DOI: 10.1002/adsc.200600286

Suzuki–Miyaura Reactions of Aryl Chloride Derivatives with Arylboronic Acids using Mesoporous Silica-Supported Aryldicyclohexylphosphine

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Received: June 23, 2006; Published online: January 8, 2007

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The Suzuki–Miyaura reactions using mesoporous-supported aryldicyclohexylphosphine as ligand have been investigated. The catalysts were based on SBA-15 type mesoporous silica which was transformed in a four-step synthesis leading to a phosphine-containing hybrid material The most productive catalytic system studied was generated *in situ* from this material and the homogeneous palladium complex, $Pd(OAc)_2$. Other catalytic systems were studied for comparison [homogeneous cataysts, a "preformed" catalyst obtained by reaction of $PdCl_2(PhCN)_2$ and the phosphine-containing material]. Variations involving the solvent system, the substrate aryl chloride and the arylboronic acid reactant were also studied. For both *in situ* and preformed catalyst systems, high conversions and yields are obtained for activated aryl chlorides. Success of the reaction for unactivated aryl chlorides was limited to the catalyst formed *in situ*. The catalyst formed *in situ* was also shown to be reactive under aqueous reaction conditions in the cross-coupling of 1-(4-chlorophenyl)ethanone with phenylboronic acid.

Keywords: aryl chloride derivatives; organic-inorganic mesostructured hybrid materials; palladium immobilization; Suzuki–Miyaura coupling reactions

Introduction

Biaryl derivatives are important substructures in fine chemistry and are of industrial interest in a wide range of applications including the preparation of pharmaceuticals, herbicides, polymers, materials, liquid crystals and ligands for catalysis.[1] Among the different methodologies available for the formation of C−C bonds, the palladium-catalyzed cross-coupling reaction of aryl halides with boronic acids, the so-called Suzuki–Miyaura reaction,[2–9] is one of the most general and powerful routes for the preparation of biaryl compounds.

Because of economic and environmental concerns, numerous efforts have been devoted to the development of catalytic systems which can be efficiently recovered and recycled while keeping the intrinsic activity and selectivity of the active center. Heterogeneous palladium catalysts immobilized on activated carbon,[10–15] silica[16–19] or organic polymers[20–23] have been recently reported and represent attractive alternatives to the homogeneous systems. Various methods are available for the anchoring of transition metal complexes onto organic or inorganic carriers: including entrapment, adsorption, ion-pair formation and covalent binding. Several examples of non-covalent immobilization on a silica matrix can be cited: the fluorous reversed-phase silica gel described by Bannwarth,[24–26] the heterogeneous detergents based on silica gel obtained by Oehme[27] and zeolites containing $PdCl_2$ studied by Garcia.[28] Nevertheless, the attachment of the metal complex to the support by covalent bond formation provides many advantages over the non-covalent approach, the main one being to reduce leaching and thus palladium contamination of the products. In the last five years, several palladium complexes based on a silica matrix have been developed by sol-gel processes or by anchoring procedures onto mesoporous silica (SBA, MCM type, etc). Oxime[29,30] or imine[31] carbapalladacycle complexes, carbene-bearing palladium complexes[32] Pd(II) complexes with N-N[33–38] or N-X (X = O, S)[39] chelation and triolefinic Pd(0) complex[40,41] have been described and their performances examined in the cross-coupling reactions of aryl iodides or aryl bromides with arylboronic acids. Generally, yields up to 90% were obtained for the desired coupling product.

From an industrial point of view, aryl chlorides, despite their lack of reactivity, are more interesting substrates as they are cheaper and readily accessible raw materials. Only few examples of palladium catalysts on silica supports capable of activating chloroarenes towards C–C bonds formation reactions have been described in the literature.[29,30,32,34,38] Generally, the yields vary in a range situated between 60 and 90% in the case of activated aryl chlorides. The recyclability of these catalytic solids, which is a key point in the development of heterogeneous catalysts, was not systematically addressed by all authors. Corma et al.,[29,30] however, have demonstrated that the oxime carbapalladacycle complex anchored onto a mercaptopropyl-modified silica surface could be reused eight times in the Suzuki reaction of *p*-chloroacetophenone and phenylboronic acid in water without noticeable decreases in activity. Pleixats et al.,[38] on the other hand, have shown a significant decreases of conversion of *m*-chlorobenzonitrile upon recycling for each of the five consecutive cycles performed, using silica materials containing di(2-pyridyl)methylamine-palladium dichloride complex as heterogeneous catalyst.

In homogeneous catalytic systems, electron-rich and sterically hindered phosphines[42–52] seem to be the best ligands for the cross-coupling reactions of aryl chlorides with arylboronic acids.

Recently, one of the authors has described the use of a new bulky and basic aryldicyclohexylphosphine based on D-glucosamine[53] or immobilized on polystyrene or polystyrene/polyethyleneglycol copolymer[54] as an effective ligand for the palladium-catalyzed cross-coupling reaction of activated aryl chlorides with arylboronic acid in organic or organic-aqueous mixtures. To extend the scope of these initial studies, and potentially prepare mechanically and chemically more stable heterogeneous catalysts, we chose to tether the aryldicyclohexylphosphine on an inorganic oxide. It is well known that the type of support material used may be a crucial factor in the performance of the supported catalyst,[55] whether for its mechanical properties, inductive electronic effects or chemical stabilization of active species. Mesostructured porous silicas (e.g., MCM-41, MCM-48, SBA-15) attained our attention as catalytic support due to their specific surface (which can reach 1000 $m^2 \cdot g^{-1}$) and the possibility of tuning pore size between 2–10 nm, properties which are also accompanied by very high thermal and mechanical stability.

In the present contribution, we report on the preparation of aryldicyclohexylphosphine anchored onto mesoporous SBA-15 type silica material using a stepwise patterning approach. The applicability of the two supported metal complexes obtained from the silica-modified phosphine, respectively, $Pd(OAc)_2$ and $Pd(C_6H_5CN)_2Cl_2$, to the cross-coupling reaction of various aryl chlorides with arylboronic acids is also described.

Results and Discussion

Stepwise Synthesis of Phosphine-Functionalized SBA-15 Silica Material

The general approach used for heterogeneous catalyst synthesis was the immobilization of the phosphine ligands on the surface of preformed mesoporous SBA-15 type silica. As mentioned above, numerous examples of phosphine ligands tethered to oxide surfaces have been reported, and a common drawback to that approach is the reaction of the grafted phosphine functional groups with the oxide surface leading to non-coordinative phosphine oxides and consequently to catalyst leaching.[56] Thus, we adopted a multi-step tethering protocol in which an initial functional anchor is introduced, the surface is then deactivated by silylation, and the phosphine is then generated in two steps. Jones had previously demonstrated the possibility of obtaining patterned surface modified by aminopropyl functional groups.[57,58] In this study, the functional group is introduced in a protected form as an imine, the structure of which determines the patterning of the eventual functional groups on the surface. The proof-of-concept studies cited above used a very bulky trityl-containing patterning agent, and thus the amino groups were relatively widely spaced on the surface. In our case, we wished to generate chelating ligand systems, and so we chose a less bulky patterning agent containing a benzyl group (Figure 1). The benzylimine silane, **1**, was easily obtained by condensation of benzaldehyde and 3-aminopropyltrimethoxysilane in methanol at room temperature. Note that Jones has very recently published the utilization of this patterning agent to produce higher loadings

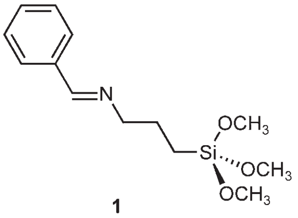

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Figure 1. Patterning agent for silica surface modification.

while maintaining site isolation between amine sites on an SBA-15 silica surface.[59]

The hybrid material was produced by post-synthetic modification of an SBA-15 type mesoporous silica.[60–62] This class of support was chosen for the very large pore aperture, which would facilitate the introduction of bulky ligands, metal complexes and substrates. The patterning agent, **1**, was reacted with a suspension of calcined SBA-15 in dry toluene at 80 °C overnight. The reaction likely proceeds *via* the condensation of surface silanols of the oxide support with the siloxane groups of **1**. After the reaction period, the solid was washed by Soxhlet extraction with CH_2Cl_2 for 15 h, which assured the total removal of physisorbed organic precursor to give **1.SBA-15**.

We characterized **1.SBA-15** by a battery of spectroscopic and quantitative methods (thermogravimetric analysis, elemental analysis, solid state ^{29}Si, and ^{13}C NMR, infrared spectroscopy, nitrogen sorption, and powder XRD). These data are in good accord with the recent Jones publication of a nearly identical species prepared at room temperature (see Supporting Information for data not included in this discussion).[59]

A highly ordered mesostructured hybrid material was obtained with an organic content of 1.7 mmol/g dry SiO_2 (from elemental analysis). The ^{29}Si CP-MAS NMR (Supporting Information) exhibited peaks at −53, −60 and −69 ppm (T^1, T^2 and T^3 sites, respectively) confirming the formation of a covalent bond between the organosilane silicon and the surface. One should note that there is a peak at 48 ppm in the ^{13}C CP-MAS NMR (Figure 2; bottom) of **1.SBA-15** indicating the presence of residual methoxy groups at the point of attachment with the surface, which is also consistent with the presence of not fully condensed T^1 and T^2 sites.

The overall synthetic process after the initial grafting of the patterning agent employed is given in Scheme 1. At each stage, the chemical transformations were monitored by CP-MAS ^{13}C NMR spectroscopy (Figure 2).

The residual surface silanol groups were first capped with chlorotrimethylsilane (resulting in material **2.SBA-15**) in order to avoid interactions with the silica surface in later steps. This was confirmed by the appearance, in the ^{13}C NMR spectrum of **2.SBA-15** (Figure 2), of a new resonance at −1.25 ppm characteristic of the carbons of the trimethylsilyl group in addition to the peaks attributed to the propyl-imino-benzyl fragment. The nitrogen analysis of this material was not significantly different from that of **1.SBA-15** (1.65 mmol g^{-1} *vs.* 1.7 mmol g^{-1}).

The imine-grafted fragment was then transformed into the corresponding amine by acid hydrolysis (**3.SBA-15**, nitrogen microanalysis, 1.3 mmol g^{-1}). The clean conversion to the amine was evidenced by the

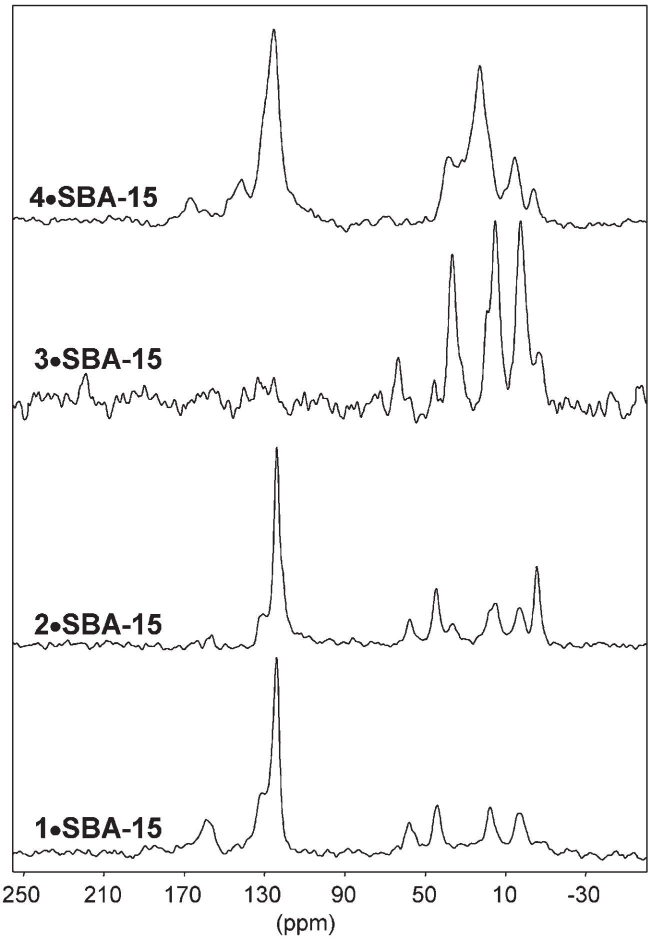
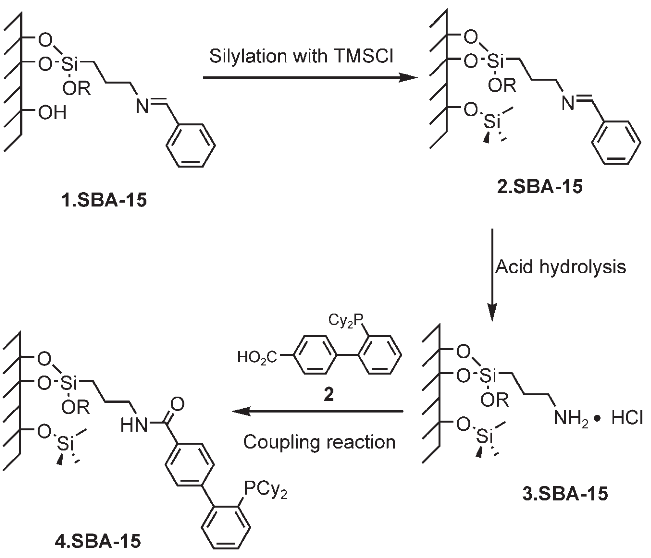


Figure 2. Mesoporous silica-supported dicyclohexylarylphosphine, stepwise synthesis followed by CP-MAS ^{13}C NMR spectroscopy.



Scheme 1. Mesoporous silica-supported dicyclohexylarylphosphine prepared by stepwise transformation of a benzyl-imino-grafted species.

total disappearance of the aromatic (123–134 ppm) and the imine (162 ppm) carbons in the ^{13}C NMR (Figure 2) with the concomitant appearance of a new resonance at 40 ppm typical of the carbon adjacent to an amine functionality. Note that most of the amines in **3.SBA-15** were obtained as their corresponding salts due to the protonation of the nitrogen by HCl (Cl/N molar ratio of 0.86) under the deprotection conditions.

Finally, the direct condensation of 2′-(dicyclohexylphosphino)biphenyl-4-carboxylic acid, **2**, with the amine functionalities of **3.SBA-15** in the presence of 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (EDC·HCl), 1-hydroxybenzotriazole (HOBT) and $NaHCO_3$ as the base afforded the desired SBA-15 silica supported dicyclohexylphosphine material (**4.SBA-15**). The presence of a base was necessary to trap the hydrochloric acid of the coupling reagent (EDC) and to neutralize the protonated amines of **3.SBA-15**.

In the ^{13}C CP-MAS NMR of **4.SBA-15** (Figure 2, top) one observes clear evidence for a condensation reaction in the appearance of a broad, very intense resonance in the aromatic region of the spectrum (127 ppm). Interpretation of the alkyl region is impossible due to the broadening of peaks and overlap between the different alkyl species peaks present. More significantly, one discerns the appearance of a weak peak which can be interpreted as a carbonyl resonance at 169 ppm.

The ^{31}P CP-MAS NMR of **4.SBA-15** (Figure 3) exhibits an intense signal at −15.0 ppm, which can be attributed to the grafted phosphine ligand (the ^{31}P NMR spectrum of **2** exhibits a single peak at −12.0 ppm), and a weak resonance at 52.9 ppm, which may be due to some oxidation of the phosphorus species. The phosphorus analysis (0.7 %wt) corresponds to a **4.SBA-15** loading of only 0.3 mmol/g SiO_2 suggesting that the condensation reaction (Figure 3) between the carboxylic acid-derived phosphine and the aminopropyl-functionalized silica was not complete (~20 % yield). This yield is somewhat disappointing, and a potentially coordinating amino ligand in the final material may be present. An independent route in which the fully developed ligand system is synthesized and isolated prior to grafting is under way.

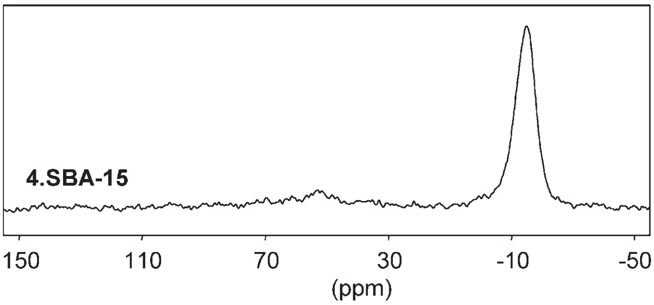


Figure 3. CP-MAS ^{31}P NMR of mesoporous silica-supported dicyclohexylarylphosphine.

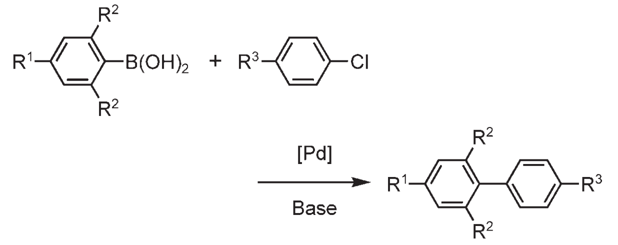
Physicochemical (X-ray powder diffraction) and textural property data (nitrogen sorption isotherms) for the different hybrid materials have been gathered in the Supporting Information. X-ray diffraction patterns of the supported organic species show three clear peaks in the 2θ-range of 0.6–3°, typical of ordered hexagonal mesophases with d(100) spacing varying from 90 to 105 Å. This result indicates that the ordered structure of the organic-inorganic hybrids has been maintained throughout the post-synthetic transformations. Nitrogen adsorption-desorption measurements show a type IV isotherm typical of mesoporous solids. Relatively narrow pore diameter distributions were observed for all materials with median pore diameters between 49 and 58 Å. The surface area was determined by BET at each step of the synthesis. In accordance with the Jones observation, the grafting of the patterning agent **1** resulted in a sharp decrease in surface area (to 350 $m^2 \cdot g^{-1}$). This parameter was relatively unaffected by the methylation and deprotection steps (**2.SBA-15**, 395 $m^2 \cdot g^{-1}$; **3.SBA-15**, 410 $m^2 \cdot g^{-1}$) whereas the final condensation step leading to the incorporation of the bulky phosphine ligand produces another sharp decrease in specific surface area (**4.SBA-15**, 200 $m^2 \cdot g^{-1}$).

This phosphine-containing mesoporous hybrid material, **4.SBA-15**, was used as a support for the palladium catalyzed Suzuki cross-coupling of various aryl chlorides with boronic acids. Thus, $PdCl_2(PhCN)_2$ (0.5 equivalents per phosphine as determined by microanalysis) was introduced into a dichloromethane slurry of **4.SBA-15** at room temperature. After several hours, the new material **5.SBA-15** was recovered by filtration and washed several times with CH_2Cl_2. The resultant yellow solid was analyzed by microanalysis (1 %wt Pd, P:Pd ratio of 1.8:1). In the catalytic studies, this pre-made catalyst is compared to relevant homogeneous and heterogeneous model species, including *in situ* systems based on **4.SBA-15** with different palladium sources.

Catalysis

The cross-coupling Suzuki–Miyaura reactions of various aryl chlorides with arylboronic acids (Scheme 2) were examined under different reaction conditions and the results are shown in Table 1.

Since water is known to increase the activity of the Suzuki–Miyaura catalyst,[63] three kinds of solvents were used: toluene, water or a 3/2/2 toluene/EtOH/H_2O mixture. (Note that it is necessary to change the nature of the base in each case due to solubility and



Scheme 2. Palladium-catalyzed Suzuki–Miyaura cross-coupling of aryl chlorides and boronic acids.

stability issues.) The reactions were catalyzed with 0.2% M of palladium-catalyst in the presence of 3 equivalents of base and with an aryl chloride/arylboronic acid ratio of 1 to 1.1. When the reactions were conducted in toluene, K_3PO_4 was used as the base at 100 °C; when water was the solvent, K_2CO_3 was the base at 100 °C; and in the case of a 3/2/2 toluene/EtOH/H_2O solvent mixture, Na_2CO_3 was used as the base at 80 °C (the reaction temperature is limited by the boiling point of ethanol). Two heterogeneous palladium catalysts were used: the catalyst formed *in situ* from 0.2% M of $Pd(OAc)_2$ or $PdCl_2(PhCN)_2$ and 0.6% M of supported phosphine **4.SBA-15** and the supported palladium-catalyst **5.SBA-15** with no additional phosphine. (Note that, as mentioned in the characterization section of the paper, as the yield of the **3.SBA-15** to **4.SBA-15** coupling reaction was low, one cannot rule out coordination of some palladium to surface amino ligand moieties. We therefore ran a control experiment using **3.SBA-15** under optimized conditions (entry 8). Very low yield was observed in this experiment suggesting that the surface amino ligands are not involved in a major way in the catalyst activity discussed below.)

For comparison, some homogeneous model reactions were investigated. Given that ligand-free $Pd(OAc)_2$ catalyzes the coupling reaction of aryl iodides and aryl bromides under standard conditions,[5,9,64–69] and aryl chlorides at high temperature (up to 150 °C) or under microwave radiation,[13,70–73] three control runs were performed with $Pd(OAc)_2$. Regardless of the solvent system, no conversion was observed (Table 1, entries 1–3). The addition of three equivalents of phosphine, 2′-(dicyclohexylphosphino)biphenyl-4-carboxylic acid **2**, leads to complete conversion of the 1-chloro-4-nitrobenzene starting material

Table 1. Suzuki-Miyaura reactions of various aryl chlorides with arylboronic acids.[a]

Entry	R^1	R^2	R^3	Catalytic system	Solvent[b]	Conversion[c] (Yield[d]) [%]
1	H	H	NO_2	$Pd(OAc)_2$	Toluene	0
2	H	H	NO_2	$Pd(OAc)_2$	Toluene/EtOH/H_2O (3/2/2)	0
3	H	H	Ac	$Pd(OAc)_2$	Water	0
4	H	H	NO_2	$Pd(OAc)_2$ + $ArPCy_2$·**2**	Toluene/EtOH/H_2O (3/2/2)	100 (96)
5	H	H	NO_2	$Pd(PPh_3)_2Cl_2$[e]	Toluene	6
6	H	H	NO_2	$Pd(PPh_3)_2Cl_2$[e]	Toluene/EtOH/H_2O (3/2/2)	98
7	H	H	NO_2	$Pd(OAc)_2$ + **4.SBA-15**	Toluene	20
8	H	H	NO_2	$Pd(OAc)_2$ + **3.SBA-15**	Toluene/EtOH/H_2O (3/2/2)	3
9	H	H	NO_2	$Pd(OAc)_2$ + **4.SBA-15**	Toluene/EtOH/H_2O (3/2/2)	100 (95)
10	H	H	NO_2	$PdCl_2(PhCN)_2$ + **4.SBA-15**	Toluene/EtOH/H_2O (3/2/2)	99 (98)
11	Me	H	NO_2	$Pd(OAc)_2$ + **4.SBA-15**	Toluene/EtOH/H_2O (3/2/2)	91 (90)
12	H	Me	NO_2	$Pd(OAc)_2$ + **4.SBA-15**	Toluene/EtOH/H_2O (3/2/2)	95
13	H	H	CHO	$Pd(OAc)_2$ + **4.SBA-15**	Toluene/EtOH/H_2O (3/2/2)	53
14	H	H	CN	$Pd(OAc)_2$ + **4.SBA-15**	Toluene/EtOH/H_2O (3/2/2)	97 (68)
15	H	H	Me	$Pd(OAc)_2$ + **4.SBA-15**	Toluene/EtOH/H_2O (3/2/2)	90 (81)
16	H	H	Ac	$Pd(OAc)_2$ + **4.SBA-15**	Water	78 (62)
17	H	H	NO_2	**5.SBA-15**[e]	Toluene/EtOH/H_2O (3/2/2)	94 (92)
18	H	H	CHO	**5.SBA-15**[e]	Toluene/EtOH/H_2O (3/2/2)	27
19	H	H	CN	**5.SBA-15**[e]	Toluene/EtOH/H_2O (3/2/2)	100 (89)
20	H	H	Me	**5.SBA-15**[e]	Toluene/EtOH/H_2O (3/2/2)	0
21	Me	H	NO_2	**5.SBA-15**[e]	Toluene/EtOH/H_2O (3/2/2)	100 (90)
22	H	H	Ac	**5.SBA-15**[e]	Water	0

[a] *Reaction conditions:* [Ar-Cl] = 0.07 M; [Ar-Cl]/[arylboronic acid]/[base]/[Pd system] = 1/1.1/3/0.002 (the ratio of added phosphine/Pd was 3/1); 20 h.

[b] In the case of toluene, the base was K_3PO_4, and the reaction temperature was 100 °C; in the case of water, the base was K_2CO_3, and the reaction temperature was 100 °C; in the case of toluene/EtOH/H_2O, the base was Na_2CO_3 and the reaction temperature was 80 °C.

[c] The conversions were determined by GC.

[d] Isolated chemical yield after column chromatography.

[e] No additional phosphine.

with phenylboronic acid in the mixed solvent system (Table 1, entry 4). In the same way, we studied the reactions catalyzed from $Pd(PPh_3)_2Cl_2$ without additional phosphine. A very low conversion (6%) was obtained when toluene was employed as solvent (Table 1, entry 5), and an almost quantitative conversion (98%) when the 3/2/2 toluene/EtOH/H_2O mixture was used as solvent (Table 1, entry 6). Thus, Suzuki–Miyaura reactions are quite dependent on the experimental conditions, and especially on solvents and palladium complexes used.

In the study of heterogeneous catalysts prepared *in situ*, we first examined the influence of solvents and palladium precursors (Table 1, entries 7, 9, 10). In the case of catalysts formed from $Pd(OAc)_2$, only 20% conversion was obtained in toluene (Table 1, entry 7), whereas full conversion and a 95% yield were determined when the mixed toluene/EtOH/H_2O medium was used (Table 1, entry 9). Changing to $PdCl_2(PhCN)_2$ as palladium precursor in the mixed solvent system also provided excellent conversion (99%) and yield (98%) (Table 1, entry 10).

Different substrates, three activated aryl chlorides and one unactivated aryl chloride, were studied in the mixed solvent system using $Pd(OAc)_2$ (Table 1, entries 9, 11–15). Differences were observed between activating groups in three runs involving aryl chlorides bearing electron-withdrawing groups ($R^3 = NO_2$, CHO and CN) (Table 1, entries 9, 13 and 14). Nitro and cyano substitution of the aryl chloride leads to the corresponding biaryl compounds in high conversion (>97%) whereas the aldehyde substituted aryl chloride gave only 53% conversion.

Most surprisingly, the *in situ* catalyst formed from **4.SBA-15** and $Pd(OAc)_2$ effectively catalyzed the reaction of an *unactivated* susbstrate, 1-chloro-4-methylbenzene, which bears an electron-donating group, with phenylboronic acid (Table 1, entry 15), leading to very high conversion (90%) and a good yield (81%). Note that in the case of the same aryldicyclohexylphosphine supported on organic polymer (polystyrene or polystyrene/polyethylene glycol copolymer),[54] no yield or a very low yield (<30%) were obtained under the same reaction conditions. Thus, the support seems to have a great influence on the activity of the palladium complex on the Suzuki–Miyaura reaction.

The effect of the structure of the boronic acid reactant was studied. The reaction of 1-chloro-4-nitrobenzene with 4-methylphenylboronic acid was compared to that with the more sterically encumbered reactant 2, 6-dimethylphenylboronic acid (Table 1, entries 11 and 12): very similar conversions of 91% or 95%, respectively, were obtained indicating little or no effect.

The use of the preformed supported palladium-catalyst **5.SBA-15** was studied in five cross-coupling reactions in the mixed solvent system. In the case of aryl chlorides bearing electron-withdrawing groups, 1-chloro-4-nitrobenzene and 4-chlorobenzonitrile, the Suzuki–Miyaura reactions with phenylboronic acid led to excellent conversions and very good yields (Table 1, entries 17 and 19). As seen with the catalyst formed *in situ*, the aldehyde substituted substrate, 4-chlorobenzaldehyde, led to poor conversion (27%) (Table 1, entry 18). Contrary to the result with the catalyst formed *in situ*, the unactivated substrate, 1-chloro-4-methylbenzene underwent no measurable reaction with phenylboronic acid at 80 °C (Table 1, entry 20). Again, the 4-methylphenylboronic acid reactant was shown to be effective when coupled with 1-chloro-4-nitrobenzene (Table 1, entry 21), as full conversion and a 90% of yield were obtained.

Finally, for economic and environmental concerns, we have tested the performance of the catalysts in the cross-coupling reaction between 1-(4-chlorophenyl)-ethanone and phenylboronic acid using water as solvent (Table 1, entries 16 and 22). In the case of preformed catalyst, **5.SBA-15**, no conversion was observed under favorable conditions, whereas from catalyst prepared *in situ* [$Pd(OAc)_2$ + **4.SBA-15**], a conversion of 78% was obtained with an isolated chemical yield in 1-biphenyl-4-ylethanone of 62%. These first results seem to show that the silica-supported palladium catalyst prepared *in situ* is more active and/or stable than the preformed catalyst for the Suzuki–Miyaura reaction.

Conclusions

In summary, we have described the stepwise synthesis of an aryldicyclohexylphosphine functionalized SBA-15 silica material using a patterning approach and demonstrated its efficiency as a support for the palladium-catalyzed Suzuki–Miyaura cross-coupling of various substituted aryl chlorides with arylboronic acids. The novel supported catalyst systems were studied under a variety of reaction conditions with varying substrates and reactants. Two principle new catalysts were studied, that obtained *in situ* from the phosphine-modified SBA-15 mesoporous hybrid material, **4.SBA-15**, and a palladium precursor, and that obtained and isolated from the prior reaction of the precursor with **4.SBA-15**. For both systems, high conversions and yields are obtained for activated aryl chlorides. Success for the reaction of unactivated aryl chlorides was limited to the catalyst formed *in situ*. The catalyst formed *in situ* was also shown to be reactive under aqueous reaction conditions in the cross-coupling of 1-(4-chlorophenyl)ethanone with phenylboronic acid. Further studies are conducted and will be reported in due course to address the recyclability of these novel catalytic systems especially in water.

Experimental Section

General Remarks

All manipulations were conducted under strict inert atmosphere or vacuum conditions using Schlenk techniques. The solvents were dried using standard methods and stored over activated 4 Å molecular sieves. Methanol was dehydrated by reaction with magnesium ethoxide prepared from magnesium turnings and iodine. Tetraethoxysilane (TEOS), poly-(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymer (Pluronic 123, MW: 5000), redistilled benzaldehyde, 4-chlorobenzonitrile, 1-chloro-4-nitrobenzene, 1-chloro-4-methylbenzene were purchased from Aldrich Chemical and used without further purification. 4-chlorobenzaldehyde, phenylboronic acid, 4-methylphenylboronic, 2, 6-dimethylphenylboronic acid, 1-iodo 2-bromobenzene, *n*-butyllithium 1.6M in hexanes were obtained from Acros and palladium chloride from Alfa. $PdCl_2(PhCN)_2$ was prepared according a procedure described elsewhere.[74] Aryldicyclohexylphosphine, $ArPCy_2$, was synthesized in three steps following the procedure reported by Konovets et al.[53,54]

Characterization

All solid-state NMR spectra were recorded on Bruker DSX-300 or Avance-500 spectrometers equipped with a standard 4 mm probehead. The spinning rate was typically 10 kHz. ^{13}C, ^{29}Si and ^{31}P NMR spectra were obtained by use of cross-polarization (contact time 5 ms). To achieve a good polarization transfer, a ramp was used on the X channel. Recycle delays were typically 1 s (a study on the ^{1}H nucleus showed that it was sufficient to allow all protons to fully relax). ^{1}H, ^{13}C and ^{29}Si MAS spectra were referenced to tetramethylsilane. ^{31}P MAS spectra were referenced to 85% H_3PO_4.

X-ray powder diffraction (XRD) data were acquired on a Bruker D5005 diffractometer using Cu Kα radiation ($\lambda =$ 1054184 Å). A Netzsch thermoanalyser STA 409PC was used for simultaneous thermal analysis combining thermogravimetric (TGA) and differential thermoanalysis (DTA) at a heating rate of $5\,^{\circ}C\,min^{-1}$ in air. Nitrogen adsorption and desorption isotherms were measured at 77 K. The organic-inorganic hybrids were evacuated at 160 °C for 24 h before the measurements. Specific surface areas were calculated following the BET procedure. Pore size distribution was obtained by using the BJH pore analysis applied to the desorption branch of the nitrogen adsorption/desorption isotherm.

The palladium content determinations for **5.SBA-15** catalyst were performed by ICP-AES spectroscopy from a solution obtained by treatment of the catalyst with a mixture of HBF_4, HNO_3 and HCl in a Teflon reactor at 180 °C.

Liquid NMR spectra were recorded on a Bruker AC-300 spectrometer and referenced as following: ^{1}H (300 MHz), internal $SiMe_4$ at $\delta = 0.00$ ppm, ^{13}C (75 MHz), internal $CDCl_3$ at $\delta = 77.2$ ppm, and ^{31}P (121 MHz), external 85% H_3PO_4 at $\delta = 0.00$ ppm. Flash chromatography was performed at a pressure slightly higher than atmospheric pressure using silica (Merck Silica Gel 60, 230–240 mesh).

GC analyses were performed on a Shimadzu GC-14B chromatograph equipped with a FID detector, a C-R6 A integrator and a Quadrex OV1 column (30 m × 0.25 mm). Helium was used as carrier gas (initial temperature120 °C, heating rate $10\,^{\circ}C\,min^{-1}$ up to 250 °C).

Synthesis of 3-*N*-Benzylideneaminopropyltrimethoxysilane Patterning Agent (1)

A slight excess of benzaldehyde (2.13 g, 0.02 mol) was stirred at room temperature with 3-aminopropyltrimethoxysilane (3 g, 0.016 mol) in dry methanol overnight. The reaction mixture was then filtered and methanol was removed under vacuum. The crude benzylimine product was obtained in 70% yield. ^{1}H NMR (CD_2Cl_2, 200 MHz): $\delta = 0.76$ (m, 2H, $SiCH_2$), 1.86 (m, 2H, $SiCH_2CH_2$), 3.64 (11H, N-CH_2 and CH_3O), 7.4 (3H, phenyl), 7.8 (2H, phenyl), 8.3 (1H, N = CH-Ph); ^{13}C NMR (CD_2Cl_2, 50 MHz): $\delta = 6.8$ (CH_2Si), 24.2 (CH_2CH_2-Si), 50.8 (CH_3O), 64.0 (N-CH_2), 128.0, 128.5, 130.4, 136.7 (phenyl), 160.6 (N = CH).

Preparation of Silica-Supported Aryldicyclohexylphosphine

Mesoporous SBA-15 type silica was used as support and was prepared by the acid-catalyzed, non-ionic assembly pathway described by Margolese et al.[75] The structure directing agent (Pluronic 123) was removed quantitatively from the as-synthesized material by calcination at 500 °C overnight under air as evidenced by TGA analysis and infrared spectroscopy. Prior to the grafting reaction, the surfactant-free mesoporous silica was rigorously dried under a flow of nitrogen at 200 °C. The aryldicyclohexylphosphine functionalized SBA-15 was prepared in four steps:

Synthesis of Benzyliminopropyl Functionalized SBA-15 Silica, 1.SBA-15

Compound **1** (1.0 g, 3.74 mmol) was added to a suspension of SBA-15 silica (2 g) in dry toluene and stirred at 25 °C for two hours to allow the diffusion of the molecular precursor into the channels of the pores. The reaction mixture was then heated at 80 °C overnight. The resulting solid was filtered under nitrogen, washed thoroughly with a small amount of toluene followed by Soxhlet extraction with CH_2Cl_2 and finally dried at 30 °C under vacuum. ICP-AES analysis: 15.40%wt C, 2.07%wt H, 1.82%wt N. The organic content of **1.SBA-15** was found to be $1.7\ mmol\,g^{-1}SiO_2$ derived from nitrogen analysis (see Supporting Information).

Residual Silanol-Capping Reaction, 2.SBA-15

The remaining silanol groups in **1.SBA-15** were capped by silylation with chlorotrimethylsilane at 60 °C in toluene for 3 h. The excess of silane was removed by washing the solid with dry toluene. ICP-AES analysis: 12.71%wt C, 2.35%wt H, 1.74%wt N. The organic content of **2.SBA-15** was found to be $1.65\ mmol\,g^{-1}SiO_2$ derived from nitrogen analysis (see Supporting Information).

Aminopropyl-Functionalized SBA-15 Silica, 3.SBA-15

Aminopropyl-grafted fragments were generated by acid hydrolysis of the imino functionalities in **2.SBA-15**. Typically, 1 g of **2.SBA-15** was suspended in a 2/2/1 solution of H_2O/MeOH/HCl (37% wt) and stirred at room temperature overnight. The solid was filtered, washed thoroughly with water, methanol and THF and then dried under vacuum at room temperature. ICP-AES analysis: 5.74%wt C, 2.06%wt

H, 1.51 %wt N, 3.33 %wt Cl. Note that most of the primary amines (>85 %) were protonated by HCl. The organic content of **3.SBA-15** was found to be 1.3 mmol g^{-1}SiO$_2$ derived from nitrogen analysis (see Supporting Information).

Aryldicyclohexylphosphine Functionalized SBA-15 Silica, 4.SBA-15

Phosphino-binding sites were introduced through the condensation of carboxylic acid-derived aryldicyclohexylphosphine, **2**, with aminopropyl-functionalized SBA-15 silica in the presence of coupling reagents. Typically, a mixture of **3.SBA-15** (192.3 mg, 1.3 mmol g^{-1}SiO$_2$ of NH$_2$ groups), carboxylic acid, **2** (100 mg, 0.253 mmol), EDC.HCl (78 mg, 0.405 mmol), HOBT (68 mg, 0.506 mmol) and NaHCO$_3$ as the base (55 mg, 0.655 mmol) in DMF (20 mL) was stirred at room temperature for 48 h. The solid was collected by filtration under nitrogen, washed with deaerated DMF, methanol and water and Soxhlet extracted with dichloromethane. Finally, the solid was dried under reduced pressure at 25 °C overnight. ICP-AES analysis: 0.7 %wt P. The organic content of **4.SBA-15** was found to be 0.3 mmol g^{-1}SiO$_2$ derived from phosphorus analysis (see Supporting Information).

Palladium-Bound Aryldicyclohexylphosphine Functionalized SBA-15 Silica, 5.SBA-15

Two equivalents of **4.SBA-15** (0.3 mmol g^{-1}SiO$_2$ of phosphine ligand) were reacted with one equivalent of bis(benzonitrile)palladium dichloride at room temperature in dichlormethane by adapting a procedure reported elsewhere.[76] The initial white organic functionalized silica material turned yellow upon reaction. The solid was then filtered, washed carefully with CH$_2$Cl$_2$ (10 mL × 3) and dried under vacuum. The metal complex immobilized silica material was referred to as **5.SBA-15** and was used in the catalytic experiments without additional palladium or phosphine introduction. ICP-AES analysis: 0.61 %wt P, 1 %wt Pd with a P/Pd molar ratio of 1.8.

Typical Cross-Coupling Procedure in Toluene or in Water

The supported palladium catalyst [Pd(OAc)$_2$ (0.45 mg, 2 μmol)/**4.SBA-15** (26.57 mg, 6 μmol, based on phosphorus analysis 7 %wt P) or **5.SBA-15** (21.28 mg, 2 μmol, based on palladium analysis 1 %wt Pd)], K$_3$PO$_4$ (636.8 mg, 3.0 mmol) and solvent (6 mL) were placed in a flask under argon. The solution was stirred for 30 min at room temperature. A mixture of aryl halide (1.0 mmol), and arylboronic acid (1.1 mmol) in solvent (8 mL) was then added. The resulting mixture was stirred at 100 °C for 20 h. After cooling to room temperature, the heterogeneous solution was filtered, and the filtrate was concentrated in vacuo to give the corresponding crude biaryl compound, which was purified by flash chromatography on silica gel to give the pure coupling product (AcOEt/petroleum ether: 1/30).

Typical Cross-Coupling Procedure in a 3/2/2 Toluene/EtOH/H$_2$O Solvent System

The supported palladium catalyst [Pd(OAc)$_2$ (0.45 mg, 2 μmol)/**4.SBA-15** (26.57 mg, 6 μmol, based on phosphorus analysis 0.7 %wt P) or **5.SBA-15** (21.28 mg, 2 μmol, based on palladium analysis 1 %wt Pd)] and toluene (3 mL) were placed in a flask under argon. The solution was stirred for 30 min at room temperature. Aryl halide (1 mmol) and arylboronic acid (1.1 mmol) dissolved in a mixture of toluene (3 mL) and EtOH (4 mL) were then added in the flask, followed by addition of Na$_2$CO$_3$ (317.97 mg, 3 mmol) in water (4 mL). The resulting mixture was stirred at 80 °C for 20 h. After cooling to room temperature, the heterogeneous solution was filtered, and the two phases of the filtrate were separated. The EtOH/H$_2$O layer was washed twice with toluene, and the combined organic phases were dried over Na$_2$SO$_4$. Evaporation of the solvent under reduced pressure gives the corresponding crude biaryl compound, which was purified by flash chromatography on silica gel to give the pure coupling product. (AcOEt/petroleum ether: 1/30).

Acknowledgements

KG and RS thank the French Ministry of Education for a fellowship.

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