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Strong evidence of solution-phase catalysis associated with palladium leaching from immobilized thiols during Heck and Suzuki coupling of aryl iodides, bromides, and chlorides

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Abstract

A 3-mercaptopropyl-functionalized silica, SH-SBA-15, is used both as a support for palladium acetate, Pd-SH-SBA-15, and as a selective poison of soluble palladium complexes. Pd-SH-SBA-15 is used as a precatalyst for Heck and Suzuki couplings of an aryl iodide, bromide, and chloride under a range of reaction conditions. In all reactions in which metal-free SH-SBA-15 is added, the catalysis associated with either homogeneous palladium acetate or from Pd-SH-SBA-15 ceased. This strongly suggests that (i) SH-SBA-15 can be used as an effective scavenger and poison of soluble palladium and (ii) catalysis with Pd-SH-SBA-15 is solely associated with leached metal. Supporting evidence is given from hot filtration tests, self-quenching behavior of partially metalated Pd-SH-SBA-15, and poisoning by other solid-phase poisons such as poly(4-vinylpyridine), Quadrapure TU, and 3-mercaptopropyl-functionalized silica gel. It is postulated that the SH-SBA-15 poisons by over coordination of soluble monomeric or dimeric palladium, which rules out catalysis by palladium nanoparticle surfaces. SH-SBA-15 is an effective and selective poison of homogeneous palladium species and can be used as a test for heterogeneity of palladium catalysts developed for Heck and Suzuki reactions.

Keywords: Heck reaction; Suzuki reaction; Mercaptopropyl silica; Palladium nanoparticle; Three-phase test; Palladium; Leaching; Supported catalysts; Selective catalyst poison

1. Introduction

Palladium-catalyzed carbon–carbon coupling reactions, such as the Heck [1] and Suzuki [2] reactions, represent an extremely important class of chemical transformations. A multitude of soluble and immobilized palladium precatalysts have been developed that are active and selective, but complications for commercial operations exist due to high metal cost and stringent requirements for removal of residual metal from exit streams. For example, palladium-catalyzed reactions are often used by pharmaceutical companies in the synthesis of medicinal molecules and must meet government requirements of <5 ppm residual metal in product streams [3]. These cost and purification pressures have spurred significant research in two distinct areas: (i) development of highly active homogeneous catalysts that are active at ppm metal concentrations and (ii) immobilization of palladium so that it can be recovered and reused [4,5].

The quest for a commercially viable, highly active, recoverable, and reusable palladium catalyst for Heck and Suzuki reactions is still ongoing despite the vast number of attempts and strategies used to date. Despite the many claims of heterogeneous catalysis by supported palladium, when more rigorous testing is undertaken, it is most often found that the true active species are from leached metal [5–17]. In fact, in a thorough review of the literature, we have asserted that there is no direct evidence for a truly heterogeneous palladium Heck or Suzuki coupling catalyst-based palladium nanoparticle- or macroparticle-catalyzed turnovers [5]. However, many authors do not attempt to assess the nature of the truly catalytic species and instead appear to assume that the form of palladium added to the reactor is the active catalyst. When authors do use various reaction tests to attempt to discern the location of the active species (i.e., leached palladium vs solid-phase palladium), re-

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sults can be easily misinterpreted. This is because many of the tests historically used to discern heterogeneous catalysis and recyclability, such as hot filtration and comparing final yield after recycling, give ambiguous results for Pd(0)-catalyzed coupling reactions [5]. This is due to three facts: (i) Even trace amounts of soluble palladium metal can be very catalytically active [11,18–21], meaning that only ppm of palladium need to leach to effect the catalysis; (ii) multiple deactivation pathways exist for soluble palladium, including redeposition on supports, formation of palladium black, and overcoordination by strongly binding ligands; and (iii) due to leaching and deposition (especially once all the aryl halide is consumed) the palladium can be partitioned among different solid phases as well as in solution [22–24]. The lifetime of active palladium species are therefore very sensitive to reaction conditions and to manipulations of the reaction solution both during and after catalysis. Commonly used heterogeneity tests must be carefully interpreted and supported by other methods. In previous studies, we introduced solid poisons to show that Pd(II) immobilized by pincer ligands [12,25,26] and Pd(II) encapsulated in a polymeric matrix [9] are not heterogeneous catalysts, but are simply reservoirs of leached active palladium. In two recent reviews, we suggested that immobilized thiols metalated with palladium warranted further investigation as a class of heterogeneous palladium precatalysts for C–C coupling reactions [5,27]; some authors have asserted that they leach active species, whereas others claim they give truly heterogeneous catalysts (vide infra).

Thiol-modified surfaces have been previously metalated with palladium and used for Heck and Suzuki reactions. Li and Jiang immobilized 3-mercaptopropyltriethoxysilane on a silica surface and then metalated with either palladium acetate or H_2PdCl_4 [28]. These materials where then used in the Heck coupling of iodobenzene with various olefins. Tests for heterogeneity included recycling the catalyst three times and comparing final yields. Wang and Liu used polymers containing bidentate mercapto-hydroxyl ligands that were metalated with palladium acetate, adsorbed onto silica, and used in Heck couplings [29]. Leaching of palladium was detected and attributed to reduction of Pd(II) by the olefin, followed by oxidative addition of the aryl halide. The palladium in the postreaction solution could be recovered by centrifuging away the precatalyst material and then adding nonmetalated support material to scavenge the leached metal, which was then successfully used in a subsequent Heck reaction. The authors also pointed out that materials with S:Pd ratios >6 exhibited no catalytic activity.

Cai, Song, and Huang condensed 3-mercaptopropyltriethoxysilane with fumed silica and metalated with Pd(II) chloride, which was reduced to Pd(0) [30]. This material was used as a precatalyst for the Heck reaction of aryl iodides with styrene and acrylic acid. Heterogeneity was implicitly tested by studying the activity on two successive runs, which decreased in activity by only 3% each time. Later, these same authors reported the synthesis of a similar material metalated with $Pd(PPh_3)_4$, which was used for a Sonogashira coupling with Cu(I) iodide as cocatalyst [31]. Choudary et al. [32] synthesized a bifunctional catalyst by tethering 3-mercaptopropyltrimethoxysilane to a silica gel surface and then partially reacted the thiols with a cinchona alkaloid. The material was metalated with Pd(II) chloride, which was assumed to only bind with the thiols, and the cinchona alkaloid was metalated in situ with $OsSO_4$. Heterogeneity tests of the catalyst were performed by testing activity of filtrates both from partially converted solutions and after addition of fresh reagents to completed reactions.

All of the above-mentioned publications suggested that palladium can be bound to an immobilized thiol surface and then used as a precatalyst for Heck reactions. However, the two primary tests used to prove or suggest heterogeneity—hot filtration and final yield after recycling—may be ambiguous (vide supra) and are not conclusive [5]. Up until the point of these publications (2002), the question had been unanswered as to whether catalysis from metalated, immobilized thiols is a result of leached or bound metal. To further complicate things, three recent, more detailed reports using similar precatalysts suggest different types of active species; two claim truly heterogeneous catalysis, and one claims that all catalysis is from leached species.

In 2004, Shimizu et al. [33] reported a careful and detailed characterization of a mesoporous silica, FSM-16, grafted with 3-mercaptopropylsiloxanes and metalated with palladium acetate to form Pd-SH-FSM. This was the first work to confirm that most of Pd atoms are bound to two sulfur atoms and are in a Pd(II) oxidation state on these types of mercaptopropyl-modified silica supports. Pd-SH-FSM was used as a precatalyst for both Heck and Suzuki reactions of activated bromides. The bulk of the reactions studied were Suzuki couplings, whereby the Pd-SH-FSM was reported as active, recoverable, and recyclable. EXAFS data indicated that most of the palladium was still bound to thiols after the reaction, and no detectable amount of palladium nanoparticles were observed in TEM. Only 0.05% of the bound Pd was found in the filtrate after reaction, and truly heterogeneous catalysis was asserted. However, because palladium can redeposit once aryl halide is consumed [22,34,35], and only traces of Pd are needed for high activity under some conditions, this is a lower bound on the amount that could have been in solution during the reaction. Under Heck conditions, only 0.01% of Pd was reported to have leached, but in this case small nanoparticles (2–14 nm) were observed by TEM, the appearance of which is suggestive of palladium leaching followed by nanoparticle formation and redeposition onto the support. EXAFS and XANES data indicated that most of the Pd was similar to that of the fresh catalyst. Tests for heterogeneity included hot filtration, in which the authors used 10 times less initial palladium (0.1%) than under standard conditions (1.0%), after which no activity was observed. The Pd-SH-FSM catalyst was recycled up to five times with no loss in productivity (based on final yield). However, careful comparison of the kinetics between the first and fifth runs show a dramatic decrease in the initial rate of reaction after recycling. The combined data from this report were interpreted as supporting the hypothesis that the thiol-supported palladium was a heterogeneous catalyst.

Also in 2004, Crudden et al. [36] studied mercaptopropyl-modified SBA-15, both co-condensed and postgrafted with 3-mercaptopropyltrimethoxysilane, both of which were metalated

Table 1
Summary of results obtained using mercaptopropyl-modified silica materials as supports for $Pd(OAc)_2$ precatalysts in Heck and Suzuki couplings

Author	Solvent		Halide		2nd reagent		Base		Catalysis	
	Heck	Suzuki	Heck	Suzuki	Heck	Suzuki	Heck	Suzuki	Heck	Suzuki
Shimizu Pd-SH-FSM-16 (S:Pd = 2.8)	NMP (403 K)	DMF (403 K)	4-Bromoaceto phenone	4-Bromoanisole	Ethyl acrylate	$PhB(OH)_2$	KOAc	K_2CO_3	Surface	Surface
Crudden Pd-SH-SBA-15 (S:Pd = 4)	DMF (393 K)	DMF H_2O DMF/H_2O (353 K, 363 K, 373 K)	4-Bromoaceto phenone	4-Chlorobenzene 4-Chloroacetophenone 4-Bromopyridine 4-Bromotoluene 4-Bromoanisole 4-Bromobenzaldehyde	Styrene	$PhB(OH)_2$	NaOAc	K_2CO_3	Surface[a]	Surface
Davis Pd-SH-SBA-15 (S:Pd = 1.6)	DMF (353 K, 373 K)	N/A	Iodobenzene	N/A	*n*-Butyl acrylate	N/A	NEt_3	N/A	Leached	N/A

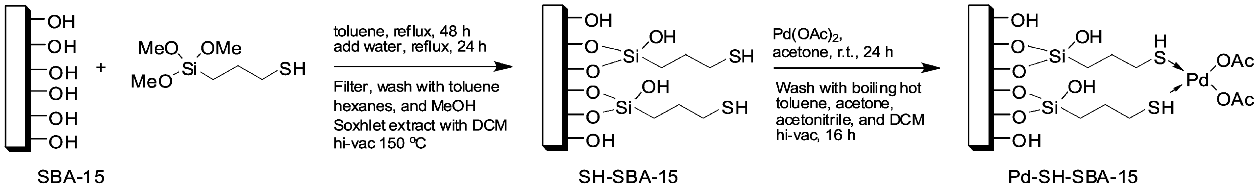
[a] Surface catalysis is implied Heck reactions in [36] and more explicitly stated in [39] where catalysis is claimed as "leach-proof."

with palladium acetate. Most of the reactions tested involved Suzuki couplings of either aryl bromides or aryl chlorides, but a smaller number of Heck couplings also were performed. It was found that only the co-condensed material exhibited effective catalytic behavior (S:Pd = 4:1), whereas the grafted material was inconsistent, with most of the prepared materials showing no activity. A significant achievement was the ability to catalyze the Suzuki reaction of chloroacetophenone (2 mol% catalyst, H_2O as solvent) with phenyl boronic acid, with the reaction proceeding to 93% (yield = 80%) at 80 °C and 99% (yield = 96%) at 90 °C. To test for heterogeneity for the Suzuki reaction, the activity of a small amount of soluble palladium acetate (0.5 ppm) was measured. Only 5% conversion of bromoacetophenone with phenylboronic acid was achieved as compared with 99% with Pd-SH-SBA-15. This was taken as evidence that the ppm levels of thiol-ligand–free palladium leached from the Pd-SH-SBA-15 could not have been the source of catalysis. A hot filtration test was also performed, with only a small amount of conversion observed in the filtrate. Finally, a three-phase test [37,38] was performed, in which an aryl bromide or aryl chloride was immobilized. Soluble aryl halide was added, and conversions of both soluble and supported reagent were estimated. Most of soluble reagent was consumed, however only small amounts of surface-bound reagent were converted in some cases. Thus, in this case, the combined data also supported the conclusion that the vast majority of catalysis was from surface-bound palladium. Later reports further strengthened the findings, describing these materials as "leach-proof catalysts [39]."

In contrast, another report suggested exactly the opposite—that all catalysis associated with thiol-supported palladium species was associated with leached, soluble species [40]. In this 2005 contribution by Ji et al., the Heck reaction of iodobenzene with *n*-butyl acrylate in DMF with triethylamine as base was investigated using both Pd(II) and prereduced Pd(0) forms of the mercaptopropyl-silica supported precatalyst. These authors performed various tests to determine whether catalysis was heterogeneous or from leached metal. In the presence of insoluble poly(4-vinylpyridine) (2% cross-linked) (PVPy), almost all catalytic activity was ceased. A series of hot filtration experiments were conducted; in contrast to previous work, a significant amount of activity was observed for filtrates free of solid precatalysts. In the case of Pd-SH-SBA-15 after 1 h, the conversion of the filtrate (76%) was nearly the same as the regular reaction (80%). The authors found that iodobenzene was required for leaching of active palladium, which implies that oxidation of immobilized Pd(0) is a cause of leaching. This is consistent with previous observations that aryl iodides can pull Pd(0) into solution from Pd(0) nanoparticle surfaces [6,11,14,41]. Finally, effluents from a continuous reaction system were found to be catalytically active, confirming the presence of leached active metal. The final conclusion was that activity of Pd-SH-SBA-15 for the Heck reaction under these conditions is solely from leached palladium.

Shimizu, Crudden, and Davis each studied similar types of palladium-immobilized catalysts using mercaptopropyl-modified silicas as supports but under markedly different conditions from each other (Table 1). Conclusions differed as to whether the catalysis was from supported or leached metal. In each case, the conclusions drawn by the authors appear reasonable based on the data presented. Unfortunately, a direct comparison of the results is difficult due to variations in reaction conditions from author to author. Shimizu and Crudden primarily looked at Suzuki reactions with activated bromides whereas Davis focused on Heck reactions of iodobenzene. The more general question as to whether mercaptopropyl-modified materials can act as a supports for heterogeneous catalysis for both Heck and Suzuki reactions was thus still unanswered.

Toward this end, here we report on the use of a mercaptopropyl-modified silica, SH-SBA-15, as a tethered ligand for palladium and introduce its use in unmetalated form as a selective poison of soluble, active palladium. Metalation with palladium acetate yields an immobilized palladium precatalyst, Pd-SH-SBA-15, which was used for Suzuki and Heck reactions under the same conditions reported by Shimizu [33], Crudden [36], and Davis [40] both with and without SH-SBA-15 added as poison. In all cases in which bare SH-SBA-15 was used as poison, no catalysis was observed. This is quite remarkable as SH-



Scheme 1.

SBA-15 is the exact same material used as the catalyst support and should not affect the catalysis occurring from truly heterogeneous palladium species on separate but identical particles. Thus, our poisoning results strongly suggest that under all conditions tested here, catalysis is solely associated with leached palladium species. Poisoning by SH-SBA-15 also implies that the active soluble catalytic species is not from nanoparticle surfaces but rather from molecular or dimeric palladium, which is consistent with the work of de Vries [20,42,43], Schmidt [24], Rothenberg [44] and Fiddy [45].

2. Experimental

2.1. General

All organic materials were purchased from commercial sources. Palladium on carbon (10 wt%), Quadrapure TU (thiourea-functionalized polystyrene, 3.3 mmol/g), and 3-mercaptopropyl-functionalized silica gel (1.2 mmol/g) were purchased from Sigma Aldrich and used without further treatment. *N*,*N*-dimethylformamide and butyl acrylate were dried with calcium hydride for 24 h, distilled under an argon atmosphere, and stored at 278 K until use. Acetone used for metalations was dried over sieves for 24 h at room temperature, distilled under argon atmosphere, and stored in a N_2 dry box (Plas Labs, Lancaster, MI). Nitrogen physisorption was performed using a Micrometrics ASAP 2010 with pore size distributions determined using the BJH method applied to the adsorption isotherms. Surface areas from N_2 physisorption were determined using the BET method. Hexagonal ordering of the mesopores was verified X-ray diffraction (PANalytical X'Pert PRO) using Cu$K\alpha$ radiation. Loadings of organically modified supports were determined from simultaneous thermal analysis (Netzsch STA 409 PG Luxx) and verified by elemental analysis (Desert Analytics, Tucson, Arizona). Organically modified silica materials were stored in a N_2 dry box to prevent moisture adsorption. FT-Raman analyses were performed on a Bruker FRA-106 with 1028 scans collected for each sample with a 100 kW laser source. Gas chromatography was performed on a Shimadzu GC-17A equipped with a flame ionization detector and a HP-5 column. The column treatment program was the same as previously reported [12].

2.2. Synthesis of organically modified mesoporous silica

Large-pore SBA-15 (110 Å) was synthesized by literature methods, using the triblock poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (EO–PO–EO) nonionic surfactant as the structure-directing agent and 1,3,5-trimethylbenzene (TMB) as a swelling co-solvent [46]. The as-prepared material was calcined using the following temperature program: (1) increasing the temperature (1.2 K/min) to 473 K, (2) heating at 473 K for 1 h, (3) increasing the temperature (1.2 K/min) to 823 K, and (4) holding at 823 K for 6 h. Before functionalization, the SBA-15 was dried under vacuum (5 mTorr) at 473 K for 3 h and stored in a dry box (BET surface area = 780 m^2/g; average pore diameter = 110 Å). Complete removal of the organic surfactant was confirmed by TGA analysis.

Organic modification of SBA-15 was achieved by mixing a toluene (120 mL) suspension of SBA-15 (4.1 g) and 3-mercaptopropyltrimethoxysilane (10 g) at reflux temperature for 48 h under an argon atmosphere. Water (1.8 mL) was then added to promote the cross-linking and the mixture was heated at reflux for an additional 24 h. The solids were then filtered and washed with copious amounts of toluene, hexanes, and methanol to remove unreacted silanes. Recovered solids were Soxhlet-extracted with dichloromethane at reflux temperature for 3 days. The resulting white solids were collected, kept under vacuum (5 mTorr) at room temperature overnight, dried at 423 K for 3 h under vacuum (5 mTorr), and stored in a nitrogen glove box. FT-Raman analysis exhibited a strong peak at 2571 cm^{-1}, which is in the normal range found for S–H stretching. A loading of 7.5 wt% of sulfur (2.3 mmol S/g solids) was found by elemental analysis (BET surface area = 320 m^2/g; average pore diameter = 80 Å).

2.3. Metalation of organically modified SBA-15

Palladium acetate (450 mg, 2 mmol) was dissolved in 50 mL of dry acetone. This solution was added to SH-SBA-15 (1.1 g), resulting in an orange-brown suspension, which was stirred at room temperature for 24 h (Scheme 1). The solids were filtered using a 150-mL fritted funnel (medium-sized frit) and washed with 3 × 100 mL each of boiling acetone, toluene, acetonitrile, and dichloromethane. The recovered solids were orange-brown in color. The solids were then exposed to high vacuum (5 mTorr) for 16 h to remove any physisorbed solvent, resulting in orange-brown solid particles. A loading of 11.06 wt% palladium (1.04 mmol Pd/g solids) was determined by elemental analysis based on the average of two EA tests for Pd (10.9 and 11.21 wt%), giving a S:Pd ratio of 1.7. This material was used for most of the experiments. Two other partially metalated batches were made by mixing (i) 9 mg palladium acetate, 110 mg SH-SBA-15, and 5 mL acetone and (ii) 45 mg palladium acetate, 200 mg SH-SBA-15, and 25 mL acetone. Materials were washed using a scaled-down filtration procedure (60 mL fritted funnel and 3 × 50 mL each of solvent). Final Pd loadings and S:Pd ratios were (4.1%, 5.7) and (8.4%, 2.6), respectively.

2.4. Heck reactions

Various reaction conditions for Heck reactions were studied. For most of the reactions, the precatalyst Pd-SH-SBA-15 (1.2 mg, 1.25E−03 mmol Pd, 0.05 mol% Pd to aryl halide) was added to a three-necked flask and connected to a condenser linked to a Schlenk line. The system was purged with argon, and then a solution of N,N-dimethylformamide (5 mL), aryl halide (2.5 mmol), base (7.5 mmol) and diethylene glycol dibutyl ether (2.5 mmol, GC standard) was added. The mixture was magnetically stirred and preheated at reaction temperature for 25 min, at which time n-butyl acrylate (3.75 mmol) was added to initiate reaction. Periodically, 0.1-mL samples were withdrawn, dissolved in 1.5 mL of acetone at room temperature, filtered through a small plug of silica gel loaded in a cotton plugged pipet, and analyzed by gas chromatography. In reactions in which homogeneous palladium acetate was used as the precatalyst, n-butyl acrylate was added before the preheating, and the reaction was initiated by adding 0.1 mL of a 0.0125 M solution of palladium acetate in DMF. Exceptions to reaction conditions described above are noted where necessary.

2.5. Suzuki reactions of 4-bromoacetophenone or 4-chloroacetophenone

2.5.1. DMF as solvent

Aryl halide (1.0 mmol) and hexamethylbenzene (0.5 mmol, GC standard) were dissolved in 5 mL of DMF. The solution was added to a glass reactor with precatalyst (1.0% for bromoacetophenone and 2.0% for chloroacetophenone), K_2CO_3 (2.0 mmol), and phenyl boronic acid (1.5 mmol). The suspension was purged with argon, sealed, and immersed in an oil bath at 353 K and magnetically stirred for 6 or 8 h. Reactions in DMF were analyzed by taking a 0.1-mL sample, which was dissolved in 1.5 mL acetone at room temperature, filtered through a small plug of silica gel loaded in a cotton plugged pipet, and analyzed by gas chromatography.

2.5.2. H_2O as solvent

Precatalyst (1.0% for bromoacetophenone and 2.0% for chloroacetophenone), K_2CO_3 (2.0 mmol), aryl halide (1.0 mmol), phenyl boronic acid (1.5 mmol), hexamethylbenzene (0.5 mmol, GC standard), and 5 mL of double-distilled H_2O were added to a glass reactor and magnetically stirred at 353 K for 6 to 24 h. In the original report of these conditions, hexamethylbenzene was used as an internal standard [36]. In this work, hexamethylbenzene was again included in the reaction, but because the reaction was in water, we developed an alternate method to assess the conversion of aryl halide based on a GC calibration file composed of known concentrations of aryl halide and 4-acetyl-biphenyl (product) with DGDE as standard. Reactions were extracted with 3 × 10 mL of dichloromethane. The DCM was then evaporated, and a known amount of DGDE in 5 mL of acetone was added. A 0.1-mL sample of solution was dissolved in 1.5 mL of acetone, passed through a small plug of silica gel loaded in a cotton plugged pipet, and analyzed by GC. The final conversion was determined by comparing the ratio of aryl halide and DGDE to the calibration file.

2.6. Hot filtration

A Heck reaction solution was allowed to reach 20–30% conversion of iodobenzene, and the solids were filtered off under static vacuum by means of a swivel frit [47] connected to an empty reaction flask. The filtrate was kept at reaction temperature, and conversion was monitored by GC.

2.7. Catalyst poisoning

In most of the reactions, the catalyst poison was added to the reaction flask before the addition of reaction solution. Poly(4-vinylpyridine) was used in 350 equivalents of pyridine sites to total palladium unless noted otherwise. When Quadrapure TU, SH- SBA-15, or 3-mercaptopropyl-functionalized silica gel was used as a poison, the molar ratio of poison to palladium was 35 to 1 unless stated differently. In reactions in which the poison was added after the initiation of reaction, a glass plug in the three-necked flask was removed (briefly exposing the argon filled vessel to air for approximately 3–5 s) and the poison particles were quickly added, after which the glass plug was reinserted.

3. Results

3.1. Aryl iodide conversions

3.1.1. Comparison of activity between soluble and immobilized palladium acetate

A typical benchmark reaction for Heck couplings involves reacting aryl iodides with either styrene or an acrylate. Aryl iodides are more active than aryl bromides or aryl chlorides due to their rapid oxidative addition to Pd(0), forming a Pd(II) complex. Unless stabilizing ligands are present, Pd(0) can aggregate to from palladium black, a typically inactive form of palladium that commonly precipitates out of solution. In the presence of excess oxidizing agents such as aryl iodides, deactivation by palladium black formation can be mitigated [14,20, 41,48]. However, as the aryl iodide is consumed in the reaction, less of it is available to complex to Pd, and the distribution of Pd can shift to favor Pd(0), leading to formation of palladium nanoparticles or palladium black. The overall catalytic activity represents a balance between completing turnovers in the Heck cycle and deactivation of the palladium associated with palladium black formation or other deactivated forms of palladium, such as overcoordinated palladium with strongly binding molecules or inactive palladium redeposited on surfaces.

To compare the activity between soluble and immobilized palladium, Heck coupling reactions of iodobenzene with n-butyl acrylate were performed using two different palladium sources: homogeneous palladium acetate and immobilized palladium acetate on mercaptopropyl-modified mesoporous silica,

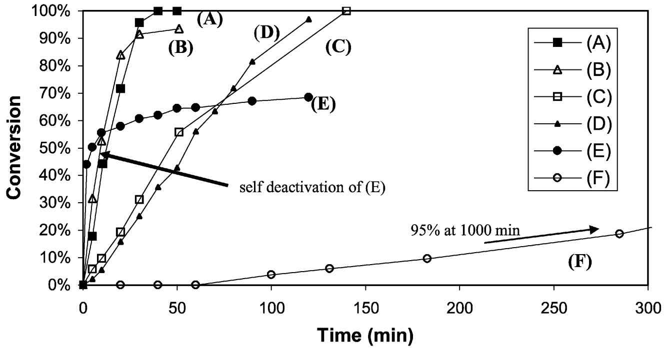


Fig. 1. Activity comparisons of Heck coupling iodobenzene with butyl acrylate using: (A) 0.05% palladium acetate at 363 K, (B) 0.5% Pd-SH-SBA-15 at 363 K, (C) 0.05% Pd-SH-SBA-15 at 363 K, (D) 0.05% palladium acetate at 343 K, (E) 1.0% palladium acetate at 363 K with start of self deactivation noted, and (F) 0.05% Pd-SH-SBA-15 at 343 K with final conversion at 1000 min.

Pd-SH-SBA-15 (Scheme 1). *N*,*N*-dimethylformamide (DMF) was used as the solvent, and triethylamine was used as the base. Comparisons of activity between soluble and immobilized palladium acetate are displayed in Fig. 1. Reactions using soluble palladium acetate rapidly went to completion at 363 and 343 K (Figs. 1A and 1D). Increasing the amount of homogeneous palladium acetate is known to result in catalyst deactivation due to the higher concentrations of Pd(0) that rapidly cluster to form palladium black [20,49]. This self-quenching was also observed under the reaction conditions studied in this report (Fig. 1E). A 1.0% loading of palladium acetate was initially faster than the 0.05% loading, but after about 5 min, the palladium began to self-deactivate, and the conversion ultimately reached a lower value of 69% at 120 min, compared with the 100% conversion at 40 min reached for the lower catalyst loading.

Reactions with Pd-SH-SBA-15 were also active but displayed lower rates than reactions using homogeneous palladium acetate at the same temperature and palladium loading. The decrease in temperature from 363 to 343 K significantly slowed the activity of Pd-SH-SBA-15, necessitating a much longer time to start, progress, and ultimately finish the reaction (Fig. 1C and F). This dramatic decrease in activity could be either due to effects inhibiting reaction on the surface (if it were to occur there) or represent the temperature influence on leaching of immobilized palladium from supported thiols. Increasing the catalyst loading of Pd-SH-SBA-15 to 0.5% resulted in a faster reaction rate (Fig. 1B), which stands in contrast to the observed behavior after homogeneous palladium acetate loadings were increased.

The increased activity by raising the Pd-SH-SBA-15 loading could be explained by one of two possible scenarios: (i) Pd(0) formed during the Heck cycle cannot aggregate due to its binding to an immobilized organic surface, and so increased activity is simply associated with more metal present, or (ii) the amount of leached palladium from the surface is low, and so the actual concentration of active catalytic species in solution is below levels that promote self-deactivation. To understand where the catalysis is occurring, tests are needed to confirm the presence of soluble palladium and determining to what extent, if any, catalysis is occurring on the surface.

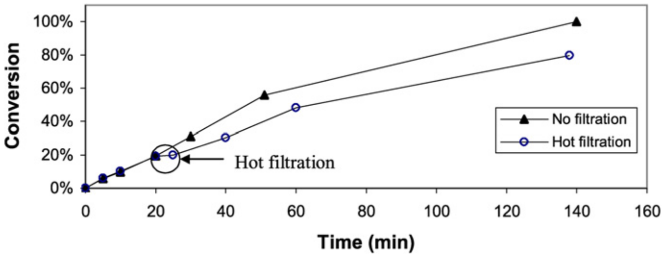


Fig. 2. Application of hot filtration to the Pd-SH-SBA-15 catalyzed Heck coupling of iodobenzene with butyl acrylate at 363 K in 5 mL DMF with triethylamine as base. Hot filtration was applied at 20 min.

3.1.2. *Hot filtration*

A strong test for assessing the presence of soluble active palladium is the hot filtration test, also known as the split test, in which solid precatalysts are filtered out of the reaction and the filtrate is monitored for continued activity [50]. A lack of filtrate activity is traditionally interpreted as a proof of heterogeneous catalysis, but this interpretation cannot be applied to palladium-catalyzed reactions without support from other tests. Heck reactions can be catalyzed by extremely small amounts of palladium (as low as 0.00001%), and the self-deactivation at high loadings described above suggests that very low loadings are ideal [5,20]. Disruptions such as hot filtration can deactivate the small amount of active metal, which can lead to the incorrect conclusion that there are no active soluble catalytic species before the filtration [5,51]. In the present work, when Pd-SH-SBA-15 (0.05%, 363 K) was hot filtered, after 20% conversion, the filtrate continued to react, indicating that some of the palladium was leaching from the surface and catalyzing the reaction (Fig. 2). A common method for determining the amount of solution versus surface catalysis is to compare the rate of activity after hot filtration to that found under normal reaction conditions. But because some of the active palladium can become deactivated during hot filtration, this method of comparison provides rough estimates at best. Other tests are needed to determine whether any heterogeneous catalysis is indeed occurring.

3.1.3. *Tests of heterogeneous catalytic activity*

In our work on assessing homogeneity/heterogeneity of catalysis associated with supported Pd precatalysts in coupling reactions, we introduced the use of solid, insoluble poisons for extinguishing solution-phase catalysis [5,9,12,25,26]. The insoluble metal scavenger poly(4-vinylpyridine), 2% cross-linked, was first used as a tool to determine whether supported catalysis was or was not occurring for palladium pincer complexes immobilized on silica or organic polymers [12,25,26], and later using Pd immobilized on amorphous silica [40] and palladium acetate encapsulated in a poly(urea) matrix [9]. No activity was observed when PVPy was used to poison Pd-SH-SBA-15, typically using 350 equivalents of pyridine sites to total palladium. The use of PVPy as a solid poison is not without its drawbacks, however. Due to the equilibrium on-off coordination of the palladium with the pyridine sites [52] and the nonporous nature of the resin, a large excess of pyridine units are required to overcoordinate the palladium (Fig. 3). This can

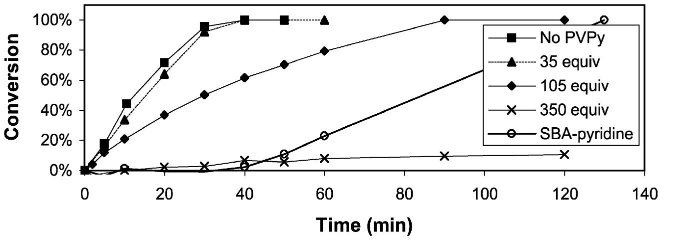


Fig. 3. Plot of iodobenzene conversion showing the effect of increased equivalencies of PVPy for poisoning of homogeneous palladium acetate catalysis of the Heck coupling of iodobenzene with butyl acrylate. Poisoning by immobilized pyridine on SBA-15 (pyridine:Pd = 35:1) is also shown for comparison. Conditions are at 363 K under argon with DMF (5 mL) as the solvent and NEt_3 as the base.

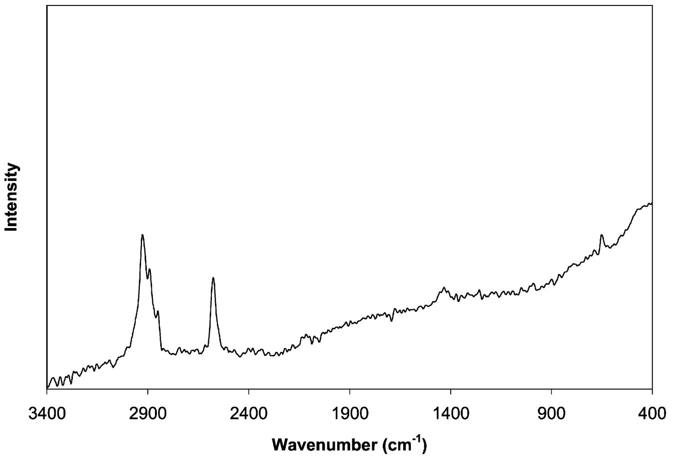


Fig. 4. FT-Raman spectrum of SH-SBA-15. The peak at 2571 cm^{-1} is assigned to an S–H stretch.

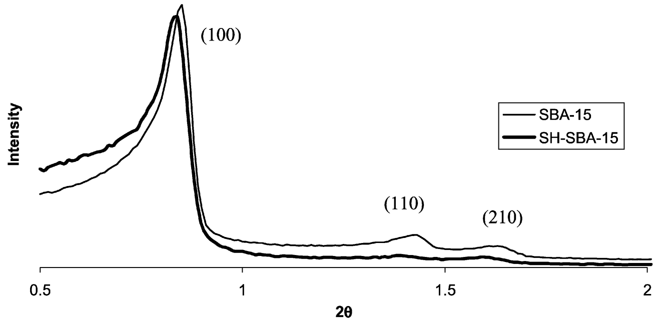


Fig. 5. XRD patterns of SBA-15 before and after mercaptopropyl-functionalization. Retainment of long range ordering is demonstrated by a strong (100) peak.

sometimes introduce a large amount of solids to the solution and may result in some pore blocking of the SBA particles from agglomerated PVPy nanoparticles or partially solvated polymer. A further disadvantage is that polymer swelling might be needed for access to many of the pyridine sites; this is largely influenced by both choice of solvent and reaction temperature. For comparison to PVPy, 2-(4-pyridylethyl)triethoxysilane was grafted onto SBA-15, Pyr-SBA-15 (1.7 mmol pyridine/g solids and pyridine:Pd = 35:1), and substituted for PVPy as a poison of palladium acetate (Fig. 3). An induction time of 40 min was observed, followed by significant activity, which is consistent with an equilibrium on-off mechanism by which soluble palladium is first rapidly overcoordinated by the immobilized pyridine sites and then eventually leaches back into solution. Under the same reaction conditions, PVPy (pyridine:Pd = 35:1) exhibited almost no initial slowing of reaction and reached full conversion by 40 min. This comparison suggests the importance of PVPy polymer swelling to make pyridine sites accessible for coordination to homogeneous palladium.

For most immobilized palladium precatalysts, the amount of leached palladium is unknown; thus, the amount of PVPy needed for poisoning becomes an optimization problem. As an example, 350 equivalents of PVPy did not completely stop catalysis when soluble palladium acetate (0.05%) was used, but did quench activity from Pd-SH-SBA-15. Comparing these results provides a qualitative estimate for the amount of palladium leached from Pd-SH-SBA-15 and indicates that not all palladium was removed from the surface when the supported precatalyst was used. More importantly, the quenching of activity by PVPy is strong evidence for catalysis solely by leached species, but due to its previously mentioned drawbacks, a more elegant selective poison is desired to provide supporting evidence.

Mercaptopropyl-modified surfaces, such as SH-SBA-15, have been used as effective palladium scavengers [36,53–55] as well as scavengers for other metals, such as silver and mercury [56]. SH-SBA-15 is a rigid mesoporous solid that does not swell under reaction conditions, a previously mentioned drawback of ligands immobilized on polymers such as PVPy. We thus hypothesized that the same SH-SBA-15 material used as a support for palladium acetate immobilization could also act as a selective poison of soluble palladium acetate if used in excess. Before its use as a selective poison, the presence of S–H groups was verified by FT-Raman spectroscopy (Fig. 4). The presence of long-range order and a hexagonal structure, as expected for SH-SBA-15, was verified by XRD (Fig. 5).

Bare, palladium-free SH-SBA-15 was used to poison catalysis of the Heck coupling of iodobenzene with n-butyl acrylate using either homogeneous palladium acetate or Pd-SH-SBA-15 (Fig. 6). In all cases, the presence of an excess of bare SH-SBA-15 to palladium of 35–1 resulted in complete cessation of activity. SH-SBA-15 was a more effective poison than PVPy and required less material (e.g., 20 mg of SH-SBA-15 vs 50 mg of PVPy), perhaps due to binding site accessibility. As shown in Fig. 3, 35 equivalents of PVPy had almost no poisoning effect, whereas Pyr-SBA-15 stopped activity for 40 min, after which activity was observed. In contrast, SH-SBA-15 completely shut down activity even after 16 h, demonstrating its superior performance as a poison and also demonstrating the better ability of immobilized thiols to retain palladium compared with immobilized pyridines. Also, because it is the same material as that used for the catalyst support, no poison-induced pore blocking occurs. To probe whether poisoning is from the organic functionalization of SBA-15 and not from anything else inherent to the SBA-15, a control reaction was performed in which 50 mg of SBA-15 was substituted for SH-SBA-15 and tested as a poison. No difference in the kinetic profile was observed between reactions with and without SBA-15, confirming that poisoning

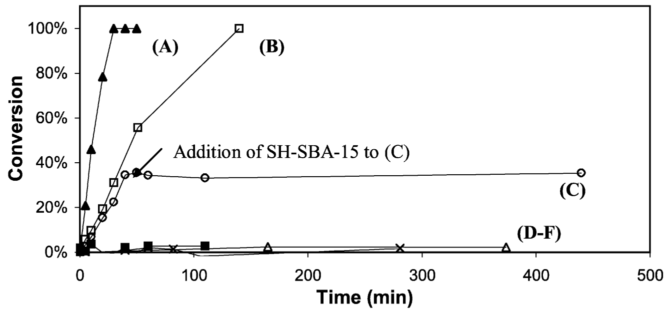


Fig. 6. Plot of iodobenzene conversion with SH-SBA-15 used as a poison and either palladium acetate or Pd-SH-SBA-15 as catalyst: (A) control reaction at 363 K using SBA-15 instead of SH-SBA-15 as an ineffective poison of palladium acetate, (B) Pd-SH-SBA-15 activity without any poison, (C) cessation of Pd-SH-SBA-15 activity by adding SH-SBA-15 poison after 40 min of reaction, (D) cessation of Pd-SH-SBA-15 activity at 363 K by adding SH-SBA-15 at start of reaction, (E) cessation of Pd-SH-SBA-15 activity at 343 K by adding SH-SBA-15 at start of reaction, and (F) cessation of palladium acetate activity by adding SH-SBA-15 at start of reaction.

was caused by mercaptopropyl modification of the surface and is not inherent to the SBA-15 material. A second control experiment was conducted in which 1-propanethiol was mixed with Pd-SH-SBA-15 (4:1, propanethiol:Pd) under normal Heck reaction conditions. Kinetic activity was significantly slowed but did reach a maximum of 40% conversion after 20 h. A complementary reaction using SH-SBA-15 (4:1, SH-SBA-15:Pd) as the poison resulted in complete cessation of activity up to 33 h. These tests highlight the importance of immobilizing the thiol groups to increase poisoning capacity. This is most likely explained by a high local sulfur concentration of the bound thiols in which captured palladium is rapidly overcoordinated by neighboring thiols before it can be released back into solution.

When SH-SBA-15 was mixed with Pd-SH-SBA-15 at either the beginning of the reaction or after the reaction has initiated, no additional conversion was observed (Fig. 6). This is strong evidence that all catalysis previously observed in this work with Pd-SH-SBA-15 was solely from leached palladium, which agrees with observations made by Davis [40]. To determine the lower bound of required poison, the equivalency of SH-SBA-15 to Pd was decreased from 35 to 4, and no reaction of iodobenzene with *n*-butyl acrylate was observed up to 2000 min (0.05% catalyst, 363 K, DMF, NEt_3). Further decreasing the equivalency to 1 resulted in a slow conversion to 58% after 700 min, which remained constant up to 1900 min. This indicates that SH-SBA-15 is an effective poison of leached palladium from Pd-SH-SBA-15 and can be effective in much lower amounts than PVPy.

The ability of the SH-SBA-15 to effectively poison these precatalysts implies that the active catalyst species consists of only a small number of Pd atoms and not from the surface of Pd nanoparticles. Due to the rigid, cylindrical structure and large pore size of SH-SBA-15, it is difficult to envision the mercaptopropyl groups overcoordinating the entire surface of a Pd nanoparticle, whereas complexes of one to a few Pd atoms could be completely coordinated. Alternatively, it is also possible that the capture of free metal ions from solution by the SH-SBA-15 could prevent the aggregation of palladium to form nanoparticles. In this scenario, a demonstrated lack of nanoparticle surface catalysis would not be substantiated by the use of insoluble poisons. However, the rapid quenching of catalysis by addition of poison once activity has commenced (Fig. 6, curve C), presumably when nanoparticle formation could have already occurred, is suggested as evidence that if nanoparticles are formed, their surface is inactive, as postulated above. Collectively, this evidence suggests Heck catalysis by molecular or dimeric palladium as postulated by de Vries [5,20,42,43] and Schmidt [5,24] and supported by Rothenberg [44] and Fiddy [45]. Further testing to conclusively demonstrate lack of activity of nanoparticle surfaces by the use of insoluble poisons is outside the scope of this paper, but is suggested as a potentially interesting future work.

3.1.4. *Probing mercaptopropyl ligand leaching*

An alternative mechanism for poisoning of Pd-SH-SBA-15 by SH-SBA-15 is that the mercaptopropyl groups leach and poison surface-bound palladium. In this case, the poisoning experiments using SH-SBA-15 could not conclusively support a leaching mechanism of Pd-SH-SBA-15. However, if mercaptopropyl leaching were occurring for SH-SBA-15, then it would also be expected to occur for the mercaptopropyl groups used to immobilize palladium acetate on Pd-SH-SBA-15, unless the presence of palladium acetate somehow prevented this from happening. Mercaptopropyl leaching from SH-SBA-15 was explicitly probed by exposing 50 mg of SH-SBA-15 to reaction conditions for 1 h and then hot-filtering the solids. The filtrate was kept at 363 K, and homogeneous palladium acetate (0.1 mL of a 0.0125 M solution in DMF) was added. Complete conversion was reached in <30 min; therefore, it is unlikely that significant leaching of thiols occurred under these conditions. An important assumption for this interpretation is that any leached thiols can survive the hot-filtration process without redepositing on the surface (recall that leached palladium often redeposits). Otherwise, the observed activity of the filtrate could not confirm the absence of thiol leaching. Assuming nearly full coverage of the silica surface with silanes, small amounts of leached silane, if they existed, likely would not find bare silica surfaces on which to redeposit. Thus, we would expect leached silane redeposition to be unimportant. To investigate the retention of the mercaptopropyl groups on the silica surface, the recovered solids from the hot filtration were rinsed with boiling hot toluene, dichloromethane, and acetone and exposed to hi-vacuum (5–6 mTorr) to remove any physisorbed organic material. Presence of residual S–H bonds was confirmed by FT-Raman analysis of both the untreated SH-SBA-15 and the SH-SBA-15 recovered from hot filtration. A strong FT-Raman peak at 2175 cm^{-1} was observed for both materials and assigned as an S–H stretch. The activity of the filtrate and FT-Raman analysis suggest that thiol leaching does not occur at a level that would allow poisoning of Pd-SH-SBA-15 if it were a heterogeneous catalyst. As noted in Section 3.1.3, a large amount of leached thiol giving a S:Pd ratio in excess of 4:1 would be required to completely poison hypothesized surface-mediated catalysis.

Table 2
Results of Heck coupling reactions of bromoacetophenone and various reagents[a]

Entry	Alkene	Base	Catalyst (mol%)	Temperature (K)	SH-SBA-15	Time (min)	Conversion (%)	Condition[b]
1[c]	Ethyl acrylate	KOAc	1.00%	403	No	210	100	3-Neck
2[c]	Ethyl acrylate	KOAc	1.00%	403	Yes	300	0	3-Neck
3	Styrene	NaOAc	0.50%	393	No	900	75	Sealed
4	Styrene	NaOAc	0.50%	393	Yes	900	0	Sealed
5	Butyl acrylate	NaOAc	0.12%	393	No	1350	87	Sealed
6	Butyl acrylate	NaOAc	0.12%	393	Yes	1350	5	Sealed
7	Butyl acrylate	NaOAc	0.12%	393	No	180	91	3-Neck
8	Butyl acrylate	NaOAc	0.12%	393	Yes	2000	0	3-Neck
9	Butyl acrylate	NaOAc	0.05%	393	No	165	93	3-Neck
10	Butyl acrylate	NaOAc	0.05%	393	Yes	1400	0	3-Neck
11	Butyl acrylate	NEt_3	0.05%	393	No	1400	27	3-Neck
12	Butyl acrylate	NEt_3	0.05%	393	Yes	1400	0	3-Neck

[a] Reactions conditions used 1.0 mmol aryl halide, 1.5 mmol alkene, 2 mmol base, 1.0 mmol DGDE (internal standard for GC), and 5 mL of DMF under argon atmosphere unless otherwise noted.

[b] Reactions using a 3-neck flask were under an atmosphere of argon using a Schlenk line and a mercury bubbler. Reactions under sealed conditions were inside a glass tube purged with argon and sealed with a Teflon-lined screw cap.

[c] Amounts used were 3.0 mmol bromoacetophenone, 4.5 mmol ethyl acrylate, 4.5 mmol KOAc, 1.0 mmol benzonitrile (internal standard for GC), and 5 mL of *N*-methyl-2-pyrrolidone, NMP [33].

3.2. Aryl bromide conversions

The previous results are strong evidence that Heck catalysis of aryl iodides from palladium immobilized on a mercaptopropyl surfaces is solely from leached palladium. This is consistent with the accumulated literature on Heck coupling [5]. However, when aryl bromides are substituted for aryl iodides, the effect on surface versus solution catalysis is less clear, especially when thiol-supported precatalysts are used. Previous works suggested possible heterogeneous catalysis from palladium immobilized on mercaptopropyl-modified surfaces for couplings between bromoacetophenone and either styrene [36] or ethyl acrylate [33] using inorganic bases instead of a soluble organic base. Conditions in which heterogeneous catalysis was suggested were replicated in this work, with the addition of using bare SH-SBA-15 as a selective poison (Table 2). Additional experiments were also conducted using the aryl bromide under the same conditions reported previously in this study for reactions involving iodobenzene (0.05% catalyst, DMF, NEt_3, butyl acrylate, 363 K). Without a poison present, Pd-SH-SBA-15 was an effective catalyst for the reactions listed in Table 2. Interestingly, in all cases in which SH-SBA-15 was added as a selective poison, little or no product formation was observed; confirming that activity observed for bromoacetophenone reactions was associated with leached palladium. Therefore, substituting an aryl bromide for an aryl iodide or substituting an organic base with an inorganic base does not appear to promote heterogeneous catalysis in this case.

Table 3
Results for Heck couplings of aryl halide with butyl acrylate[a] using various bases

Entry	Aryl halide	Base	Temperature (K)	SH-SBA-15	Time (min)	Conversion (%)
1	Iodobenzene	NEt_3	393	No	30	100
2	Iodobenzene	NaOAc	393	No	300	100
3	Iodobenzene	NaOAc	383	Yes	1600	0
4	Iodobenzene	NaOAc	383	No	285	95
5	Iodobenzene	NaOAc	363	No	270	31
					960	48
6[b]	Iodobenzene	NaOAc	363	No	300	37
					1600	93
7	Iodobenzene	MDA	393	No	30	97
8	Bromoacetophenone	MDA	393	No	530	0
9	Bromoacetophenone	KOAc	393	No	270	87

[a] Reaction conditions are 2.4 mmol aryl halide, 3.6 mmol butyl acrylate, 4.8 mmol base, 2.4 mmol DGDE (GC standard), and 5 mL DMF under argon atmosphere. Precatalyst is Pd-SH-SBA-15 (0.05%).

[b] 0.00125 mmol of homogeneous palladium acetate was substituted for Pd-SH-SBA-15.

3.3. Impact of the type of base

Comparing the activity under various conditions demonstrated that reactions using sodium acetate as the base produced a higher yield than comparable reactions using triethylamine (Table 2; entries 7, 9, and 11). To probe the effect of base on both leaching and activity, various bases were used, with iodobenzene and bromoacetophenone as the aryl halide and either palladium acetate or Pd-SH-SBA-15 as the catalyst (Table 3). The higher conversion of bromoacetophenone found when using sodium acetate instead of organic base was not observed for iodobenzene; instead, the opposite was true, with higher conversions achieved when NEt_3 rather than NaOAc was used as the base. Using methyl(dicyclohexyl)amine (MDA), a base previously described as more active for couplings involving activated aryl bromides [57], produced no activity with bromoacetophenone but significant activity for iodobenzene. Thus, the exact role of the base on activity is currently not clear with respect to leaching or stabilization of the leached catalytic species. In general, the use of inorganic bases instead of organic bases promotes bromoacetophenone activity but lowers iodobenzene activity. Changing the base does not promote heterogeneous catalysis; all SH-SBA-15 poisoning experiments

Table 4
Results from Heck[a] reactions of chloroacetophenone and Suzuki[b] reactions of chloroacetophenone and bromoacetophenone [36]

Entry	Aryl halide	Reaction	Catalyst loading	Base	Temperature (K)	SH-SBA-15	Time (h)	Conversion (%)
1	Chloroacetophenone	Heck	0.12%	NaOAc	393	No	48	0
2	Chloroacetophenone	Heck	1.00%	NaOAc	393	No	24	0
3	Chloroacetophenone	Suzuki	2.00%	K_2CO_3	353	No	24	50
4	Chloroacetophenone	Suzuki	2.00%	K_2CO_3	353	Yes	24	0
5	Bromoacetophenone	Suzuki	1.00%	K_2CO_3	353	No	8	100
6	Bromoacetophenone	Suzuki	1.00%	K_2CO_3	353	Yes	8	0

[a] Reactions conditions are 1.0 mmol chloroacetophenone, 1.5 mmol n-butyl acrylate, 2.0 mmol base, 1.0 mmol DGDE (internal standard), and 5 mL of DMF under argon atmosphere in a 3-neck flask.

[b] Reaction conditions are 1.0 mmol aryl halide, 1.5 mmol phenyl boronic acid, 2.0 mmol base, 0.5 mmol hexamethylbenzene, and 5 mL H_2O under argon atmosphere in sealed reaction tube.

resulted in no activity (Table 2; entries 2, 4, 6, 8, 10, and 12 and Table 3; entry 3).

3.4. Reinterpretation of literature regarding activated bromide reactions

In this work, all of the data strongly suggest that observed Heck catalysis is associated with leached palladium, which stands in contrast to interpretations based on previous compilations of data [33,36] (vide supra). A careful examination of these past works from the standpoint of metal leaching as the primary mode of catalysis leads to some alternative explanations for the previously observed behavior. For the Heck reaction of 4-bromoacetophenone with ethyl acrylate, Shimizu observed 0.01% palladium leaching and the appearance of 2–14 nm palladium nanoparticles. The formation of nanoparticles is consistent with palladium leaching from the surface, aggregation during the reaction on formation of Pd(0), and then redeposition back onto the surface. A hot filtration test was performed on the Pd-SH-FSM precatalyst, but the conditions were with 10 times less catalyst than normal reaction conditions (0.1% vs 1.0%). It is possible that a smaller total amount of palladium was leached, which was deactivated during the hot-filtration test (vide supra). A lack of observed activity could occur as a result of deactivation of soluble active palladium species [51]. The authors report conversions up to 95% within 2 h using a loading 0.0013 mol% of immobilized palladium, and after recycling for 5 times, the authors again were able to achieve around 95% conversion, but this time in about 8 h. The lower rate of recycling is consistent with increased metal leaching or deactivation of the catalyst by leaching and redeposition. Overall, the data from Shimizu can be reinterpreted from the standpoint of metal leaching as the primary or only catalytic mode. One major difference between the current study and the work of Shimizu is the use of SBA-15 instead of FSM-16 as the silica support, but given the similar surface characteristics, it is unlikely that this difference in support material would change whether the catalysis is occurring heterogeneously or homogeneously. The impact of the slight difference in the S:Pd ratios between the study by Shimizu (2.8) and the present study (1.7) is discussed in more detail later. To compare our conditions with Shimizu's conditions, select tests were also conducted with a material with a 2.6 S:Pd ratio in this work.

3.5. Aryl chloride conversions and Suzuki reactions

The ability to use aryl chlorides for Heck, Suzuki, and other aryl couplings is of strong interest because these molecules are commonly cheaper than analogous iodides or bromides. However, the carbon–chlorine bond is stronger and more difficult to activate. Many homogeneous palladium complexes have been found to catalyze Heck and Suzuki reactions of aryl chlorides, but these usually require specific combinations of ligands, base, and solvent [5,58]. Attempts to couple chloroacetophenone with n-butyl acrylate in the Heck reaction met with no success using Pd-SH-SBA-15 at either 0.05% or 1.0% loadings (Table 4). However, a Suzuki reaction with chloroacetophenone and phenyl boronic acid (5 mL water, 2.0 mol% catalyst, K_2CO_3, 353 K) after 24 h resulted in 50% conversion, and Suzuki couplings of bromoacetophenone (1 mol% catalyst) went to completion in 5 h. Like the work described above on Heck reactions, no activity was observed with additional SH-SBA-15 present as a poison in any case. Thus, Pd-SH-SBA-15 is suggested to act as a source of leached palladium for Suzuki reactions of aryl chlorides and bromides under these conditions, just as it did for Heck reactions of aryl iodides and bromides.

A series of selective poisoning experiments were conducted to both probe the effectiveness of other poisons for the Suzuki coupling of bromoacetophenone with phenyl boronic acid and to confirm the poisoning results of SH-SBA-15 (vide supra) (Table 5). Control reactions of homogeneous palladium acetate were compared with Pd-SH-SBA-15 and to palladium on carbon (Pd/C), which is a precatalyst known to operate by a leaching mechanism. Two solvents (DMF and H_2O) were used, and Suzuki couplings were carried out under normal reaction conditions. In addition to SH-SBA-15, two other poisons were tested, Quadrapure TU [9] and 3-mercaptopropyl-functionalized silica gel ($SH\text{-}SiO_2$). Previously, Quadrapure TU was used as a poison in high-temperature Heck reactions (90 and 110 °C) and extinguished all activity using carbon-supported precatalysts or supposedly "leach-proof" Pd-EnCat [9]. Interestingly, for most of the tests with Quadrapure TU, some activity was observed for all three precatalysts, although this activity was significantly lower than that without the addition of Quadrapure TU. We attribute this finding to two primary phenomena. First, a small amount of activity was observed at room temperature before submersion into an 80 °C oil bath. Quadrapure TU is an or-

Table 5
Results from selective poisoning of different palladium precatalysts for Suzuki[a] reactions of bromoacetophenone with phenylboronic acid

Precatalyst	Solvent	Time (h)	Conversion with poison			
			None	SH-SBA-15	Quadrapure TU	SH–SiO_2
$Pd(OAc)_2$	DMF	6	100	0	0, 20	0
	H_2O	6	100	0	20	0
Pd-SH-SBA-15	DMF	6	94	0	6	0
		8	100	0	–	–
	H_2O	6	80	0	30	0
Pd-C	DMF	6	48	0	0	0
	H_2O	6	76	0	–	–

[a] Reaction conditions are 1.0 mmol bromoacetophenone, 1.5 mmol phenylboronic acid, 2.0 mmol K_2CO_3, 0.5 mmol internal standard (hexamethylbenzene for H_2O and DGDE for DMF), 1.0% catalyst, and 5 mL solvent under argon atmosphere in sealed reaction tube. The molar ratio of poison to palladium was 35 for all poisons.

ganic polymer resin that requires swelling of the pore structure to increase access of poisoning sites to solubilized palladium. Therefore, observed activity could be due to soluble palladium catalysis before the polymer sufficiently swelled sufficiently to allow Pd diffusion into the polymer matrix. Second, when water is used as the solvent, the bromoacetophenone melts, creating a separate organic liquid phase that forms a small globule. Most of the Pd-SH-SBA-15-based particles were observed to preferentially collect inside the bromoacetophenone globule whereas the Quadrapure TU beads (average particle size ∼500 µm) were suspended in the water or stuck to the outer surface of the organic phase. Under these conditions, the diffusion of palladium from the Pd-SH-SBA to the Quadrapure TU may be further hampered, thereby allowing some catalysis to occur. Thus, under these conditions, application of Quadrapure TU as a poison is not ideal. Indeed, choosing the proper solid poison to assess catalysis requires forethought and sometimes screening, and ambiguous or marginal information may be obtained in some cases. For example, when using supported precatalysts that are soluble under reaction conditions (e.g., polymer-supported precatalysts), solid-phase poisons such as Quadrapure TU may give ambiguous results [27,59]. However, in this work, no activity was observed with all tests using SH-SBA-15 or SH-SiO_2, confirming the selective poisoning ability of tethered thiols and indicating that the catalysis occurring without the presence of tethered poisons is associated with leached metal.

3.6. Reinterpretation of literature regarding activated bromide reactions

Crudden used a number of techniques to assess the heterogeneity of the Suzuki reactions catalyzed using mercaptopropyl-functionalized silica-supported palladium precatalysts. One of these was a hot-filtration test on a Suzuki coupling of bromoacetophenone with phenylboronic acid. When care was taken to charge the filtrate with fresh base and phenylboronic acid, an increase in conversion from 12 to 17% was observed in the filtrate. This was interpreted as evidence that some leached species were present, but that these were responsible for only a small amount of the catalysis occurring, with most attributable to heterogeneous catalysis. As noted above, the marginal increase in conversion after filtration also could be a reflection of the relatively small amount of solubilized palladium that survived the hot-filtration process. A test using a trace amount of soluble catalyst (0.5 ppm of palladium acetate; 0.00023 mol% catalyst) resulted in <5% conversion, leading to the conclusion that small amounts of solubilized palladium could not account for the observed activity for Pd-SH-SBA-15 [36]. The strongest evidence for heterogeneous catalysis came from the use of the three-phase test in which soluble aryl bromides were reacted to a much greater extent than immobilized aryl bromides. Combining all these previous data, the conclusion that some heterogeneous catalysis was occurring appeared reasonable.

Our observation that addition of bare, unmetalated porous mercaptopropyl-modified support completely suppressed catalysis in both Heck and Suzuki reactions brings new data to be considered. These data can best be interpreted by the hypothesis that leached, soluble palladium plays a key role in the catalysis. Like all other ligand–metal complexes, there exists an equilibrium between bound and free metal species in solution. Based on the results presented here, alkyl–thiol groups bind Pd more strongly than pyridyl groups, and thus the mercaptopropyl-modified support is effective in significantly limiting the amount of soluble species that are in solution. One hypothesis explaining the combined data is that solely leached palladium species are active for the observed coupling reactions. This is the most likely explanation for the data in our assessment, because it is consistent with the literature [5]. An alternate hypothesis is that only traces of palladium at defect sites on the surface are active, and these species are more likely to leach than most of the other sites. Thus, the addition of solid poison captures these species as they leach into solution, removing them from the solid precatalyst and rendering it inactive. In the context of the current catalyst system, one might envision palladium species bound to a single thiol as more likely to leach (and perhaps be active on the solid surface), whereas species bound by two or more thiol ligands are inactive and less likely to leach. This latter hypothesis seems less likely, because addition of a solid poison at a midpoint of a reaction should not result in instantaneous deactivation of active solid supported species. Instantaneous deactivation is most consistent with all of the catalysis being associated with reactions promoted by soluble catalytic species (Fig. 6c). The trend of increased deactivation with an increasing amount of excess surface thiol on partially metalated surfaces supports the notion that in the presence of sufficient bare, accessible thiol, all palladium species can be overcoordinated and thus be unavailable for leaching and catalysis.

Can the previously reported data suggesting heterogeneous catalysis [36] be rationalized in light of these new results? Both the filtration test and three-phase test data were used to suggest catalysis by solid-supported species. We suggest that a positive result for each test—observations of activity in the filtrate after filtration of a solid precatalyst and of conversion of solid-bound reactants in the three-phase test—can serve as definitive evidence of some leaching of catalytic species when no background reaction exists. But in our opinion, the negative of each test is potentially ambiguous when applied to palladium-catalyzed coupling reactions. As noted above and in previous work [5,9], the competing rates of palladium deactivation, redeposition, and aggregation all can influence the clarity of these tests. For example, both the filtration and three-phase tests gave results suggesting limited (but not zero) solution-phase activity in past studies of Suzuki couplings of bromoacetophenone [36]. In the three-phase test using bromoacetophenone, the soluble bromoacetophenone was at 50% conversion, whereas only 3% of the supported aryl bromide was converted after 5 h. Increasing the reaction time to 13 h increased the soluble component yield to 97% and the immobilized yield to 7%. Combined with the observation that a trace amount of soluble catalyst (0.5 ppm of palladium acetate; 0.00023 mol% catalyst) resulted in <5% conversion of bromoacetophenone in a Suzuki coupling, it was suggested that small amounts of solubilized palladium could not account for the observed activity for Pd-SH-SBA-15. Furthermore, in a three-phase test using soluble chloroacetophenone, after 24 h, the yield of soluble aryl chloride was 80% and no conversion of the tethered chloride was observed. Thus, it was suggested that heterogeneous sites were responsible for the aryl chloride activity. However, this analysis based on previous data needs to be reexamined in light of our new results. The earlier analysis neglects the role that the immobilization of palladium plays in both protecting palladium from aggregation and controlling how palladium is released into solution (e.g., at what rate, what temperature), making the trace soluble $Pd(OAc)_2$ test difficult to compare with reactions using immobilized palladium. If the palladium leached from Pd-SH-SBA-15 is from oxidative addition of aryl halide, then the initial homogeneous source of Pd(II) into solution will be different from homogeneous palladium acetate, which is important with respect to reduction and deactivation pathways. Also, it is possible that the trace amount of homogeneous palladium acetate was deactivated during the heating of the reaction solution before catalysis could occur, whereas in an immobilized state, the palladium might remain dormant until the temperature is high enough to promote both the controlled leaching and subsequent catalysis. In addition, this analysis does not consider the role that tethering of a reactant in the three-phase test plays on its reactivity.

The ability of aryl halides to stabilize solubilized palladium increases according to the ease of oxidative addition (I > Br > Cl). With regards to the three-phase test, the ease of oxidative addition and the availability of aryl bromide may play a crucial role not only in promoting leaching, but also in preventing palladium deactivation and in inhibiting redeposition. In addition, the rate of reaction of supported aryl halide may be significantly slower than the homogeneous counterpart for steric reasons. As noted by Crudden, the aryl bromide conversion data show quite clearly that there is at least some active leached metal. The rise in yield of supported aryl halide with time could alternatively be suggestive of a slow rate of reaction resulting from its immobilization on surface. Unfavorable competition for the small amount of homogeneous palladium between soluble and supported aryl halide could slow the reaction of the immobilized reagent until most of the soluble boronic acid component is consumed by both Suzuki coupling and self-coupling, but even then the palladium could be inaccessible due to Pd–Pd agglomeration or redeposition. Therefore, whereas the three-phase data clearly show the presence of leached, active palladium, they do not conclusively show, in our eyes, that most of catalysis is occurring on the surface. As demonstrated in this study, the ability of SH-SBA-15 to poison catalysis under similar conditions provides strong evidence that the catalysis of the soluble component is more consistently interpreted, in light of the combined data of Shimizu, Crudden, Davis and the present work, as resulting from leached palladium.

3.7. *Effect of S:Pd ratio on activity*

One additional variable warranting investigation is the role of the S:Pd ratio. Previous reports have suggested that this ratio is important to the observed reactivity when using solid precatalysts. In 1988, Wang and Liu reported their findings that macromolecular palladium chelates exhibited no activity in the Heck coupling of iodobenzene with ethyl acrylate when a S:Pd ratio of $\geqslant 6$ was used [29]. Reducing the ratio to 3:1 produced a moderate increase in activity, and further reduction to 2:1 gave the highest yields. These findings highlight the importance of the S:Pd ratio for catalyst activity and demonstrate that overcoordination by sulfur can slow or quench catalysis. It is important to note that these ligands were first complexed to palladium before immobilization and thus do not provide any insight into how immobilized thiols coordinate to free palladium.

In 2005, Crudden synthesized two different mercaptopropyl-modified SBA-15 supports. The first of these was made by post-grafting the mercaptopropyltrialkoxysilane with the preformed SBA-15. Out of 10 batches, only 3 exhibited any level of catalytic activity. Reasons for the lack of activity were not known at that time. The S:Pd ratio was not reported, but, based on the reported thiol loading and assuming that all available palladium acetate was bound to the surface during metalation, a ratio of 8.8 was calculated. A possible explanation for the lack of activity is that the large excess of available sulfur sites could conceivably bind leached palladium (or prevent any leaching) and self-quenches the catalysis. Indeed, when we reduced our palladium content of Pd-SH-SBA-15 from 11.06 wt% (S:Pd = 1.7) to 8.45 wt% (S:Pd = 2.6) and 4.6 wt% (S:Pd = 5.3) we observed a decrease in the Heck coupling of bromoacetophenone with butyl acrylate with each successive increase in the S:Pd ratio (Table 6). For the Heck coupling of iodobenzene, an increase in S:Pd ratio from 1.8 to 5.3 resulted in a small amount of Heck coupling of iodobenzene for one run (22% after 1300 min) and no activity for two replicates (standard conditions) (Table 6). This catalyst also was inactive for a Heck coupling of bromoacetophenone with *n*-butyl acrylate (standard conditions with data taken to 24 h). Decreases in activity resulting from increases in the S:Pd ratio were also observed for Suzuki reactions of bromoacetophenone and phenylboronic acid. To probe the maximum capacity of SH-SBA-15 to quench catalysis by homogeneous palladium acetate, a reaction was performed in

Table 6
Effect of S:Pd ratio on activity of Pd-SH-SBA-15 precatalysts[a]

S:Pd	Halide	Reaction	Solvent	Conversion (%)	Time (min)
1.8	Iodobenzene	Heck	DMF	100	130
	Bromoacetophenone	Heck	DMF	93	165
	Bromoacetophenone	Suzuki	DMF	100	480
	Bromoacetophenone	Suzuki	H_2O	80	360
2.6[b]	Bromoacetophenone	Heck	DMF	14	1130
	Bromoacetophenone	Suzuki	DMF	42	360
	Bromoacetophenone	Suzuki	H_2O	31	360
5.3	Iodobenzene	Heck	DMF	0, 0, 22	1300
	Bromoacetophenone	Heck	DMF	0	1440

[a] Experiments conducted under normal Heck and Suzuki reaction conditions.
[b] Addition of 35 equivalents of SH-SBA-15 poison resulted in no activity under similar Heck and Suzuki conditions when using a Pd-SH-SBA-15 precatalyst with a S:Pd ratio of 2.6.

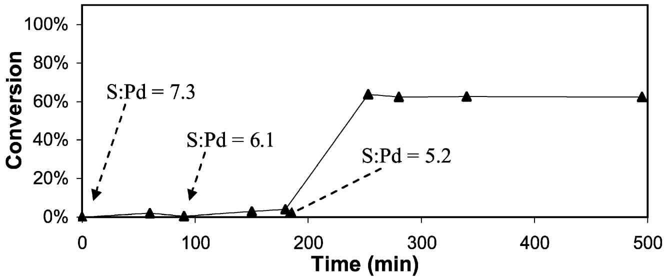


Fig. 7. Plot of iodobenzene conversion (DMF, 90 °C, NEt_3) with SH-SBA-15 used as a poison with a 0.1 mL dose of 0.063 mmol/L of $Pd(OAc)_2$ in DMF added at time zero (S:Pd = 7.3) followed by additions of 0.02 mL added at 90 min (S:Pd = 6.1) and 180 min (S:Pd = 5.2).

which palladium acetate was dosed into a reaction containing SH-SBA-15 (Fig. 7). Activity was not observed until the S:Pd ratio was decreased to 5.2, after which rapid conversion followed by a quenching of catalysis was observed. This cessation is likely a reflection of the rate at which the partially metalated SH-SBA-15 is able to bind additional palladium against the rate of catalysis by the unbound palladium.

3.8. *Utility of Pd-SH-SBA-15 as a practical Heck and Suzuki precatalyst*

Although these new data suggesting catalysis by leached species speak to nature of the true catalytic species, they do not address the functional utility of these precatalysts. The previous data on Suzuki couplings promoted by catalysts of this type strongly suggest that the amount of palladium in solution after reaction is quite small. Shimizu found that after reaction, the palladium levels in solution for Pd-SH-FSM were 0.5 ppm for Suzuki reactions and 0.1 ppm for Heck reactions of activated bromides [33]. Crudden reported that for Suzuki reactions using Pd-SH-SBA-15, the palladium leaching levels ranged from 0.003 to 0.75 ppm, depending on reaction conditions, and that for Heck coupling of bromoacetophenone with styrene, the palladium in solution was 0.27 ppm [36]. However, the total amount of palladium leached was generally <0.2 ppm at a S:Pd ratio of 2:1. Another recent report also suggests that only traces of palladium remained in solution after reaction [60]. These low levels of palladium leaching suggest that either the leached species are very active (i.e., if all conversions are catalyzed by the amount of palladium in solution after the reaction), or that a redeposition process is at play, whereby larger amounts of leached palladium are active during reaction, with some or most of the palladium redepositing on the SH-SBA-15 surface after reaction. After recovery, this redeposited palladium may be available for further reaction, as was similarly found for other immobilized palladium precatalysts [16,52,61,62]. However, if the S:Pd ratio is >2:1, then palladium capture and overcoordination by excess surface thiols may result in a partial or complete deactivation of catalysts, as was observed for partially metalated SH-SBA-15 surfaces (vide supra). Either way, the amount of palladium in the products after reaction appears to be sufficient to make the precatalyst useful for producing nearly palladium-free Heck and Suzuki coupling products.

A very recent report[1] of thiol-supported palladium precatalysts also suggests only traces of palladium are found in solution after reaction [63]. Although the nature of the true catalytic species was not addressed in this work, our results presented here strongly suggest that this system also is simply a precatalyst that liberates soluble catalytic species in solution.

4. Conclusion

In summary, a mercaptopropyl-modified mesoporous silica, SH-SBA-15, was successfully synthesized and used as a solid support for immobilization of palladium acetate, Pd-SH-SBA-15. The metalated material was used as a catalyst for both Heck and Suzuki reactions under a range of conditions. Metal-free SH-SBA-15 was shown to be an effective poison of both homogeneous palladium acetate and Pd-SH-SBA-15 used as precatalysts for Heck and Suzuki reactions. Therefore, we assert Pd-SH-SBA-15 is simply a reservoir of leached palladium, which is in agreement with previous findings by Davis et al. [40] with regard to Heck reactions using iodobenzene and suggests that previous analysis of heterogeneous catalysis with these precatalysts in Heck and Suzuki couplings may need to be reinterpreted in light of the new data presented here [33,36].

This work introduces SH-SBA-15 as a new selective poison for elucidating solution versus surface catalysis by palladium and demonstrates its use as a more effective and versatile poison than poly(4-vinylpyridine) and Quadrapure TU. Thus, selective poisons tethered onto silica substrates, such as SH-SBA-15 and SH–SiO_2, are a better class of materials for the selective poisoning of palladium than are poisons tethered to insoluble organic

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[1] Note that the authors measured palladium solution content after passing the reaction solution through celite, washing with water, which was discarded, and drying the organic with $MgSO_4$. This procedure was most likely chosen to mimic procedures used in the pharmaceutical industry and thus gives a good representation of how much metal contamination would be found in the organic product stream. However, the used workup procedures could have removed a significant amount of soluble metal from the reaction solution through deposition of palladium metal on celite and dissolution in the aqueous phase. Thus palladium levels of the final workup are not reflective of palladium levels in the final reaction solution.

polymers. The ability of insoluble, selective poisons to poison homogeneous palladium is dependent on the ratio of binding sites to soluble palladium. Therefore, control reactions in which known amounts of homogeneous palladium complexes are poisoned should be performed first to (i) verify poisoning ability and (ii) determine the proper amount of selective poison required to quench catalysis if all available immobilized Pd were to leach into solution. The three-phase test can provide positive confirmation of catalysis from leached Pd, but lack of activity may not confirm strictly heterogeneous catalysis. Quenching of palladium-catalyzed reactions by SH-SBA-15 suggests that the active catalyst comprises at most a few atoms of palladium and reactivity is not from catalysis on palladium nanoparticle surfaces.

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