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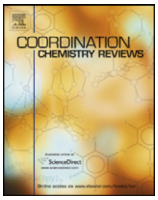

Review

Silica-supported palladium: Sustainable catalysts for cross-coupling reactions☆

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ABSTRACT

Heterogeneous palladium (Pd) catalyst systems are among the most widely used for the formation of carbon–carbon and carbon–nitrogen bonds. The majority of the novel heterogeneous catalysts are based on silica supports, primarily because silica displays some advantageous properties, such as excellent stability (chemical and thermal), good accessibility and porosity, and the fact that organic groups can be robustly anchored to the surface to provide catalytic centers. This review aims to give insight into the state of art in the field of the synthesis and the application of silica-supported Pd catalysts in carbon–carbon and carbon–nitrogen coupling reactions.

1. Introduction

The emergence of the chemistry of transition metals in the 1960s has profoundly changed the science of organic synthesis. Used in catalytic or stoichiometric quantities, these metals have provided exceptional gizmo for the development of countless synthetic protocols, with superb reactivity and selectivity. Palladium is a transition metal which offers excellent opportunities for catalytic reactions. Many Pd-catalyzed reactions were developed over the past three decades and the growing number of scientific publications in this area shows its high demand. There are two main reasons for the growing interest in this field. The first is that this catalyst system provides a simple and practicable method for creating carbon–carbon and carbon–nitrogen bonds under sustainable conditions with excellent yield, and at the same time, due to mild reaction conditions, it is highly tolerable by many func-

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☆ This article is dedicated to the memory of El Wacham Thami, admirable grandfather and an irreplaceable person.

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tional groups, which bodes well for the total synthesis of complex drug molecules, wherein it is required to selectively couple the molecules at specific positions without affecting other functional groups. Heck, Suzuki, Sonogashira, Stille, and Buchwald–Hartwig are among the predominantly used reactions that are catalyzed by Pd. These reactions were mostly carried out by homogeneous catalytic systems, because of their high reactivity, high turnover numbers, milder reaction conditions, and notably the possibility of coupling of the widely available and low-cost aryl chlorides [1]. However, the efficient separation and subsequent recycling of homogeneous transition metal catalysts remains a scientific challenge and an aspect of economical relevance. One of the best ways to overcome this problem is the use of heterogeneous catalysis, because of profound advantages of straightforward recovery and reuse of the catalyst from the reaction mixture by simple filtration, decantation, and recently by magnetic altercations [2]. Simplification of workup protocols and handling of catalysts is an especially important factor for industrial applications of catalysts. Importantly, without any further purification, these leach-proof catalysts leave no remnants of metal in the end product, since metal contamination is highly regulated by the pharmaceutical industry.

Palladium can be immobilized on several solid supports such as organic polymers [3,125], layered clays [4], and activated carbon [5]. However, silica as a solid support is the choice of everyone, because of its wide accessibility, excellent stability, porosity, and the fact that organic groups can be robustly anchored to its surface to generate catalytic sites [6]. The present review aims to describe the performances of silica-supported Pd catalysts in various cross-coupling reactions.

2. Silica-supported palladium catalysts for carbon–carbon bond formation

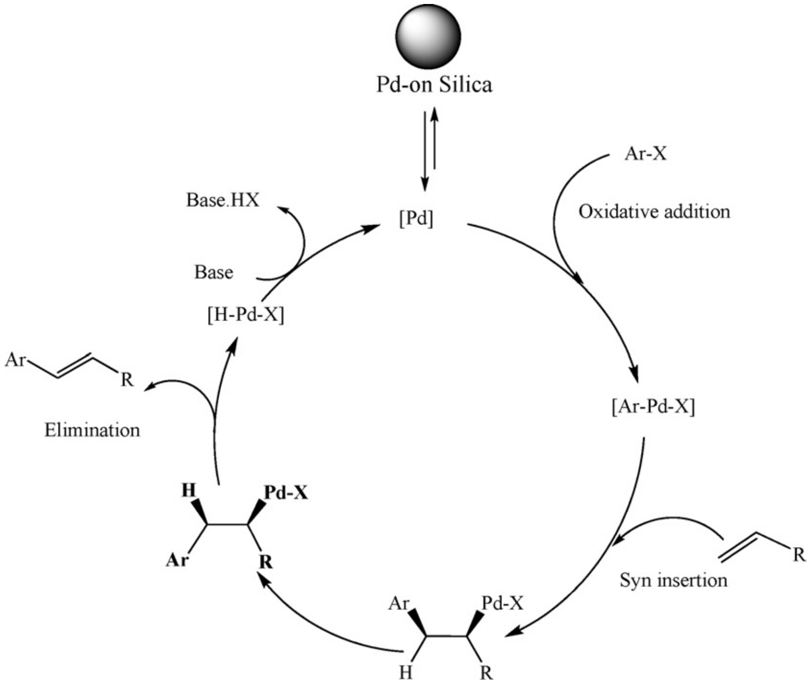
2.1. Heck reactions

The Heck reaction is one of the most noteworthy and comprehensively used reactions for the formation of carbon–carbon bonds, which allows the arylation, alkylation, or vinylation of various alkenes by their coupling with aryl halides [7,8]. Heck-type reaction was first developed by Mizoroki et al. [9] and Heck and Nolly [10]. Because of the simplicity and high reactivity of this protocol, it has been used for a wide range of functional groups. There are many examples of utilization of this method on an industrial level for fine chemical synthesis [11]. Academic and industrial interest in this reaction has increased in recent years, because of its tolerance for almost any solvent and functional group on the substrates, its high selectivity, and its moderate toxicity [11,12].

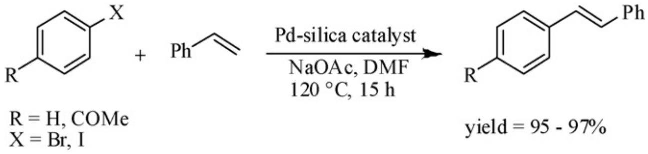
The typical catalytic cycle of the Heck reaction involves a postulated molecular, homogeneous Pd catalyst that cycles between the Pd^0 and Pd^{II} oxidation states during the course of the catalytic reaction [13]. Silica-supported Pd catalyst also works similarly (Scheme 1) [14]. In the first step, catalytically active soluble Pd complexes are formed by the coordination with the polar reaction solvent and base. Afterwards, oxidative addition of aryl halide (Ar–X) to these Pd complexes occurs to yield [Ar–Pd–X], which subsequently complexes with CH_2=CHR. After addition of Ar–Pd across C=C and β-hydrogen elimination, ArCH=CHR and BH^+X^- are produced and Pd^0 is regenerated, which then deposits back on to the surface of the support (re-deposition).

A variety of Pd complexes supported on silica, such as Pd(II)–pincer complexes [15], Pd(II)–schiff-base complexes [16], Pd(II)–carbometallated palladacycle [17] complexes, Pd(II)-nonsymmetrical salen-type coordination complexes [18], Pd(II)-thiol and Os-cinchona alkaloid complexes [19], have been reported, which catalyze Heck reaction excellently with negligible Pd leaching [20]. Other materials such as functionalized silica-Pd, sol–gel entrapped Pd, Pd nanoparticles in silica, and ionic liquid-coated Pd in silica, also showed high catalytic activity for Heck reactions [21]. This part focuses on some of the recently developed important silica-supported Pd catalysts for Heck reaction.

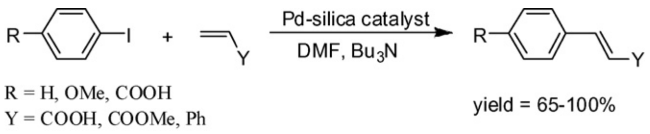
Jana et al. reported Pd(0) immobilized into the silica-based mesoporous material to develop catalyst Pd(0)-MCM-41, which was highly active in C—C coupling reactions. $[Pd(NH_3)_4]^{2+}$ ions have been incorporated into the mesoporous material during synthe-



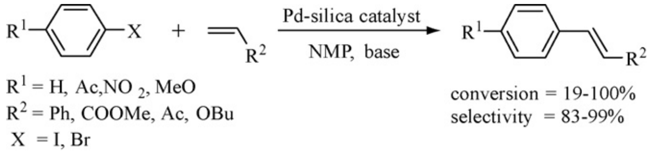
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 6.

sis of MCM-41 and subsequently upon treatment with hydrazine hydrate. Pd(0)-MCM-41 showed high catalytic activity toward C—C bond formation reactions like Heck and Sonogashira coupling, with high TONs. This catalyst was also efficient in the activation of aryl chloride to give impressive conversion in cross-coupling reactions under mild conditions [22].

Mercaptopropyl-modified SBA-15 Pd-encapsulated material was used by Crudden et al. as a catalyst for the Heck reactions, with negligible Pd leaching (Scheme 2) [23]. Even after using loadings as high as 2%, only 3 ppb of Pd were observed in solution, accounting for only 0.001% of the added catalyst. Most amazingly, heterogeneity tests including hot filtration tests and a three-phase test have demonstrated that the catalysis occurs on the surfaces as well as in the pores of the silicate.

A series of polymeric amine–Pd(0) complexes have been prepared from organic silica via immobilization on fumed silica, and showed high activity for Heck arylation of aryl iodides and conjugated alkenes (Scheme 3). A variety of substituted products were obtained in high yields [24].

High catalytic activities, selectivities, and stabilities have been reported in the Heck reaction catalyzed by pyridine-functionalized silica-supported Pd catalysts; for example, Pd complexes immobilized on silica functionalized with acetylpyridines are active and stable catalysts in the Heck reaction of iodobenzene with ethyl acrylate, as well as in the carbonylation of iodobenzene [25]. Clark et al. have also reported C—C coupling of iodobenzene using pyridinium–Pd complexes immobilized on MCM-41 with a minimal level of Pd leaching and TONs of around 2000 mmol of methyl cinnamate/mmol Pd in the fifth cycle [26].

Sugi and co-workers prepared Pd complexes immobilized on pyridine–carboimine and quinoline–carboimine-functionalized mesoporous FSM-16 [27]. These immobilized complexes can be sufficiently applied for the Heck vinylation and even for the Suzuki coupling of aryl bromides as active and re-usable catalysts with minimal leaching of Pd species into solution and with stability at higher reaction temperatures. Using quinoline–carboimine as ligand can offer higher conversions than pyridine–carboimine. Molnar and co-workers prepared sol–gel entrapped Pd-silica catalyst, which was generated via simultaneous self-assembling of mesoporous MCM-41 silica and Pd-particle generation [28]. Three different catalysts with varying Pd loadings were prepared and these catalysts showed high activity and selectivity in the Heck coupling reactions of iodo and bromoarenes. In most of the reactions, complete *E* selectivity was observed, whereas in the transformations of styrene, products of α-coupling were found (Scheme 4).

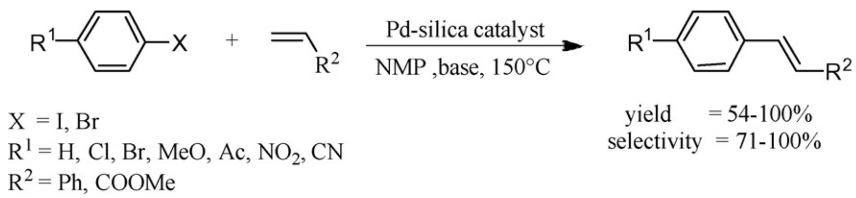
A silica-ethylthioglycolate material (Scheme 5), which readily binds with Pd, was prepared and tested for Heck reactions. The materials showed high catalytic activity and recyclability, with no evidence of Pd leaching [29].

Various other supported catalysts using trichlorosilane, dichloromethylsilane, chlorodimethylsilane, dichlorophenylsilane or chlorodiphenylsilane have been prepared. These Pd-on-silica catalysts were applied in the reaction of iodo and bromoarenes with styrene and aliphatic vinylic compounds (Scheme 6) [30].

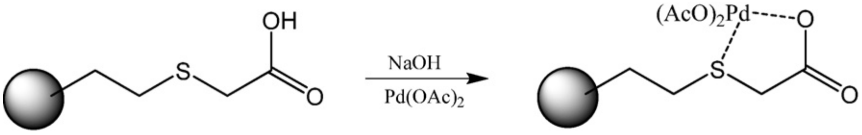
All catalysts proved to be active in the Heck coupling. The conversion values were between 19 and 100%, whereas the selectivities were found to be in the range 83–99%. It was noteworthy that even less reactive activated bromoarenes, such as *p*-bromoacetophenone and *p*-bromonitrobenzene, reacted satisfactorily with methyl acrylate. Bromobenzene and chlorobenzene, in turn, did not react. Moreover, the highly selective formation of the corresponding *E* isomers was characteristic in all cases. The catalyst was re-used 20 times without any loss of activity.

Blum and co-workers also employed a sol–gel entrapped version of the $PdCl_2(PPh_3)_2$ catalyst for the Heck coupling process. This heterogeneous catalyst is characterized by extremely simple preparation. It is a completely leach-proof, highly porous material (typical N_2-BET surface areas of 490 $m^2 g^{-1}$, and average pore diameters of 27 Å) and is air stable for many months [31].

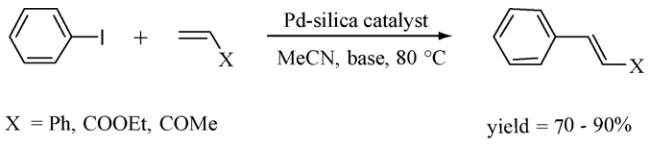
Assortment of nanocomposite silica aerogels were synthesized using anhydrous $Pd(acac)_2$ as the metal source and tetraethoxysilane as the silica source, with no reduction step required to obtain



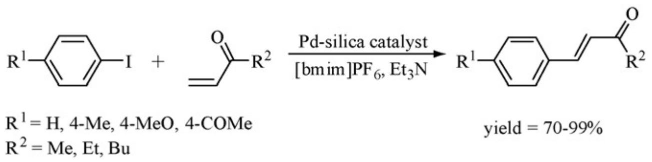
Scheme 4.



Scheme 5.



Scheme 7.



Scheme 10.

metallic particles of Pd(0). The silica wet gels were prepared in a two-step, acid-base-catalyzed sol–gel process and then impregnation of the wet gels. As-synthesized matrix catalyzes the Heck reaction with good 70–90% yield (Scheme 7) [32].

Kim et al. also prepared the silica gel entrapping Pd nanoparticles through a two-step procedure by heating a mixture of $Pd(PPh_3)_4$, tetra(ethylene glycol), and $Si(OMe)_4$ and treating the resulting black suspension with water. Washing and drying the resulting gel gave a grey powder that was used as the catalyst in the Heck reaction [33]. Pd nanoparticles were also supported on fluorinated silica hybrid material, by sol–gel process. This material showed high catalytic activity for Heck coupling reaction under microwave irradiation (Scheme 8). Recycling studies have shown that the catalyst can be readily recovered and reused several times without significant loss of activity [34].

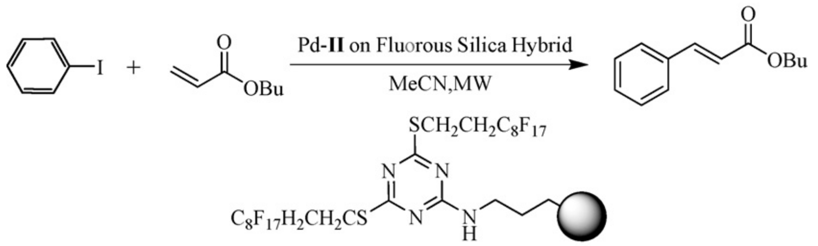
The immobilization of phosphine-free perfluoro-tagged Pd nanoparticles on fluorous silica gel showed high catalytic activity for Heck reactions, with high yields of vinylic substitution products (Scheme 9). This solid-supported Pd catalyst can be readily recovered and reused several times without significant loss of activity. Interestingly, reactions can be carried out in the presence of air, without any specific precaution [35].

Yokoyama and co-workers reported high conversions of the Heck reactions in ionic liquid $[bmim]PF_6$ (bmim = *N*-butyl *N*-methyl imidazole) with $Pd(II)/SiO_2$ catalyst in absence of any ligands, with yields from 70 to 99% (Scheme 10) [36].

Pd catalyst in an ionic liquid in silica pores was also synthesized by Suzuki and co-workers and investigated for Heck reactions with high efficiency and recyclability. Immobilization of the Pd catalyst on silica with the aid of an ionic liquid is pretty simple and involves a suspension of spherical amorphous silica in a solution of $Pd(OAc)_2$ in $[bmim]PF_6$ and THF, which was then evaporated to dryness to afford a free-flowing immobilized solid catalyst [37]. Among the ionic liquids tested, $[bmim]PF_6$ was better at holding $Pd(OAc)_2$ than [bmim]Br, $[bmim](CF_3SO_2)_2N$, or $[hmim]PF_6$ (hmim = *N*-hexyl *N*-methyl imidazole). To prevent removal of the ionic liquid layer from the silica, the Heck reaction was carried out in a hydrocarbon solvent. Reuse of the catalyst was difficult in hot toluene, due to the solubility of the ionic liquid. A decrease of the catalytic activity was observed after three cycles, during which the free-flowing nature of the catalyst was also lost.

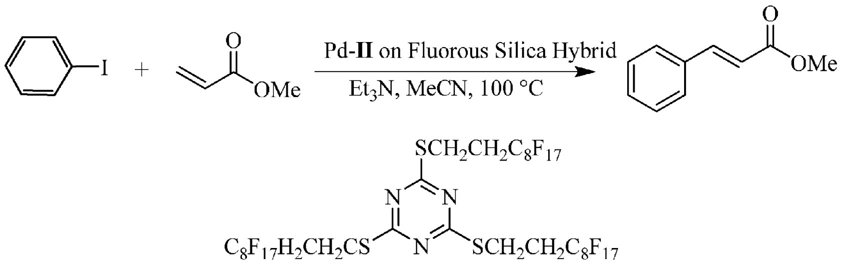
These reactions were also carried out in water as a solvent (Scheme 11) [38]. The major advantage in carrying out the reaction in water is its non-flammable, inexpensive, and non-toxic nature [39]. Other advantages are the high cohesive energy density, high dielectric constant and high internal pressure, which facilitate bimolecular reactions involving ionic intermediates. Furthermore, the use of a heterogeneous catalyst is expected to increase the Heck reaction rates by adsorption of substrates on the catalyst. Compared to the reaction in dodecane, the reaction was apparently accelerated in water, since it was completed at a lower temperature and in a shorter period of time [38].

An effort to recycle the catalyst, resulted in the removal of the ionic liquid layer from the silica gel into water, resulting in leaching of the Pd. Water entered between the ionic liquid layer and the silica gel surface, may be due to the hydrophilic nature of the latter. This concern was overcome by the immobilization of $Pd(OAc)_2$ on reversed-phase silica gels, among which hexylated (HEX), aminopropylated (NAP), and *N*,*N*-diethylaminopropylated silica gel (NDEAP) were employed (Scheme 12). These silica gels were obtained by grafting with the corresponding silane coupling reagents. $Pd(OAc)_2$ was successfully immobilized on each of the



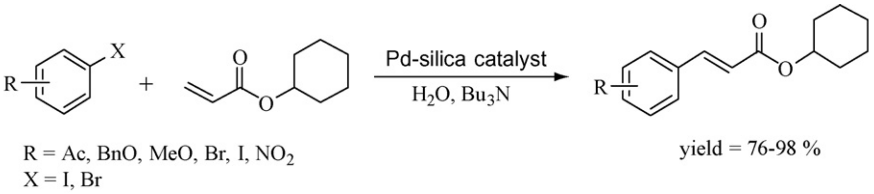
(II)

Scheme 8.

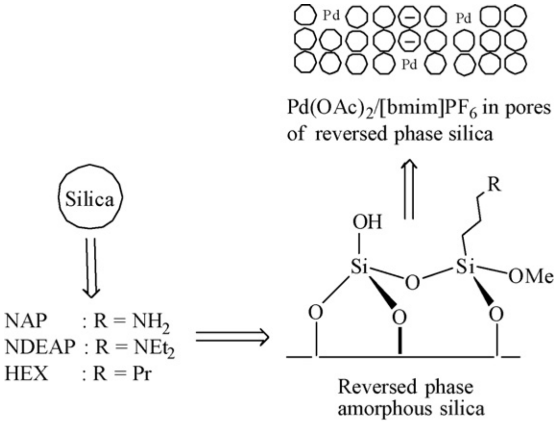


(I)

Scheme 9.



Scheme 11.



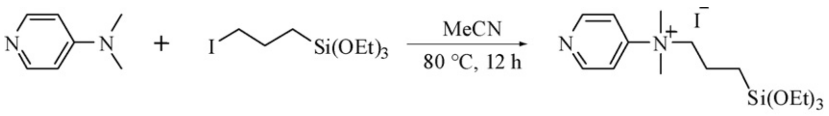
Scheme 12.

reversed-phase silica gels, except HEX, with the aid of $[bmim]PF_6$. The reactivity of these immobilized catalysts was tested in the reaction of iodobenzene and cyclohexyl acrylate. The reaction was sluggish, as compared to the catalyst immobilized on normal phase silica gel, and exhibited a highly recyclable nature and a remarkably high TON and turnover frequency (TOF) [38].

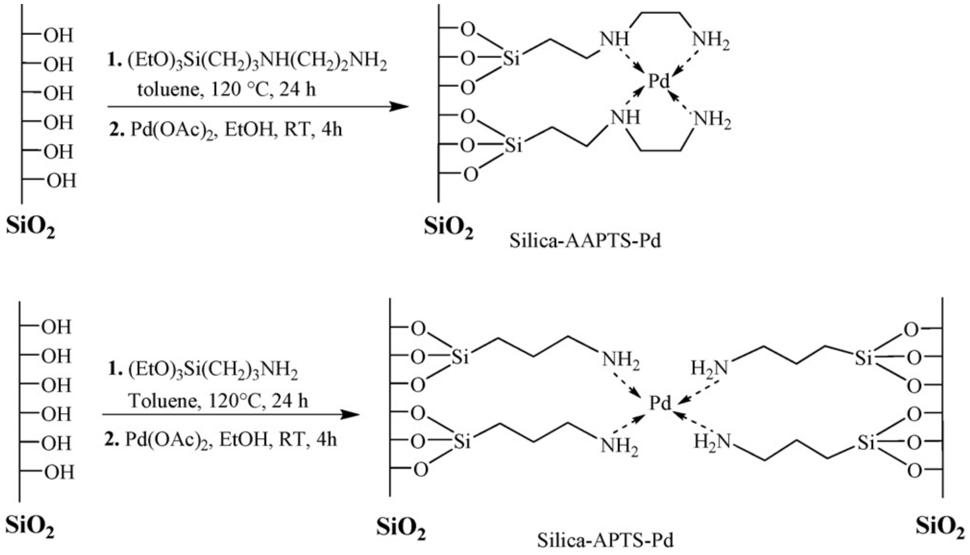
Polshettiwar, Hesemann and Moreau also prepared $Pd(OAc)_2$ encapsulated in nanostructured hybrid silica with a well-defined pyridine binding site via an ionic liquid templated sol–gel nanocasting technique for Heck and Sonogashira reactions. The organic sol–gel precursor was synthesized by refluxing 4-*N*,*N*-dimethylaminopyridine and 3-iodopropyltriethoxy-silane in a Schlenk tube, under an inert atmosphere. Notably, the reaction yielded only the ammonium salt, keeping the pyridine site intact, which was efficiently utilized for complexation with $Pd(OAc)_2$ (Scheme 13) [40].

The synthesized silica was mesoporous material with nanostructured morphology, functionalized with pyridine binding sites covalently linked to the silica support. Material showed excellent activity as a heterogeneous catalyst in Heck reaction of various aryl iodides and bromides, in addition to Sonogashira and cyanation reactions [40].

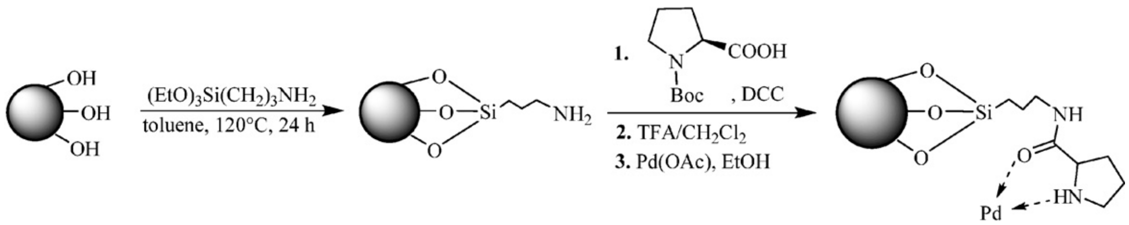
Wang and co-workers anchored palladium on organic–inorganic hybrid silica [41,42]. They prepared three different catalyst systems, first two of which was prepared in two-step procedures. The silica gel was treated with {3-[(2-aminoethyl)amino]propyl}-triethoxysilane (AAPTS) or (3-aminopropyl)triethoxysilane (APTS) and refluxed in dry toluene at 120 °C for 24 h to afford the [3-(2-aminoethyl)amino]propyl-functionalized silica gel (silica-AAPTS) or 3-aminopropyl-functionalized silica gel (silica-APTS) (Scheme 14). As-synthesized materials later reacted with palladium acetate to generate the corresponding silica-AAPTS-Pd and silica-APTS-Pd catalyst system.



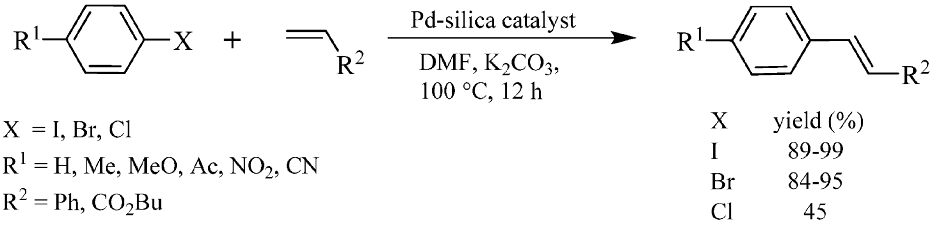
Scheme 13.



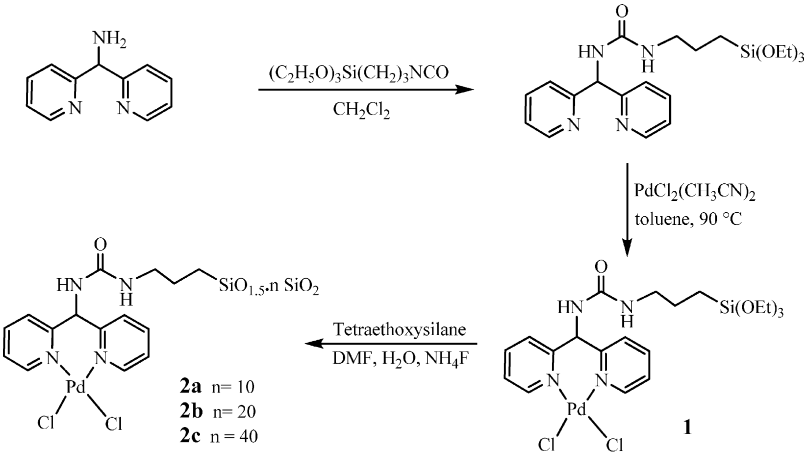
Scheme 14.



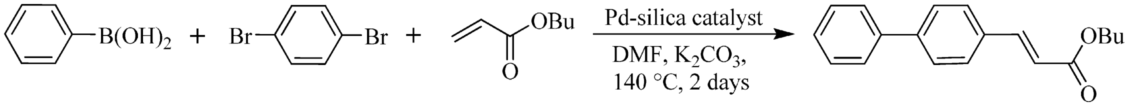
Scheme 15.



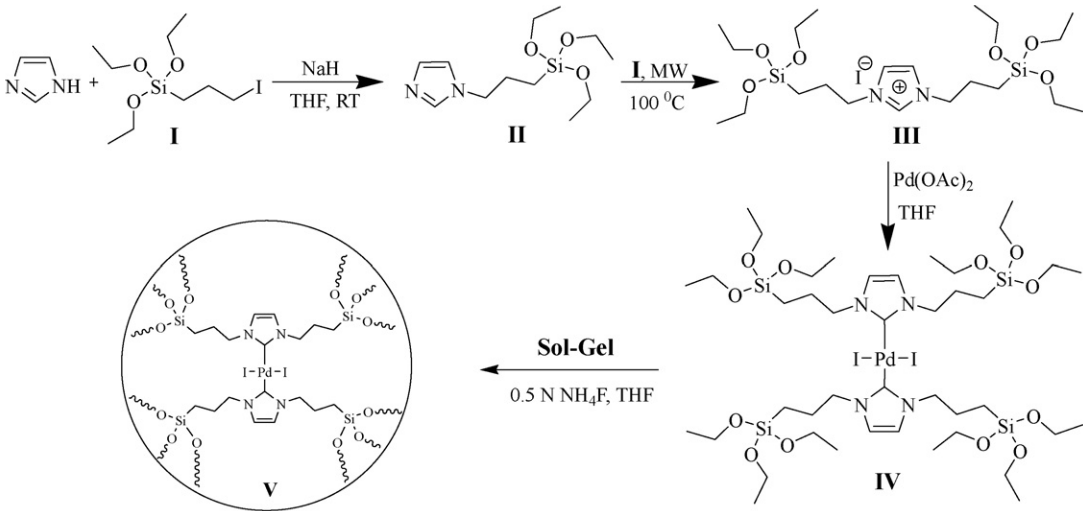
Scheme 16.



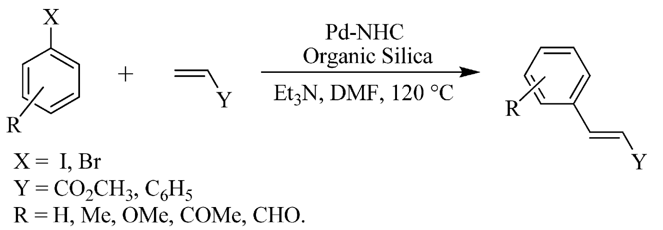
Scheme 17.



Scheme 18.



Scheme 19.

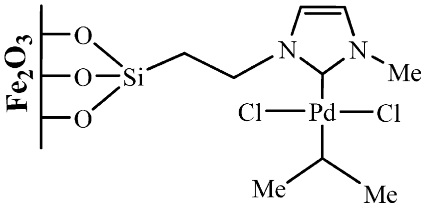


Scheme 20.

Third catalyst of this series was prepared by treating silica with (3-aminopropyl)-triethoxysilane and then resulting functionalized silica material was reacted with *N*-Boc-L-proline in the presence of *N*,*N*′-dicyclohexylcarbodiimide to afford the corresponding hybrid material. After deprotection of Boc protective group, the white solid was reacted with palladium(II)acetate to yield silica-anchored proline-palladium catalyst (Scheme 15) [43].

All above prepared materials showed excellent catalytic activity for Heck reaction of iodo-, bromo- and chloroarenes with good to excellent yields (Scheme 16). Also, catalysts were recovered and recycled by simple filtration, without any loss in activity.

Shimizu and co-workers prepared mesoporous silica-supported mercaptopropylsiloxane Pd(II) complex by stirring mercaptopropyl-functionalized FSM-16 (SH–FSM) with a solution of $Pd(OAc)_2$ in acetone at 25 °C for 12 h. Synthesized material was active and stable heterogeneous catalyst for the Heck reaction of 4-bromoacetophenone with ethyl acrylate. The aggregation behavior of Pd species during the reaction was also studied in great details and they found that the stability toward the formation of inactive Pd metal particles is the crucial factor for achieving a stable heterogeneous catalysis system, which can controlled by using the proper support. This catalyst seems to be a clean and convenient alternative with high TON and excellent recyclability without any loss of the catalytic activity [6].



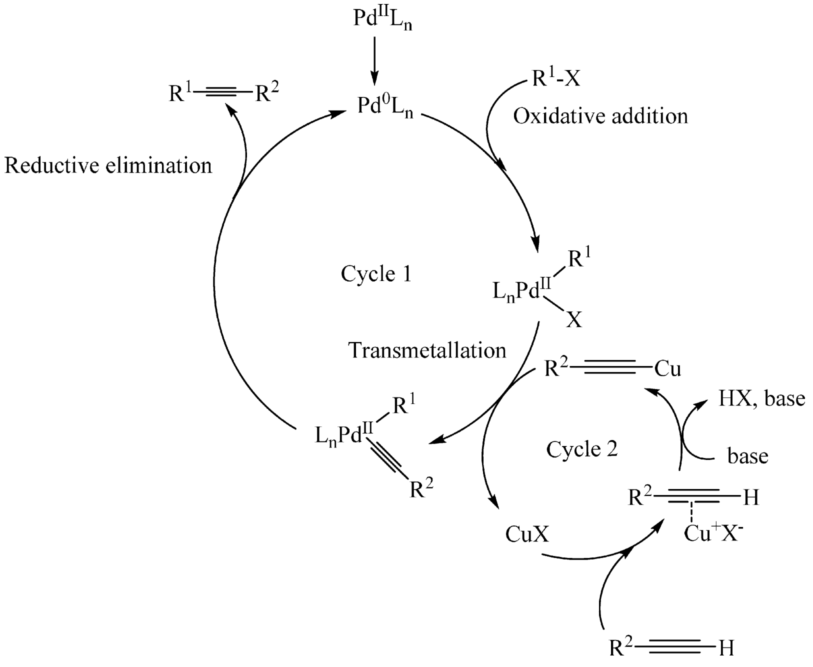
Scheme 22.

Pioneer in the field of hybrid silica, Pleixats and co-workers have prepared a hybrid silica material containing di(2-pyridyl)methylamine–palladium dichloride complex covalently bonded to the silica matrix. The di(2-pyridyl)methylamine was prepared by zinc reduction of the oxime derived from commercial di(2-pyridyl)methanone. It was immediately reacted overnight with 3-(triethoxysilyl)propylisocyanate in dichloromethane at room temperature. The resulting urea derivative was treated with $PdCl_2(CH_3CN)_2$ in anhydrous toluene at 90 °C overnight to afford the Pd(II) complex **1**. Co-gelification of the silylated monomer **1** with different amounts of TEOS (1:10, 1:20, 1:40) was performed in dimethylformamide under standard sol–gel conditions with a stoichiometric amount of water and ammonium fluoride as catalyst, leading to Pd-containing materials **2a–c** (Scheme 17) [44,45].

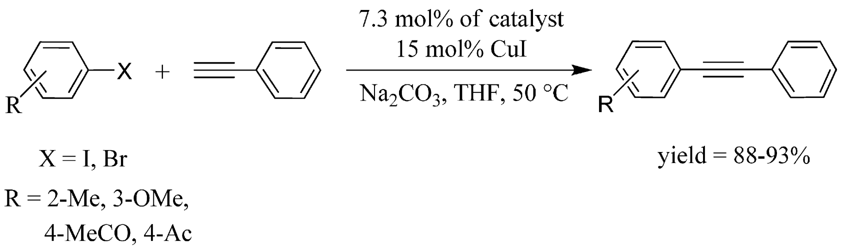
The Heck reaction between *p*-bromoacetophenone and *n*-butyl acrylate was very effective with these supported catalysts and catalyst can be reused up to five times. Using the catalyst **2b**, they also studied tandem one-pot two-step Suzuki–Heck reaction between *p*-dibromobenzene, phenylboronic acid and *n*-butyl acrylate (Scheme 18). The 4-phenyl-*trans*-cinnamic acid *n*-butyl ester was obtained in a clean and efficient one-pot process in 97% isolated yield. Hot filtration tests performed with all these coupling reactions showed that both homogeneous and heterogeneous pathways participate in the catalysis. Formation of Pd-nanoparticles during the reactions was also observed.

Recently, Karimi and Enders developed a new concept of simultaneous covalent anchoring of an *N*-heterocyclic carbene Pd/ionic liquid matrix on the silica surface; catalyst characterization indicated the formation of Pd nanoparticles within the immobilized layer. They used this material for the Heck reaction of a variety of different haloarenes. The catalyst showed high activity and could be recovered and reused for four reaction cycles [46].

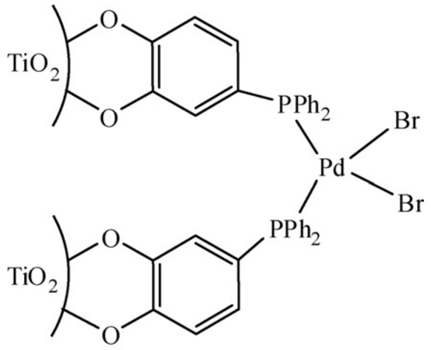
The common structural feature of most silica-Pd catalysts is the entrapment of the dopant (catalytic) molecule in the pores of silica, a phenomenon which imparts unique chemical and physical prop-



Scheme 21.



Scheme 23.



Scheme 24.

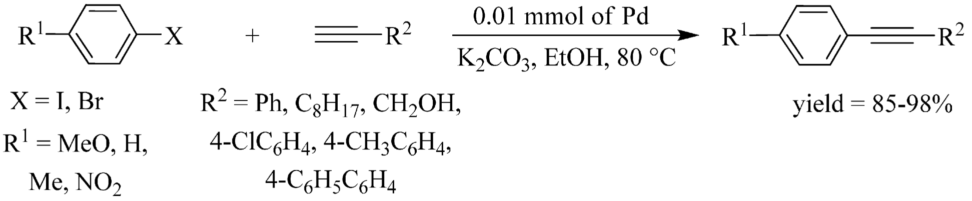
erties to resulting hybrid silica. Most of encapsulated silica catalyst contains 90% inorganic part and only 10% the catalytic part. Also, not all catalytic sites are available for reaction, since most of them are in the walls of silica and only those which are in the pores are available for catalysis. Consequently, there is need to design and synthesize pure organic silica, which does not use any inorganic sol–gel precursor, so that most of its sites are catalytically active. Polshettiwar and Varma developed a new concept of catalyst heterogenization, by synthesizing Pd–*N*-heterocyclic carbine (Pd–NHC) complex in the form of organic silica (Scheme 19). These materials showed excellent activity for C—C coupling reactions [47].

The Pd–NHC organic silica **V** was prepared in THF as shown in Scheme 14. The reaction of imidazole with 3-iodopropyl triethoxysilane (**I**) generated silylated imidazole **II**, that on reaction with 3-iodopropyl triethoxysilane (**I**) provided ionic imidazole species **III**, which on treatment with $Pd(OAc)_2$ in THF under reflux condition afforded the complex **IV**. Microwave (MW) irradiation was ideally suited for the conversion of **II** to ionic liquid **III**, which normally requires an extended period of 12 h for the completion of the reaction. This may be due to selective absorption of microwaves by reactants and polar intermediates, which accelerate the reaction rate [48].

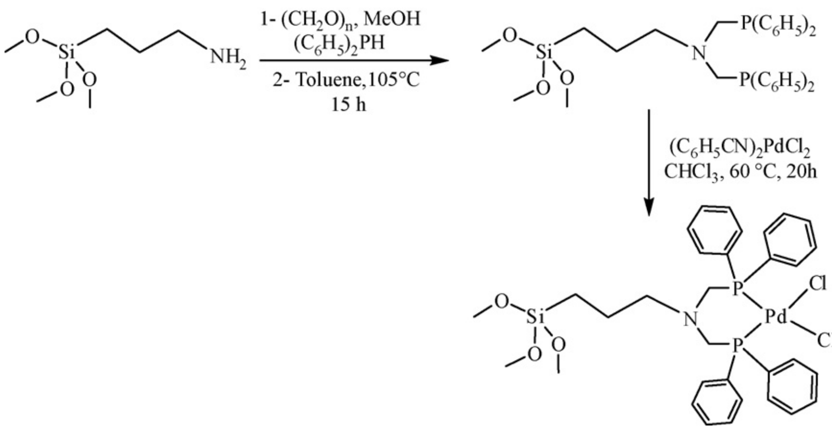
The scope of this catalyst was studied for Heck reaction of various aryl halides and alkenes (Scheme 20); aromatic iodo- and bromo-compounds reacted efficiently with alkenes to give coupling products in good to excellent yield [47].

2.2. Sonogashira reactions

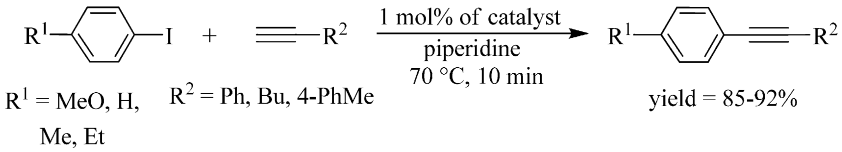
Over the last quarter century, Pd-catalyzed alkynylation has emerged as an important method for the synthesis of alkynes [49,50]. The preparation of conjugated aryl alkynes is of great interest in materials science and also because of their wide presence in many bioactive natural products [51–53]. The exact mechanism of the homogeneous copper co-catalyzed Sonogashira reaction is unknown and is generally supposed to take place through two independent catalytic cycles, as shown in Scheme 21. While the first



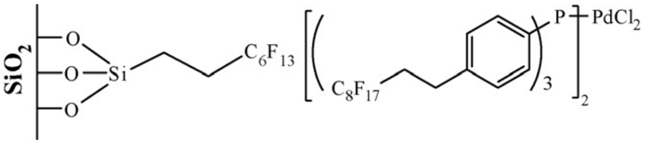
Scheme 25.



Scheme 26.



Scheme 27.



Scheme 28.

cycle involving Pd is classical from C—C cross-coupling formation, the second cycle generally involving copper (I) iodide is still poorly understood [54].

Few techniques have been developed to study this coupling process using heterogeneous catalysts in order to detect surface transient organometallic intermediates [55,56]. However, unanticipated findings can add further complications to the already intricate mechanisms. The factors that affect the rates of the Sonogashira reaction are not completely understood, however, the steric and electronic properties of the ligands and catalysts are determining parameters. The aim of this part of the review is to provide the reader with a concise update on the recent applications of silica-supported catalysts in the Sonogashira reactions. Gao and co-workers grafted a Pd/*N*-heterocyclic carbene complex onto the surface of soluble maghemite nanoparticles (γ-Fe_2O_3) stabilized by oleate surfactants (Scheme 22) [57].

The partial solubility of the nano-particles in many organic solvent is due to their small dimensions (11 nm ± 10%) and organic coating. The superparamagnetism of the maghemite core allows the particles to be magnetically concentrated and re-dispersed using a small permanent magnet positioned externally. Using 7.3 mol% of catalyst and Na_2CO_3 as the base in the presence of THF, this catalyst provided nearly quantitative yields for electron-rich and electron-poor aryl iodides and bromides (Scheme 23).

No significant loss of the catalytic activity of the immobilized catalyst was observed after several reaction cycles and recycling of the nanoparticles was achieved by magnetic concentration, and washing and air drying without further purification. The authors believe that catalytic activity is due to an easier access to the surface active sites.

It is worth noting – even if it is out of the main scope of the present review – that McDonagh and co-workers were able to propose the functionalization of titanium dioxide with Pd through a strongly bound catecholate ligand (Scheme 24) [58].

This catalyst has been characterized by solid-state ^{31}P NMR spectroscopy and diffuse-reflectance IR spectroscopy on $W(CO)_5$ derivatives. Using triethylamine and in the presence of copper iodide, a preliminary study showed that the Pd phosphane complex supported on TiO_2 catalyzed the Sonogashira coupling of phenylacetylene with 4-iodonitrobenzene. A complete conversion and selectivity in the desired coupling product was obtained after 24 h at room temperature. Deactivation of the Pd catalyst, however, was observed after recycling three times.

The catalytic activity of silica-APTS-Pd in Sonogashira coupling reaction have described by Li and Wang [59]. In the absence of a copper promoter and phosphane ligand, good to excellent yields of the coupling products were obtained from iodides in EtOH at 80 °C for 6 h, and from electron-poor and electron-rich bromides in DMF at 110 °C for 8 h (Scheme 25).

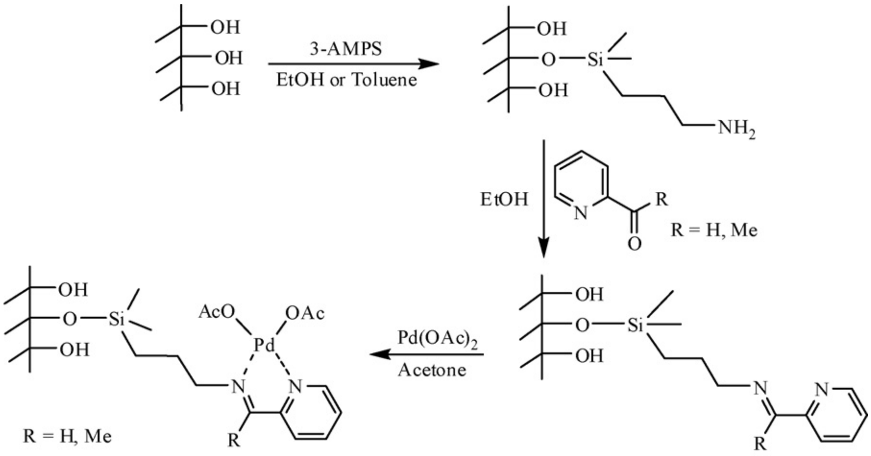
The authors indicated that after simple filtration and work-up procedures, the silica-supported Pd was recovered and was used for 30 consecutive trials without any decreases in activity.

A partially analogous 3-aminopropyl-functionalized silica gel was synthesized by a two-step protocol commencing from aminopropyltrimethoxysilane (Scheme 26) [60].

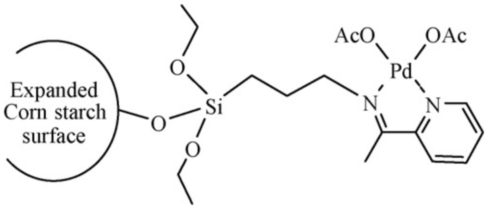
This silica-supported Pd catalyst was successfully used in a series of copper-free Sonogashira coupling reactions, but had a more limited scope and only useful for aryl iodides (Scheme 27).

The authors indicated that the piperidine can be used as both a base and solvent and the supported catalyst is stable over several months, under an inert atmosphere. The catalyst could be recycled by simple filtration and washing with toluene, although a slight reduction in the yield of the coupled product and an increase in the reaction time were noted.

An interesting example of supporting a phosphane ligand on silica without covalent bonding can be seen in the case of perfluoro-tagged Pd complex which was immobilized on a fluorous-modified silica gel (Scheme 28) and used in the Sonogashira coupling



Scheme 29.



Scheme 30.

of 4-nitrobromobenzene and phenylacetylene in the presence of CuI/nBu$_2$NH in DME as solvent at 100 °C for 14 h. High yields of 98, 97, and 71% were obtained for three successive experiments using 2 mol% of catalyst; whereas with 0.2–0.002 mol% loading, the catalytic activity and the recyclability dropped significantly [61].

A study on a more diverse array of substrates would be necessary to determine the scope of these catalysts. Based on an similar concept, catalytic Pd(OAc)$_2$/n TPPTS, n = 2, 5 [TPPTS = P(m-C$_6$H$_4$SO$_3$Na)$_3$] systems immobilized in an aqueous film supported on a mesoporous silica was shown to be successful for the coupling of phenylacetylene with iodobenzene in the presence of catalytic amounts of CuI and triethylamine as base. The authors believe that the solids behave essentially as a reservoir of highly soluble species, from which the leaching species might be a lipophilic Pd/phosphane intermediate with a C≡CPh group, thus making the system inadequate for recycling [62].

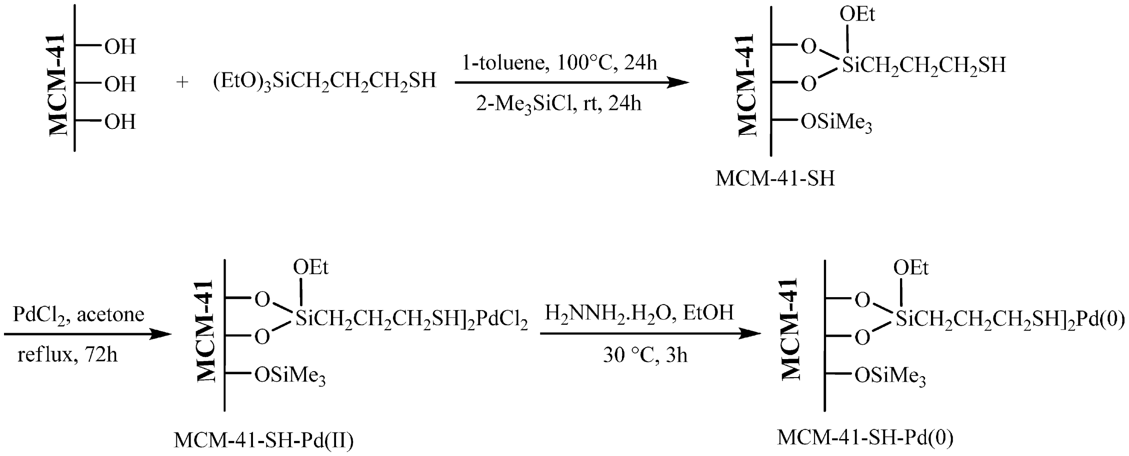
Macquarrie and co-workers have examined the Sonogashira cross-coupling by using silica-supported Pd complexes which were obtained recently by reaction of amino-containing silanes with silica gel (Scheme 29) [63].

A variety of electron-poor aryl iodides were successfully alkynylated in good yields by employing 0.1–1 mol% of catalyst in the presence of undecane and Et$_3$N as a base and no copper co-catalyst. These catalysts could be filtered and reused, showing a partial loss of performance after the third cycle.

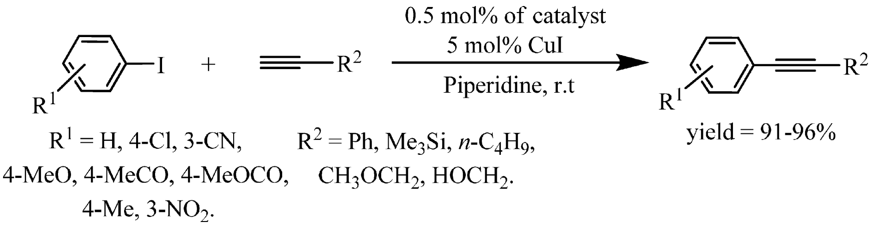
In an independent study, the same group has also examined the Sonogashira cross-coupling using related supported Pd catalyst which is anchored to the surface of expanded corn starch (Scheme 30) [64].

The authors have shown that supported Pd can catalyze the coupling of electron-poor aryl iodides with phenylacetylene. In presence of DABCO as base at 100 °C using microwave heating, the catalyst system provided the product in high yields without the need of any co-catalyst like CuI and with no Pd leaching. In contrast to silica gel-based materials, which have been proven by XPS to contain Pd(II), this starch-derived catalyst has been shown to contain Pd(0) nanoclusters produced after conditioning of the surface, which are stabilized by the supported material. The heterogeneous catalyst can be readily recovered by filtration and subsequently washed with methanol and gently dried under vacuum before reusing several times without marked loss of catalytic activity.

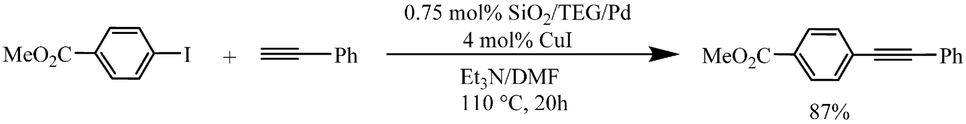
Cai and co-workers have recently developed a novel MCM-41-supported sulfur Pd(0) complex and explored its catalytic properties in Sonogashira coupling reaction. This mesoporous material (MCM-41) was conveniently synthesized from commercially available γ-mercaptopropyltriethoxysilane via immobilization on MCM-41, followed by reacting with Pd chloride in acetone,



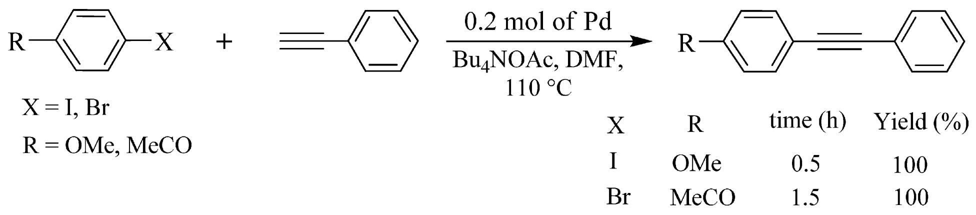
Scheme 31.



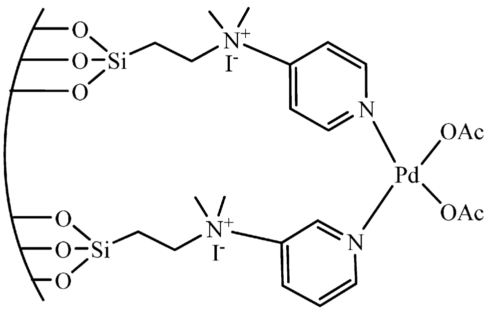
Scheme 32.



Scheme 33.



Scheme 34.



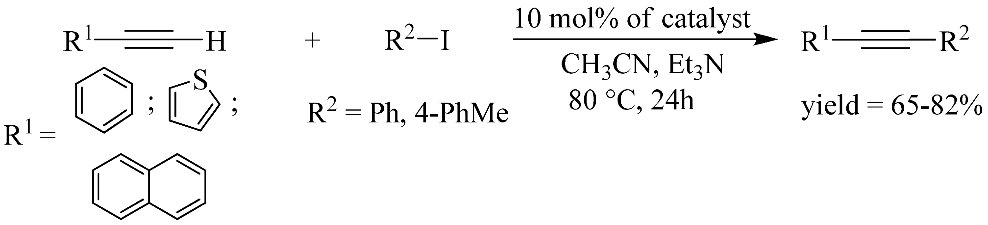
Scheme 35.

and then reduction with hydrazine hydrate in ethanol (Scheme 31) [65].

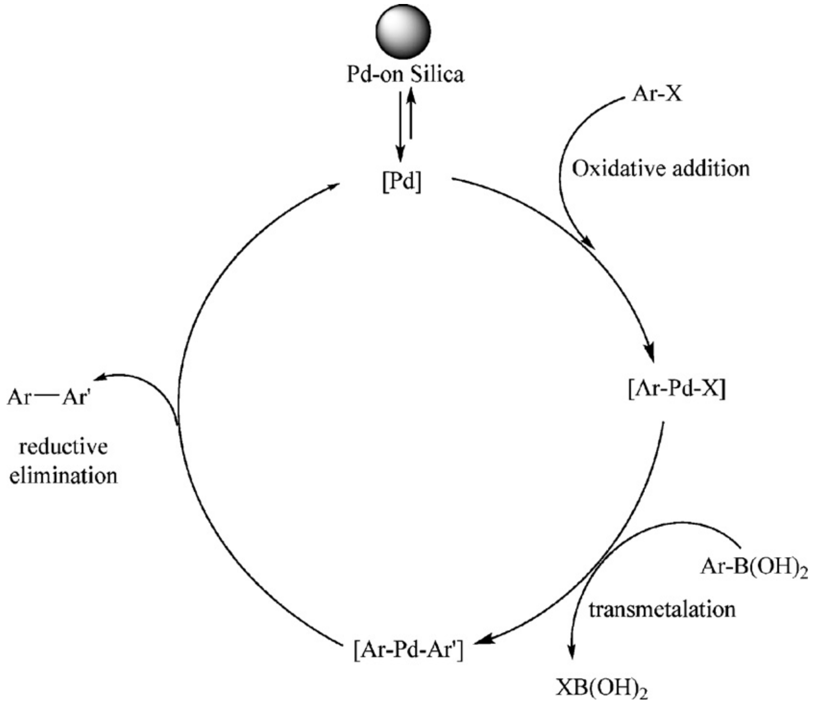
Using piperidine as both the solvent and the base and in the presence of CuI as the co-catalyst, this novel MCM-41-supported sulfur Pd(0) provided a very efficient system for Sonogashira coupling reaction of activated and unactivated aryl iodides with terminal alkynes (Scheme 32). The authors indicated that the conversion of iodobenzene with 1-hexyne can be maintained above 95% after five recycling steps by using 0.5 mol% of catalyst.

The catalyst obtained by encapsulation of Pd nanoparticles in a silica matrix (SiO_2/TEG/Pd) showed high catalytic activity in the Sonogashira coupling of methyl 4-iodobenzoate with phenylacetylene (Scheme 33) [33].

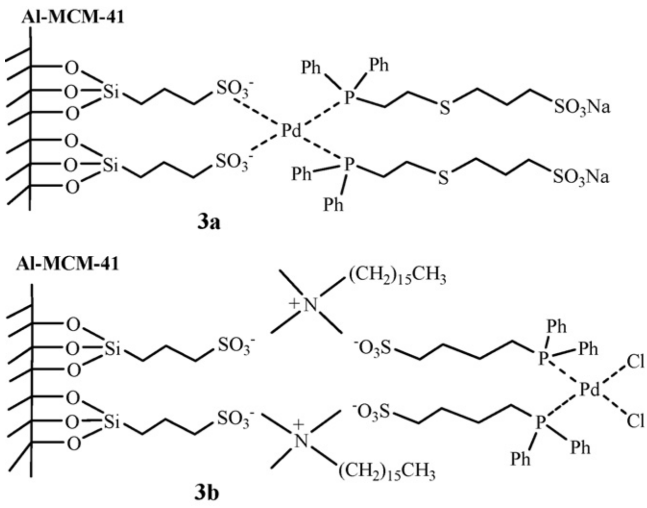
The preliminary experiments on the Sonogashira were conducted by using the hybrid silica material **2b** [45]. Suitable conditions were found for very fast copper- and phosphine-free Sonogashira couplings between phenylacetylene and aryl bromides and iodides (Scheme 34). Nonetheless, the *p*-chloroacetophenone did not react with phenylacetylene under prolonged heating in analogous conditions. The recyclability of the catalyst (five runs) was much better for *p*-bromoacetophenone than for *p*-iodoanisole.



Scheme 36.



Scheme 37.



Scheme 38.

Finally, it is worth noting that Moreau and co-workers described a new nanostructured hybrid silica bearing pyridine binding sites which can be prepared in a template assisted hydrolysis polycondensation of tetraethylorthosilicate and the ionic precursor *N*,*N*-dimethyl-pyridin-4-yl-(3-triethoxysilyl-propyl)-ammonium iodide using *N*-dodecyl-*N*′-methyl-imidazolium bromide as structure directing agent (Scheme 35) [40].

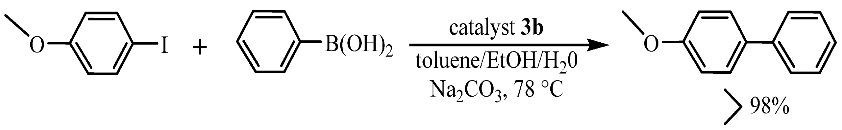
After treatment with Pd acetate, this material was tested in the Sonogashira reaction of aryl halides with terminal alkynes. The copper-free reactions were carried out in refluxing acetonitrile in the presence of 10 mol% of catalyst and 2 equivalents of triethylamine as base, with good to excellent yields (Scheme 36). However, the coupling of aryl bromides was not reported for this system.

2.3. Suzuki–Miyaura reactions

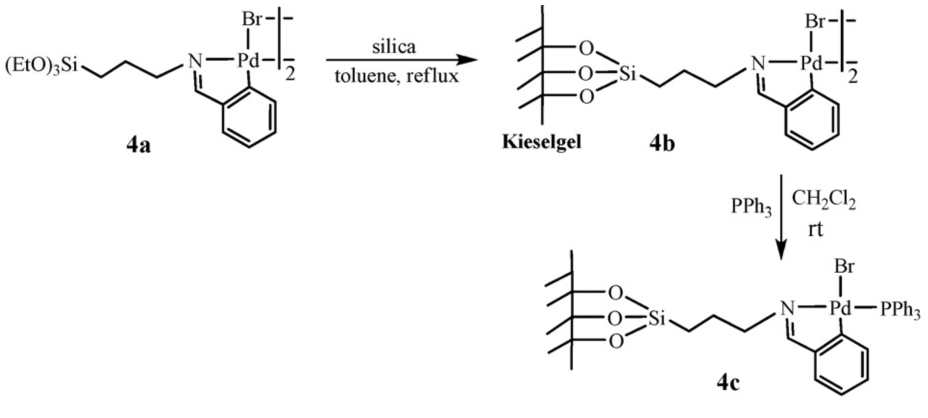
The biaryl substructure is a widely occurring component of biologically active and functional molecules [66–69]. Its importance is reflected in the immense economic value of pharmaceuticals including Valsartan [70,71] and Telmisartan [72,73], and agrochemicals such as Boscalid [74]. As alternatives to the homogeneous Pd-phosphine catalysts, Pd on carbon [75,76], on silica or polymer supports [77–79], and on mesoporous materials can be used [80,81]. Silica-supported Pd catalysts useful for Suzuki cross-coupling reactions can be prepared in various ways providing different structures and activity. Pd can directly be deposited onto silica, or it can be anchored as a complex. Also, these systems can be reversed in such a way that a lipophilic catalyst is physisorbed on reversed-phase silica gel or fluorous reversed phase silica gel (FRPSG). In general, Suzuki coupling reactions catalyzed by solid-supported Pd follow the usual reaction mechanism (similar to homogenous catalysis), but the full understanding of mechanism in heterogeneous conditions still remains an open question (Scheme 37).

Starting from surfaces functionalized with propylsulfonic groups, Kosslick and co-workers prepared the MCM-41-supported Pd. The alkylsulfonated support is prepared by bi- or tridentate anchoring of mercaptopropyltriethoxysilane on the walls of Al-MCM-41, followed by oxidation with hydrogen peroxide to the corresponding sulfonic acid. These functionalized supports are contacted with a mixture of $Pd(OAc)_2$ and a water-soluble phosphine ligand such as $Ph_2P(CH_2)_2S(CH_2)_3SO_3Na$, or with the preformed precursor $PdCl_2[Ph_2P(CH_2)_4SO_3K]_2$ (catalyst **3a**, Scheme 38). Moreover, the alkylsulfonated Al-MCM-41 material may be amphiphilized by the adsorption of the surfactant cetyltrimethylammonium bromide (catalyst **3b**), followed by exposure to the same precursor complex. The quaternary ammonium ion not only changes the surface polarity, but also serves as phase transfer agent in the Suzuki reaction [82].

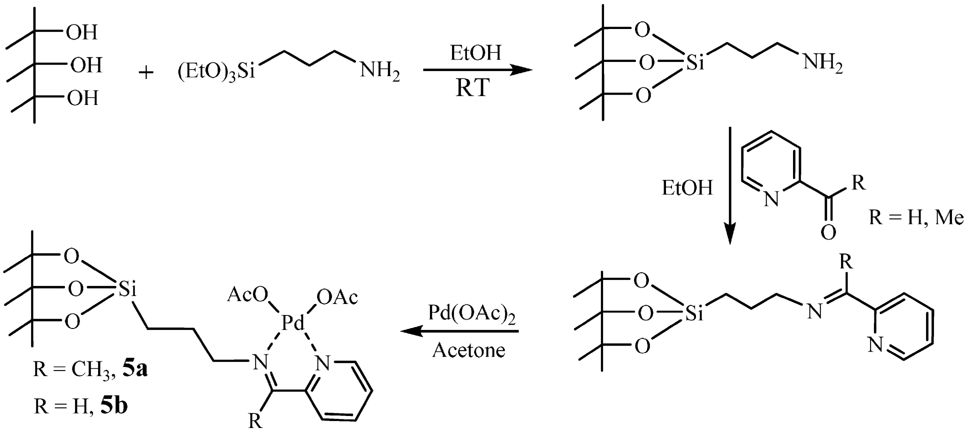
Reactions with two liquid phases and a solid catalyst were performed using the sulfonated materials **3a** and **3b**. For instance, *p*-iodoanisol was reacted with phenylboronic acid in a biphasic toluene/ethanol/water mixture, with Na_2CO_3 as base and with the amphiphile cetyltrimethylammonium bromide (CTAB) as phase transfer agent (Scheme 39). The amphiphilized catalyst **3b** displays a much enhanced activity in comparison with the parent catalyst **3a** (90% conversion versus 2% conversion in 10 min). This was ascribed to a micellar effect, with the amphiphilic solid improving the mixing of the two liquid phases. However, a subsequent run with **3b** revealed a decreased activity, possibly due to loss of the quaternary ammonium compound from the support. The authors indicated that the active species may not only be the anchored Pd(II) com-



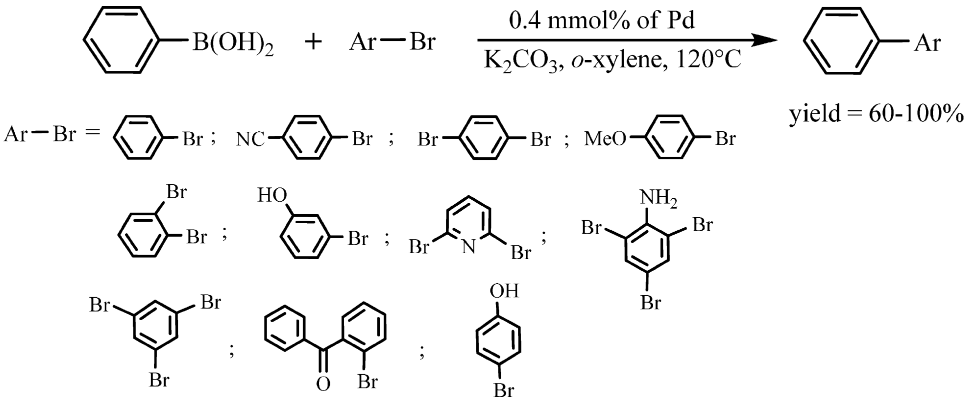
Scheme 39.



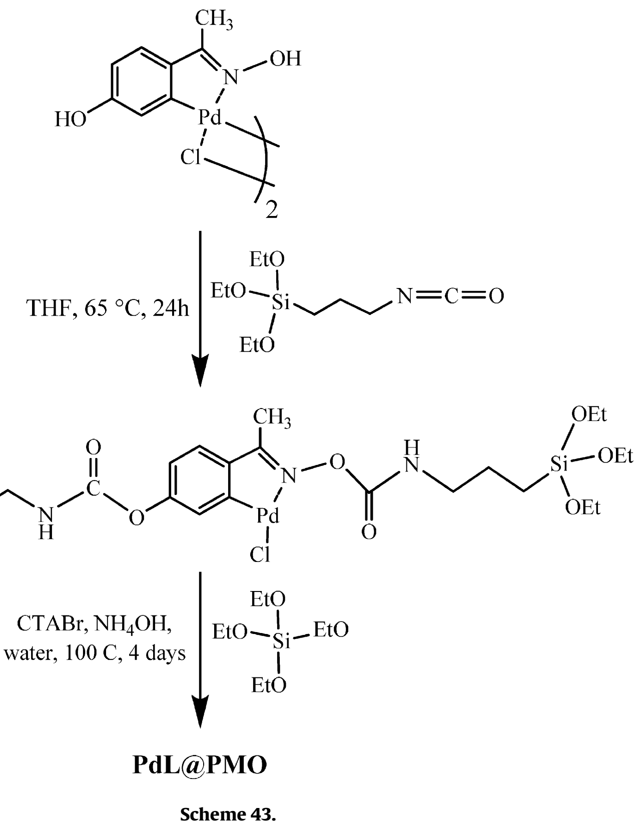
Scheme 40.



Scheme 41.

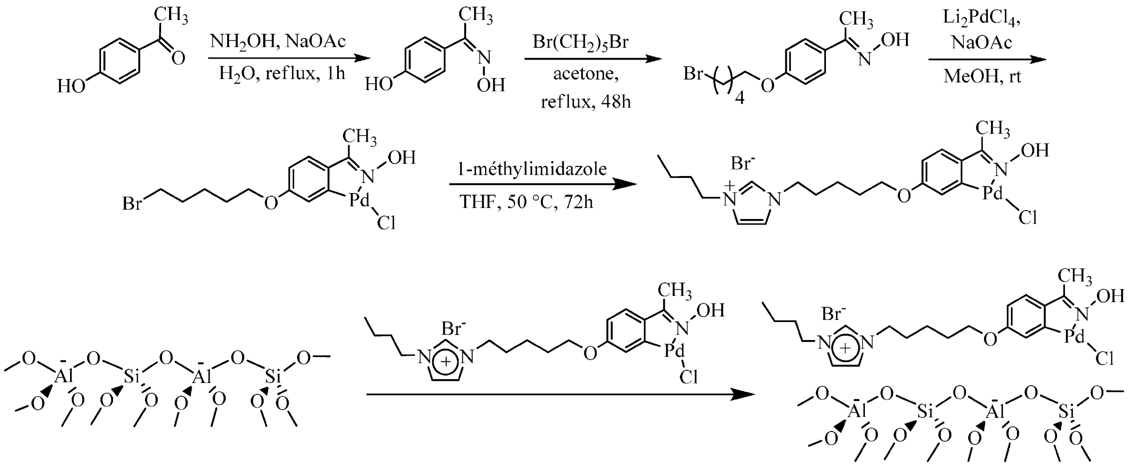


Scheme 42.

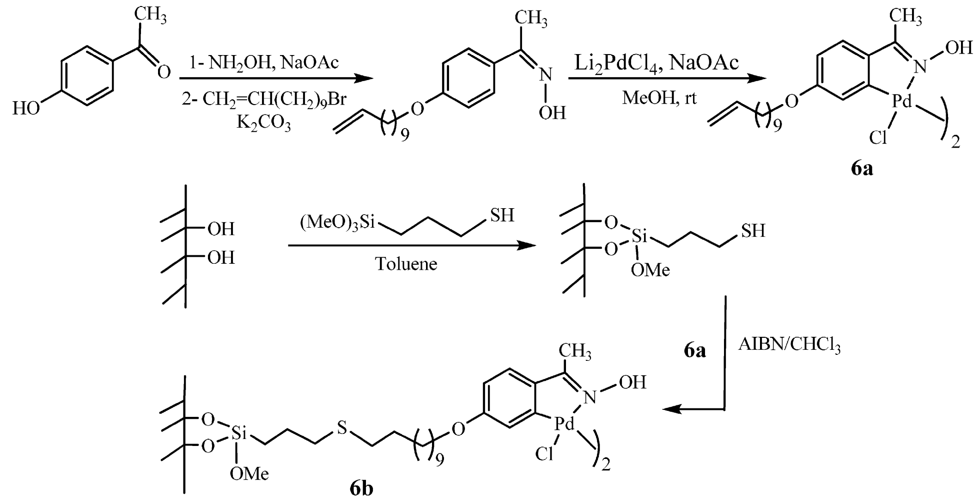


PdL@PMO

Scheme 43.



Scheme 44.



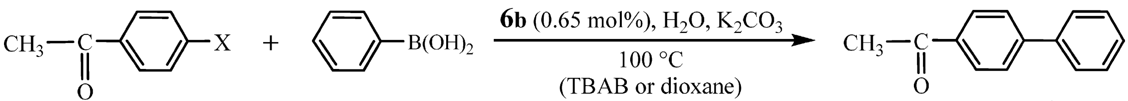
Scheme 45.

plexes, but also deposited Pd(0) clusters, formed by decomposition of Pd(II) reaction intermediates.

Alternatively, Bedford and co-workers prepared the silica-supported imine palladacycle catalysts and compared their catalytic properties in the Suzuki coupling of aryl bromides with phenylboronic acid [83]. As shown in Scheme 40, the catalyst **4b** was prepared by grafting of the dimeric palladacycle **4a** on mesoporous silica (Merck Kieselgel, 100 Å), the latter giving the catalyst **4c** by a treatment with a solution of triphenylphosphine.

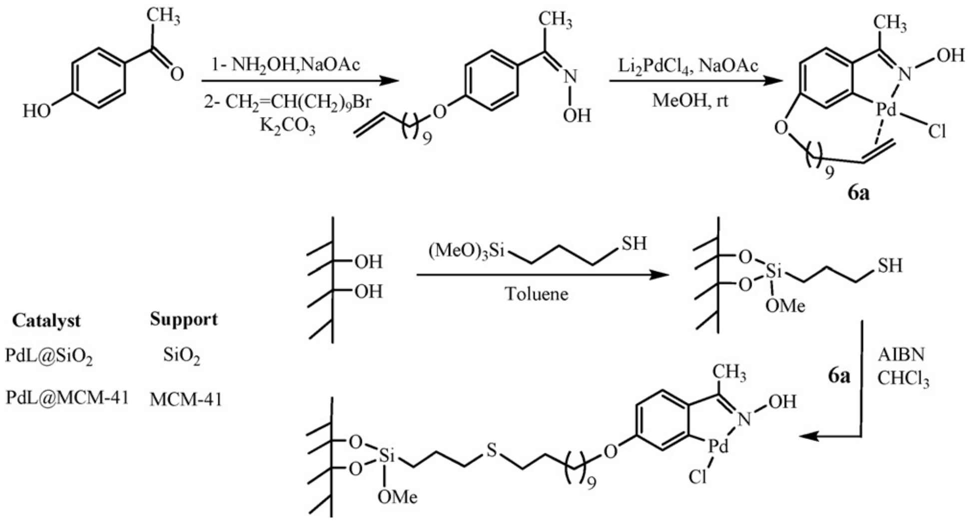
In this case, when the coupling of 4-bromoanisole with phenylboronic acid catalyzed by **4b** was stopped after 6 h, the coupling product was obtained with 69% yield; removal of the silica by filtration, addition of more phenylboronic acid and base, and heating for a further 19 h gave only a poor yield (11%) of the desired product. The catalyst **4c** initially showed much higher activity than **4b**. However, in contrast to the results obtained with **4b**, attempts to recycle the PPh_3 modified catalyst **4c** remained unsuccessful with essentially complete loss of activity being observed between the first and second runs. Experiments with these silica-supported imine palladacyclic complexes have shown that small Pd(0) clusters are likely the active catalysts in many Suzuki reactions.

Clark and co-workers reported the synthesis of novel silica-supported Pd complexes incorporating nitrogen-containing ligands which were obtained by the anchoring of Pd on the surface of modified silica (Scheme 41) [84]. The catalyst **5a** has been investigated in the Suzuki cross-coupling of aryl bromides with phenylboronic

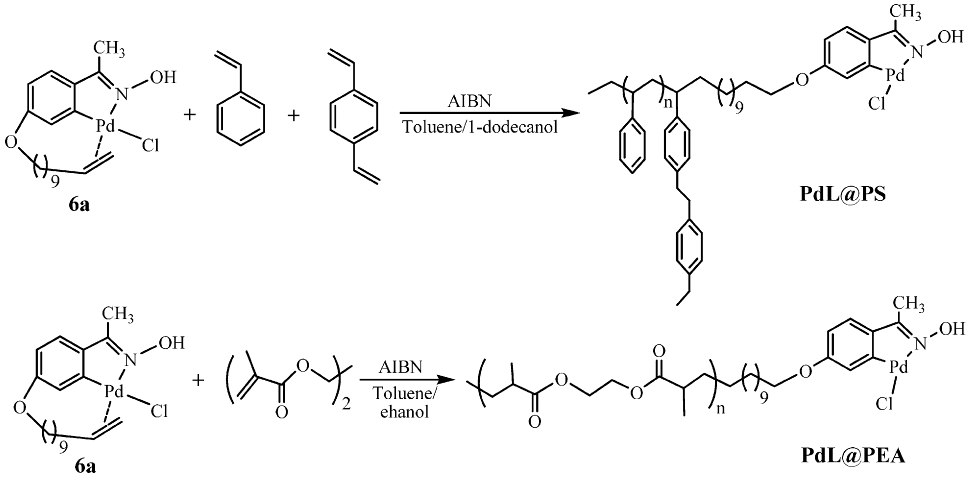


		Conversion %
X = Br	Water/TBAB	62
Br	Water	99
Cl	Water	91
Cl	Water/TBAB	55

Scheme 46.



Scheme 47.

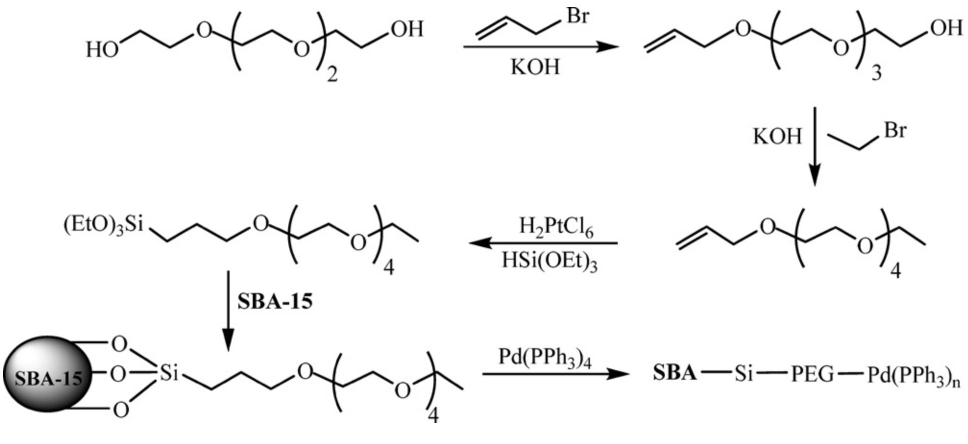


Scheme 48.

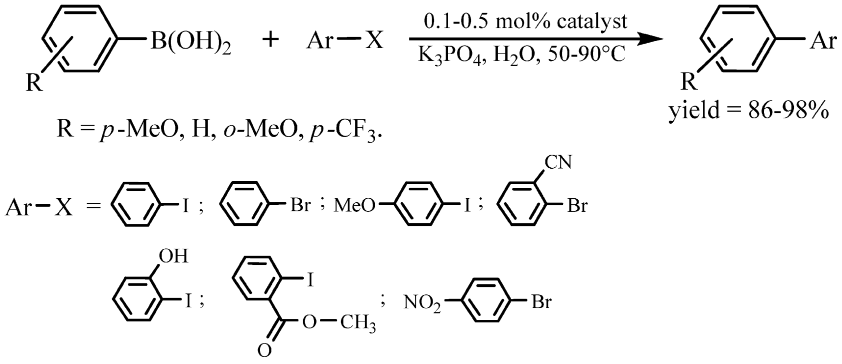
acid using K_2CO_3 as base and *o*-xylene as solvent. Good results were obtained with a wide range of aryl bromides by using 0.4 mmol% Pd. The catalyst can be also used for consecutive Suzuki reactions in a single step and hence successfully applied to the synthesis of polyaryls (Scheme 42).

The catalyst **5a** was found to be more active than **5b**; this difference may be due to the electronic effect of a methyl group, which ultimately increases the electronic environment around the Pd. The authors indicated that no change in the catalyst structure has been observed on the basis of surface analysis and simultaneous thermal analysis even after using seven times.

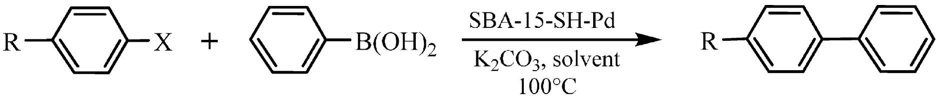
Among the successful homogeneous Pd catalysts, carbapalladacycles derived from electron-rich aromatics having a heteroatom in such a position that allows formation of a ring encompassing the



Scheme 49.



Scheme 50.



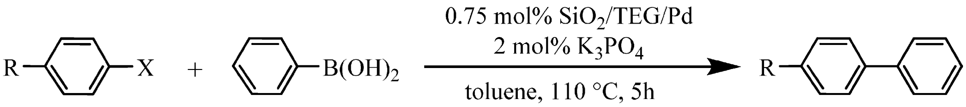
X	R	Solvent	yield%
Cl	H	DMF	67
Cl	MeCO	H_2O	96
Br	Me	DMF/H_2O	82
Br	MeO	H_2O	96
Br	HCO	H_2O	97

Scheme 51.

Pd atom, are known to be very active. Using the two free hydroxyl groups of the above carbapalladacycle, Corma and co-workers have functionalized it in a simple way by reaction with triethoxysilane molecule and prepared a periodic mesoporous organosilica (PMO) containing up to 15 wt% of this complex (Scheme 43) [85]. The catalytic activity of PdL@PMO was tested for the Suzuki coupling of a series of aryl bromides and chlorides with phenylboronic acid in water in the presence of K_2CO_3 as base. This catalyst showed good activity for aryl bromides but it was inactive for aryl chlorides. The initial catalytic activity of these PMO materials was significantly higher than that of a related amorphous silica catalyst containing the same carbapalladacycle covalently anchored to amorphous silica. Leaching studies, either filtering the solid in hot solution or three-phase-test attaching one of the reagents to a solid, demonstrated that there is a contribution to the catalysis of leached species from the solid into the solution. The solid can be reused although a progressive deactivation caused by complex degradation and mesopore collapse has been observed.

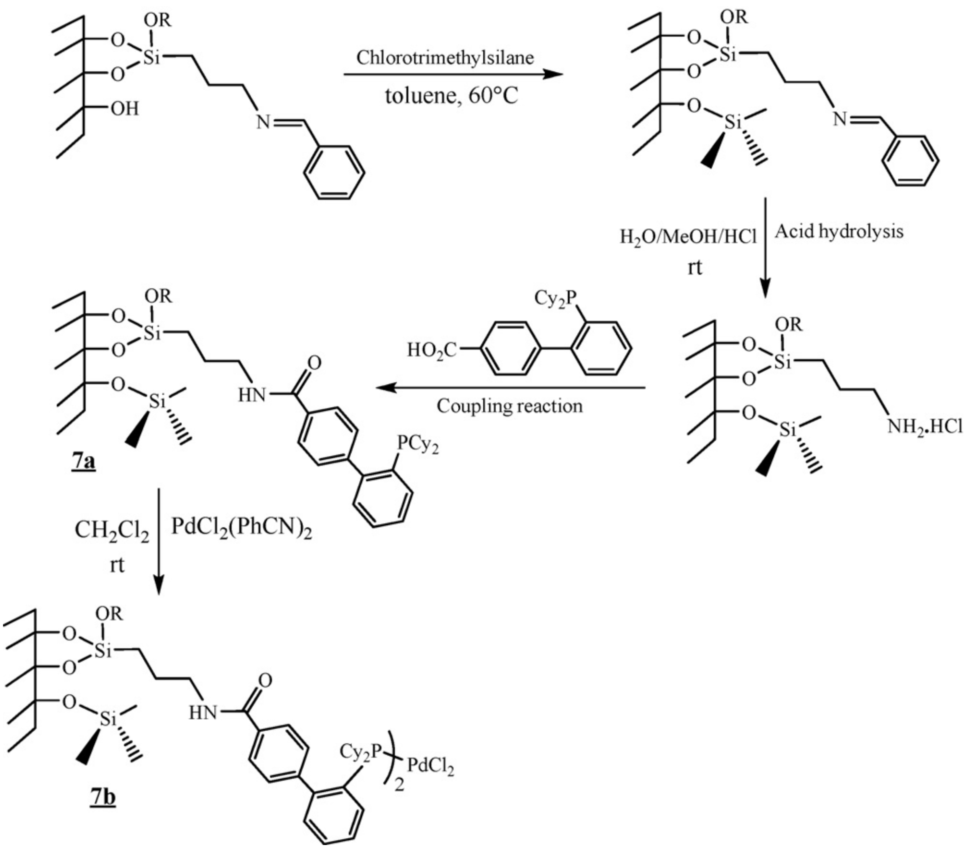
An alternative strategy to the covalent anchoring for binding active catalytic sites to the surface of mesoporous silicas is the “Coulombic” interaction between negative charges of the aluminosilicate framework and positively charged species. $[SiO_4]^{4-}$ tetrahedral sharing the edges are neutral, but when a Si atom is isomorphically substituted by an Al atom to form $[AlO_4]^{5-}$, a negative charge is introduced in the framework. Each negative charge of the framework requires the presence of a charge compensating cation in order to ensure the electroneutrality of the solid. The synthetic route of this ionophilic palladacyle and the resulting electrostatic binding between this organometallic complex and the aluminosilicate support are shown in Scheme 44 [86].

The imidazolium-tagged carbapalladacycle electrostatically bound to Al/MCM-41 was used as a catalyst for the Suzuki cou-

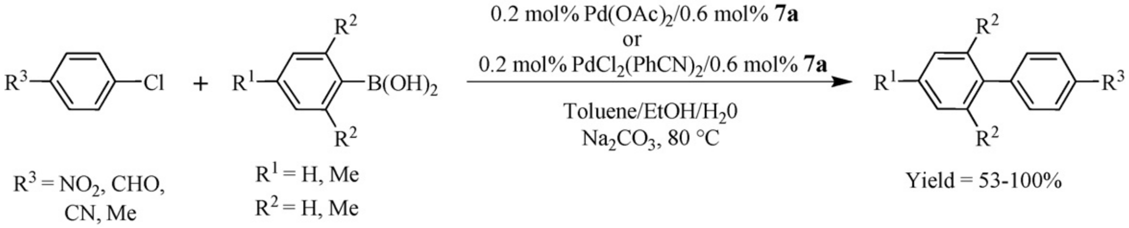


X	R	Yield %
I	CO_2Me	100
Br	H	86 (12h)
Br	CO_2Me	100
Br	CHO	98
Br	CF_3	98
Cl	CO_2Me	‹5

Scheme 52.



Scheme 53.

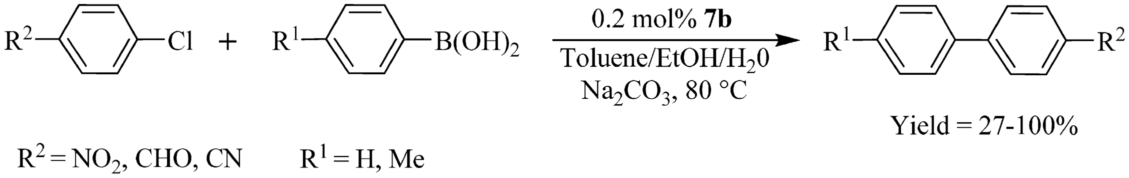


Scheme 54.

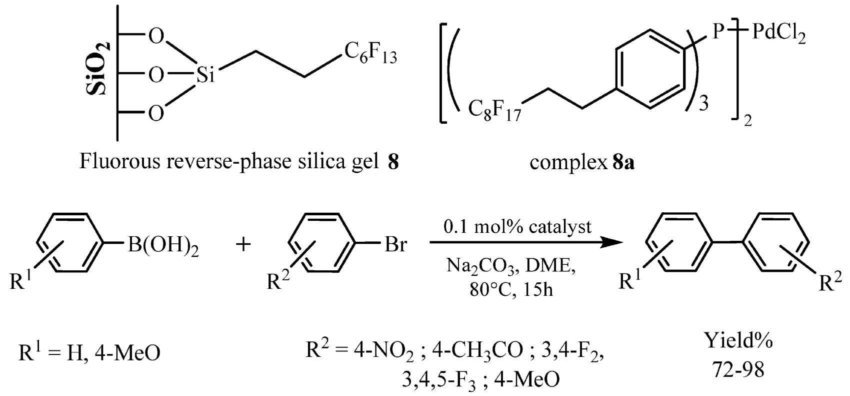
pling in toluene and DMF as solvent. Better results were obtained in the latter aprotic polar solvent, in good agreement with the general behavior of the catalytic activity of the soluble parent carbapalladacycle.

Conducting reactions in aqueous media can be advantageous, particularly for large-scale industrial applications, as a result of the ease of purification as well as the environmental friendliness and low-cost of water [87]. An important observation regarding Suzuki couplings was reported in 2003 by Corma and co-workers, who established that an oxime-carbapalladacycle complex covalently anchored onto mercaptopropyl-modified silica catalyzed cross-couplings of halobenzenes with phenylboronic acid in aqueous media (Scheme 45). The preparation of this catalyst (**6b**) is based on the synthesis of an oxime carbapalladacycle having a terminal C=C double bond group in a long alkyl chain (**6a**) that will enable the anchoring of the complex. This undecenyl derivative of the Pd complex was prepared from the corresponding oxime starting from 4-hydroxyacetophenone (Scheme 45) [88]. The covalent bond between the mercaptopropyl functionalized silica and the Pd complex was formed through a radical chain mechanism using AIBN as initiator.

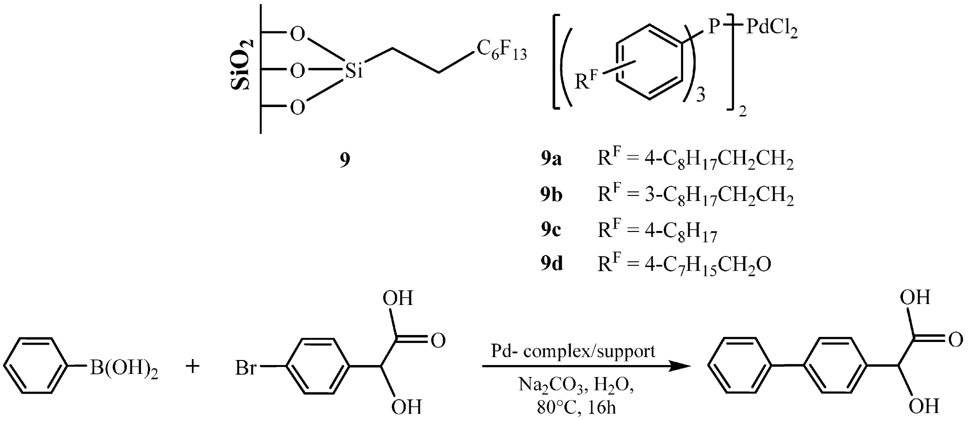
By using the catalyst **6b**, the 4-bromoacetophenone reacted with phenylboronic acid to give the expected product with a good yield in aqueous media. This catalyst also provided a high yield in the



Scheme 55.



Scheme 56.



9a $R^F = 4\text{-}C_8H_{17}CH_2CH_2$

9b $R^F = 3\text{-}C_8H_{17}CH_2CH_2$

9c $R^F = 4\text{-}C_8H_{17}$

9d $R^F = 4\text{-}C_7H_{15}CH_2O$

catalyst	yield%
9a	99
9b	88
9c	94
9d	85

Scheme 57.

cross-coupling of 4-chloroacetophenone with phenylboronic acid (Scheme 46).

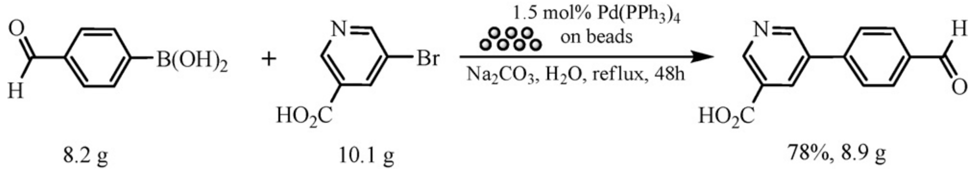
The authors indicated that after filtration and washing with ethanol and ether, the silica-supported Pd was recovered and was used eight times without a noticeable decrease in the activity.

In a subsequent study, the same research group expanded the initial results to the preparation of a related catalyst using MCM-41 as support, but authors specify that complex **6a** is a monomeric rather than a dimer as previously reported. The monomeric nature of complex **6a** suggests that the terminal C=C double bond is somehow interacting with the Pd, disfavouring the dimer formation (Scheme 47) [89]. Unfortunately a definitive confirmatory structure determination based on a single crystal has not yet being available.

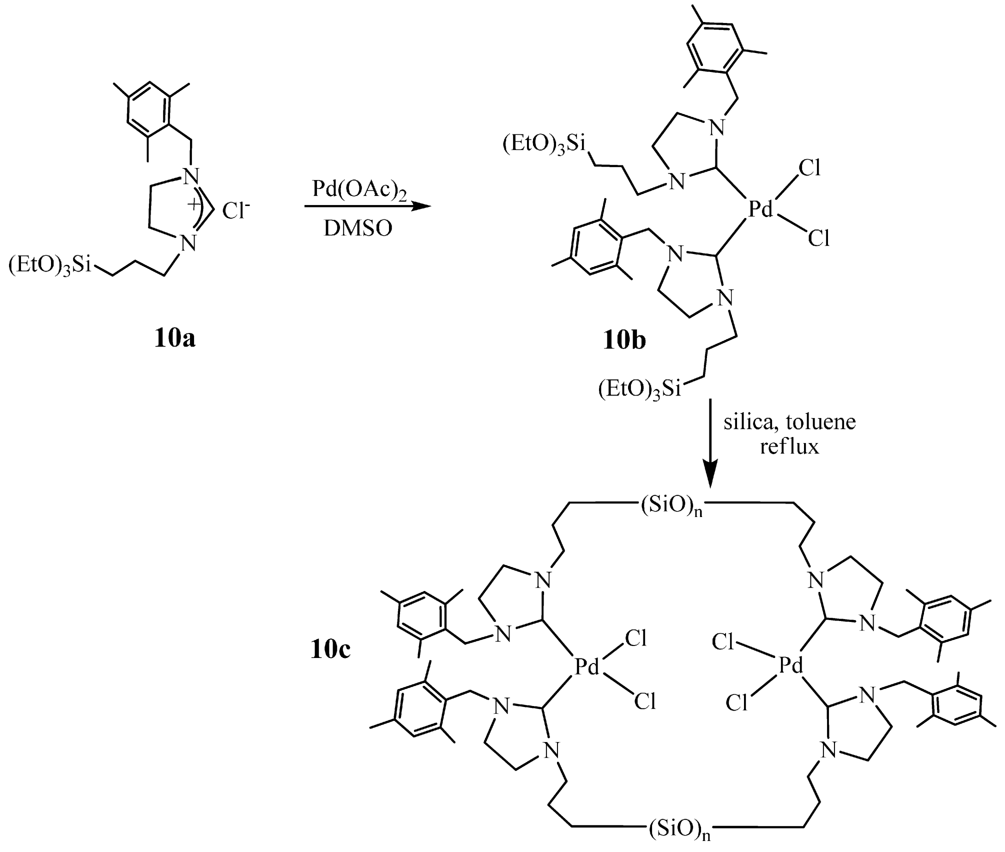
A different type of solid catalyst where the oxime carbapalladacycle complex is anchored on two different polymeric backbones was also prepared. One of these polymeric catalysts termed as PdL@PS was obtained starting from complex **6a** having the terminal C=C double bond upon copolymerization with styrene and *p*-divinylbenzene (Scheme 48). The second polymer (PdL@PEA) was obtained starting from ethylene glycol bis(methacrylate) as monomer through copolymerization with lesser amounts of terminal C=C double bond complex **6a** in the presence of toluene/ethanol as solvent (Scheme 48).

These catalysts have been tested for the Suzuki cross-coupling of 4-chloroacetophenone with phenylboronic acid as model reaction. The differences in activity depending on the support were remarkable; the Pd complex was more active for the reactions in water when supported on silica in comparison with mesoporous MCM-41 or polymeric supports derived from styrene or methyl acrylate.

Xiao and co-workers later described the synthesis of a new Pd catalyst supported on PEG modified mesoporous silica. This mesoporous catalyst was obtained from tetra(ethylene glycol) by



Scheme 58.



Scheme 59.

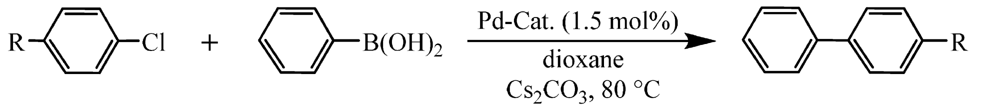
allylation reaction in the presence of KOH which was followed by etherification with ethyl bromide (EtBr). Platinum-catalyzed hydrosilylation of product obtained with $HSi(OEt)_3$ afforded the organosilane, which was used for grafting onto the surface of SBA-15 to support the Pd catalyst (Scheme 49) [90].

The prepared catalyst was used to catalyze Suzuki coupling reactions in water using K_3PO_4 as the base. Under the various conditions explored, the catalyst provided good yields for a range of substrates which incorporate electron-donating and electron withdrawing substituents at *ortho* or *para* positions (Scheme 50).

Xiao and co-workers have also noted that this catalyst system provided the desired product under low catalyst loading conditions such as 10^{-2} to 10^{-3} mol%. The catalyst could be recycled several times with no detectable deactivation and no leaching of the catalyst to the organic layer. The high activity and stability of this catalyst system are attributed to the mesoporous structure of material.

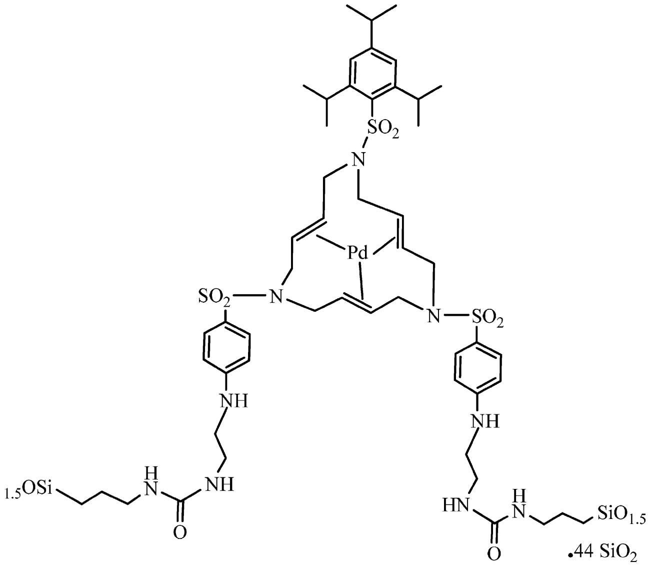
Crudden et al. have shown that the functionalization of SBA-15 with mercaptopropyltrimethoxysilane leads to an effective catalyst for Suzuki reactions of less reactive aryl chlorides and bromides in organic and aqueous solutions (Scheme 51). The SBA-15-SH-Pd catalyst was reused four times without any loss of catalytic activity when another equivalent of the reactants and base were added. Heterogeneity tests such as hot filtration experiments and three-phase tests show that the reaction was occurring predominantly via surface-bound Pd [23].

Similar to mercaptopropyl ligands, aminopropyl ligands were grafted to amorphous silica by reaction with the corresponding aminopropyltriethoxysilane [91]. These modified silica were loaded with Pd nanoparticles by treating with $Pd(OAc)_2$ and initially tested in Suzuki reaction of phenylboronic acid with 4-bromoanisole in the presence of K_2CO_3 and with toluene as solvent. The obtained results showed that the choice of organic modification has a crucial role in determining the activity and recyclability of the catalyst, optimum behavior was found when chelating diamines and triamines were used as organic modifiers. The optimized catalysts are also active in the coupling of a range of aryl bromides and phenylboronic acids; after three catalytic runs they show virtually no loss in activity, but the activity decreased in further runs.



R	Catalyst	Yield%
OMe	**10a**/$Pd(OAc)_2$	93
Me	**10a**/$Pd(OAc)_2$	91
OMe	**10c**	88
Me	**10c**	85

Scheme 60.



Scheme 61.

Shimizu and co-workers also studied the activity of mesoporous silica-supported mercaptopropylsiloxane Pd(II) complex, Pd-SH-FSM, in the coupling of 4-bromoanisole with phenylboronic acid (1 mol% catalyst, K_2CO_3, DMF, 130 °C) and compared with the other supports [6]. The Pd-SH-FSM catalyst prevented Pd metal aggregation, but gave a similar performance when compared with the SH-functionalized amorphous silica. Lower palladium leaching was observed for Pd-SH-FSM in comparison with Pd-FSM, Pd-Y zeolite or Pd-C, the two latter catalysts showing, however, higher yields of the products (83 and 86%, respectively). Nonetheless, a wider substrate scope would be desirable.

The catalyst SiO_2/TEG/Pd consisting of Pd nanoparticles encapsulated in a silica matrix showed high catalytic activity in the Suzuki coupling of aryl iodides and aryl bromides but was less active toward aryl chlorides [33]. The reusability was tested in the coupling of phenyl boronic acid and methyl 4-bromobenzoate. The catalyst could be reused three times without losing activity (Scheme 52).

More recently, Dufaud and co-workers have prepared an aryldicyclohexylphosphine anchored onto mesoporous SBA-15 type silica material for use in Suzuki–Miyaura cross-coupling reactions. The benzyliminopropyl functionalized SBA-15 silica was prepared by heating the benzylimine silane with a suspension of calcined SBA-15. The remaining silanol groups in supported benzylimine were capped by silylation with chlorotrimethylsilane at 60 °C in toluene for 3 h. After removal of the excess silane, the imine-grafted fragment was then transformed into the corresponding amine which was condensed with 2′-(dicyclohexylphosphino)biphenyl-4-carboxylic acid to give the supported dicyclohexylphosphine material **7a**, the latter giving the silica-supported Pd catalyst **7b** after treatment with bis(benzonitrile) Pd dichloride at room temperature in dichloromethane (Scheme 53) [92].

Scheme 62.

The performances of two heterogeneous Pd catalysts formed *in situ* from $Pd(OAc)_2$ or $PdCl_2(PhCN)_2$ and **7a** have been evaluated in cross-coupling Suzuki reactions. For both systems, high conversions and yields were obtained for activated aryl chlorides with phenylboronic acid (Scheme 54). However, under these conditions, aldehyde substituted aryl chloride couples in a modest (53%) yield.

The efficiency of the supported Pd-catalyst **7b** was also examined (Scheme 55) and this catalyst gave satisfactory results in terms of product yield for the coupling of 1-chloro-4-nitrobenzene and 4-chlorobenzonitrile with phenylboronic acid; however, low yield has been reported for the coupling of 4-chlorobenzaldehyde (27%). Also, no data for recycling experiments were reported.

An important contribution in the development of Suzuki chemistry of aryl bromides was described by Bannwarth and co-workers in 2002. In this study, they noted that the immobilization of perfluoro-tagged Pd catalysts on FRPSG exhibit high activities in Suzuki couplings of electron-deficient aryl bromides with aryl boronic acids in 1,2-dimethoxyethane as solvent and the presence Na_2CO_3 at 80 °C (Scheme 56) [61]. For the immobilization of the complex, FRPSG **8** was shaken with a solution of perfluoro-tagged bis(triarylphosphine)palladium complex **8a** in Et_2O, and the solvent was evaporated. This catalyst could be recycled without significant decrease of activity.

Bannwarth and co-workers also provided the first application of a pre-catalyst supported on FRPSG in the Suzuki cross-coupling of phenylboronic acid with 4-bromo-α-hydroxy-benzene acetic acid using water as the sole reaction solvent (Scheme 57) [93]. A complete conversion of expected product was obtained with 0.1 mol% of **9a–d** immobilized on **9**.

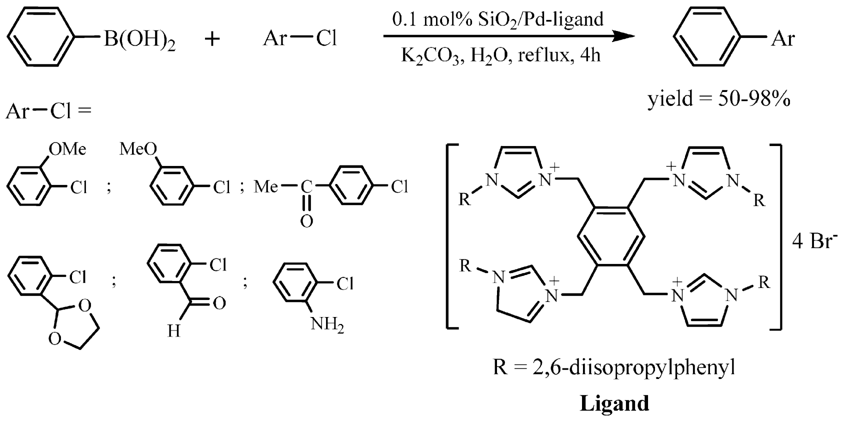
The FRPSG-supported catalyst was removed by simple decantation or filtration, and the catalyst could be reused several times without significant loss of efficiency. An advantage of this strategy compared to conventional covalent catalyst immobilization is that the same support can be used for different catalysts, without the need for a separate linker unit.

In this context, Williams and co-workers have employed reverse phase glass (silica) beads as a support for the palladium catalysed Suzuki reaction of several boronic acids with a large variety of water-soluble aryl iodides and bromides in neat water [94]. In general, the reactions were completed in 1.5–4 h, with low palladium leaching and with the formation of variable amounts of the homocoupling products in some cases. The recycling of the catalyst has been briefly examined in the coupling of 3-Bromophthalic acid with 4-carboxyphenyl boronic acid. Recycled catalyst was used in a repeat reaction without any appreciable loss of activity. Unfortunately, a very low yield or no product was obtained in the coupling of aryl chlorides. Nonetheless, it is noteworthy that this methodology could be extended to a larger-scale synthesis (Scheme 58).

A few electron-rich imidazolidine carbene Pd catalysts supported on the mesoporous silica have been prepared and tested for the Suzuki reaction [95]. The immobilized catalyst **10c** was prepared by reaction of 1-(2,4,6-trimethylbenzyl)-3-(propyltriethoxysilane)imidazolidinium chloride with the $Pd(OAc)_2$ in DMSO followed by grafting onto the surface of mesoporous silica (Scheme 59).

The resulting catalyst **10c** showed excellent activity in Suzuki coupling of unactivated chloroarenes (Scheme 60). The authors indicated that this catalyst was recovered and re-used with a small decrease in activity.

The group of Pleixats prepared a hybrid organic–inorganic material containing a macrocyclic palladium(0) complex covalently



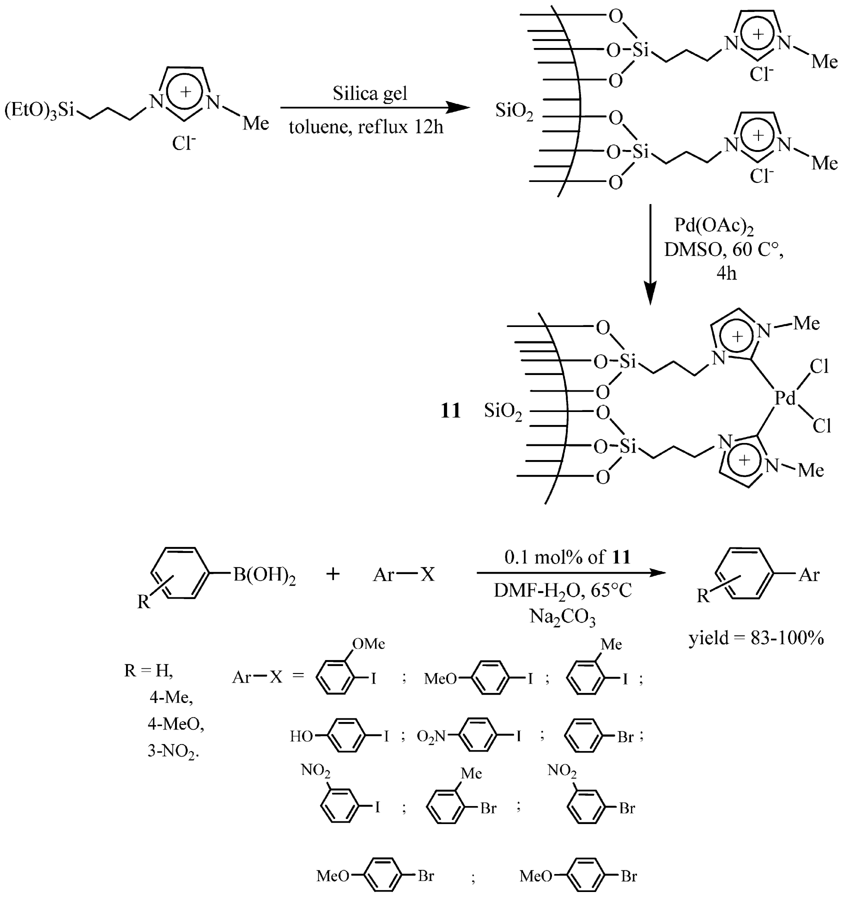
Scheme 63.

bonded to a mesoporous silica matrix obtained from tetraethyl orthosilicate (Scheme 61) [96,97]. The catalyst exhibited good activity in Suzuki cross-coupling reactions with cinnamyl bromide and activated aryl iodides and has been reused up to five cycles, although a progressive decrease in activity has been observed. With non-activated aryl iodides fairly good conversions can be attained in the first cycle, but efficient recycling was not achieved. Metal leaking does not seem to be the reason of this shortcoming.

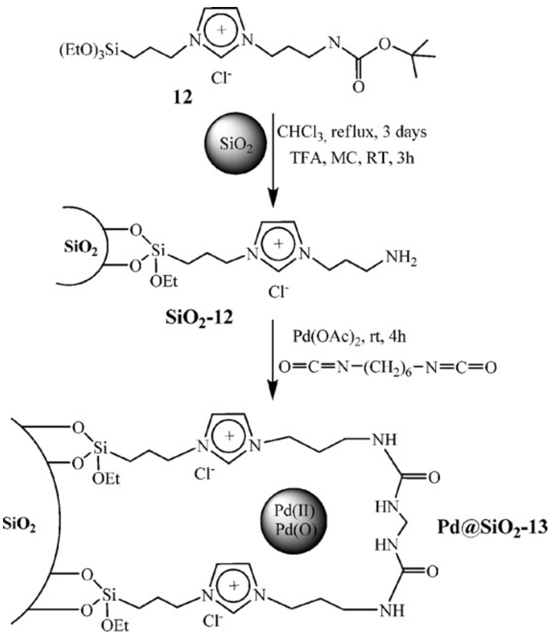
In this same context, the activity of catalysts **2a–c** has been evaluated in the coupling of 4-bromoacetophenone with phenylboronic acid (0.2 mol% Pd, K_2CO_3, DMF/H_2O, 110 °C, 45–60 min) [44]. The reaction was fast, leading to the expected desired product in excellent isolated yield, even after 10 consecutive cycles. Unfortunately, the coupling of 3-chlorobenzonitrile with phenylboronic acid was much slower, with an incomplete and significant decrease of conversion upon recycling.

The same research groups have also described the synthesis of organic–inorganic hybrid silica materials from monosilylated imidazolium and disilylated dihydroimidazolium salts in acidic conditions using $NaBF_4$ and 1-cetyl-3-methylimidazolium chloride as cationic surfactant (Scheme 62) [98]. The catalytic systems formed by palladium acetate and hybrid silica materials show catalytic activity in Suzuki–Miyaura cross-couplings with challenging aryl bromides and chlorides.

These catalysts are efficiently recovered in case of aryl bromides. However, activity and recyclability with aryl chlorides are mod-



Scheme 64.



Scheme 65.

est. Also, *in situ* formation of palladium nanoparticles has been observed in recycling experiments.

In 2003, the research groups of Zhang developed a silica-supported NHC-carbene palladium catalyst for the cross-coupling of aryl bromides with phenylboronic acid in neat water under air [99]. In this case, highly electron-rich substrates such as methoxy-substituted aryl bromides, as well as several nitrogenated heteroaryl bromides, gave the desired products in moderate to excellent yield. Activation of aryl chlorides was also achieved by employing the same catalyst in refluxing *n*-butanol under air (Scheme 63).

It is worth noting that the solid-supported complex can be stored for more than two months without significant loss of activity and can be reused 2–3 times in the coupling of aryl bromides and phenylboronic acid.

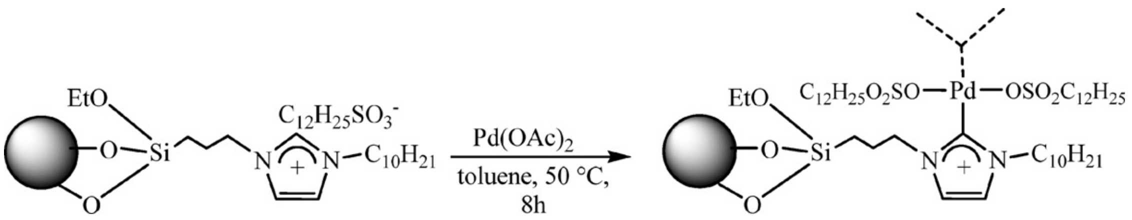
An important observation regarding Suzuki couplings was reported very recently by Jin and co-workers, who established that silica gel-supported *N*-heterocyclic carbene–Pd, prepared by reaction of silica-supported imidazolium chloride with $Pd(OAc)_2$, catalyze cross-couplings of deactivated aryl iodides and electron-rich, electron-neutral, and electron-poor aryl bromides with arylboronic acids containing electron-donating and electron-withdrawing substituents with high yields in an aqueous medium (Scheme 64) [100].

Encouraged by these results, the authors have also tested the coupling of several aryl chlorides in the presence of 1 mol%. The reaction of chlorobenzene with phenylboronic acid proceeded smoothly to afford desired product with high yield. However, low yields were observed in the coupling of substituted aryl chlorides. This catalyst could be simply recovered and reused without a significant loss of catalytic activity as well as air-stable to allow easy use.

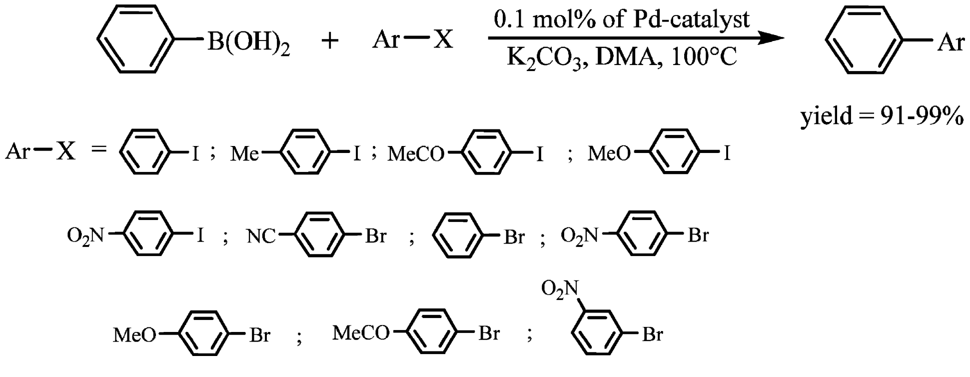
Lee and co-workers have prepared the Pd nanoparticles captured onto spherical silica particles and they have evaluated their catalytic activity in the Suzuki reactions. The synthesis of this material starts by the modification of the surfaces by grafting of the *N*-Boc-protected amine and triethoxysilyl bifunctionalized ionic liquid followed by reaction with a suspension of silica particles. After refluxing, the silica particles were separated and the Boc protection group was removed by treatment with trifluoroacetic acid to provide silica particles **SiO_2-12**. The latter react with $Pd(OAc)_2$ and then an excess amount of 1,6-diisocyanatohexane to provide silica particles **SiO_2-13** (Scheme 65) [101].

Suzuki–Miyaura coupling between phenylboronic acid and 4-bromoacetophenone was carried out in the presence of Pd@SiO_2-**13** (5 mol% based on Pd content) in DMF at 130 °C for 18 h. After the completion of the reaction, the catalyst was recovered by simple filtration and could be reused several times without any loss in catalytic activity.

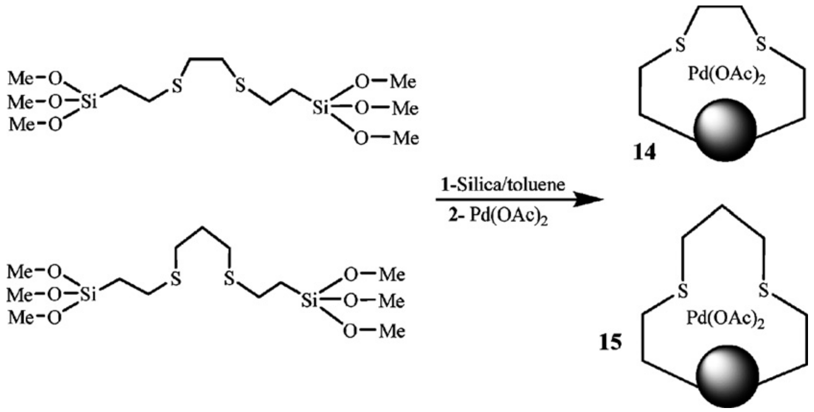
Another *N*-heterocyclic carbene–palladium (NHC–Pd) complex immobilized on ~10 nm silica nanoparticles were synthesized by Tandukar and Sen (Scheme 66) [102]. Because of the very high surface area and small size, these nanoparticles remain suspended in a variety of solvents with the catalyst sites readily accessible to the reactants. The catalyst showed excellent activity towards



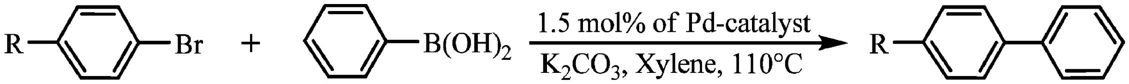
Scheme 66.



Scheme 67.

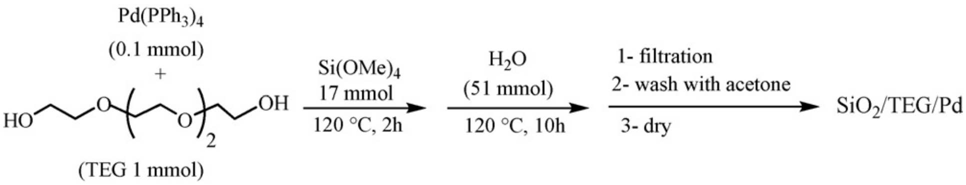


Scheme 68.



R	Catalyst (yield %)	
H	**14** (99)	**15** (99)
MeO	**14** (99)	**15** (99)
Me	**14** (99)	**15** (98)
Cl	**14** (99)	**15** (99)

Scheme 69.



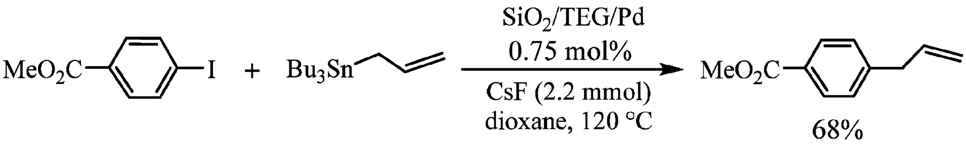
Scheme 70.

Suzuki coupling reaction of different aryl iodides and bromides with phenyl boronic acid using isopropanol: H_2O as solvent. Recycling of the catalytic system was possible in the synthesis of 4-phenyl toluene from 4-iodotoluene and phenyl boronic acid, with only a slight loss of activity (from 95 to 90% yield after five cycles).

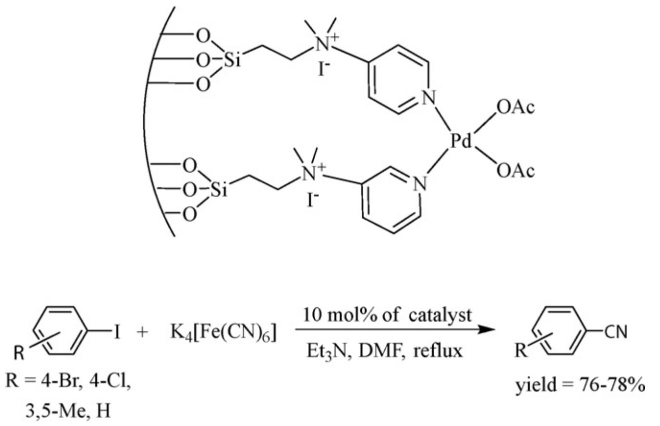
Wang and co-workers have also demonstrated that the catalyst silica-APTS-Pd can be used in the Suzuki reaction of aryl bromides and iodides. In the presence of 1 mol% of the above Pd catalyst, the best results were obtained with K_2CO_3 as the base in DMA at 100 °C [42]. The system was efficient for the coupling of aryl iodides and activated bromides with phenylboronic acid (Scheme 67). However, the coupling of nonreactive aryl chlorides such as chlorobenzene and 4-methylchlorobenzene with phenylboronic acid required a higher catalyst loading and elevated temperatures. The recyclability of this silica-supported Pd catalyst was also examined using the standard procedure of the reaction of iodobenzene and phenylboronic acid. The results revealed that catalyst could be recovered and recycled by simple filtration and reused for more than 15 consecutive trials without significant loss of catalytic activity.

Sullivan and co-workers have reported new silica immobilized di(ethylthio)ethane and di(ethylthio)propane Pd catalysts having two sulfur donor atoms in the immobilized ligands to enhance binding through sulfur coordination. The silica-supported derivatives, silica–$(CH_2CH_2S(CH_2)_2SCH_2CH_2)$–silica and silica–$(CH_2CH_2S(CH_2)_3SCH_2CH_2)$–silica were formed from the trimethoxysilyl compounds by grafting to commercial silica. Post-modification with $Pd(OAc)_2$ gave materials **14** and **15** with likely structures (Scheme 68) [103].

Using catalysts **14** and **15**, the cross-coupling of bromobenzene, 4-bromoanisole, 4-bromotoluene, and 4-cholorobromobenzene



Scheme 71.



Scheme 72.

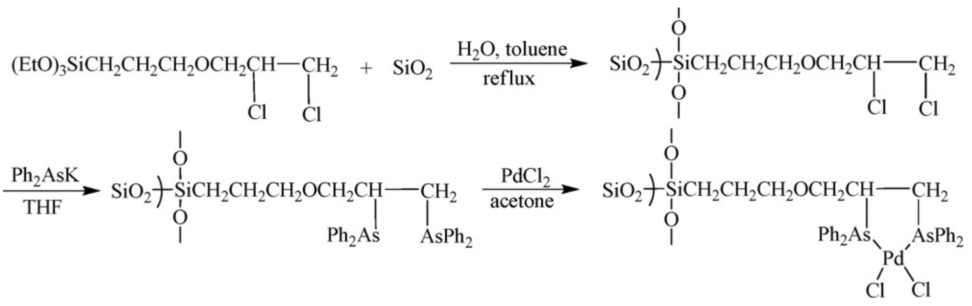
with phenylboronic acid was achieved in satisfactory yields (Scheme 69). The limitations of these catalysts were found with chloroanisole, which not converted under same conditions. These catalysts could be recycled three times using different aryl iodides and phenylboronic acid.

2.4. Stille reactions

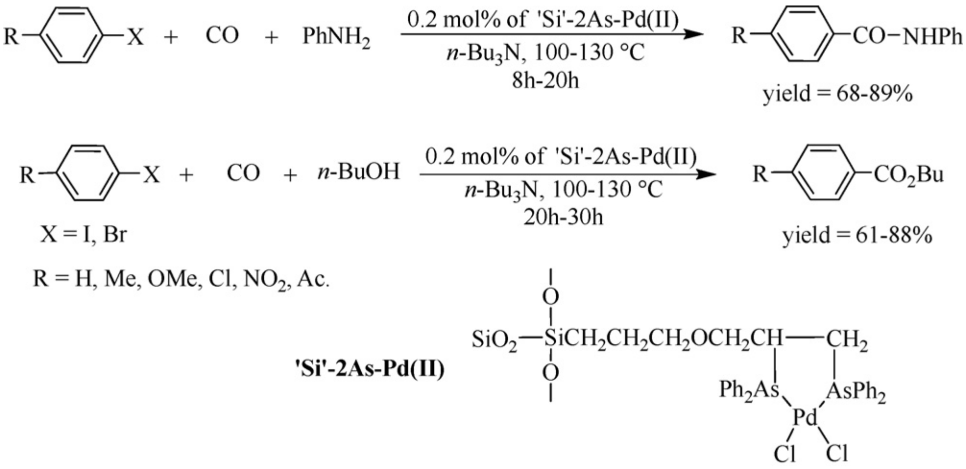
The cross-coupling reaction using organostannane compounds known as the Stille reaction has widespread use in organic synthesis [104–106]. This is due to the growing availability of the organostannanes, their stability to moisture and air, and excellent compatibility with a large variety of functional groups. The Stille cross-coupling has played a pivotal role in a number of total syntheses, such as those of Rapamycin [107] and dynemicin [108,109]. In heterogeneous catalysis, most catalysts are supported on carbon [110,111] and on potassium fluoride/alumina [112]. To the best of our knowledge, the Stille reaction using silica-supported Pd has only rarely been explored. A highly active Pd catalyst on amorphous silica (SiO_2/TEG/Pd) for Stille couplings was prepared via sol–gel of Pd nanoparticles obtained from $Pd(PPh_3)_4$ in tetra(ethylene glycol) and tetramethoxysilane (Scheme 70) [33]. During this process, PPh_3 was oxidized to the triphenylphosphine oxide, which was recovered from the final filtrate of the catalyst preparation in more than 90% yield. This heterogeneous catalyst showed high catalytic activity in the Stille coupling of aryl iodides with allyltributylstannane (Scheme 71).

2.5. Cyanation reactions of aromatic halides

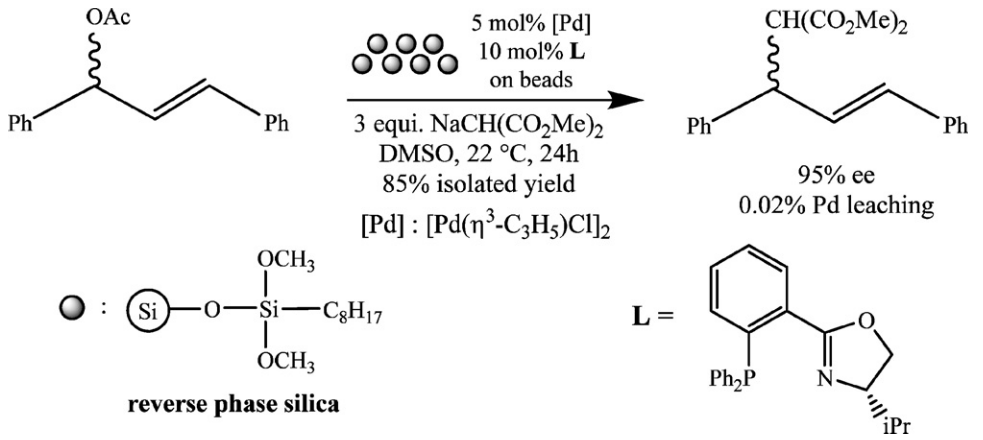
Cyanation of aryl halides is a common and useful transformation in organic synthesis. Not only products containing the nitrile group are biologically important [113] but the nitriles are also valuable in installation of functionalities such as aldehydes, amines, amidines, acids, and acid derivatives [114]. For many years, the only method for cyanation of an aryl halide required stoichiometric CuCN and harsh conditions [115]. The Pd-catalyzed cyanation of aryl halides has been reported as a more convenient alternative [116]. The nanostructured hybrid silica bearing pyridine binding sites showed high catalytic activity in the cyanation reactions. Using 10 mol% of catalyst, $K_4[Fe(CN)_6]$ as the source of cyanide, and triethylamine as a base in refluxing DMF, this catalyst system provided interesting results in the cyanation reactions of various aryl iodides (Scheme 72) [40]; however under the same conditions, the catalyst was not effective for the coupling of aryl bromides and chlorides.



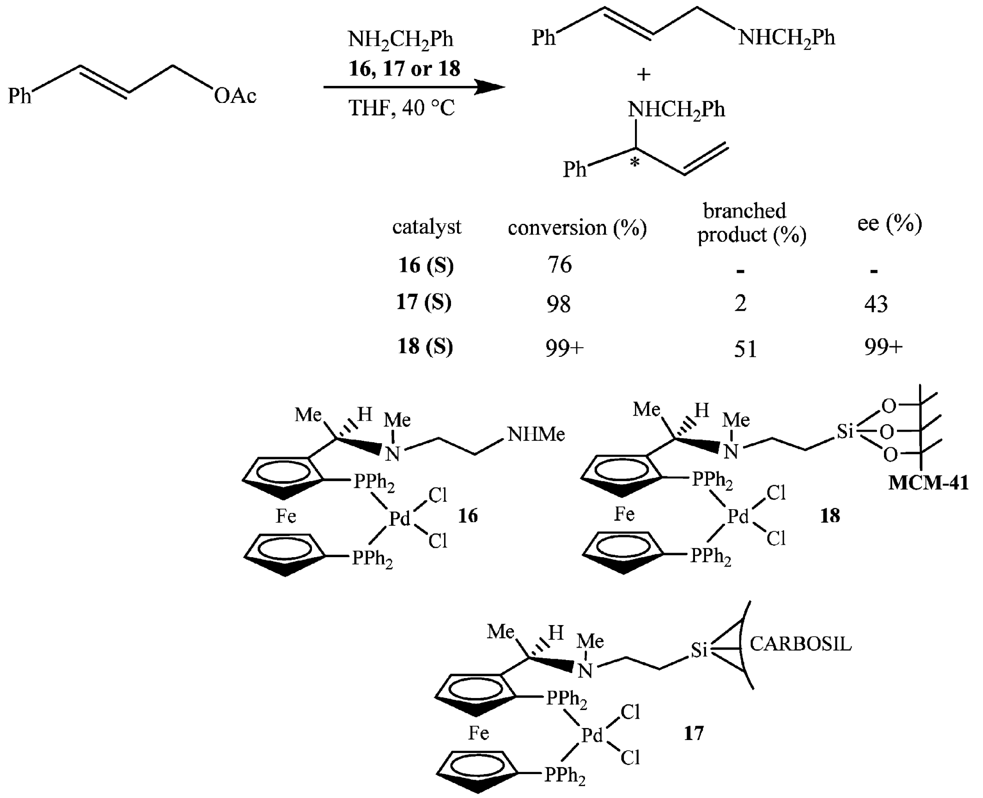
Scheme 73.



Scheme 74.

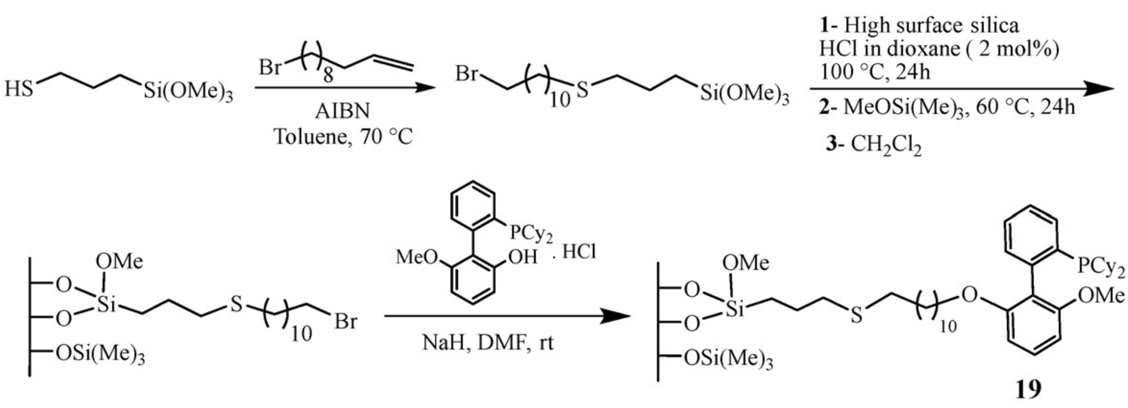


Scheme 75.

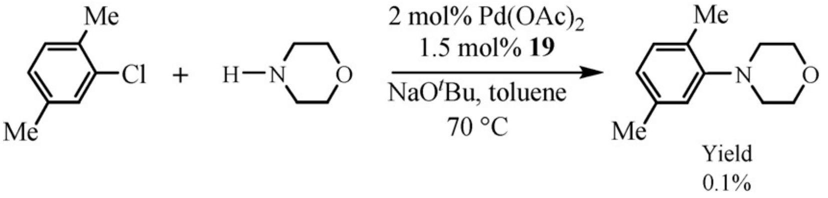


catalyst	conversion (%)	branched product (%)	ee (%)
16 (S)	76	-	-
17 (S)	98	2	43
18 (S)	99+	51	99+

Scheme 76.



Scheme 77.



Scheme 78.

2.6. Carbonylation reactions

The Pd-catalyzed carbonylation of aryl halides and triflates furnishes a powerful method for synthesizing an array of carbonyl compounds, such as aldehydes, esters, and amides [117]. Pd on carbon was used in the presence of PPh_3/TsOH/LiCl to synthesize 2-arylpropionic acids by carbonylation of 1-aryl-1-chloroethanes [118]. Cai and co-workers have reported the synthesis of a silica-supported bidentate arsine Pd complex. This catalyst has been prepared from 4-oxa-6,7-dichloroheptyltriethoxysilane via immobilization on fumed silica, followed by reacting with potassium diphenylarsenide in THF and then the reaction with Pd chloride (Scheme 73) [119]. This arsine Pd complex is an efficient catalyst for Heck carbonylation of aryl iodides and activated aryl bromides under atmospheric pressure of carbon monoxide (Scheme 74). The catalyst showed high activity and could be recovered and reused.

3. Silica-supported palladium catalysts for carbon–nitrogen bond formation

3.1. Amination of allylic acetates

The discovery of the Pd-catalyzed allylic alkylation [120] has initiated an intense research effort directed towards the synthesis of useful allylic building blocks [121]. A number of homogeneous chiral ligands have been developed for this kind of reaction [122,123]. This reaction has rarely been studied in its heterogeneous form [124–127]. Williams and co-workers have reported successful use of reverse phase silica in heterogeneous enantioselective allylic substitution reactions [128]. The chiral phosphine-oxazoline **L**, simply incorporated into reverse phase silica, successfully catalyzed the reaction of 3-acetoxy-1,3-diphenylpropene with sodium salt of dimethyl malonate, affording the malonate substituted product in high yield and excellent ee (95%) (Scheme 75). When the reaction was performed in DMSO, the enantioselectivity and product yield of the reaction was high and also the level of Pd leaching was low. Unfortunately, recycling experiments were not reported for this system.

Immobilized ferrocenyl Pd-complexes **17** and **18** have been reported by Johnson et al. [129]. The two catalysts were tested in allylic amination of cinnamyl acetate. Catalyst **18**, immobilized on inner walls of the mesoporous MCM-41, exhibited superior catalytic properties compared to the catalyst **17** anchored on Carbosil. The catalyst **18** showed some degree of regioselectivity for the desirable branched product (51%) and extremely high enantioselectivity (>99% ee), whereas Carbosil immobilized catalysts **17** afforded the branched product in only 2% yield and with 43% ee (Scheme 76). With the homogeneous catalyst **16**, the reaction directed solely toward the straight chain product.

3.2. Buchwald–Hartwig reactions

As a result of the pioneering efforts of Buchwald et al. [130] and Hartwig et al. [131,132] metal-catalyzed C—N bond formation has emerged as an extremely powerful tool for the synthesis of arylamines, which are important to a diverse array of fields, such as pharmaceuticals and agrochemicals [133,134]. This reaction is often catalyzed in homogeneous phase with Pd metal and phosphine ligands. The Buchwald–Hartwig reactions using silica-supported Pd have only rarely been explored. Corma and co-workers had anchored a monophosphine on high area silica supports. The first step consists of the formation of a trimethoxysilane derivative containing a long alkyl chain having terminal bromide leaving group connected through a thioether functional group. After silica functionalization with the desired loading of the brominated silyl groups, an excess of trimethylmethoxysilane was added to the reaction mixture to mask the remaining silanols of the silica surface. The resulting bromide-functionalized, high surface area silica can undergo nucleophilic substitution by monophosphine at room temperature to yield the silica-supported phosphine ligand **19** (Scheme 77) [135]. This material was then tested for the Buchwald–Hartwig amination of chloro-p-xylene with morpholine in the presence of Pd acetate. However, compared to the catalytic activities of different known supports, only trace amounts of the C—N coupling products were obtained with this catalyst system (Scheme 78).

4. Concluding remarks and outlook

As demonstrated throughout this review, impressive progress has been reported during the last few years regarding silica-supported catalysts. These catalysts offer a number of advantages, such as excellent stability, easy separation from the reaction mixture by filtration or decantation, reusability for several times with often minimal loss of activity, and wide accessibility of silica. Another advantage is the fact that silica-supported catalysts can also offer the possibility of the use of wide range of ligands. However, despite the impressive progress, a number of challenges remain untapped. The coupling of the readily available and low-cost aryl chlorides continues to pose difficulties and the difference between their activity in homogeneous and heterogeneous phases is very high. Another drawback of the heterogeneous catalysis is that the mechanism of most of the coupling reactions is still unclear. Future research in this area will help us to understand the contradictory results reporting in the field. In addition, the heterogeneous catalyst sometimes can require higher reaction temperatures and catalyst loadings and has limitations in stereoselective reactions. One of the most important parameter that help to identify the limitations and potentialities of any heterogeneous protocol is the reusability of catalyst system and metal leaching seems to be the main cause for the decrease in reactivity upon recycling and this parameter need more attention for future development. Although there have been many advances dealing with silica-supported catalysts in the last few years, there is still a long way to go before achieving the ideal procedure. With all these challenges still present in the battlefield and with the growing interest in the heterogeneous catalysis, it is certain that the silica-supported catalysts will still continue to be a fast-moving topic for the next several years.

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