

Research Article

Palladium on Layered Double Hydroxide: A Heterogeneous System for the Enol Phosphate Carbon-Oxygen Bond Activation in Aqueous Media

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In this work, a new catalytic approach for the C-O activation of enol phosphates based on a palladium supported on layered double hydroxide was developed. In this case, two different ketene aminal phosphates were used as models to study the synthesis of α -phenyl enecarbamates N-Boc/CBz under the Suzuki-Miyaura conditions. The use of an ortho-bromoaniline as precursor allowed the synthesis of the 2-phenyl indole through an arylation/Heck cyclization. Catalyst reusability enabled the synthesis of the heterocycle in moderate yields for four consecutive runs.

1. Introduction

Carbon-oxygen bonds have ubiquitous presence in several major natural and synthetic products. Among some chemical properties that contribute to their occurrence in complex systems the relative inertness of the C-O bond can be considered crucial, since the bond dissociation energy is around 60 to 110 kcal/mol depending on the functionality [1, 2]. However, recent progress in the development of metal catalysts containing specific active sites has drawn the attention of chemists to the widely existing O-containing organic compounds in virtue of their low cost as organic electrophiles. In the context of metal-catalyzed cross-coupling reactions, the use of more reliable coupling partners is desired for both economical and ecological reasons compared to the traditional halides [2–4]. Of these, some most widely exploited in synthesis are the triflates due to their high reactivity compared to aryl/alkenyl halides [5, 6]. Apart from this, there are several disadvantages concerning the use of triflates, including their high cost and some difficulties in the handling. On the other hand, the

widely existing O-electrophiles such as phenols, alcohols, ethers, and esters have more recently been considered as promising starting platforms in large-scale processes envisaging the use of biomass-derived products.

Phosphates represent one of the most important classes of esters since they have an essential role in nature [7, 8]. In general, their leaving ability occurs mostly in the presence of enzyme catalysis so their suitable activation under normal conditions depends mainly on the nucleophile along with the pH. Some palladium complexes have been known for their ability to catalyze the addition of carbon and nitrogen nucleophiles onto alkyl and allyl phosphates [9]. However, depending on the reaction conditions, a complex end mixture consisting of the S_N2 and S_N2' products can be obtained instead of the metal-catalyzed alkylation/arylation. In contrast to other enolate derivatives, enol phosphates generally have an improved stability, which avoids the formation of side products and also the production of undesirable waste material during the synthesis [10].

There have been a number of synthetic applications involving the use of enol phosphates and some correlates (e.g., phosphonates and phosphonites) as starting materials for the conversion into a variety of functional groups [2, 11–17]. In these cases, enol phosphates have mostly been useful substrates for some metal-catalyzed cross-coupling reactions, such as Suzuki-Miyaura, Sonogashira, Stille, Negishi, and Kumada mostly by palladium(0) and nickel(0) species. The earlier reports involved the seminal studies by Takai and coworkers which started exploring the alkylation of enol phosphates with trialkylaluminum [11]. By considering strategies involving both Csp^2 coupling partners, some interesting applications by the Nicolaou et al. [12] and Fuwa [16] groups have been recently described towards the total synthesis of natural products. Among some of these applications, ketene amination phosphates (α -phosphoryloxy enecarbamate) were found to be specially convenient for the construction of complex nitrogen-containing heterocycles by exploring the palladium catalysis [18–20]. However, some limitations are related to the use of specific and expensive ligands along with the relatively high amounts of catalyst.

Recently, the interest in cutting-edge heterogeneous materials exhibiting high activity for multistep synthesis has led to the emergence of different classes of catalysts with unique properties. Layered double hydroxides (LDHs) are well-known two-dimensional (2D) anionic clay materials having a brucite-like layers and formula $[M^{II}_{(1-x)}M^{III}_x(OH)_2][A^{n-}_{(x/n)}(H_2O)]$. Due to relatively weak interlayer bonding a wide tunability to compensating anions results in materials with compositional flexibility and interesting applications in catalysis, especially under basic conditions [21]. For instance, LDHs containing transition-metals intercalated in the layers or metal nanoparticles have been used as efficient catalysts for cross-couplings with aryl halides. In most cases, the layered matrix was exploited as special supports since high turnover frequencies (TOFs) were observed under relatively mild reaction conditions. Recently, our research group demonstrated that LDHs of Mg/Al with different crystallinities can behave distinctly regarding the ability for intercalation of palladium or gold species [22, 23]. The application of the Pd catalyst system in the Suzuki-Miyaura reaction with aryl bromides enabled high yields for the corresponding biaryls under neat water and room temperature [23]. As far as we know, the exploration of oxygen-based electrophiles for carbon-carbon bond formation under heterogeneous catalysis is scarce. Here, we present first results concerning the enol phosphate (ketene amination phosphate) C-O bond activation promoted by a LDH system containing palladium.

2. Experimental

All reactions were performed under air using conventional reflux glassware. All chemicals were purchased at the highest commercial grade and used as received. Analytical thin-layer chromatography (TLC) was performed by using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm thickness). Flash column chromatography was carried out by using E. Merck silica gel BW-300 (200–400 mesh).

Fourier-Transform Infrared Spectroscopy. The measurements were performed on Nicolet Magna 760 spectrophotometer with 16 accumulations and 4 cm^{-1} resolution in the $4000\text{--}400\text{ cm}^{-1}$ region. The samples were prepared in KBr pellets.

X-Ray Diffraction. The X-ray diffractograms were acquired at ambient temperature with a Rigaku diffractometer, Ultima IV model with high frequency X-ray generator (3 kW), Cu X-ray tube ($\lambda = 1.5418\text{ \AA}$), Universal Theta-2 Theta goniometer with 185 mm radius, fixed slits, and Ni Kbeta filter with 40 kV voltage and 20 mA current. Samples were analyzed on glass supports. The measurements conditions were $5 < 2\theta < 80$ degrees, 0.05° step, and a step time of 1 second.

X-Ray Fluorescence. The compounds were analyzed on a Philips spectrophotometer, model PW 2400 with rhodium lamp. Samples were fused with lithium tetraborate for the formation of pellets.

Scanning Electron Microscopy and Energy-Dispersive X-Ray Spectroscopy. The photomicrographs of scanning electron microscopy (SEM) were acquired by a JEOL JSM 6460-LV, operating between 10 and 20 kV equipped with energy dispersive X-ray spectrometer to perform the chemical microanalysis. The powders were adhered to a double-sided tape graphite attached to the sample holder. Some samples were metallized with gold for better viewing. The elemental analysis via energy dispersive X-ray spectroscopy (EDS) had the following parameters: resolution: 256×192 ; cutting time: 50 s; number of cuts: 5; acquisition time: 250 s; residence time: $712\text{ }\mu\text{s}$.

BET Analysis. Nitrogen adsorption/desorption isotherms were obtained at -196°C using the instrument Quantachrome Novawin. The samples were pretreated in vacuum at 180°C for 5 hours. The specific surface area of the materials was calculated by the BET method [24].

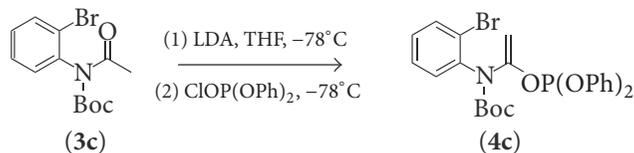
^1H NMR Analysis. ^1H NMR spectra of products **2a**, **2b**, **3a–3c**, and **4a–4c** are presented in the Supplementary Information (see Supplementary Material available online at <https://doi.org/10.1155/2017/8418939>). ^1H NMR spectra were recorded on a Varian VNMRSYS-500 spectrometer at 25°C . Chemical shift values are reported in δ (ppm) relative to tetramethylsilane with reference to internal residual solvent. Coupling constants (J) are reported in hertz (Hz). Multiplicities of signals are designated as follows: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad.

2.1. TH-LDH Synthesis Containing Pd

2.1.1. Synthesis of the Hydrothermally Treated Layered Double Hydroxide. In a 250 mL round-bottomed flask with milliliter water (100 mL), $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.006 mol, 1.538 g) and $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (0.003 mol, 1.125 g) were added with a Mg/Al molar ratio of 2. Furthermore, under strong magnetic stirring NaOH aqueous solution (1 mol L^{-1}) was added dropwise until a final pH around 10. After the coprecipitation the material obtained was hydrothermally treated (80°C) for 24 hours and

the material was filtered via common filtration and dried at room temperature.

2.1.2. Immobilization of Pd on Layered Double Hydroxide. The immobilization was processed using 0.025 mol L^{-1} solution



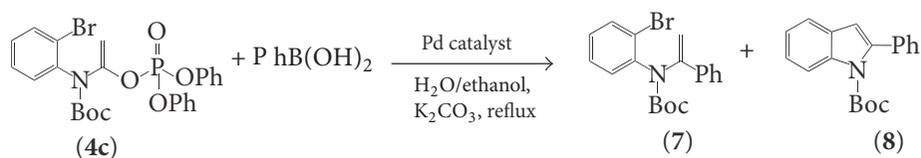
A solution of BuLi 1.04 M in hexanes (3.0 mL) was added to $i\text{-Pr}_2\text{NH}$ (0.48 mL, 3.5 mmols) in dry THF (8 mL) under Ar at 0°C . After 30 min, imide **3c** (0.384 g, 1.60 mmols) in dry THF (1.5 mL) was added at -78°C and the mixture was stirred for 1 h under the same conditions. Then, a solution of $(\text{PhO})_2\text{POCl}$ (0.65 mL, 3.12 mmols) in dry THF (2.3 mL) was

of Na_2PdCl_4 in N,N -dimethylformamide (DMF) applying the molar ratio Pd : HDL of 1 : 2 at 80°C for 24 hours.

2.2. Typical Procedure for the Synthesis of Enol Phosphate 4c

added dropwise and stirring proceeded for 1 h. Then, 5% aq NH_4OH was added and after regular work-up, the obtained residue was purified by flash chromatography (neutralized silica gel, 2% TEA) to afford phosphate **4c** (0.65 g, 78%).

2.3. Typical Procedure for the Synthesis of Product 8



A mixture of enol phosphate **4c** (0.116 g, 0.218 mmol), phenylboronic acid (0.164 g, 0.437 mmol), potassium carbonate (0.028 g, 0.656 mmol), and HT-DLH (0.012 g, 0.011 mmol) in water/ethanol (2 : 1, 5.0 mL) was refluxed for 24 h. After this period, the reaction mixture was cooled, filtered, and extracted with a mixture of ethyl acetate/dichloromethane (1 : 1, $3 \times 15 \text{ mL}$). The combined organic layers were dried with Na_2SO_4 and after filtration/evaporation of the solvent, the residue was analyzed by NMR ^1H .

3. Results and Discussion

3.1. Characterization of the Hydrothermally Synthesized LDH Catalyst. Our first studies concerning the synthesis and characterization of the coprecipitated LDH evidenced that Pd(0) was formed from the ion-exchange process mediated by N,N -dimethylformamide (DMF) [23]. For this material, it was evidenced that Pd(0) was formed during the ion-exchange process mediated by N,N -dimethylformamide. We inferred that the elementary species of palladium were inserted in the interlayer region [23]. In the following, we report the characterization of the palladium containing LDH whose matrix was submitted to hydrothermal treatment at 80°C for 24 hours.

Firstly data from X-rays fluorescence showed the incorporation of 0.5% palladium. It is worth noting that this LDH absorbs less palladium, approximately half the quantity, than coprecipitated LDH does (1.0%) [23]. Concerning this we may conclude that the crystallinity of the matrix was influenced in the incorporation of palladium, probably due to the different kinds of species that were absorbed.

To proceed to a phase analysis in the LDH matrix we obtained the X-rays diffraction patterns (Figure 1). Figure 1(a) evidences that the hydrothermally treated LDH (HT-LDH) is more crystalline than the coprecipitated one [23], as expected. There was no shift of the (003) reflection ($d = 7.66$ angstroms) due to the incorporation of palladium in the matrix (Figure 1(b)). The same behavior was observed for the incorporation of Pd by the coprecipitated LDH [23]. In contrast the XRD pattern for the Pd containing HT-LDH, Figure 1(b), presents no apparent Pd(0) peaks, which let us conclude that mostly Pd^{2+} species were incorporated in the matrix. However up to this point we cannot affirm that PdCl_4^{2-} species were intercalated in the HT-LDH material.

In order to gain more information concerning the Pd incorporation process, Fourier-transform infrared (FTIR) spectra were acquired. These spectra are shown in Figure 2 and evidence that few differences are noticed when they are compared. Basically vibrational modes corresponding to $\nu_{\text{as}}\text{CO}_3^{2-}$ at 1369 cm^{-1} , $\nu_{\text{as}}\text{NO}_3^-$ at 1384 cm^{-1} , and νOH relative to the interaction between interlayer H_2O and CO_3^{2-} at 3080 cm^{-1} [25] were kept for Pd/HT-HDL. Also the bands in the $1000\text{--}400 \text{ cm}^{-1}$ range, relative to $\delta_{\text{as}}\text{CO}_3^{2-}$ (640 cm^{-1}) and relative to Al-O and Al-OH modes (780 , 550 , and 450 cm^{-1}) [26], remained unchanged in contrast of what was previously reported for the intercalation of noble metals by LDH [25, 26]. With these results in mind it may be said that most of the chemical conditions in the interlayer region seem to be unchanged after Pd incorporation.

To further investigate this chemical system, we managed to make some visualizations of scanning electron microscopy

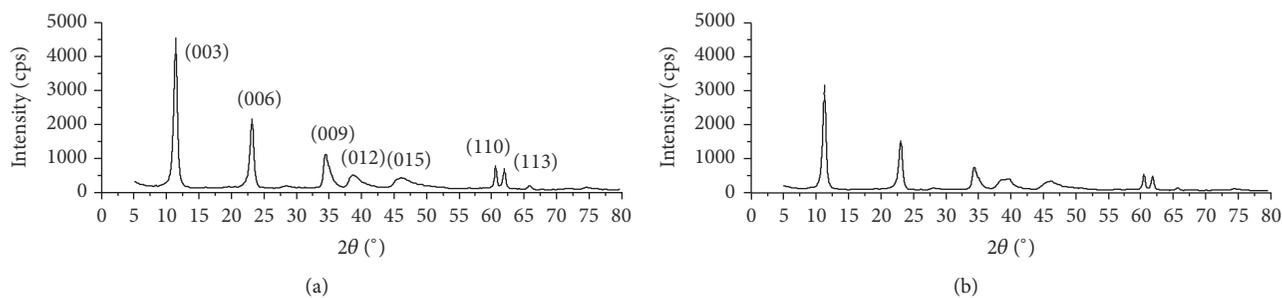


FIGURE 1: XRD patterns for the hydrothermally treated layered double hydroxide (HT-LDH) before (a) and after (b) palladium incorporation.

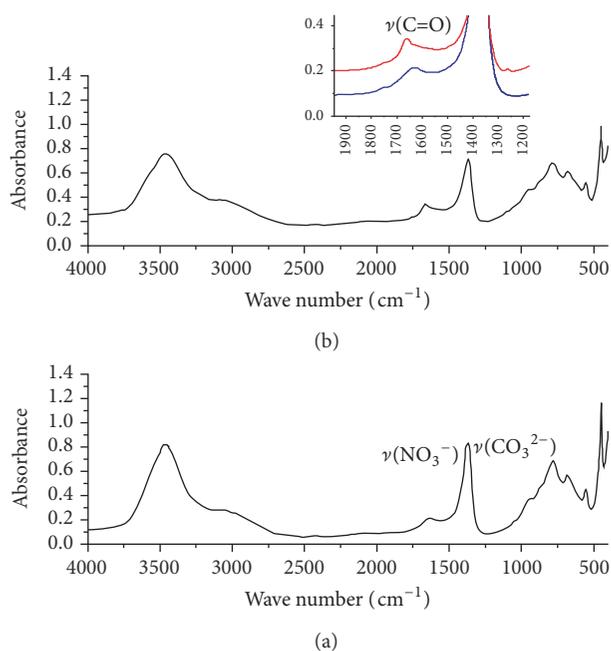


FIGURE 2: Fourier-transform infrared spectra for the hydrothermally treated layered double hydroxide (HT-LDH) before (a) and after (b) palladium incorporation. Inset: zoom of the 1900–1200 cm^{-1} region of both spectra signaling in the upper spectrum the band relative to C=O stretching mode of *N,N*-dimethylformamide.

(Figure 3). From Figure 3(a), relative to a backscattered electrons image, a phase contrast evidenced by the white brilliant particles situated on the surface of the dark grey agglomerate was noticed. This is unique since this phase contrast was not observed for the coprecipitated LDH after Pd incorporation. We also obtained the elements distributions (Pd, Cl, and Mg) throughout this agglomerate by using the energy-dispersive X-rays spectroscopy facility coupled to the SEM microscope (Figures 3(b)–3(d)). From the EDX element mapping it became clear that the brilliant phase corresponded to a higher density of the palladium and chlorine elements contrasting to a lower density of the magnesium element: rather than being caused by chemical inhomogeneity it was due to shielding of the Mg characteristic X-rays promoted by the superficial phase. This phase can be assigned as being composed of Pd and Cl; however we do not believe that this would be the precursor salt Na_2PdCl_4 , since it is very soluble in DMF. It

is more probable to correspond to some palladium chloride that precipitated from the medium due to the association with DMF. In the IR spectrum of this catalyst we zoomed in the region of 1900–1200 cm^{-1} and we evidenced one band above 1650 cm^{-1} that can be assigned as the DMF carbonyl stretching mode (see the inset of Figure 2 for the comparison of this material IR spectrum with that of LDH before Pd incorporation). Therefore although part of Pd and Cl appeared homogeneously distributed throughout the particle in Figure 3(a), probably intercalated, another part composed a second phase that precipitated over LDH particles.

The nitrogen adsorption/desorption isotherms for the Pd/HT-LDH are shown in Figure 4(a). In this isotherm it is important to note how the hysteresis loop is narrow, which is characteristic of crystalline materials. This isotherm differs entirely from materials with low crystallinity as the Pd immobilized in coprecipitated LDH, Pd/CP-LDH (Figure 4(b)). In addition the surface area of the hydrothermally treated catalyst (65.12 $\text{m}^2 \text{g}^{-1}$) is also higher than that of the coprecipitated one (7.834 $\text{m}^2 \text{g}^{-1}$). With a hydrothermal treatment step, greater crystallites that have less reactive surface are generated and consequently agglomerate less. Smaller agglomerates correspond to smaller particles with higher surface areas therefore reasoning why the surface area of the hydrothermally treated LDH is higher compared to the coprecipitated one.

3.2. Reactions. Although several synthetic methodologies have been developed to access ketene aminal phosphates, the most convenient strategy consists of the deprotonation of an enolisable ketone using a strong base, such as LDA, followed by reaction of the subsequent metal enolate with a phosphoryl chloride (Scheme 1). Also, the stability of the phosphates depends on the electronic effects imposed on the nitrogen moiety. Previously, our group reported that stable ketene aminal phosphate (α -phosphoryloxy encarbamate) derived from *N,N*-diprotected acetamide could be prepared by using *p*-methoxyphenyl (PMP) and CBz as protecting groups at the nitrogen [20]. In this case, cross-couplings under classical conditions, including the use of phosphine and arsine as ligands, were carried out to access enynes and dienes in moderate to good yields [20].

To evaluate the catalytic activity of the Pd/HT-LDH, we firstly run experiments with the PMP substituted, *N*-CBz-protected ketene aminal phosphate **4a** since this starting

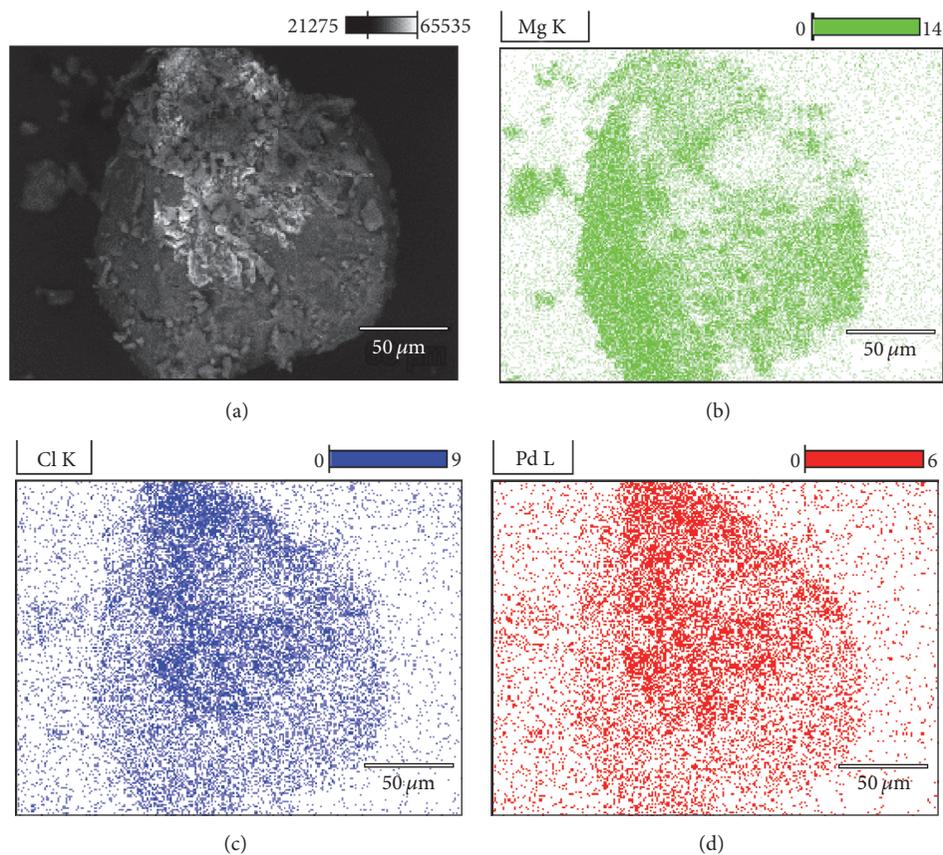


FIGURE 3: SEM-EDS visualizations for the catalyst of Pd on hydrothermally treated layered double hydroxide. (a) Backscattered electrons image; (b)–(d) EDS mapping of the elements Mg, Cl, and Pd.

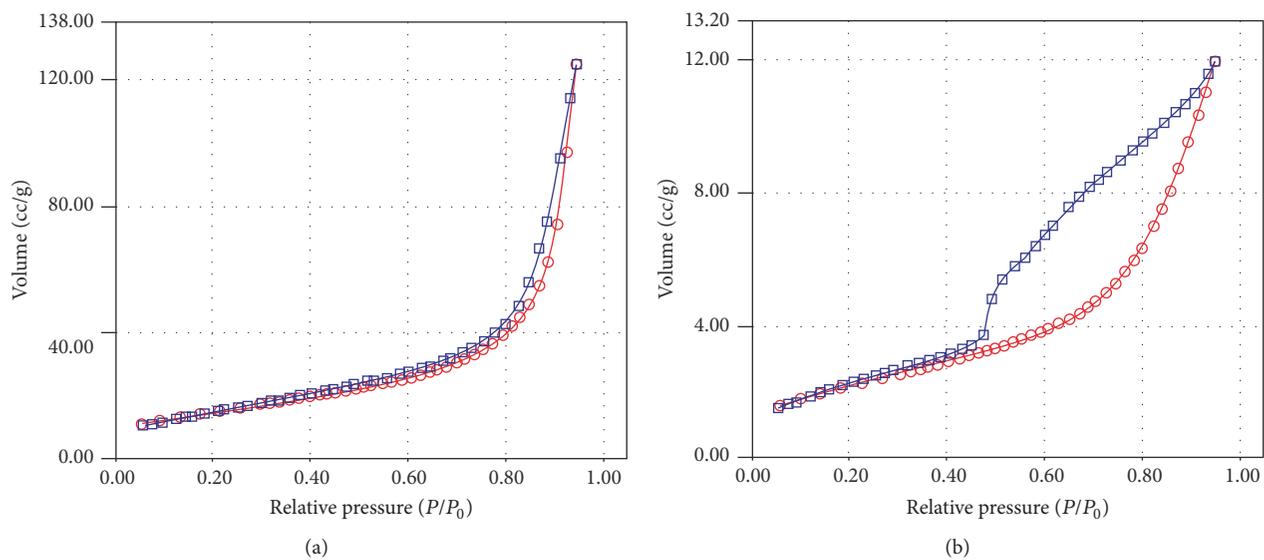
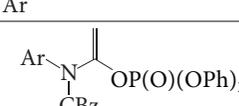
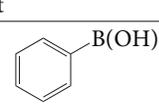
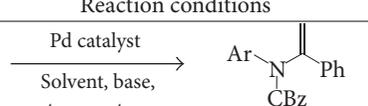


FIGURE 4: Nitrogen adsorption/desorption BET isotherms of the catalysts based on (a) hydrothermally treated and (b) coprecipitated layered double hydroxide.

TABLE 1: Screening of the reaction conditions for the synthesis of the α -phenyl-enecarbamates from the *N*-CBz protected enol phosphates.

Entry	Ar	Catalyst	Reaction conditions	Yield (%)
	 4a (Ar=4-OCH ₃) 4b (Ar=2-Br)	 5	 6a (Ar=4-OCH ₃) 6b (Ar=2-Br)	
1	4-OCH ₃	HT-LDH/Pd (1.0 mol%)	H ₂ O/EtOH, 75–80°C	–
2	4-OCH ₃	HT-LDH/Pd (1.0 mol%)	H ₂ O/EtOH, K ₂ CO ₃ , 75–80°C	41%
3	4-OCH ₃	HT-LDH/Pd (2.0 mol%)	H ₂ O/EtOH, K ₂ CO ₃ , 75–80°C	50%
4	4-OCH ₃	HT-LDH/Pd (2.0 mol%)	H ₂ O, K ₂ CO ₃ , 75–80°C	–
5	4-OCH ₃	HT-LDH/Pd (2.0 mol%)	EtOH, K ₂ CO ₃ , 75–80°C	–
6	4-OCH ₃	HT-LDH/Pd (2.0 mol%)	H ₂ O/THF, K ₂ CO ₃ , 75–80°C	72%
7	4-OCH ₃	CP-LDH/Pd (2.0 mol%)	H ₂ O/THF, K ₂ CO ₃ , 75–80°C	39%
8	4-OCH ₃	Pd nanoparticles (2.0 mol%)	H ₂ O/THF, K ₂ CO ₃ , 75–80°C	35%
9	4-OCH ₃	Pd nanoparticles (5.0 mol%)	H ₂ O/THF, K ₂ CO ₃ , 75–80°C	40%
10	4-OCH ₃	Na ₂ PdCl ₄ (2.0 mol%)	H ₂ O/THF, K ₂ CO ₃ , 75–80°C	–
11	2-Br	HT-LDH/Pd (2.0 mol%)	H ₂ O/THF, K ₂ CO ₃ , 75–80°C	n.d.

even by using the classical conditions [Pd(PPh₃)₄ 10 mol%, Et₃N, DMF, 100°C, and sealed tube]. Starting from *o*-bromoanilide, the corresponding halogenated ketene aminal phosphate was prepared for the catalytic tests. In this case, we have used the *N*-Boc-protected substrate, obtained in good yield (85%), which presented a good stability when compared to the previous one. We presume that the absence of a strong donating group (PMP) improved the stability of the (CH₃)₃C-O bond in Boc moiety [20]. The examination of the Suzuki-Miyaura reaction between phenylboronic acid and substrate **4c** in H₂O:THF (1:1), in the presence of 2.0 mol% Pd/HT-LDH and K₂CO₃, revealed the formation of the α -aryl enecarbamate **7** in 40% along with the minority cyclic product **8** (17%) when the reaction was carried out by 24 h (Table 2, entry 1). However, running the reaction by 48 h did not improve the cyclization towards the indole ring but instead led to the partial degradation of **7** (Table 2, entry 2).

According to Fuwa and coworkers, the suppression of the cyclic product can occur with the addition of H₂O and a moderate reaction temperature [32]. To evaluate if this finding follows a trend we performed a test in the presence of dry THF as the sole solvent. However, when compared to the previous condition (H₂O/THF) it gave an unsatisfactory result due to the incomplete starting material conversion and lack of selectivity (Table 2, entry 3). On the other hand, by using commercial ethanol, we have observed an almost complete consumption of the starting material as well as the formation of the cyclic product in a moderate yield (Table 2, entry 4). Based on this evidence, we argued that water could have a role in the formation of active species. Thus, our strategy involved the increase of the indole yield by using this heterogeneous catalytic system in the presence of a mixture based on water/ethanol. Under the condition involving water/ethanol (2:1), the Suzuki-Miyaura reaction

tandem cyclization with the HT-LDH took place in the presence of K₂CO₃ at 90°C for 24 h affording an inversion in the **7** : **8** ratio with an improved yield for the indole (Table 2, entry 5). However, by changing the base to cesium carbonate the efficiency of the cyclization was affected (Table 2, entry 6).

It is interesting to note that the **7** : **8** ratio can be tuned not only by changing the solvent but also through the catalyst system: by using the Pd nanoparticles stabilized by CDs, the cyclization proceeded with a poor selectivity towards **8** (Table 2, entry 7). By comparison, the coprecipitated LDH was also tested under this condition to verify the influence of the catalyst structure on the cyclization. As shown in entry 8, the reaction occurred with similar selectivity suggesting that it can be improved by the LDH structural effect involving the interlayer space.

Considering the formation of **7** and **8**, we found, in a control experiment, that the hypothetical product from intramolecular Heck reaction (indole formation) containing the phosphate moiety is not involved as the first intermediate since no reaction occurred in the absence of the phenylboronic acid. This data supports the idea of a mechanism in which the C-O bond activation occurs followed by the carbon-halogen coupling. In addition the catalyst deactivation could be a hypothesis that for prolonged times the reaction does not afford the cyclization leading to indole. However its recycling ability was showed (see Table 3) hence contrasting to the hypothesis of its deactivation. Any poisoning of the LDH by inspection of the catalyst without washing/purification using infrared spectroscopy was not detected.

To test the merit concerning the nature of the catalysis, we performed in a separate experiment a hot filtration test as a useful criterion for distinguishing between homogeneous and heterogeneous catalysis [33]. In this case, the reaction

TABLE 2: Screening of the reaction conditions for the synthesis of the 2-phenyl indole from the *N*-Boc protected enol phosphate.

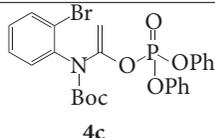
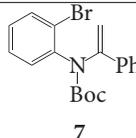
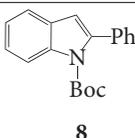
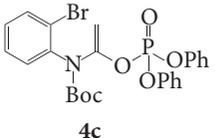
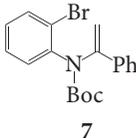
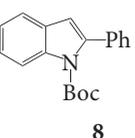
Entry	Catalyst	Reaction conditions	Yield (%)	
			7	8
	 4c		 7	 8
		Pd catalyst Solvent, base, temperature		
1	HT-LDH/Pd (2.0 mol%)	H ₂ O/THF, K ₂ CO ₃ , 80°C, 24 h	40	17
2	HT-LDH/Pd (2.0 mol%)	H ₂ O/THF, K ₂ CO ₃ , 80°C, 48 h	–	–
3	HT-LDH/Pd (2.0 mol%)	THF, K ₂ CO ₃ , 80°C, 24 h	21	13
4	HT-LDH/Pd (2.0 mol%)	Ethanol, K ₂ CO ₃ , 80°C, 24 h	38	35
5	HT-LDH/Pd (2.0 mol%)	H ₂ O/ethanol (1:1), K ₂ CO ₃ , 80°C, 24 h	27	65
6	HT-LDH/Pd (2.0 mol%)	H ₂ O/ethanol (1:1), Cs ₂ CO ₃ , 80°C, 24 h	22	48
7	PdNPs (5.0 mol%)	H ₂ O/ethanol (1:1), K ₂ CO ₃ , 80°C, 24 h	31	24
8	CP-LDH/Pd (2.0 mol%)	H ₂ O/ethanol (1:1), K ₂ CO ₃ , 80°C, 24 h	20	32

TABLE 3: Catalyst reusability¹.

Entry	Run	Yield of 8 (%)		
		7	8	
	 4c		 7	 8
		HT-LDH (2% Pd) K ₂ CO ₃ , H ₂ O/ethanol reflux, 24 h		
1	1st		65	
2	2nd		58	
3	3rd		56	
4	4th		56	

¹The reusability tests were carried under identical conditions. After each run, the catalyst was filtered, washed with water, and dried at room temperature.

medium was filtered after the end of the reaction and the catalytic activity of the supernatant was analyzed under the same conditions. Interestingly, there was no detected amount of both coupling products, indicating that only a limited number of species were leached. Examination of the catalyst recyclability (Table 3) revealed that the material can be used for four consecutive runs without significant loss in activity. Based on these results, we hypothesized that the heterogeneous catalysis could be the predominant mechanism.

4. Conclusion

In summary, we have demonstrated that a catalyst system based on layered double hydroxide containing Pd(0) is efficient for the C-O activation of acetamide-derived ketene amination phosphates. Based on anilines containing Boc or CBz as protecting groups, we started catalytic studies for the cross-coupling reactions with the phenylboronic acid. The Boc substituted *o*-brominated enol phosphate was quite stable under the catalytic conditions when compared to the CBz counterpart evidencing that the combination between the electron-donating and electron-withdrawing groups involves

a delicate balance. From the comparison with the classical catalytic conditions, the beneficial effect of this ligand-free strategy is apparent. By using the hydrothermally treated LDH containing Pd(0), the corresponding α -aryl enecarbamates were obtained in moderate to good yields. In the case of the *o*-halo substituted substrate, the conditions were tuned to improve the domino Suzuki-Miyaura/intramolecular Heck which led to the 2-phenyl indole in moderate yields. Indeed, the catalyst showed recycling potential since the activity was similar for four consecutive runs towards the 2-phenyl indole. Although improvement of the scope of the methodology requires additional studies, the advantage of using a ligand-free condition, as in challenging C-O/C-C domino reactions, is retained. Ongoing work seeks to explore additional substrates for these and related cross-coupling reactions.

5. Supplementary Information

¹H NMR spectra of all products are available online in the Supplementary Information file.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

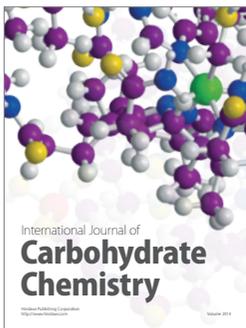
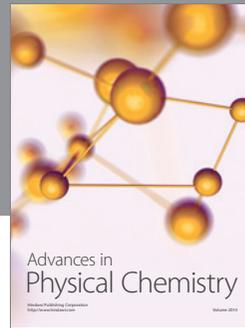
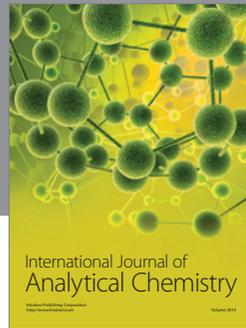
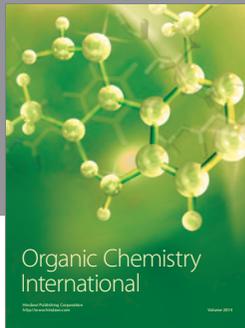
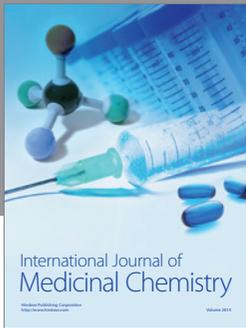
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