand is coordinated to Pd. Finally, in the spectrum of species (**5b@SiO$_2$ + TMS)** (Fig. 1, v) the signals arising from the incorporation of SiMe$_3$ groups in the final material were detected at *ca.* 0 ppm (Fig. 1, v) labeled ***b***). These results clearly show that at least the majority of the Pd-NHC complexes had been successfully anchored to the silica support without catalyst degradation.

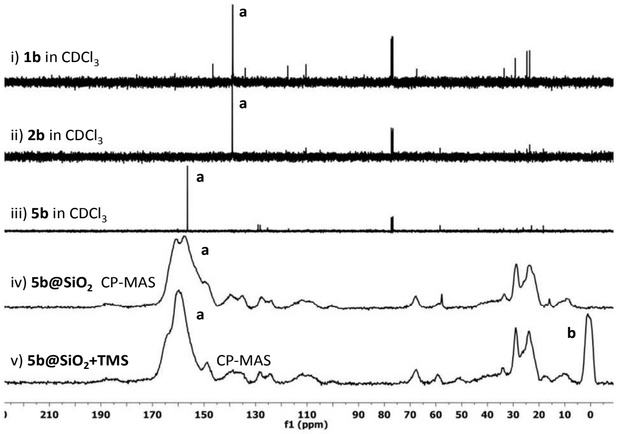


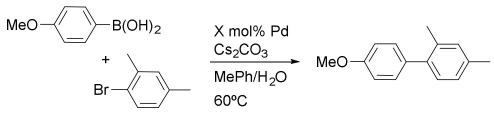
Figure 1. ^{13}C{^{1}H} NMR spectra of ^{13}C2-labeled (**5b@SiO$_2$+TMS)** and synthetic precursors: *i*) imidazolium pre-ligand **1b**; *ii*) triethoxysilyl-functionalised imidazolium pre-ligand **2b**; iii) Pd-coordinated imidazolylidene **5b**; *iv)* silica-immobilised Pd-imidazolylidene **5b@SiO$_2$**; *v*) post-immobilisation modified Pd-imidazolylidene (**5b@SiO$_2$+TMS)**; ***a***. Imidazolium/ylidene C2 carbon. ***b***. Peak corresponding to surface SiMe$_3$ groups.

Performance of the new silica-supported NHC-Pd complexes in the Suzuki-Miyaura reaction

Activity and recyclability under batch conditions

The silica-immobilised Pd complexes described above were tested in the Suzuki-Miyaura reaction of 4-methoxyphenylboronic acid and 1-bromo-2,4-dimethylbenzene. First, the reaction conditions (temperature, solvent base and catalyst loading) were optimised, see Supp. Info.. The optimal reaction conditions for these catalysts included a biphasic toluene/water mixture as solvent and Cs$_2$CO$_3$ or K$_3$PO$_4$ as base at a temperature of 60 °C. Under these conditions, an activity comparison of the different catalyst formulations was performed (Table 1). Only low to moderate yields were achieved when catalysts bearing methyl substitution at the ligand's aromatic rings (labelled "a") were used (Table 1, entries 1 and 2). Catalysts featuring isopropyl substituents showed higher activity, furnishing the biaryl product in 85% yield (Table 1, entry 4). It is also noteworthy that single anchoring of the Pd-NHC complexes provided more active catalysts than double anchoring (entry 5 vs. 4, 3). Finally, post-immobilisation modification by capping the silica surface with SiMe$_3$ groups had a very important beneficial effect on activity, enabling much faster reactions at reduced catalyst loading (Table 1, entry 7 vs. 5).

Table 1. Comparison of activity of the silica-supported catalysts in a model Suzuki-Miyaura reaction.



entry[a]	catalyst	mol% Pd	time (h)	yield (%)[b]
1	**4a@SiO$_2$**	1.5	20	40
2	**5a@SiO$_2$**	1.5	20	35
3	**4b@SiO$_2$**	1.0	5, 20	34, 58
4	**4b@SiO$_2$**	2.0	20	85
5	**5b@SiO$_2$**	1.5	20	85
6	**4b@SiO$_2$+TMS**	2.0	5	87
7	**5b@SiO$_2$+TMS**	1.0	5	88
8	**5b@SiO$_2$+TMS**	2.0	5	**>95**

[a] Conditions: 0.5 mmol ArBr, 0.6 mmol ArB(OH)$_2$, 1.0 mmol Cs_2CO_3, 1.5 mL MePh, 0.75 mL H_2O, 60 °C. [b] By GC-FID, average of two runs.

The most active catalyst formulation (**5b@SiO$_2$+TMS)** was used to briefly explore the substrate scope achievable with this system; for full details, see Supp. Info. *Ortho*-substituted coupling partners, activated bromides and chlorides and also heteroaromatic bromides and chlorides furnished the desired biaryl products in over 80% yield, except for the more challenging heteroaromatic halides, for which only 50% and 45% yields were obtained in the case of 2-bromo and 2-chloropyridine, respectively.

However, darkening of the reaction mixtures was observed in all cases, indicating the formation of Pd black and hence catalyst decomposition under these conditions. Indeed, when a series of recyclability tests were performed under these conditions, a rapid decrease in activity was observed after the first cycle and no conversion was achieved after the third cycle, see Supp. Info.

To investigate the origin of such unexpected decomposition/deactivation, the soluble complex [Pd(**1b**)(acac)Cl)] **6b** was used as precatalyst in the Suzuki-Miyaura coupling under the same reaction conditions used for their supported analogues. The formation of a black precipitate that was observed shortly after the reaction was brought to temperature indicated that catalyst decomposition was also occurring in this case, ruling out a deleterious interaction between the metallic centre and the support. It was therefore thought that the use of water as co-solvent in the reaction medium might be detrimental to the stability of these catalysts and new experiments were carried out to investigate their activity and stability under anhydrous reaction conditions.

Several NHC-Pd based heterogenised catalysts have been reported that can operate in nonaqueous solvents. A variety of systems using anhydrous solvent/base such as iPrOH/*t*-BuOK,[55,56] DMF/Cs_2CO_3[57] or xylene/K_2CO_3[58] have been used in the coupling of arylboronic acids with aryl and benzyl bromides and chlorides. In our case, further optimisation indicated that under anhydrous conditions these catalysts worked best in toluene using cesium carbonate as a base at a reaction temperature of 80 °C.

The recyclability of the one-tethered (**5b@SiO$_2$+TMS)** and the two-tethered (**4b@SiO$_2$+TMS)** catalysts was examined in the coupling of 1-bromo-2,4-dimethylbenzene with 4-methoxyphenylboronic acid under these alternative conditions. The results are shown in Figure 2.

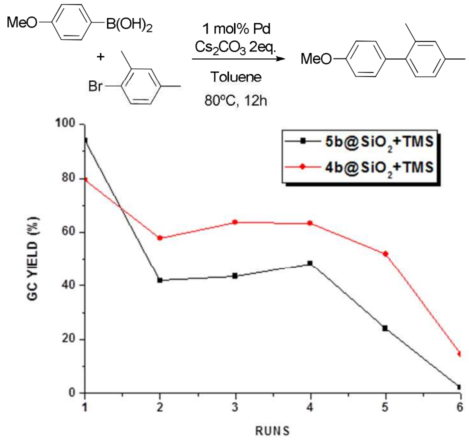


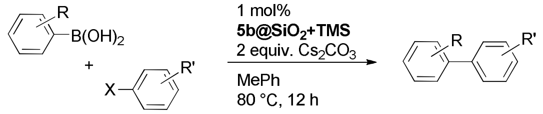
Figure 2. Performance of the supported catalysts **(4b@SiO2+TMS)** and **(5b@SiO2+TMS)** under anhydrous conditions.

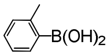
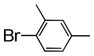
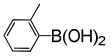
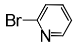
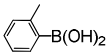
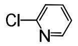
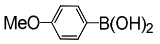
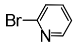
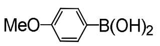
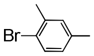
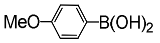
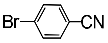
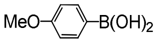
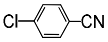
As previously observed under aqueous biphasic conditions, higher activity was achieved using the single tethered **(5b@SiO$_2$+TMS)** in the first run, yielding 95% of the biaryl product after 12 h. In the next run a large drop in catalyst activity occurred and the coupling product could only be obtained in *ca.* 40% yield. These moderate yields were maintained in the following two cycles, before the conversion dropped gradually over the next two runs, resulting in only 3% conversion in the sixth cycle. On the other hand, double tethered (**4b@SiO$_2$+TMS**), though being outperformed in the first cycle by its one-side-attached analogue, proved more robust and achieved yields in the 60% yield range over the next four cycles before eventually showing signs of degradation after the sixth reuse. No visible formation of precipitated palladium was observed in any case under these conditions and the potential leaching of Pd during each run was measured by ICP measurement (Fig. S2 in Suppl. Info.). However, no relevant amount of Pd could be

Substrate scope under batch conditions

Since the catalyst (**5b@SiO2+TMS**) was found to be reasonably stable to recycling under the conditions outlined above, this system was chosen for evaluation in the Suzuki-Miyaura coupling of sterically hindered and heteroaryl bromides and chlorides. The results are summarized in Table 2. Using *ortho*-tolylboronic acid, excellent yields were obtained with 1-bromo-2,4-dimethylbenzene and 2-bromopyridine substrates (entries 1 and 2). However, lower yield was achieved in the transformation of 2-chloropyridine using the same coupling partner (entry 3), indicating that the C-X bond activation might be rate limiting under these reaction conditions. Using 4-methoxyphenylboronic acid as coupling partner, high to excellent yields were also obtained with 1-bromo-2,4-dimethylbenzene and 4-bromo- and 4-chlorobenzonitrile (entries 5-7), although 2-bromopyridine afforded a much lower product yield (entry 4). These results show that under these conditions the *ortho*-substitution in both coupling partners and the use of substrates containing heteroatoms were tolerated and provided efficient transformations using the catalytic system (**5b@SiO$_2$+TMS**).

Table 2. Suzuki-Miyaura substrate scope for the silica-supported catalyst (5b@SiO2+TMS) employing anhydrous conditions.[a]



entry	ArB(OH)2	Ar′X	isolated yield (%)
1			82
2			90
3			43
4			55
5			91
6			92
7			83

[a]Conditions: 1 mmol ArX, 1.2 mmol ArB(OH)$_2$, 2.0 mmol Cs$_2$CO$_3$, 4 mL Toluene anh., 80 °C, 12 h

Evaluation of the performance of the new catalysts under continuous flow conditions

Next, performance of the silica-supported **(4b@SiO$_2$+TMS)** and **(5b@SiO$_2$+TMS)** was assessed under continuous flow operation. Dry methanol was used as a solvent because it offered the best compromise between catalyst activity and the solubility of the reactants and by-product salts (Figure 3a, experiments 1 and 2), for comparison, wet acetonitrile was also used as a solvent. Two solutions with different chemical composition were used in the packed bed flow reactor and the catalyst and the corresponding amounts of Pd in the catalytic bed.See Supp. Info.

Different reaction parameters were used in the flow tests. For all the experiments the temperature inside the flow reactor set at 65 °C; the total flow rate was 0.30 mL min^{-1} and the residence time was 3.5 min for experiments 1 and 2 and 1.9 min for experiment 3.

The flow experimental conditions clearly show the trend of catalyst activation-deactivation under the reaction conditions. In all three experiments we observed an initial incubation period, which could indicate the possible generation of palladium nanoclusters, although no decomposition was apparent during the experiments.[59] Full conversion of the bromide substrate was achieved with the **(5b@SiO$_2$+TMS)** catalyst after 40 min time-on-stream, see Figure 3a, empty circles. Then, as also observed under batch conditions, conversion dropped to about 40-50%, and this level of activity was maintained over the following 90 min.

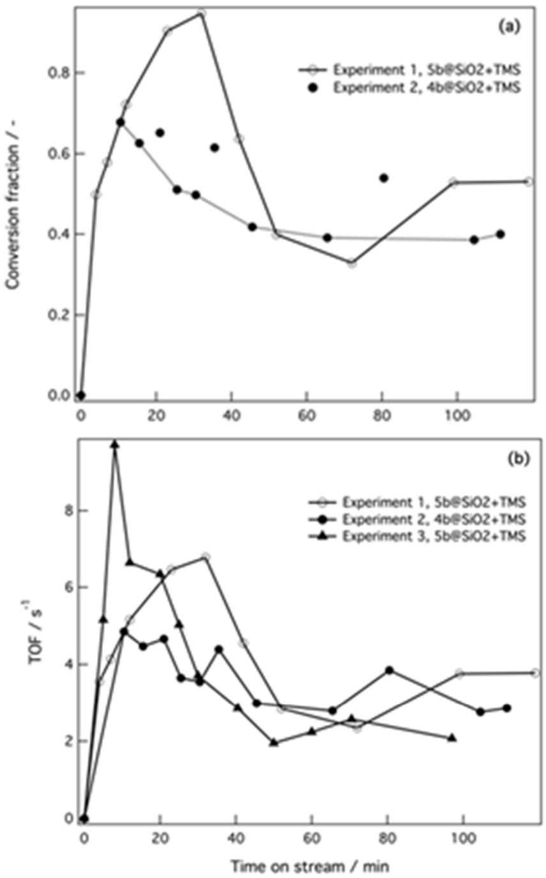


Figure 3. Experiments 1 and 2 took place in dry MeOH under anhydrous conditions. For both experiments the solution I was 0.2 M in the corresponding ArBr and the solution II was 0.4 M in base(Cs$_2$CO$_3$) and 0.2 M in boronic acid. Experiment 3 was carried out in wet acetonitrile, the solution I was 1 M in the ArBr and the solution II was 2 M in base (K$_3$PO$_4$) and 1 M in boronic acid. (a) Conversion of the Ar-Br to Suzuki coupling product vs time on stream; (b) TOF vs time on stream. Experiment numbers correspond to Table 3; lines are given for convenience of an eye. C$_0$= 0.1 M in the reactor; u$_1$= u$_2$= 0.15 mL min^{-1} in both experiments. GC conversion, mesytilene used as internal standard.

The catalyst **(4b@SiO$_2$+TMS)** also showed an incubation period after which the mixture coming out from the reactor reached a maximum conversion of 70% after 10 min on stream. In this case a smaller drop in conversion occurred compared with the single tethered catalyst, and conversion remained stable at 40-50% after two hours under continuous flow. When a biphasic aqueous-organic mixture was used (experiment 3, Figure 3b), higher initial activities (expressed as turn over frequency, TOF) were achieved, followed by a decrease of 80% in catalytic activity after 45 minutes in flow, dropping from 10 to 2 s^{-1}. Traces of the deboronation by-product as well as an unidentified by-product (possibly arising from homo-coupling) were observed for both catalysts. However, the selectivity of the Ar-Br substrate towards Suzuki coupling product was found to be 93-96%. The color of the supported catalysts changed from initial yellow to dark orange-brown over time. However, no visible Pd black was observed in the outlet flow.

The observed concentration vs time-on-stream trends for several experiments show fluctuations in concentrations. These are correlated with periodic increases in pressure drop within the packed catalyst bed caused by salt formation and its removal from the packed bed with the flow. The estimated residence time in the single-phase experiments is 3.5 min, resulting in 50-60 % conversion. The considerably faster reaction in flow compared to batch conditions is due to the high ratio of catalyst to reactant in the packed-bed microreactor. Despite the observed fluctuations the overall conversion was relatively stable over *ca.* 90 min on stream.

Conclusions

In the present work, the synthesis and characterisation of a new family of silica-immobilised Pd-NHC precatalysts is reported, following a highly modular synthesis of the functionalised ligands recently reported by our group. The introduction of trialkoxysilyl groups in the imidazolium architecture allowed the covalent attachment of the Pd complexes onto the silica support. These supported catalysts were characterized by ICP, elemental analysis, and solid state ^{13}C and ^{29}Si NMR. These catalysts were active in the Suzuki-Miyaura reaction of aryl chlorides and bromides bearing sterically hindered substituents. The stability of these catalysts improved under anhydrous conditions and the coupling of 1-bromo-2,4-dimethylbenzene with 4-methoxyphenylboronic acid was carried out five successive times by simply filtrating and washing the catalyst. Finally, **(4b@SiO$_2$+TMS)** and **(5b@SiO$_2$+TMS)** catalysts were evaluated under continuous flow operation. Moderate conversions were achieved at relatively short residence time of 3.5 min and conversion was stable during two hours in flow, confirming the increased robustness of these systems under anhydrous reaction conditions.

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Experimental Section

General considerations

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 CaH$_2$/NaH or P$_2$O$_5$, 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 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 shifts for ^{1}H and ^{13}C{^{1}H} 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} mbar prior to use. [Pd(acac)$_2$],[60] were prepared according to literature procedures. Preparative procedures for imidazolium salts **1a/b**, **2a/b** and **3a/3b** ligands and precatalysts, characterization data for all compounds and computational details can be found in the Supporting Information.

Synthesis of supported catalysts

*One-pot procedure for preparation of [Pd(**2a**)(acac)Cl@SiO$_2$]* ***4a@SiO$_2$***. A flame-dried Schlenk flask was charged with **1a** (200 mg, 0.441 mmol, 1.0 equiv.), 3-mercaptopropyl(triethoxy)silane (270 µL, 1.064 mmol, 2.4 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 at room temperature 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$_2$Cl$_2$ and evaporated again in order to fully remove the EtOH. Then the crude product was washed three times with hexane (3 mL). 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$_2$Cl$_2$. 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$_2$O$_6$PdS$_2$Si$_2$@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.

*One-pot procedure for preparation of [Pd(**2b**)(acac)Cl@SiO$_2$] (**4b@SiO$_2$**)*. A flame-dried Schlenk flask was charged with **1b** (213 mg, 0.377 mmol, 1.0 equiv.), 3-

mercaptopropyl(triethoxy)silane (228 µL, 0.905 mmol, 2.4 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 at room temperature 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. Then the crude product was washed three times with hexane (3 mL). 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@SiO$_2$** 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.

*One-pot procedure for preparation of [Pd(**3a**)(acac)Cl@SiO$_2$] (**5a@SiO$_2$**)*. 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 at room temperature 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. Then the crude product was washed three times with hexane (3 mL). 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@SiO$_2$** 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@SiO$_2$] (**5b@SiO$_2$**)*. 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 at room temperature 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. Then the crude product was washed three times with hexane (3 mL). 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 at ambient temperature, 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{^{1}H} CP-MAS and ^{29}Si{^{1}H} MAS NMR spectra of a C2 ^{13}C-labeled sample of **5b@SiO$_2$** are included in the NMR spectra section of the Supporting Information.

*End-capping treatment of silica-supported materials for the obtaining of **(4b@SiO$_2$+TMS)**, **(5a@SiO$_2$+TMS)** and **(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{^{1}H} CP-MAS and ^{29}Si{^{1}H} MAS NMR spectra of a C2 ^{13}C-labeled sample of **(5b@SiO$_2$+TMS)** are included in the NMR spectra section of the Supporting Information.

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 and flushed with N_2, and then the aryl halide was added by microsyringe if liquid. Solvent was added by syringe (4 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 then 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.

Coupling products obtained by S.M. reactions:

4-methoxy-2′,4′-dimethylbiphenyl. 4-bromo-*m*-xylene (136 µL, 1.0 mmol, 1.0 equiv.), 4-methoxyphenylboronic acid (182 mg, 1.2 mmol, 1.2 equiv.), Cs_2CO_3 (652 mg, 2.0 mmol, 2.0 equiv.), (**5b@SiO$_2$+TMS**) (60 mg, 0.01 equiv.). Purified by column chromatography using 25:1 *n*-hexane/EtOAc as eluant. ^{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 data match literature values.[61] MS (EI): m/z = 212 (H$^+$), 197, 181.

2,4-dimethyl-2′-methylbiphenyl. 4-bromo-*m*-xylene (136 µL, 1.0 mmol, 1.0 equiv.), 2-methylphenylboronic acid (164 mg, 1.2 mmol, 1.2 equiv.), Cs_2CO_3 (652 mg, 2.0 mmol, 2.0 equiv.), (**5b@SiO$_2$+TMS)** (60 mg, 0.01 equiv.). Purified by column chromatography using *n*-hexane as eluant. ^{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. [62]

2-(2-methylphenyl)pyridine. 2-bromopyridine (96 µL, 1.0 mmol, 1.0 equiv.), 2-methylphenylboronic acid (164 mg, 1.2 mmol, 1.2 equiv.), Cs_2CO_3 (652 mg, 1.0 mmol, 2.0 equiv.), (**5b@SiO$_2$+TMS)** (30 mg, 0.01 equiv.). Purified by column chromatography using 10:1 *n*-hexane/EtOAc as eluant. ^{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 (96 µL, 1.0 mmol, 1.0 equiv.), 4-methoxyphenylboronic acid (182 mg, 1.2 mmol, 1.2 equiv.), Cs_2CO_3 (652 mg, 1.0 mmol, 2.0 equiv.), (**5b@SiO$_2$+TMS)** (30 mg, 0.01 equiv.). Purified by column chromatography using 10:1 *n*-hexane/EtOAc as eluant. ^{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.

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 Et_2O, then dried under vacuum and directly reused in the next cycle.

Experimental procedure for continuous flow tests.

Catalytic activity and stability of the catalysts (**4b@SiO$_2$**) and (**5b@SiO$_2$**) 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.

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).

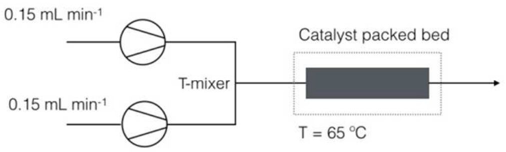

Figure 4. Scheme of a Vapourtec reactor.

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).

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