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Mesoporous silica-supported Pd catalysts: An investigation into structure, activity, leaching and heterogeneity

Jonathan D. Webb, Stephanie MacQuarrie, Kevin McEleney, Cathleen M. Crudden *

Queen's University, Department of Chemistry, 90 Bader Lane, Kingston, ON, Canada, K7M 3N6

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Abstract

Mesoporous silica functionalized by mercaptopropyl trimethoxysilane can be loaded with palladium and the resulting material used as a catalyst for a variety of coupling reactions. The ordered silicate reacts with levels of Pd leaching in the low ppm to ppb range. The catalyst can be re-used multiple times with only moderate loss of activity or structure, depending on the method of incorporation of the thiol. A grafting approach gives a significantly more stable material which is likely insulated from attack by the aqueous base, while incorporation of the thiol by co-condensation gives a material with minimal stability under the reaction conditions. Several heterogeneity tests are performed on the catalyst including three-phase tests and poisoning studies. These indicate that the effective heterogeneity depends strongly on the solvent employed and the reaction conditions. Under non-aerobic conditions with a controlled ratio of sulfur ligand to palladium, low levels of reaction due to homogeneous species are observed, but as the organic content of the solvent is increased, more reaction on an immobilized reagent (as judged through the three-phase test) is observed. In addition, these studies highlight the constraints within which the three-phase test can be an accurate assessment of heterogeneity.

Keywords: Palladium; Heterogeneous; Mesoporous; Catalysis; Coupling; Suzuki; Three-phase test

1. Introduction

The use of silica-supported Pd catalysts in general and mesoporous silica-supported catalysts in particular has gained increased attention as of late [1–10]. This is presumably driven by the widespread use and utility of Pd catalysts in industry [11–14] and the resulting difficulties with removing spent catalysts at the end of the reaction [15–17]. For this reason, heterogeneous catalysts offer significant advantages over their often times more reactive homogeneous partners since the levels of Pd remaining in solution are attenuated. However, there have been numerous cases in which the use of supposedly heterogeneous catalysts, such as the ubiquitous Pd on carbon, has resulted in leaching of Pd at levels which led to questions about the true heterogeneity of the Pd source [18,19]. Detailed independent studies by Kohler, Arai and Conlon have shown that in the case of Pd on unfunctionalized supports such as Pd/C and Pd/SiO_2, essentially all of the catalysis can be attributed to Pd into solution [20–29]. Furthermore the severity of the leaching and redeposition leads ultimately to catalyst death due to losses in solution and also agglomeration of Pd into large, less active particles on the surface. Similar studies employing Rh catalysts have also shown that even in the case of homogeneous precursors, catalysis can often be ascribed to heterogeneous Rh colloids generated under the reaction conditions [30,31].

A fundamentally different approach to heterogenizing Pd catalysts is to chemically bind known ligands to the surface of a support and use these to form strong bonds to Pd. These ligands include species such as phosphines [32,33] and *N*-heterocyclic carbenes [34,35]. In addition to these traditional ligands, pincer and palladacycle [36–38] ligands which contain a Pd–carbon bond have also been employed. The high catalytic activity of these latter ligands generated considerable controversy, since the complexes are immobilized in the Pd(II) oxidation state, which raised questions about the mechanism of the coupling re-

* Corresponding author.
E-mail address: cruddenc@chem.queensu.ca (C.M. Crudden).

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action and the possibility of a Pd(II)/Pd(IV) catalytic cycle [12,19,39].

Detailed studies of the pincer system eventually showed that with a few possible exceptions, most palladacycle-type catalysts decompose slowly under the reaction conditions, liberating active Pd(0) species that are the true catalysts for the reaction [29,40–52]. Another class of catalysts that have been developed utilize less well defined interactions for the immobilization of Pd. Examples of these catalysts include Kobayashi's incarcerated catalysts [53,54], ionic gels employed by Kirschning [55] and Mioskowski [56], Pd-containing perovskites by Ley [57,58], and the interesting case of physically immobilized catalysts using a zeolite shell by Tang et al. [59]. Intermediate between these two extremes are systems in which the support is functionalized, but the interactions between Pd and the surface are not necessarily well defined. For example, Ley's Pd EnCat catalysts contain thiourea ligands for Pd [60–62], and silica surfaces modified by thiol groups have also been described [63–65]. There are several fundamental differences between these catalysts and palladacycle type catalysts, most notably that these catalysts can act as supports for Pd(0) and/or Pd(II), and can accommodate an equilibrium between homogeneous and heterogeneous Pd, whereas pincer-type catalysts will not re-adsorb Pd after it has been released as Pd(0), at least not via the ligand that was initially used to immobilize the Pd. This is a critical difference since it complicates the interpretation of various heterogeneity tests.

As part of a study aimed at developing an effective Pd scavenger based on mesoporous silica modified with mercaptopropyl trimethoxysilane, we discovered to our surprise that after scavenging of Pd, the resulting material catalyzed the Suzuki–Miyaura reaction with low levels of leaching [64]. A similar study of the activity of Pd-loaded functionalized FSM-16 also described high catalytic activity with low leaching [63]. In order to further assess the utility, re-usability and heterogeneity of catalysts such as those prepared from thiol-modified silica, we have carried out extensive studies of leaching, catalyst integrity and heterogeneity tests such as three-phase tests and polymeric poison challenge tests. Interestingly, we find that the catalysts behave differently in different tests, which highlights the difficulty of interpreting results from only one series of tests [52]. The results of these tests, and tests of the recyclability of the material are described herein.

2. Experimental

2.1. General experimental

Reagents were purchased or obtained from the following suppliers: Pluronic 123 was donated by BASF. TEOS (tetraethylorthosilicate), mercaptopropyl trimethoxysilane (MPTMS), aminopropyl triethoxysilane (APTES), *para*-bromoacetophenone (BrPhAc), potassium carbonate, DMF, 4-bromobenzoyl chloride, *N*-methyl morpholine and *para*-dimethoxybenzene were obtained from Aldrich. Phenylboronic acid, pinacol ester was prepared from phenylboronic acid, obtained from Aldrich. Palladium acetate was obtained from Pressure Chemical Company.

2.2. Procedure for catalyst synthesis

In a typical procedure [66], Pluronic 123 (P123) (4.0 g) was weighed into a 500 mL flask with stir bar. The polymer was dissolved by adding distilled water (30 mL) and 4 h of vigorous stirring at 35 °C followed by the addition of aqueous 2 M HCl (120 mL). This solution was stirred for a further 24 h at 35 °C prior to addition of TEOS (9.0 mL) via syringe. A fine white precipitate formed after about 30 min, this solution was vigorously stirred at 35 °C for 24 h after which the suspension was heated for 48 h at 80 °C. The solution was filtered and dried under vacuum for 3 days at 80 °C. The polymer was removed via Soxhlet extraction using refluxing 95% EtOH (600 mL) for 5 days. The recovered silicate was dried at room temperature and 80 °C under vacuum both for 18 h. This procedure produced 2.5 g of a fine white powder. SBA-15 (BET SA: 1080 m^2/g, BJH absorption pore diameter: 84 Å, pore volume: 1.13 mL/g).

To prepare SBA-15-SH(g), SBA-15 (900 mg) was suspended in dry toluene (50 mL) in a round bottomed flask (100 mL) which was flushed with N_2. (3-Mercaptopropyl)-trimethoxysilane (MPTMS) (3.6 mL) was added via syringe and the mixture heated to 110 °C with stirring for 18 h. The solution was filtered and washed with Et_2O (3 × 15 mL). The recovered powder was extracted via Soxhlet using refluxing 95% EtOH (600 mL) for 24 h. The silicate was dried under vacuum at room temperature for 18 h. A white powder was recovered (625 mg). The final sulfur content varies depending on the initial batch of SBA-15 (0.6–1.1 mmol/g S) as was determined by elemental analysis. When comparing two different materials, equivalent sulfur contents were always employed. SBA-15-SH(g) (BET SA: 750 m^2/g, BJH absorption pore diameter: 72 Å, pore volume: 0.82 mL/g).

$Pd(OAc)_2$, corresponding to 50% of the loading of sulfur as determined by elemental analysis, was dissolved in THF (50 mL) and the flask flushed with N_2. SBA-15-SH(g) (500 mg) was then added and the suspension stirred for 2 h. The solution was filtered and washed with THF (3 × 50 mL). The red-orange material was dried under vacuum overnight, yielding 450 mg. The amount of Pd loaded was determined by an ICP-MS analysis of the supernatant obtained after filtration and washings of the Pd material prepared as described above. Consistent with previous work, >99.9% of the initially added Pd was scavenged from solution [64]. SBA-15-SH(g)·Pd (BET SA: 360 m^2/g, BJH absorption pore diameter: 70 Å, pore volume: 0.44 mL/g).

To prepare SBA-15-SH(cc), 4.0 g of triblock copolymer Pluronic 123 (P123) was dissolved in 150 mL of water along with 20 mL of conc. HCl and the resulting mixture stirred at 40 °C for 16 h. 8.6 mL (8.02 g, 38.5 mmol) of tetraethylorthosilane (TEOS) was then added and the mixture stirred for 5 h at 40 °C. Finally, 0.5 mL (0.525 g, 2.8 mmol, 6.8 mol%) of (3-mercaptopropyl)-trimethoxysilane (MPTMS) was added and the reaction mixture stirred for 19 h at 40 °C. The powder was then hydrothermally treated at 80 °C for 48 h with no stirring. The solid was recovered by filtration and washed with

water. The surfactant P123 was then removed by Soxhlet extraction with ethanol for 5 days. The solid was then filtered and dried under vacuum. SBA-15-SH(cc) (BET SA: 790 m^2/g, BJH absorption pore diameter: 69 Å, pore volume: 0.945 mL/g). Sulfur content was determined by elemental analysis as noted above.

114.77 mg (0.511 mmol) of $Pd(OAc)_2$ was dissolved in 75 mL of dry THF. This was stirred under an argon atmosphere for 15 min to ensure complete dissolution. SBA-15-SH(cc) 1.5157 g (1.03 mmol S) was then added to the solution and the mixture stirred under argon for 1 h at room temperature. The catalyst was filtered using a sintered glass funnel, scraped into a vial and dried overnight under high vacuum. The filtrate was collected and sent for ICPMS (which is able to detect Pd at parts per trillion levels) analysis to determine palladium content. The residual palladium in the solution was found to be <0.03% of that initially added. SBA-15-SH(cc)·Pd (BET SA: 662 m^2/g, BJH absorption pore diameter: 42 Å, pore volume: 0.688 mL/g).

2.3. General procedure for the Suzuki–Miyaura coupling reaction

Pd-SH-silica (1 mol% Pd), *p*-bromoacetophenone (50 mg, 0.25 mmol), K_2CO_3 (70 mg, 0.50 mmol), PhBpin (pinacol ester of phenyl boronic acid, 75 mg, 0.375 mmol) and 1,4-dimethoxybenzene (35 mg, 0.253 mmol) as internal standard were weighed into a sealed tube with a stir bar and flushed with Ar. Dry DMF (2.5 mL), degassed by bubbling Ar, and distilled H_2O (0.125 mL) were added via syringe. The solution was heated at 80 °C with stirring while monitoring reaction progress by GC-FID.

Recycling studies were carried out following the general Suzuki reaction procedure except scaled up so that either 50 or 100 mg of SBA-15-SH(g)-Pd were used. Following reaction/recycle the supernatant was collected for ICP-MS analysis and the recovered catalyst washed with copious amounts of EtOAc and H_2O to remove residual salts and organics. Each recycle was performed by weighing the recovered washed catalyst and calculating the amount of reagents necessary for a 1 mol% Pd reaction, it was assumed that >99% of Pd was retained by the material as validated by ICP-MS. Nitrogen adsorption isotherms of the recovered catalyst are given in Figs. S-6 and S-7 of Supporting information. Data generated from these plots are given in Table S-1. Powder XRD data for SBA-15-SH(g)·Pd before and after reaction are given in Fig. S-5 and ^{13}C CPMAS NMR data are shown in Fig. S-8. Fig. S-9 gives the nanoparticle distribution observed by TEM for catalysis run in argon.

2.4. Experimental procedure for the three-phase test

4-Bromobenzoyl chloride (1.15 g, 5.25 mmol), 3-aminopropyl trimethoxysilane-modified silica (1.00 g, Aldrich), pyridine (404 μL, 5 mmol) and dry THF (10 mL) were stirred in a round bottom flask under a nitrogen atmosphere at 40 °C for 12 h. The suspension was filtered and washed with 5% (v/v) HCl (20 mL, 3 times) followed by 0.02 M aqueous K_2CO_3 (20 mL, twice) and rinsed with distilled water (40 mL) and ethanol (40 mL). The resulting solid was washed with excess dichloromethane and dried at room temperature in air, yielding 1.14 g of a white powder. CP-MAS ^{13}C NMR (ppm), 233.7, 167.2, 130.5, 58.782, 42.0, 35.6, 30.2, 21.7, 16.7, 9.5. Calculated elemental analysis; weight %C = 10.38 (8.65 mmol/g), %H = 1.32 (13.2 mmol/g), %N = 1.51 (1.07 mmol/g), %Br = 5.60 (0.7 mmol/g).

Alternatively, 4-bromobenzamide 3-propyltriethoxysilane (**8**) was prepared for use in the three-phase test by mixing 4-bromobenzoyl chloride (2.01 g, 9.1 mmol), *N*-methyl morpholine (1.00 mL, 9.1 mmol) and THF (50 mL) in a round-bottomed flask and cooled to −15 °C. 3-Aminopropyl triethoxysilane (2.14 mL, 9.1 mmol) in THF (10 mL) was added dropwise to the cooled solution. The resulting mixture was warmed to room temperature (2 h). After that time, the solid was removed via filtration and the solvent was removed under vacuum at room temperature. The product was obtained as 3.5 g of a beige solid. ^1H NMR (ppm), 7.8 (1H, t), 7.6 (2H, d), 7.2 (2H, d), 3.5 (6H, q), 3.2 (2H, m), 1.5 (2H, m), 1.0 (9H, t), 0.3 (2H, m).

4-Bromobenzamide propyl triethoxysilane (3.5 g, 8.6 mmol) thus obtained, was mixed with pyridine (0.912 mL, 11.5 mmol) and added dropwise to a suspension of SiO_2 (1 g) in dry toluene (3 mL), under argon. The resulting mixture was refluxed for 24 h. After that time, the suspension was filtered and Soxhlet extracted with dichloromethane for 24 h. The resulting solid was dried under vacuum at room temperature, giving 1.6 g of a white powder. CP-MAS ^{13}C NMR (ppm), 223.8, 167.0, 130.4, 127.9, 59.2, 42.2, 22.3, 17.3, 9.4. CP-MAS ^{29}Si (ppm), −50.0, −52.9, −58.0, −68.3, −103.2, −112.1. Calculated elemental analysis; weight %C = 12.72 (10.59 mmol/g), %H = 1.41 (14.1 mmol/g), %N = 1.53 (1.08 mmol/g), %Br = 7.91 (0.98 mmol/g).

3. Results

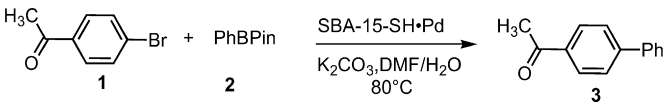
3.1. Reaction conditions

Our study began by assessing the effect of several variables on catalyst activity and leaching. Two of the key features which emerged from this study are the method of incorporation of the thiol and the ratio of thiol to Pd. In addition to SBA-15, amorphous silica was examined as a cost-effective alternative to this ordered silicate. The Suzuki–Miyaura reaction between 4-bromoacetophenone and the pinacol ester of phenyl boronic acid were chosen as the test reaction [64] (Eq. (1)). Potassium carbonate was employed as the base and the solvent was either mixtures of DMF and water, or pure water. Controls showed that no reaction occurred in the absence of added catalyst. Under these conditions, amorphous silica modified with mercaptopropyl trialkoxysilane and treated with Pd is not only catalytically active, but displays activity comparable to that of SBA-15-SH supported Pd (Supporting information, Fig. S-4).

Table 1
Catalytic activity and leaching as a function of S to Pd ratio[a]

Entry	Material	S:Pd	Yield (%)	Leaching (%) [67]
1	SiO_2-SH·Pd	1:1	86	0.3
2	SiO_2-SH·Pd	2:1	98	0.06
3	SiO_2-SH·Pd	3:1	72	0.02
4	SiO_2-SH·Pd	4:1	25	0.03
5	SiO_2-SH·Pd	8:1	0	n.e.[b]

[a] Reaction conditions: 0.75 mmol PhBpin, 0.51 mmol BrAcPh (4-bromoacetophenone), 1 mol% SiO_2-SH·Pd, 1.02 mmol K_2CO_3, 0.51 mmol *p*-dimethoxybenzene as internal standard, 20/1 DMF/H_2O (0.1 M in BrAcPh), 80 °C, 18 h.
[b] Not examined.



(1)

As previously reported [63,64], low levels of leaching were observed in the solution at the completion of the reaction. At the standard 2:1 ratio of S:Pd, the Pd concentration in solution at the end of the reaction was generally less than 0.2 ppm, and often as low as several ppb. This corresponds to between 0.05 and 0.3% of the initially added Pd (Table 1) [67]. At a 1:1 ratio of sulfur to Pd, catalysts displayed increased leaching (compare entries 1 and 2). As the ratio of sulfur to Pd increased, the catalytic activity decreased (see Fig. S-5 in Supporting information) such that at ratios of 8:1 or greater, no catalytic activity was observed (Table 1). We chose 2:1 as the optimum S:Pd ratio since scavenging studies showed that this ratio was the most effective at removing Pd from solution [64] and since it gave the most active catalyst. Under these conditions, we examined the reactivity and leaching of the SBA-15-derived materials prepared by grafting (SBA-15-SH(g)) and by sol–gel co-condensation (SBA-15-SH(cc)) methods for the incorporation of the mercaptopropyl functionality. The effect of the atmosphere of the reaction was also examined.

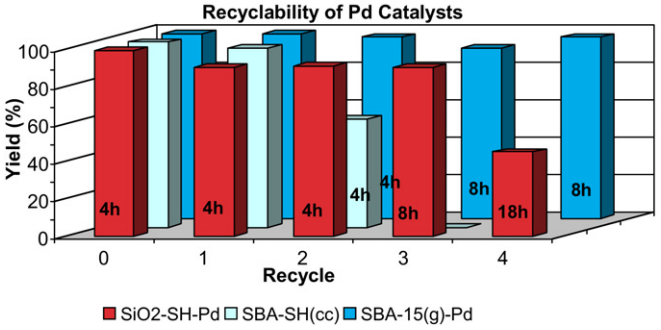
The reactions can be performed in air or even oxygen, although better results are obtained in argon in terms of rate of reaction, turnover and leaching. In air, reactions require between 6 and 8 h to go to completion, while in argon, they are generally complete in 4 h. As expected, reactions run in air display small amounts of homocoupling of the boronate ester, which continues to be observed after the Suzuki–Miyaura reaction is complete until all of the excess boronate ester is consumed (Table 2).

The turnover numbers of the various catalysts were also assessed in air and argon and were found to be higher in all cases in argon. SBA-15-SH(g)·Pd reacted with a total turnover number of >10,000 in argon compared to 5100 in air. This corresponds to a reaction time of 24 h for 97% yield at a loading of 0.009 mol%. By comparison, amorphous silica reacted with a total turnover number of 6800 in argon and 5100 in air.

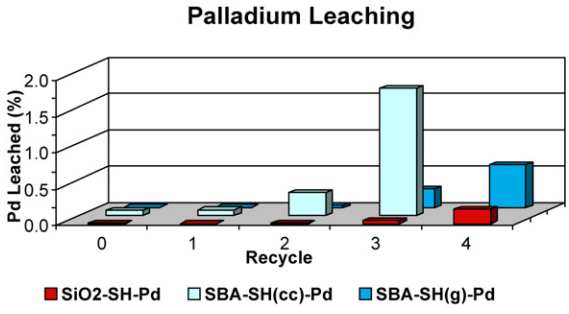
Table 2
Pd leaching in solution relative to support, atmosphere and method of thiol functionalization

Entry	Catalyst support	Conditions	Yield	Pd leaching (%)[a]
1	SBA-15-SH(g)	Air, 8 h	98–99[b]	0.32 ± 0.05
2	SBA-15-SH(g)	Argon, 4 h	98–99	0.12 ± 0.05
3	SBA-15-SH(cc)	Air, 18 h	90–98	0.17 ± 0.09
4	SBA-15-SH(cc)	Argon, 4 h	90–95	0.22 ± 0.09

[a] Pd leaching is given as a of added Pd (see Ref. [67]). In all cases less than 0.5 ppm Pd is observed.
[b] 16 biphenyl observed (1.5 equivalents of $PhB(OH)_2$, 1 equivalent of ArBr).



(A)



(B)

Fig. 1. Effect of recycling on catalyst yield (A) and leaching (B).

3.2. Recyclability

In addition to the total leaching and overall catalytic activity, recyclability is obviously a critical feature of supported catalysts. Employing SBA-15-SH(g) in which the thiol was introduced by grafting on a previously synthesized material, we found that the material displayed minimal loss of activity after 4 runs (Fig. 1). In contrast, catalysts prepared using a co-condensation method for thiol incorporation [68a], were quickly deactivated [68b]. Interestingly, this drop in activity occurred concomitantly with an increase in leaching. As will be shown subsequently, the loss of activity with the co-condensed catalyst was coincident with a loss of order of the support (*vide infra*).

Amorphous silica-supported catalysts had intermediate behavior in terms of recyclability and leaching, with activity dropping off after the fourth use. In this case, 18 h was necessary for 90% conversion, and then eventually only 45% conversion obtained on the fifth run. Again, loss of activity appeared to be coincident with increased leaching, although Pd leaching was

Table 3
Recycling studies[a]

Entry	Pd catalyst	Run	Yield [time]	Pd leaching (%) [ppm]
1	SBA-15-SH(g)·Pd	1	99 [4 h]	0.036 [0.011]
2	SBA-15-SH(g)·Pd	2	99 [4 h]	0.008 [0.006]
3	SBA-15-SH(g)·Pd	3	97 [4 h]	0.032 [0.018]
4	SBA-15-SH(g)·Pd	4	91 [8 h]	0.26 [0.11]
5	SBA-15-SH(g)·Pd	5	97 [8 h]	0.59 [0.13]
6	SiO_2-15-SH·Pd	1	98 [4 h]	–
7	SiO_2-15-SH·Pd	2	90 [4 h]	0.001 [0.003]
8	SiO_2-15-SH·Pd	3	91 [4 h]	0.008 [0.005]
9	SiO_2-15-SH·Pd	4	90 [18 h]	0.04 [0.017]
10	SiO_2-15-SH·Pd	5	45 [18 h]	0.2 [0.072]

[a] See Section 2 for details.

still relatively low (0.2% of the initially added catalyst, corresponding to 0.07 ppm Pd in solution, Table 3).

3.3. Catalyst integrity and leaching

Although the hydrothermal stability of SBA-15 has been well documented [69], the conditions of the Suzuki–Miyaura reaction are significantly harsher than simply hydrothermal treatment since the reaction is performed with aqueous base. Considering that the wall sizes in SBA-15 are on the order of 3 nm, dissolution/decomposition of the support under the reaction conditions is a concern.

Thus the various catalysts were treated with DMF and water at 80 °C for varying times with and without base. As shown in Fig. 2, the leaching after 24 h is on the order of 0.05% (0.013 ppm) for all three catalysts. This value does increase upon the inclusion of base (potassium carbonate) in the mixture, but not substantially. Consistent with the recycling study, the co-condensed catalyst showed greater sensitivity to base. We attribute these results to the greater protective effect of the grafting conditions, in which the surface is rendered more hydrophobic than the co-condensed material, where greater portions of unprotected silica are exposed to the reaction media.

3.4. Catalyst support

In addition to assessing the loss of Pd from the support upon treatment with base, it is obviously crucial to determine whether or not the support itself survives the reaction conditions, a fact which becomes more important as the cost of the support increases. The integrity of the silicate was assessed in several ways. Transmission electron microscopy of catalyst recovered from the reaction showed that the overall structure was largely maintained (Figs. 3A and 3B (before use) and Figs. 4A and 4B (after use)), although some destruction of the framework porosity is evident at the edges of the particles. Similarly to Shimizu et al. [63], we observed Pd nanoparticles on the surface (Fig. 4A), none of which were larger than the pores (6 nm). The distribution of nanoparticles is shown in Fig. S-8 (Supporting information), which demonstrates that the nanoparticles range in size from 1 to 6 nm, with the majority in the 3–5 nm range.

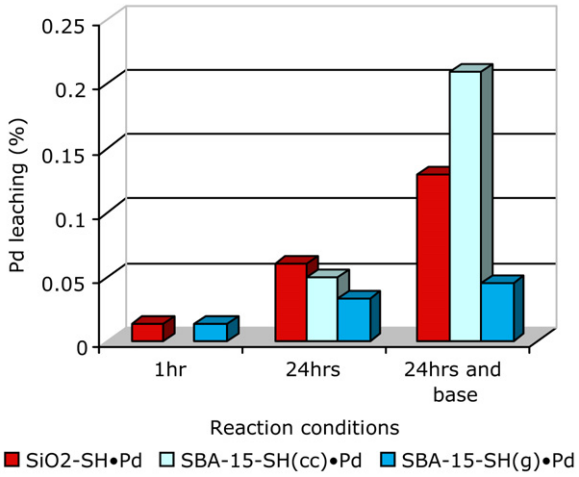


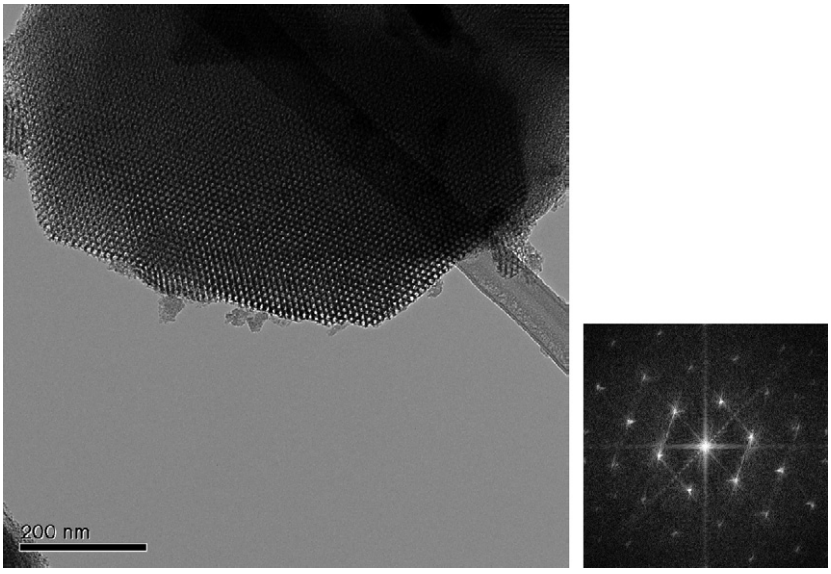
Fig. 2. Treatment of various materials with solvent and base.

Catalysts which were employed in reactions run under an air atmosphere showed no evidence of Pd nanoparticles either by TEM (Fig. 5) or XRD, although the latter technique may not be useful at the low concentrations of Pd(0) which are likely present on the support. Again the high order maintained in the catalyst after the reaction is especially evident in the electron diffraction (inset).

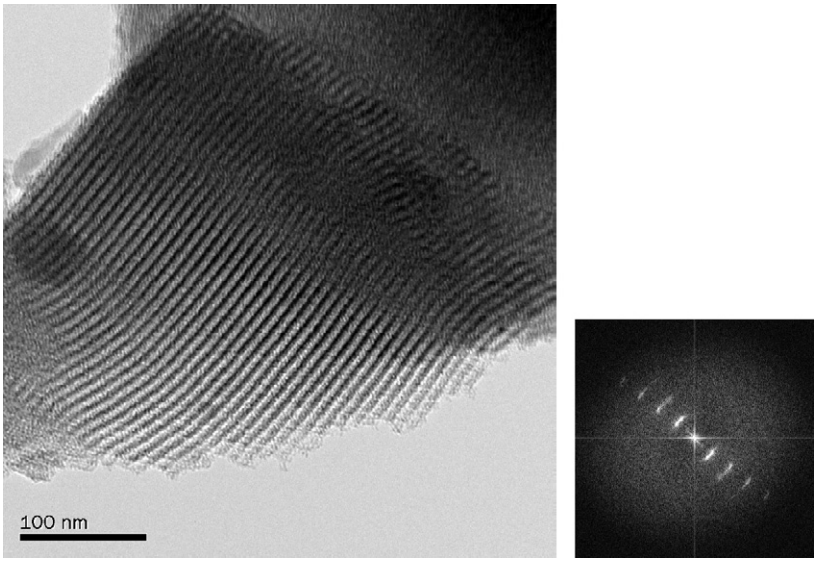
Although the microscopy results are generally satisfying in terms of the retention of order of the material, we also examined the supported catalyst by physisorption analysis after reaction since this is a bulk-characterization technique. As shown in Figs. S-6 and S-7 (Supporting information), there is a moderate loss of order after each run, in which the material is exposed to aqueous base at 80 °C for 4 h [70]. Fig. 6A shows fresh catalyst before use and the same catalyst after it has been used three times. Similar studies with the co-condensed material illustrated the dramatic difference between the two methods of grafting. As shown in Fig. 6B, the material prepared by co-condensation is dramatically more sensitive, having lost a significant amount of order after only one run. As noted previously, the two materials have similar overall thiol loading as determined by elemental analysis, indicating that the effect observed is related to the method of incorporation [71].

3.5. Heterogeneity tests

In the initial study of MPTMS-modified SBA-15 as a catalyst support for the coupling of boronic acids [64], the heterogeneity of the catalyst was assessed by two of the standard techniques in the area, three-phase tests and a hot filtration test [52]. In the hot filtration test, a portion of the reaction mixture is filtered from the suspended catalyst mid-way through the reaction, and the filtrate is tested for catalytic activity. The observation of activity in the filtrate is indicative of soluble Pd present in solution. Since catalyst redeposition on support upon partial cooling of a solution can occur prior to or during filtration, a negative test is not sufficient to declare a catalyst to be truly heterogeneous [19]. Also since many Pd-catalyzed coupling reactions employ sparingly soluble reagents and starting



(A)



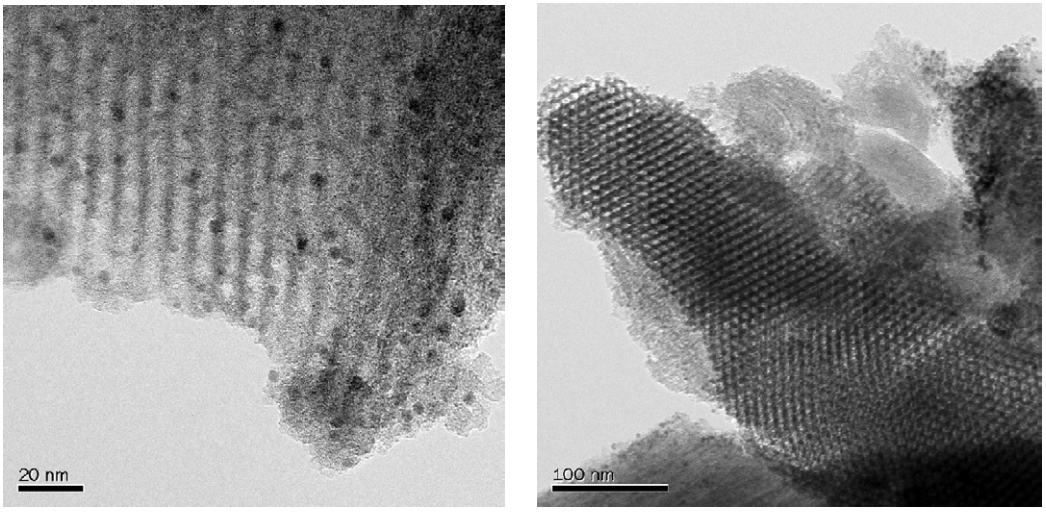
(B)

Fig. 3. Different views of SBA-15-SH·Pd before use.

materials (such as boronic acids), it is essential to ensure that these are exposed to the filtrate and are not removed during filtration. In the initial study, approximately 5% reactivity in the filtered phase was detected, indicating that some catalytically active Pd was being released from the surface.

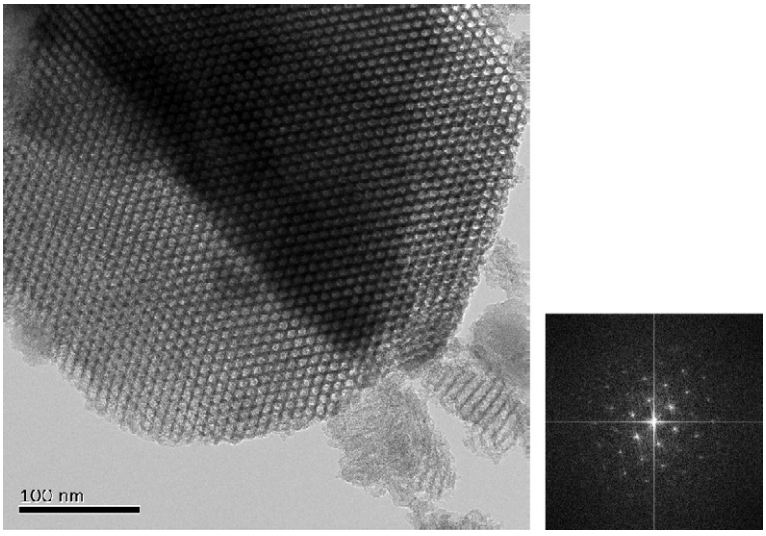
However, due to the difficulties noted with the hot filtration test, a three-phase test was performed, which is believed to be one of the most definitive tests for heterogeneity since it actually tests for the presence of active, catalytically competent Pd in solution [62,72]. This test was developed in the late 70's by Rebek and Zimmerman to test for the presence of reactive intermediates [72]. The concept is that reactive intermediates in solution can be detected by allowing them to react with an immobilized substrate which can later be filtered and analyzed. The test is performed by immobilization of an aryl halide and addition of solution phase reagents along with the "heterogeneous" catalyst in question [18,62]. After reaction for a prescribed amount of time, the immobilized substrate is cleaved from the second support to determine whether or not any reactive catalyst was present in solution. The test is considered to be an indication of the release of active Pd from support, since the supported reagent and supported catalyst are unlikely to react together. However, there are pitfalls associated with this test as well. As elegantly demonstrated by Davies and co-workers at Merck, it is important to add a soluble aryl halide, since it is believed that oxidative addition with this soluble reagent is the main pathway for bringing Pd into solution [18]. Moreover, the presence of soluble aryl halide provides an opportunity to ensure that an active catalyst is in fact generated since the coupling of the two soluble species can be detected and quantified.

Thus, we carried out the three-phase test with grafted and sol–gel-modified mesoporous materials and also amorphous silica-based catalysts. Supported aryl bromide **4** was prepared by coupling of 4-bromobenzoyl chloride with aminopropyl

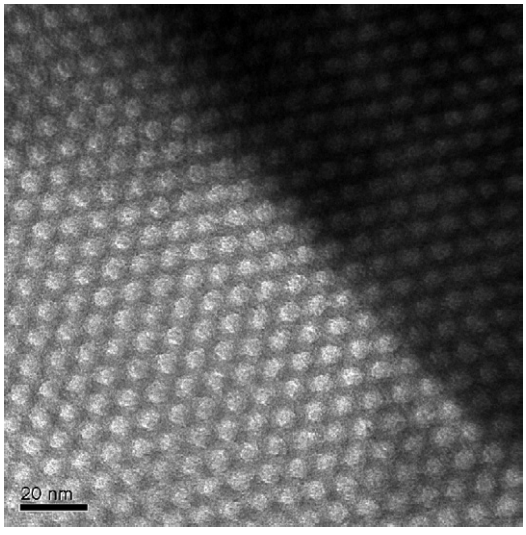


(A) (B)

Fig. 4. SBA-15-SH·Pd after use (argon, 4 h).

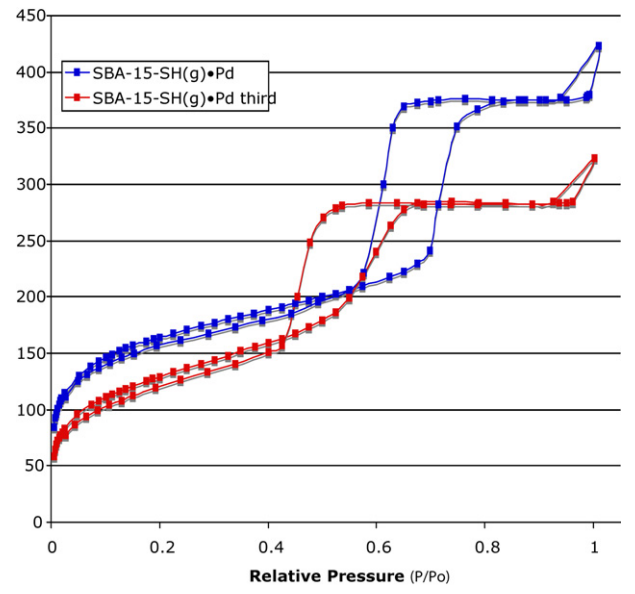


(A)

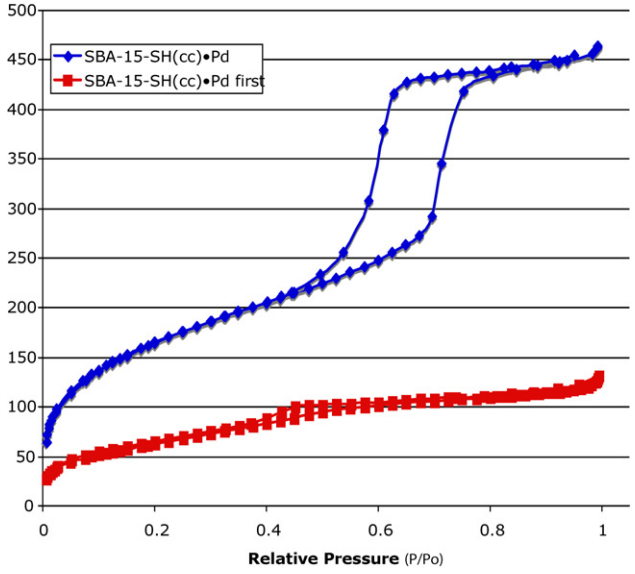


(B)

Fig. 5. TEM image of SBA-15-SH·Pd after reaction in air.



(A)



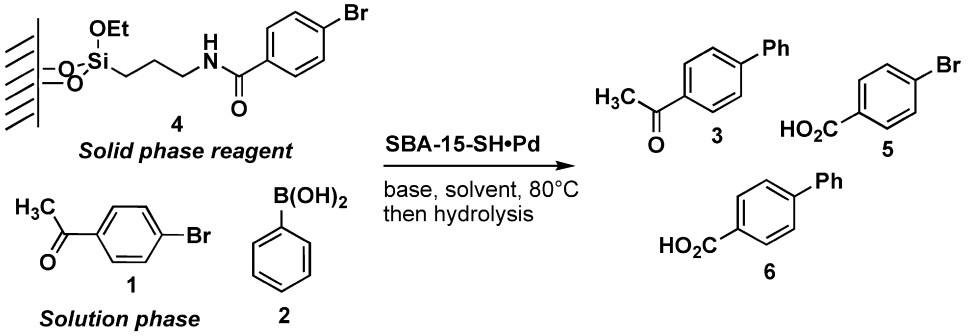
(B)

Fig. 6. Nitrogen physisorption analysis of SBA-15-SH(g)·Pd (A) before use (blue) and after three reactions (left); and of SBA-15-SH(cc)·Pd (B) before use and after one run in argon.

triethoxysilane-modified silica according to the method of Corma et al. Bromoacetophenone (**1**) and phenyl boronic acid (**2**) (in excess) are dissolved in the solution. Finally, the immobilized catalyst is the third phase (Scheme 1). In order to test for the presence of catalytically active Pd in solution, supported halide **4** and soluble halide **1** are reacted with phenyl boronic acid under typical reaction conditions. The soluble fraction is monitored for the presence of 4-phenylacetophenone (**3**) which indicates the generation of an active catalyst. The silica supported reagent is then separated from the solution, and the amide bond cleaved with base. The critical species in this experiment is compound **6**, whose presence gives an indication of the amount of active Pd that has left the surface of SBA-15 and has reached the solid-phase reagent **4**.

As shown in Table 4, all three materials gave results consistent with our previous study, namely at reaction times similar to those normally employed, low levels of **6** were observed, generally on the order of 2–10% reaction on support. Since the S:Pd ratio has been proposed to be an important feature in the functional heterogeneity of the material, the three-phase test was performed on a material prepared with different ratios of Pd to sulfur. At a S:Pd ratio of 1:1, greatly increased reaction on support was observed, entry 5, indicating that the three-phase test was at least qualitatively assessing the escape of catalytically competent Pd. Alternatively, increasing the S:Pd ratio from 2:1 to almost 3:1 decreased the yield of the homogeneous reaction compared to the material that had a ratio of only 2:1, while the ratio of bromobenzoic acid to phenyl benzoic acid ratio remained high (entry 4, 94:6). Higher reaction on support was also observed for the 2:1 materials when the reaction times were extended (entries 6 and 7). In addition, greater reaction on support is observed when the reaction is run in air (entry 8). Finally, in order to ensure that the reaction is not starved of boronic acid, the three-phase test was repeated with an even greater excess (three equivalents) of boronic acid (entry 9). It is clear that the extent of reaction on support increases, implying that competition between the soluble aryl halide and the supported aryl halide favors reaction in solution at the expense of reaction on support. This is an important feature of the three-phase test that needs to be considered when its results are used to assess catalyst heterogeneity.

One other feature from Table 4 which deserves comment is with regard to the overall yield of compound **3**, resulting from coupling in solution. In virtually all of the cases where



Scheme 1. Application of the three-phase test to the Suzuki–Miyaura reaction.

Table 4
Three-phase test for assessment of the presence of catalytically active Pd in solution[a]

Entry	Catalyst	S:Pd ratio	Reaction conditions	Yield of **3** (%)	**5**:**6**
1	SBA-15-SH(g)·Pd	2:1	5 h, argon	48	98:2
2	SBA-15-SH(cc)·Pd	2:1	5 h, argon	42	90:10
3	SiO_2-SH·Pd	2:1	5 h, argon	94	90:10
4	SiO_2-SH·Pd	3:1	5 h, argon	45	94:6
5	SiO_2-SH·Pd	1:1	5 h, argon	93	65:35
6	SBA-15-SH(g)·Pd	2:1	13 h, argon	55	82:18
7	SBA-15-SH(cc)·Pd	2:1	20 h, argon	42	85:15
8	SBA-15-SH(cc)·Pd	2:1	20 h, air	56	58:42
9	SBA-15-SH(cc)·Pd[b]	2:1	5 h, air, excess $PhB(OH)_2$	69	73:27

[a] Reaction conditions: 0.75 mmol PhBPin, 0.51 mmol BrAcPh (4-bromoacetophenone), 1 mol% SiO_2-SH·Pd, 1.02 mmol K_2CO_3, 0.51 mmol *p*-dimethoxybenzene as internal standard, 20/1 DMF/H_2O (0.1 M in BrAcPh), 80 °C.
[b] Reaction performed with 3 equivalents of boronic acid.

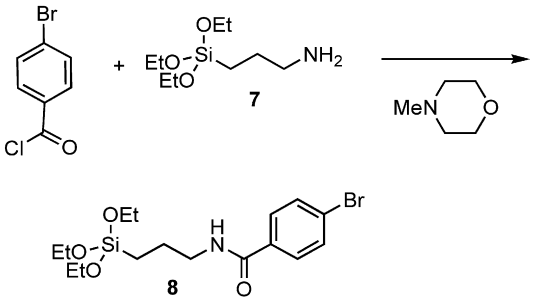
Table 5
Three-phase test using supported amide **8**[a]

Entry	Catalyst	S:Pd ratio	Reaction time (h)	Yield of **3** (%)	**5**:**6**
1	SBA-15-SH(g)·Pd	2:1	5	74	94:6
2	SBA-15-SH(cc)·Pd	2:1	5	63	94:6
3	SiO_2-SH·Pd	2:1	5	95	60:40
4	SBA-15-SH(g)·Pd	2:1	24	90	60:40

[a] See Section 2 for details.

mesoporous silica is employed as the support, lower yields are observed in the presence of the supported aryl halide than they are in its absence. This led us to consider the possibility that any free amines on the surface of the supported aryl halide were acting alternatively as a sink for Pd that is released from the support, or as a poison for active soluble Pd. Based on elemental analysis, the supported amide reaction was incomplete and ca. 0.3 mmol/g of free NH_2 groups were present on the support. Because of the small amount of Pd that is added and the large amount of the supported reagent, the ratio of free amine to Pd was 35:1.

Considering these facts, a new supported reagent was prepared such that no free amines would be on the surface (Eq. (2)). Concurrent with this study, we assessed the ability of a variety of poisons to inhibit the reaction (vide infra).



(2)

Using the new supported aryl halide, we were able to achieve higher catalytic activity in the soluble portion of the three-phase test (Table 5). Interestingly, the amorphous silica catalyst again showed a higher level of reaction on support indicating greater leaching or poorer capture of catalytically active material. Also consistent with the results previously obtained, the leaching becomes more evident as the reaction is left to a longer time, such that at 24 h with the grafted mesoporous catalyst, substantial (40%) reaction was observed on the supported aryl halide (entry 4).

Thus the three-phase data, when repeated under more forcing conditions, give a picture of a catalyst that does show activity in solution at varying levels depending on the conditions. In order to benchmark the catalyst vs other known systems, we attempted the reaction with Pd/C under our now standard conditions. This unfortunately was not successful since Pd/C was not an effective catalyst in water (1% yield after 5 h).

Therefore, we assessed the heterogeneity of the catalyst in other solvents, particularly in combinations of DMF and water as this is a commonly employed solvent for Suzuki–Miyaura reactions, and was employed for many of the reactions described in this study. In this case, the reaction was much more sensitive to the presence of the supported aryl halide and initially no conversion was observed in either solution or on support. However, the use of the amide **8** along with gentle stirring to prevent mechanical decomposition of the catalyst did give a system which was catalytically competent, providing compound **3** in reasonable yields. Remarkably, in terms of the three-phase test, the trends observed in DMF/water were quite different from those observed in water. Again the yields of the homogeneous reaction were moderate to good, but the yield on support did not increase as expected, even after extended time. Thus using the grafted catalyst, a 74% yield of **3** was obtained after 5 h and a 94:6 ratio of **4**:**5** after hydrolysis. Extending the reaction time to 24 h increased the yield of **3** to 90%, however the ratio of **4**:**5** remained at 94:6. Since this was inconsistent with the results we obtained in water, where increased time always led to increased reaction on support, we carried out the reaction with Pd/C, which is known to act via leached Pd species. Again we found only low levels of reaction on support (94:6) indicating that in DMF/water, the three-phase test is not meaningful for this system, since Pd/C is known to leach active Pd.

Searching for an alternative method to assess the catalytic activity, we carried out the reaction in the presence of Quadrapure-TU and polyvinylpyridine, two of the most commonly employed poisons. In addition, the effect of adding aminopropyl-modified silica was also examined, as it mimicked the effect of the three-phase material. For reactions in DMF/water, the addition of Quadrapure-TU had a moderate effect, slowing but not stopping the reaction as shown in Fig. 7. Interestingly, with the exception of PL-thiourea, the other scavengers took approximately 5 h before the reaction was completely stopped, although the initial rate of reaction was decreased. As shown by monitoring the reaction at extended times, the reaction continued to occur with PVP and Quadrapure-TU, although at a greatly diminished rate. This is likely attributable to slow release of Pd from the surface of these scavengers. Similar results were observed for the grafted catalyst (see Supporting information). With this catalyst, the addition of silica-supported amines and thiols [73] were also

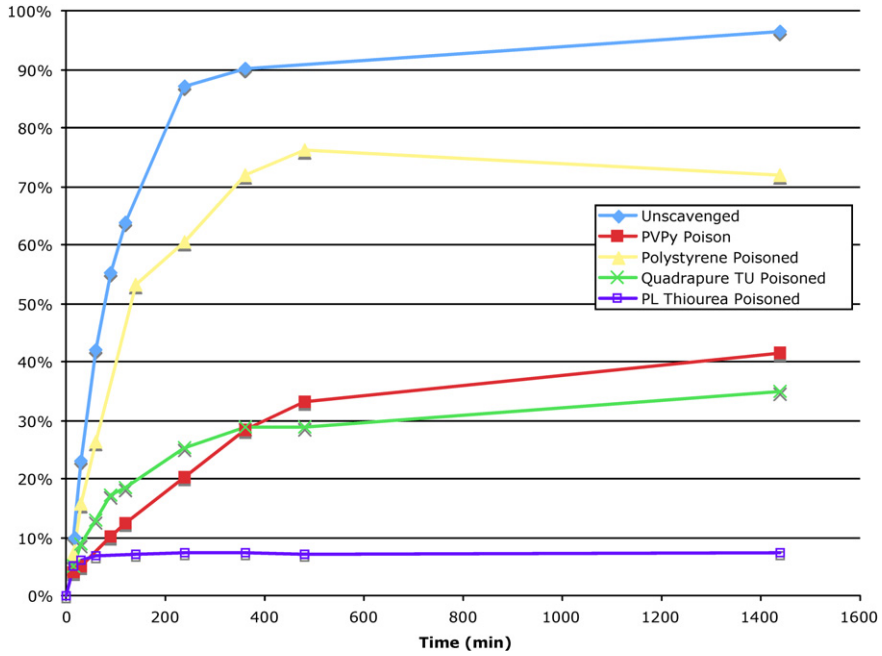


Fig. 7. Effect of various polymeric poisons on the activity of SBA-15-SH(cc)·Pd.

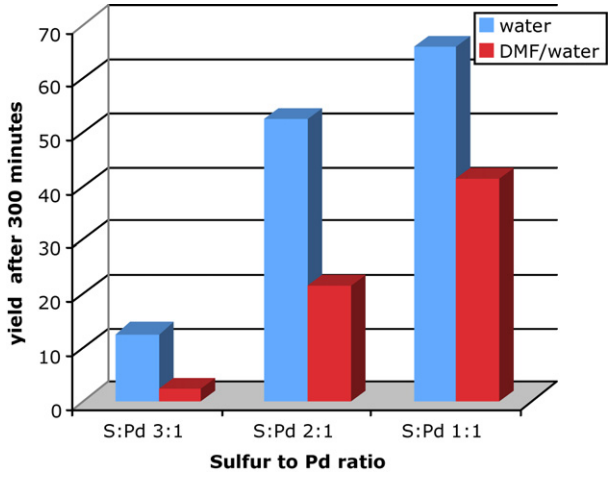


Fig. 8. Effect of Quadrapure-TU on the reaction of the amorphous silica prepared at different sulfur to Pd ratios.

attempted at ratios of 35:1 (heteroatom:Pd) in order to mimic the amount of unreacted amine present on the surface of the supported aryl halide. These tests resulted in a complete cessation of catalytic activity, confirming the scavenging capability of these materials, and the likelihood that the reaction was characterized by a release and catch mechanism. This analysis also explains the results obtained with respect to the thiol:Pd ratio as described in Table 1. At ratios such as 8:1, Pd is held more efficiently on the support and is then not able to escape into solution.

Examining the effect of Quadrapure-TU on the reaction of the amorphous silica prepared at different sulfur to Pd ratios, provided an interesting trend (Fig. 8). The yield of the desired product was assessed after 300 min, a time at which the unpoisoned reaction is usually complete. As shown in Fig. 8, a significantly greater yield was observed for the reaction performed with the 1:1 catalyst compared with the 3:1 catalyst which is in some ways counterintuitive based on the fact that greater leaching and solution activity is undoubtedly occurring for the 1:1 S:Pd catalyst.

However, based on the kinetics of the scavenging, the correct interpretation of these results is likely that a greater degree of reaction has occurred in solution for the 1:1 catalyst before the scavenger has a chance to become fully active.

4. Discussion

The development of Pd catalysts that do not lead to contamination of organic products at the end of a reaction is an important advance in the preparation of pharmaceutical compounds because of the great difficulty associated with removing Pd from these often highly functionalized compounds [15]. How these catalysts actually function is another question since many have been shown to act more correctly as reservoirs for soluble Pd, which may be solubilized as the oxidative addition product or as small Pd nanoclusters [74,75]. A complicating factor in the analysis of the heterogeneity of Pd catalysts is that the reaction which is generally employed as a test is the Mizoroki–Heck reaction, which is often run at temperatures as high as 140 °C [39]. Considering the large number of Pd complexes that function as asymmetric catalysts for this reaction [76,77] and others, the possibility of preparing a supported catalyst that remains bound to the surface seems to be only a question of choosing the correct ligand and conditions. However, the high activity of leached Pd [74] remains a problem and thus the question of whether *any* activity can be ascribed to surface-bound Pd for catalysts reported to date is questionable.

Several tests have been developed to assess the activity of surface vs homogeneous Pd. In fact, most of these tests determine only whether activity is present in solution, not whether

active species are present on support. One such test is the hot-filtration test, where activity of a solution after removal of the supposedly supported catalyst is examined. The presence of high levels of activity is then indicative of the presence of soluble Pd species. However, this test can be complicated by the fast redeposition of Pd on the surface which means that the observation of no activity in solution is not an indicator of surface catalysis. One of the tests which proved useful in discerning whether or not any activity could be attributed to surface-bound Pd in the case of pincer ligands is the polymeric-poison challenge test. In this approach, an insoluble poison is added to the reaction to trap any reactive Pd species, and then cessation of reaction is taken as evidence that the reaction was indeed catalyzed by leached Pd. This test also has some difficulties, since the polymeric poisons have been shown to bind to surfaces and inhibit reaction merely by preventing access to the surface [34], although the magnitude of this effect can be assessed in part by examining the effect of added polystyrene on the reaction. In addition, the quantity of the poison that is needed to inhibit the reaction may need to be optimized. Most importantly, however, for catalysts in which there is some equilibrium between soluble and bound Pd, these poisons may serve only to scavenge Pd from the support and hold it in an inactive form. Thus cessation of activity may not differentiate between the presence of *active* Pd in solution and the mere presence of Pd in solution. A better test of whether persistent catalytically active material is present in solution has been believed to be the three-phase test.

In this test, an aryl halide is tethered to the surface of a support and conversion on this support is deemed to result from the loss of catalytically active Pd from the surface. In this way, the three-phase test is superior to the hot filtration test, since the supported aryl halide is present at the time of the reaction, no filtration step is necessary. However, a fact which is often ignored is that in its original inception, the three-phase test was designed to capture intermediates from solution which had a certain lifetime. In the case of Pd catalysis, the Pd species must be sufficiently long-lived to diffuse from the surface on which it was originally supported and reach the supported reagent. Other factors which need to be considered are solvation of the two surfaces which may inhibit reaction at the surface, and the inherently slower rates of reaction of insoluble reagents. This will likely change with the nature of the Pd species involved, particularly as a function of the aryl halide since the ease of the individual steps in the catalytic cycle will control the nature of the most abundant catalytic species (MACS).

For example, based on the work of Reetz, the oxidatively added Pd(II) species is likely the MACS when aryl iodides are employed as the substrate [75]. With aryl bromides, there is evidence that the transmetallation step is also the rate determining step [28], and with aryl chlorides, a completely different step controls the nature of the resting state of the catalyst [78]. The solubility and the rate of deposition of the species that is most abundant will then have a significant impact on the observation of soluble Pd. With few exceptions [28,39,50,75], this point has not received much attention in the literature.

Interestingly, in the case of mercaptopropyl trialkoxysilane-modified silicates as supports for Pd, various heterogeneity tests have given divergent results. Thus the addition of poisons to the reaction mixture slows or stops the solution reaction while the three-phase test shows the presence of only small amounts of active Pd in solution. This led us to examine the three-phase test in more detail. As described in the results section, the three-phase test does give an accurate picture of the reaction, but only under appropriate conditions. Key features to consider are that the reaction between the supported reagent and leached Pd occurs at a decreased rate compared with reaction between Pd and soluble reagents. Thus, in order to observe reaction on support, it is important to run reactions to extended times/higher conversions, and also to increase the amount of coupling partner (in this case boronic acid) to ensure the availability of this reagent for coupling on support. Finally, it is instructive to probe the three-phase test with an appropriate homogeneous catalyst, or, as we demonstrated, with a heterogeneous catalyst that is known to leach Pd. In our case, we employed Pd/C to test the effectiveness of the three-phase test which showed that the test is unreliable in DMF/water, possibly due to differential solvation of the various surfaces involved. Although this did not prove feasible in water, the response of the three-phase test to prolonged reaction times and increases in $PhB(OH)_2$ imply that the test is effective in this medium, and that it provides at least a qualitative measure of the amount of active Pd that leaches from the surface.

5. Conclusions

In conclusion, the recyclability, stability and heterogeneity of thiol-modified silicates have been examined. It was shown that depending on the reaction conditions, thiol-modified materials which have been loaded with Pd can be highly active and recyclable catalysts. The method of introducing the thiol is critical to maintain structural integrity, since catalysts prepared by co-condensation undergo rapid reduction in surface area and mesoporosity upon exposure to aqueous base. This loss of order is coincident with a decrease of catalytic activity. In contrast, the material prepared by grafting of the thiol on the surface of pre-formed support retains most of its activity and structure up to 5 runs, although slight decreases in both are noted. Compared with amorphous silica, this particular catalyst is the most recyclable among those examined.

The effectiveness of the various heterogeneity tests described in the literature has also been probed, and it was demonstrated that like many other heterogeneity tests, both the three-phase test and the poison-challenge test need to be interpreted carefully. In particular, it is important to validate the three-phase test with catalysts known to leach Pd, or with conditions known to promote leaching. These results, in concert with poison-challenge tests can provide at least a qualitative picture of catalyst activity and heterogeneity. In the case of thiol-modified mesoporous silicates, they indicate that the material likely functions in a release and catch mechanism due to the strong binding of the Pd to the thiolated surface and the effectiveness of this material as a scavenger for Pd.

Acknowledgments

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Supporting information

Characterization data (physisorption analysis, pXRD analysis) of SBA-15-SH·Pd before and after use, conversion vs time plots for the reaction of amorphous silica at different S:Pd ratios, for SBA-15-SH(g) and for these two materials in the presence of various poisons can be found in the online version of this article.

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