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Graphical Abstract

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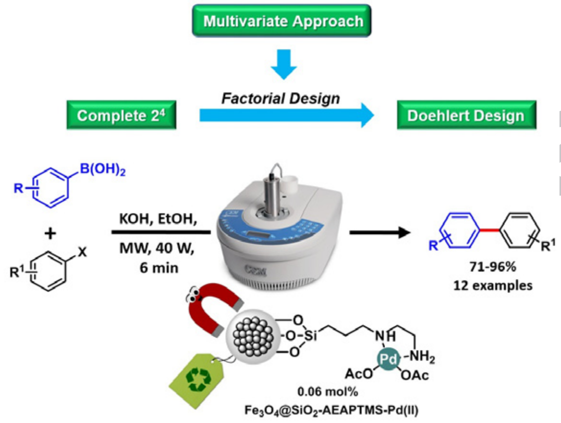

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ABSTRACT

A magnetically recoverable catalyst [Fe_3O_4@SiO_2-AEAPTMS-Pd(II)] was prepared, fully characterized and had its catalytic activity evaluated on the Suzuki cross-coupling reaction under microwave irradiation. The reaction conditions for the synthesis of biaryl compounds was optimized in two stages - an initial fractional design 2^4, in which the parameters reaction time, temperature, solvent and catalyst loading were evaluated, followed by a Doehlert design. The factorial design proved to be a viable approach for obtaining the optimal reaction conditions based on a relatively small number of experiments. Additionally, the biaryl derivatives synthesized by this method were obtained with good to excellent yields (71 to 96%) and the recovery and reuse of the palladium catalyst was also evaluated.

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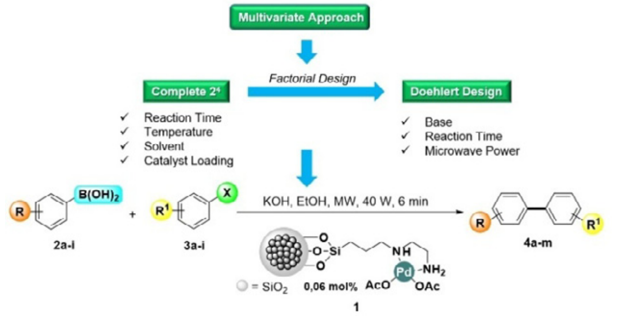
1. Introduction

Catalytic reactions play an important key role in organic synthesis, since they allow the improvement of methods that are used to prepare highly-valuable organic compounds.[1] Following this lead, several research groups have dedicated their efforts to develop more environmentally-benign catalysts for a wide range of organic transformations.[2] Literature surveys show that heterogeneous catalysts take a prominent place in this field, mainly due to some particular features such as easy recoverability and reusability.[3] In this sense, iron oxide magnetic nanoparticles (MNPs) have emerged as an important class of materials for the immobilization of new catalysts owing to their large surface area, high chemical stability, high saturation magnetization values, and both low cost and toxicity.[4] More importantly, MNPs fill the gap between homogeneous and heterogeneous catalysis[5] in terms of activity, selectivity and removal from the reaction medium, since the separation of these types of materials can be easily achieved by using an external magnetic field. Consequently, the generation of residue is minimized, thereby contributing to the development of greener synthetic protocols.[6] Magnetite (Fe_3O_4) is among the most studied MNPs as supports, mainly due to its super-paramagnetic properties, biological compatibility[7] and a wide variety of synthetic methods for its preparation which leads to different morphologies and size distributions.[8] The palladium-catalyzed Suzuki cross-coupling reaction constitutes a very powerful approach for the formation of new C-C bonds.[9] This methodology is used to synthesize a wide range of products, namely biaryl moieties, which can be found in a great number of biologically active compounds, such as valsartan, felbinac and imatinib, among others.[10]

Considering that the Suzuki-Miyaura reaction has been widely applied as an important tool in organic synthesis, there has been a growing interest in and accordingly the development of greener, more sustainable approaches to chemistry.[11] In this way, several new magnetically recoverable palladium-based catalysts have been developed in the last few years and extensively applied in batch,[12] and more recently, in flow processes.[13]

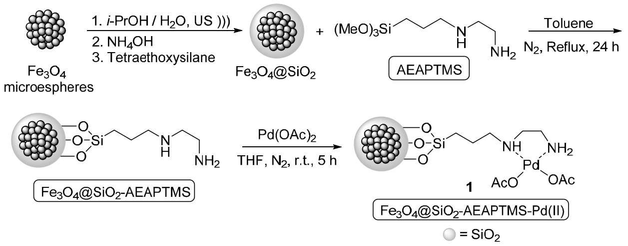
It is well known that most organic reactions are optimized in a univariate approach, being performed one variable at a time. However, according to Leardi,[14] "…this approach would be valid only if the variables to be optimized would be totally independent from each other", which is certainly not the case for most reactions. In this way, it can be assumed that during the optimization of the reaction conditions, the interaction among the different factors being evaluated is highly relevant and can contribute to the obtainment of the best conditions with fewer experiments. Thus, the optimization in a multivariate approach enables the development of mathematical models that can be used to predict the response for any possible setting, even untested regions. Although the experimental design[15] can reduce the number of reactions, thereby reducing the generation of waste and increasing the quality of information that can be obtained, and this approach being already very common in industry, only a few reports from academic groups on this sort of chemistry have been disclosed using this tool.[16]

Bearing these factors in mind, and continuing our ongoing research into the development of greener methodologies,[17] in this paper we report the synthesis of a novel magnetically recoverable Fe_3O_4@SiO_2-AEAPTMS-Pd(II) catalyst for the Suzuki cross-coupling reaction under microwave irradiation via a multivariate approach using factorial design (Scheme 1).



Scheme 1. General design of experiments.

The catalyst Fe_3O_4@SiO_2-AEAPTMS-Pd(II) **1** was prepared following the steps described in Scheme 2. Initially, the magnetite microspheres were prepared through a solvothermal method,[18] followed by a silica-coating step using the well-known Stöber method.[19]. Next, the amino ligand *N*-[3-(trimethoxysilyl)propyl]ethylenediamine (AEAPTMS) was anchored onto the surface of Fe_3O_4@SiO_2 in anhydrous toluene under reflux for 24 h. The obtained Fe_3O_4@SiO_2-AEAPTMS powder was then treated with palladium acetate in tetrahydrofuran (THF) under N_2 atmosphere, at room temperature for 5 h, to generate the Fe_3O_4@SiO_2-AEAPTMS-Pd(II) catalyst **1**. The catalyst was fully characterized by a variety of analytical techniques e.g. x-ray diffraction (XRD), transmission electron microscopy with energy-dispersive x-ray spectroscopy (TEM-EDX), scanning electron microscopy (SEM), X-ray photoelectron spectroscopy (XPS), elemental analysis (EA), inductively coupled plasma optical emission spectrometry (ICP-OES) and vibrating sample magnetometer (VSM).



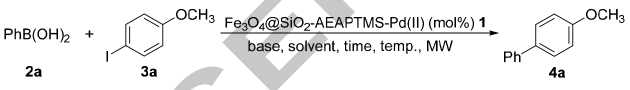
Scheme 2. Preparation of catalyst Fe_3O_4@SiO_2- AEAPTMS-Pd(II).

We have started our characterization studies by evaluating the crystalline structure of the Fe_3O_4 microspheres and the Fe_3O_4@SiO_2-AEAPTMS-Pd(II) catalyst **1** by X-ray diffraction (XRD). The high angle X-ray diffraction pattern of Fe_3O_4 microspheres (black line in Figure S1 in the ESI) showed the typical peaks of the spinel structure of magnetite (2 = 30.1, 35.4, 43.1, 53.5, 57.0, 62.6), while the diffractogram of the final catalyst showed an additional broad peak around (2 =23.3), related to the presence of amorphous silica in the sample. In addition, no characteristic peaks of the palladium nanoparticles were observed, which may be a result of the presence of well-dispersed small particles of the palladium species, or to the presence of a non-crystalline palladium phase.[20] However, the presence of Pd on the catalyst was confirmed by TEM-EDX (see Figure S2 in the ESI). Additionally, the exact concentration of Pd was determined by ICP-OES and the obtained valued was 1.3 wt%.

Aiming to investigate the morphology and size distribution of both the support and the final catalyst, TEM and SEM analyses were conducted (see Figure S3 in the ESI). The SEM images show that the obtained Fe_3O_4 microspheres (Figure S3a) are spherically shaped and a detailed statistical particle count revealed an average size of 227±28 nm (Figure S3b). The TEM image of $Fe_3O_4@SiO_2$ (Figure S3c) confirms the formation of core/shell-structured magnetic silica microspheres with a shell thicknesses of approximately 51,4±5,9 nm. As for the final catalyst, it was possible to notice the presence non-uniformly distributed Pd nanoparticles, with a mean diameter range 9.03±1,23 nm in the surface of the catalyst (Figure S3e) (See the ESI for further details).

In addition, the catalyst **1** was also analysed by XPS in order to determine the oxidation state of the palladium species present in the material. The XPS elemental survey scans of the surface of the fresh catalyst **1** (see Figure S4a in the ESI) showed peaks ascribed to silicon (Si), carbon (C), palladium (Pd), nitrogen (N) and oxygen (O). A closer look at the Pd3d region reveals the presence of two peaks at 337.43 ($3d_{5/2}$) and 342.62 ($3d_{3/2}$), attributed to Pd(II), and other two peaks at 335.84 ($3d_{5/2}$) and 339.97 ($3d_{3/2}$), assigned to Pd(0). The intensities of the peaks clearly indicate that the palladium species are present predominantly in +2 oxidation state (88%) with a lower content of Pd(0). Then, magnetic properties of the synthesized materials were evaluated by VSM at room temperature. The magnetization curves for Fe_3O_4 and $Fe_3O_4@SiO_2$-AEAPTMS-Pd(II) are presented in Figure S5 in the ESI; the values of saturation magnetization for the Fe_3O_4 microspheres and the $Fe_3O_4@SiO_2$-AEAPTMS-Pd(II) were 29.2 and 7.85 emu/g respectively. The significant decrease in the saturation magnetization is due to the formation of the thick silica layer over the surface of the magnetic microspheres, with its further functionalization with the organic ligand and the Pd salt. It is worth mentioning that the magnetic curves show no hysteresis for both two samples, suggesting that both Fe_3O_4 and $Fe_3O_4@SiO_2$-AEAPTMS-Pd(II) catalyst exhibit superparamagnetic behavior, thus being easily dispersed and recovered from reaction medium with the aid of a magnetic field.

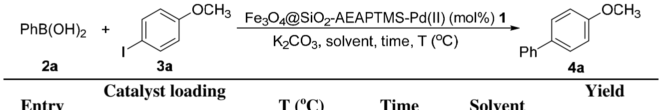
Having the catalyst fully characterized in hand, we moved to evaluate its catalytic activity in the Suzuki reaction and study how different parameters could affect its outcome by using factorial design. In that way, the reaction between phenyl boronic acid **2a** and 4-iodoanisol **3a** was chosen as a model reaction for the optimization studies (Scheme 3) and a series of experiments were performed using a multivariate approach.



Scheme 3. Suzuki cross-coupling reaction between phenyl boronic acid and 4-iodoanisol.

The first stage of the optimization involved an experimental design, which can be used as a powerful tool for identifying the most important variables among many others. Based on literature survey, four experimental factors (solvent, time, temperature and catalyst loading), were selected for testing (Table 1).[21]

Table 1. Full factorial design and results for the optimization of Suzuki cross-coupling reactions. Coded levels (-1 and +1) are in parenthesis.[a]

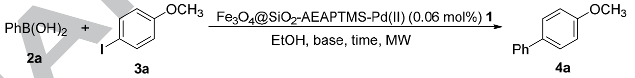


Entry	Catalyst loading (mol%)[b]	T (ºC)	Time	Solvent	Yield (%)[c]
1	0.06 (-1)	25 (-1)	30 (-1)	H_2O (-1)	0
2	0.6 (+1)	25 (-1)	30 (-1)	H_2O (-1)	0
3	0.06 (-1)	100 (+1)	30 (-1)	H_2O (-1)	32
4	0.6 (+1)	100 (+1)	30 (-1)	H_2O (-1)	51
5	0.06 (-1)	25 (-1)	120 (+1)	H_2O (-1)	0
6	0.6 (+1)	25 (-1)	120 (+1)	H_2O (-1)	0
7	0.06 (-1)	100 (+1)	120 (+1)	H_2O (-1)	83
8	0.6 (+1)	100 (+1)	120 (+1)	H_2O (-1)	69
9	0.06 (-1)	25 (-1)	30 (-1)	EtOH (+1)	0
10	0.6 (+1)	25 (-1)	30 (-1)	EtOH (+1)	0
11	0.06 (-1)	100 (+1)	30 (-1)	EtOH (+1)	52
12	0.6 (+1)	100 (+1)	30 (-1)	EtOH (+1)	68
13	0.06 (-1)	25 (-1)	120 (+1)	EtOH (+1)	0
14	0.6 (+1)	25 (-1)	120 (+1)	EtOH (+1)	5
15	0.06 (-1)	100 (+1)	120 (+1)	EtOH (+1)	81
16	0.6 (+1)	100 (+1)	120 (+1)	EtOH (+1)	81

[a] Unless otherwise specified, all the reactions were performed with phenylboronic acid (1,5 mmol) **2a**, 4-iodoanisol (1.0 mmol) **3a**, $Fe_3O_4@SiO_2$-AEAPTMS-Pd(II) **1** and K_2CO_3 (1,5 mmol) in the presence of solvent (10 mL) in a 2 necked round bottom flask. [b] (-1 low and +1 high levels). [c] Yields were determined through CG-MS.

These preliminaries experiments, which were performed using a full factorial design (2^4), indicated that the most important variables were temperature, time and their interaction. The other variables presented negligible effects in the studied range. Posteriorly, a Doehlert design[22] was performed to further study the variables that showed to exert important effects, as well as variables that are known to influence the Suzuki Cross-coupling reaction.

Table 2. Doehlert design results for the optimization of Suzuki cross-coupling reactions. Coded levels (-1 and +1) are in parenthesis.[a]



Entry	Time (min)	Base	Power (W)	Yield (%)[b]
1	6.0 (0)	KOH (-0.12)	40 (0)	92
2	6.0 (0)	KOH (-0.12)	40 (0)	90
3	6.0 (0)	KOH (-0.12)	40 (0)	94
4	11.0 (1.0)	KOH (-0.12)	40 (0)	83
5	8.5 (0.5)	Na_2CO_3 (1.0)	40 (0)	51
6	8.5 (0.5)	K_2CO_3 (0.6)	70 (0.817)	88
7	1.0 (-1.0)	KOH (-0.12)	40 (0)	69
8	3.5 (-0.5)	Et_3N (-1.0)	40 (0)	0
9	3.5 (-0.5)	Cs_2CO_3 (-0.52)	10 (-0.817)	38
10	8.5 (0.5)	Et_3N (-1.0)	40 (0)	2
11	8.5 (0.5)	Cs_2CO_3 (-0.52)	10 (-0.817)	90
12	8.5 (0.5)	Cs_2CO_3 (-0.52)	10 (-0.817)	87
13	3.5 (-0.5)	Na_2CO_3 (1.0)	40 (0)	23
14	6.0 (0)	Na_3PO_4 (0.68)	10 (-0.817)	2
15	3.5 (-0.5)	K_2CO_3 (0.6)	70 (0.817)	90
16	6.0 (0)	K_3PO_4 (-0.84)	70 (0.817)	86
17	11.0 (1.0)	Na_2CO_3 (1.0)	70 (0.817)	80

[a] Unless otherwise specified, all the reactions were performed with phenylboronic acid (1,5 mmol) **2a**, 4-iodoanisol (1.0 mmol) **3a**, $Fe_3O_4@SiO_2$-AEAPTMS -Pd(II) (0.06 mol%) **1** and base (1.5 mmol) in the presence of solvent (1,5 mL) under microwave irradiation. [b] Yields for isolated products.

In this context, microwave irradiation has been pointed in the last decades as one of the most efficient and sustainable energy sources, since it allows to reduce the reaction time, to improve the reaction yields and the product purity, when compared to experiments involving conventional heating.[23] Despite of the controversy surrounding microwave-induced reactions, they have been widely used in organic synthesis.[24] Therefore, we have decided to use a microwave reactor in this stage of the study, and the microwave power was considered a factor, rather than temperature. Time and type of base were the other evaluated experimental factors (Table 2). With the factorial design performed (second stage), 10 coefficients were calculated: b0 (intercept or constant), b1, b2 and b3 (linear coefficients for variables 1, 2 and 3), b11, b22 and 33 (quadratic coefficient for variables 1, 2 and 3) and its interactions b12, b13 and b23.

The significance of these coefficients was verified using analysis of variance (Anova) and only two coefficients were significant at a 95% of confidence level. The proposed model was expressed by eqn (1).

$$\text{Yield} = 87 - 53\,(\text{base})^2 \qquad \ldots\ldots\ldots\ldots\ldots(1)$$

As can be observed in this equation, only the quadratic coefficient for the type of base was significant (b22). A surface response was generated and the best conditions (for high yields) were obtained when KOH was used as a base (Figure 1).

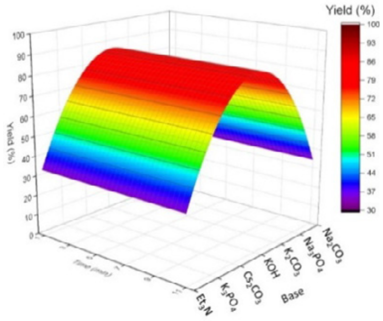
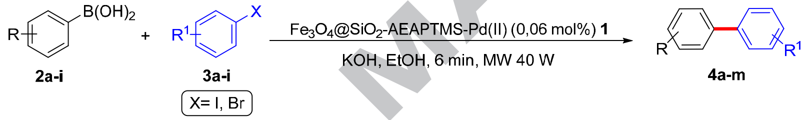
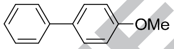
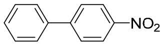
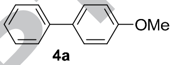
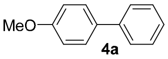
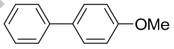
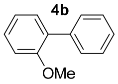
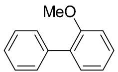
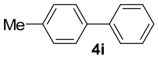
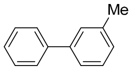
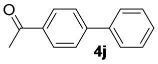
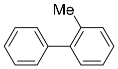
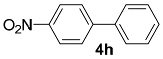


Figure 1. Response surface plot of the yield *vs* the two independent factors time and base.

As may be seen from Figure 1, the factors time and power were not significant and, therefore, can be fixed in a more economic condition (at lower the levels, for instance). With the optimal conditions in hands, that is, catalyst loading (0.06 mol%), base (KOH) solvent (EtOH), time (6 min.) and microwave irradiation power (40 W), we have extended the protocol to a broader range of aryl iodides and boronic acids, in order to evaluate the scope and limitations of this approach (Table 3). Initially, a set of reactions was performed with phenyl boronic acid and different aryl iodides (entries 1–10). In most cases, excellent yields were achieved. However, it could be observed that steric effects exerted some influence during the cross-coupling reactions; substituents attached to the *para* and *meta*-positions of the aryl iodides furnished better yields (Table 3, entries 1 and 5) than the same substituents in the *ortho* position (entries 4 and 6). On the other hand, the electron-donating (Table 3, entries 1, 5 and 7) and electron-withdrawing (entries 9 and 10) nature of the groups attached to the *para* and *meta* positions or the aromatic ring did not exert any influence on the yield. Additionally, 4-bromoanisol could also be used to generate the product, albeit with a lower yield when compared with 4-iodoanisol (entries 3 *vs* 1). In another set of experiments, we promoted the coupling changing the boronic acid component and, once again, the products were formed with high yields (entries 11–18). Moreover, our protocol also allowed the Suzuki cross-coupling of a heteroaromatic boronic acid, providing the corresponding product in excellent yield (entry 17).

Table 3. Suzuki cross-coupling reaction catalyzed by Fe_3O_4@SiO_2-APPTS-Pd(II) under microwave irradiation.[a]



Entry	RB(OH)$_2$	R^1	Product	Yield (%)[b]	Entry	RB(OH)$_2$	R^1	Product	Yield (%)[b]
1	H	4-OMe	 OMe 4a	94	10	H	4-NO$_2$	 NO$_2$ 4h	96
2[c]	H	4-OMe	 OMe 4a	ND[e]	11	4-OMe	H	 MeO 4a	92
3[d]	H	4-OMe	 OMe 4a	74	12	2-OMe	H	 OMe 4b	92
4	H	2-OMe	 MeO 4b	71	13	4-Me	H	 Me 4i	91
5	H	3-Me	 Me 4c	87	14	4-COMe	H	 4j	93
6	H	2-Me	 Me 4d	80	15	4-NO$_2$	H	 O$_2$N 4h	95

7	H	4-NH_2	96	16	3-Cl	H	85
8	H	H	95	17		H	95
9	H	3-CF_3	84	18		H	96

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[a] Unless otherwise specified, all the reactions were performed with boronic acid (1.5 mmol) **2a-i**, aryl halide (1.0 mmol) **3a-i**, Fe_3O_4@SiO_2-AEAPTMS-Pd(II) (0.06 mol%) **1**, KOH (1.5 mmol), EtOH (1,5 mL) under microwave irradiation (40 W) for 6 min. [b] Yields for isolated products. [c] Without base. [d] 4-bromoanisol was used. [e] Not detected

The development of economic and environmentally friendly methods is one of our prime concerns. These concepts have prompted us to further improve our protocol and perform an evaluation of the recyclability of the catalyst. The Suzuki cross-coupling reaction between phenyl boronic acid **2a** and 4-iodoanisol **3a** was chosen as a model for the recycling test. After the completion of reaction, the catalyst **1** was readily separated from the reaction mixture employing an external magnet, washed with water and ethanol and reused for the next cycles. The results (Figure 2) have indicated that the catalyst can be recycled up to three cycles with a small drop in the product yield.

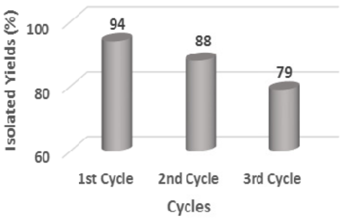
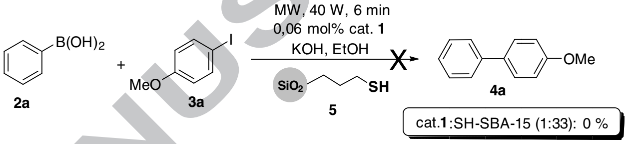


Figure 2. Recyclability of the prepared catalyst Fe_3O_4@SiO_2-AEAPTMS-Pd(II) catalyst **1** for the Suzuki cross-coupling reaction of phenyl boronic acid **2a** with 4-iodoanisol **3a** under MW irradiation.

TEM and XPS analyses were then used to evaluate the recycled catalyst after the 1st reaction cycle. The TEM images (see Figure S6 in the ESI) demonstrated that the morphology of Fe_3O_4@SiO_2-AEAPTMS-Pd(II) did not change after one reaction cycle when compared to the fresh catalyst. However, it is noteworthy that the Pd nanoparticles were now randomly deposited on the silica layer and had both their amount and size increased (from 9 nm in the fresh catalyst to 30 nm, Figure S6). This result was also confirmed by XPS (see Figure S7 in the ESI), since the intensities of the two peaks at 335.12 ($3d_{5/2}$) and 339.69 ($3d_{3/2}$) clearly indicated a significant increase in the content of Pd(0) (36%) after the first cycle. However, most of the palladium species are still present predominantly in the +2 oxidation state [peaks at 337.79 ($3d_{5/2}$) and 342.97 ($3d_{3/2}$), 64%].

Several authors have argued that the real active catalytic species in the Suzuki reaction are resulting from leached palladium species from the catalyst, that return to the support at the end of the reaction.[25] In this view, the authors have suggested a (quasi)homogeneous mechanism in which the heterogeneous catalyst seems to be simply a reservoir of leached palladium. In this context, different experiments have been applied to answer this question, including (1) hot-filtration, (2) three-phase and (3) solid poisoning test. To gain more insights into which type of catalysis is operating in our reaction system, we performed a solid phase poisoning test (Scheme 4). Under optimized conditions and following a previously reported protocol,[26] the cross-coupling between phenyl boronic acid **2a** and 4-iodoanisole **3a** was carried out in presence of the commercially available 3-mercaptopropyl-functionalized silica (SiO_2-SH) as a selective palladium scavenger with a molar ratio of scavenger **5:**Pd of 33. In this case, the presence of an excess of SiO_2-SH lead to a complete loss in the catalytic activity, with no product formation being verifiable by thin layer chromatography (TLC).



Scheme 4. Solid phase poisoning test.

Based on this result, we infer that our heterogeneous catalyst may be acting simply as a reservoir of leached palladium, with the catalyst becoming soluble during the oxidative addition step and redeposited on the surface after the reductive elimination step, similar to the mechanisms described in the previous reports.[11d,25g,27] However, the magnetic nature of the catalyst significantly improves the recovery of the palladium species from the reaction medium. This result was confirmed by the ICP-OES analysis of the reaction medium, which showed no detectable amount of Pd after the removal of the catalyst.

2. Conclusions

In summary, we have described the synthesis and characterization of a novel Fe_3O_4@SiO_2-AEAPTMS-Pd(II). The optimization of the Suzuki cross-coupling reaction using this catalyst was conducted through a factorial design; in the first stage, two factors (temperature and time) and their interaction were identified using a full factorial design as the most important variables. During the second stage, the optimal conditions for the Suzuki cross-coupling were obtained using the Doehlert matrix. The analysis of the responses obtained in the second stage showed that the nature of the base strongly influences the yield, with KOH being the one that afforded the better yield. Other factors such as time and microwave power were not significant and were fixed in more economic conditions. The optimized protocol could be applied to a wide range of substrates, and the products were obtained with yields ranging from 71 to 96% under microwave irradiation in only 6 minutes of reaction. Moreover, owing to its magnetic behavior, the nanocatalyst could be easily recovered and reused for three times with only a small loss of its catalytic activity. The use of a scavenger (SH-SBA-15) allowed us to conclude that the immobilized palladium catalyzed the reaction in a dissolution and redeposition way.

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Supplementary Material

Electronic Supplementary Information (ESI) available can be found, in the online version, at XXX.

Highlights:

- A magnetically recoverable Pd(II) catalyst was prepared and fully characterized.
- The reaction conditions were optimized through a Factorial Design.
- The products were obtained with yields ranging from 71 to 96%.
- The catalyst was easily recovered and reused for three times.