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PVP-Pd nanoparticles as efficient catalyst for nitroarene reduction under mild conditions in aqueous media

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The catalytic activity of PVP-Pd nanoparticles synthesized by electrochemical methods was explored in nitroaromatic hydrogenation reaction. In this transformation, the colloidal nanocatalyst proved to have outstanding catalytic activity under sustainable reaction conditions. This mild process efficiently reduced the nitroaromatic group at room temperature, without high pressure of molecular hydrogen and in aqueous medium. Furthermore, several functional groups were tolerated, given the corresponding substituted arylamines in excellent yields and with high TOF. In addition, one-pot reactions and tandem process were explored, in which nitroaromatic hydrogenation reaction was included in the synthesis of modified amines. This methodology was effectively incorporated in tandem reactions and one-pot procedures, achieving *N*-arylamines functionalized in good isolated yields. Finally, comparison of sustainable chemistry metrics analysis demonstrated that this methodology is a reliable approach to perform the nitro compound hydrogenation process.

Introduction

The synthesis of highly functionalized amines is an important goal in modern organic chemistry. Amine functional groups are ubiquitous among natural and pharmaceutical products, and key intermediates in the preparation of fine chemical products like dyes, chemical fibers, pesticides, rubber additives, etc.[1] Several methods were developed to synthesize functionalized amines, such as catalytic amination of aryl halides,[2] or reduction of functional groups like imine, nitrile, etc.[3–5] The catalytic hydrogenation of nitro compounds by noble metal catalyst (Pt, Pd, Ni, Rh and, more recently, Au) is the most traditional and widely used method for the industrial production of amines.[6–9] The catalytic reduction of nitro compounds is a widespread methodology; however, it suffers from several drawbacks such as the use of a large amount of metal catalysts, organic reaction medium, and expensive or harmful hydride source, or under high molecular hydrogen pressure. In some cases, harsh reaction conditions were required (e.g., high temperature), under which the amine products could be susceptible to degradation. Moreover, nitro compound hydrogenation is usually limited in complex structures like pharmaceutical intermediates, since these compounds typically contain other sensitive functionalities. All these features restrict the applicability of procedures, making them non-environmentally friendly. Thus, development of sustainable or "green" methodologies represents a challenging task for both catalysis and organic synthesis progress. [10–12] The concept behind green chemistry principles is to reduce the impact of any chemical processes on the environment. Accordingly, the use of safer chemicals and the prevention of primary pollutions are endorsed.[13–15] Sustainable chemistry transformation could be accomplished by application of this philosophy to the planning of any process, like solvent selection, avoiding the use of hazard reagents, or reducing waste generation.[16–18]

Regarding Pd-catalyzed nitroaromatic hydrogenation, there is a plethora of methods available to perform this reaction, with both homogeneous and heterogeneous catalysts. However, fewer examples of homogeneous Pd catalytic systems using water or alcoholic reaction media at room temperature have been reported.[19–21] Even though homogeneous systems usually show higher selectivities than heterogeneous, the homogeneous complexes present the disadvantage of decomposing in several reaction media, or of incorporating sophisticated, toxic and expensive ancillary ligands.

In relation to heterogeneous catalyst, in the last decades the development of nanocatalysts has drawn special attention. This is due to the high-level activities and selectivities shown by nanoparticles (NPs),[22,23] attributes related to high surface-to-volume ratio and raised surface energy of the NPs, making their surface atoms particularly active.[24,25] Considering the growing environmental concern, different Pd NPs catalytic systems were developed to perform the hydrogenation reaction. There are a number of reports devoted to performing the reduction of nitro compounds by employing Pd-heterogeneous nanocatalysts in aqueous medium[26–29] or at room temperature,[12,30–34] or a combination of both.[35–38] However, the methodologies are still far away from employing less amount of reducing agent, avoiding the use of expensive hydride source like silanes, toxic hydrazine, or high pressure of molecular hydrogen. [39–41] In general, heterogeneous catalysts are stable and can be easily re-cycled; nonetheless, these show fewer selectivities than

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those of homogeneous ones, and harsh reaction conditions may be necessary in order to achieve high conversions.[42]

The use of colloidal NPs as catalysts provides a way to combine the main advantages of homogeneous and heterogeneous catalytic systems, setting up a bridge between them.[5] In addition, metal colloidal clusters are well dispersed in the reaction medium, their cluster size may be effectively controlled, and they are usually weakly stabilized by capping agent, leaving their surface exposed and available to participate in the catalysis.[43]

Recently, we synthesized small-size Pd NPs stabilized by PVP by electrochemical methods.[44,45] The use of PVP as stabilizer allowed NPs to be disperse in aqueous medium. PVP also shows several advantages like low toxicity, inexpensiveness and thermal stability. The catalytic activity of the electrochemically obtained nanocatalyst in Suzuki and Heck coupling reactions was outstanding for colloidal NPs, and PVP-Pd NPs proved to be reusable and stable for several months.[44,45] Therefore, in the search of new catalysts with high selectivity in the reduction of nitro compounds and under environmentally friendly reaction conditions, the catalytic activity of the PVP-Pd NPs electrochemically synthesized was explored. The selectivity for the nitro group reduction was examined under several conditions, employing $NaBH_4$ as safe source of hydrogen.[29,36,46] In addition, incorporation of nitro group hydrogenation by PVP-Pd NPs in one-pot consecutive reactions was also examined.

Experimental Section

1. General Methods

All materials were commercially available and used as received. $PdCl_2$, KNO_3, PVP [poly-(*N*-vinyl-2-pirrolydone), Mw=10,000 Da, HCl 35 %, *p*-chloronitrobenzene, *o*-chloronitrobenzene, nitrobenzene, *p*-nitroaniline, *p*-dinitrobenzene, *o*-nitrophenol, *m*-nitrophenol, methyl *m*-nitrobenzoate, *p*-nitroacetanilide, 2-chloro-3-nitropyridine, 5-nitroquinoline, styrene, 1,1-diphenylethylene, *p*-nitroacetophenone, *p*-chloroaniline, *o*-chloroaniline, nitrobenzene, *p*-aminoaniline, *o*-aminophenol, *m*-aminophenol, methyl *m*-aminobenzoate, *p*-aminoacetanilide, benzophenone, *p*-iodonitrobenzene, phenylboronic acid, benzaldehyde, di-*tert*-butyl dicarbonate ($(Boc)_2O$), ethanol 98 %, methanol HPLC grade, $NaBH_4$ (AF granules) 98%, $Pd(AcO)_2$, BINAP, K_3PO_4, K_2CO_3, KI, and Na_2SO_4 were used without purification. Silica gel (0.063-0.200 mm) was used in column chromatography. All solvents were analytical grade and distilled before use.

GC analyses were performed on a gas chromatograph with a flame ionization detector, equipped with VF-5 30 m x 0.25 mm x 0.25 µm column. GC-MS analyses were performed on a GC/MS QP 5050 spectrometer equipped with a VF-5ms, employing a 30 m x 0.25 mm x 0.33 µm. Ionization was achieved by electronic impact (70eV) and detection setup positive mode. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz respectively on a Brüker Advance II 400 spectrometer in $CDCl_3$, DMSO-d_6 or acetone-d_6. Coupling constants (*J*) are given in Hz. An Autolab PGSTAT100 (ECO CHEMIE) potentiostat was used for the synthesis of PVP-Pd NPs in the galvanostatic mode. PVP-Pd NPs observation by Transmission Electron Microscopy (TEM) was performed with a JEM-Jeol 1120 microscope operating at 80 kV, at the IFFIVE Research Institute, INTA, Córdoba, Argentina (See Figure S1 and S2, Supporting Information). In order to characterize NPs by TEM, samples were prepared depositing a drop of colloidal PVP-Pd NPs solution on a formvar-carbon coated cooper grid and dried at room temperature. The total content of palladium was determined by Atomic Absorption in a Perkin Elmer Analyst 600, using ET (electro thermal mode with graphite furnace) at the ISIDSA Institute, Universidad Nacional de Córdoba, Córdoba, Argentina. Aqueous solutions were prepared from analytical grade chemicals and Milli-Q-Millipore water.

2. Experimental Procedures

2.1. Representative procedure for the nitroaromatic reduction by PVP-Pd NPs

The following reaction procedure is representative: into a 25 mL bottom round flask equipped with a magnetic stirrer, *p*-chloronitrobenzene **1** (0.25 mmol) was dissolved in EtOH (0.5 mL) and 0.90 mL of colloidal dispersion of PVP-Pd NPs was added. Finally, under vigorous stirring, a solution of 1 mmol of $NaBH_4$ in H_2O (2 mL) was dropped. At this stage, an intense colour change took place, and effervescence evolution was observed. After 15 minutes under vigorous stirring, a decolouration occurred. The reaction was stirred for 1 hour at room temperature. The mixture was finally diluted with water and then extracted three times with ethyl acetate (5 mL each). The reaction mixture was analysed by GC and GC-MS after being dried with anhydrous Na_2SO_4. The amine product was compared with authentic samples by GC, GC-MS and ^1H NMR. The product was quantified by CG employing benzophenone as internal standard.

Several reactions were analysed by HPLC. In these cases, once the reaction was completed, MeOH HPLC grade was added until final dilution of 1:100. Then, 1 mL of this solution was filtered and analysed in HPLC equipment, using the external standard method for quantifying the amine products.

For competition reactions: when performing a competition reaction, the same procedure was followed, incorporating alkene 1,1-diphenylethene (**14**) together with *p*-chloronitrobenzene **1**, before adding $NaBH_4$.

2.2. Representative procedure for one-pot synthesis of 4-amine biphenyl (16), by consecutive Suzuki-nitro hydrogenation reaction catalysed by PVP-Pd NPs

For Suzuki cross-coupling reaction: into a 25 mL bottom round flask equipped with a magnetic stirrer, *p*-iodonitrobenzene (0.25 mmol) was dissolved in EtOH (0.5 mL). Then, phenylboronic acid (0.375 mmol), K_3PO_4 (1 mmol) and 1 mL of water were added. Finally, 0.90 mL of colloidal dispersion of PVP-Pd NPs was added. The reaction was stirred overnight at 50

ºC. After this, the mixture was cooled down before proceeding with the hydrogenation reaction.

Hydrogenation of *p*-nitrobiphenyl: to the previous reaction mixture, EtOH (0.5 mL) and 2 mmol of $NaBH_4$ in H_2O (4 mL) were dropped. After 45 minutes under vigorous stirring, a decolouration occurred. The reaction was stirred for 2 h at room temperature. Finally, the mixture was diluted with water and then extracted three times with ethyl acetate (5 mL each). The reaction mixture was analysed by GC and GC-MS after being dried with anhydrous Na_2SO_4. The amine product was compared with authentic samples by GC, GC-MS and ^1H NMR. The 4-aminebiphenyl (**16**) was isolated by column chromatography on silica gel eluting with pentane:ethyl acetate gradient (100:00→70:30), obtained as a yellow solid.

2.3. Representative procedure for the synthesis of *N*-protected arylamines with benzaldehyde (17) or di-*tert*-butyl dicarbonate (18)

After the hydrogenation protocol was performed over *p*-chloronitrobenzene **1** (section 1.2), 0.75 mmol of benzaldehyde (**17**) or di-*tert*-butyl dicarbonate (**18**) were added to the mixture. The reaction was stirred for 3 h at room temperature. The mixture was finally diluted with water and then extracted three times with ethyl acetate (5 mL each). The reaction mixture was analysed by GC and GC-MS after being dried with anhydrous Na_2SO_4. The N-protect amine product was compared with authentic samples by GC, GC-MS and ^1H NMR. Imine product **19** was purified by sublimation in a Büchi microdistillation system at 70 °C, obtained as a white solid. N-Boc protect amine **20** was isolated by column chromatography on silica gel eluting with pentane:ethyl acetate gradient (100:00→70:30), obtained as a pale-yellow solid.

2.4 Representative procedure for the synthesis of *N2*-(4-chloro phenyl)pyridine-2,3-diamine (22)

Catalytic amination of 2-chloro-3-nitropyridine: in a Schlenk tube, *p*-chloroaniline **2** (0.25 mmol), 2-chloro-3-nitropyridine **23** (0.25 mmol), K_2CO_3 (1mmol), $Pd(AcO)_2$ (2 mol%), BINAP (2 mol%), KI (3 mol%), and toluene (1 mL) were placed together with a magnetic stirrer. The reaction was stirred for 24 h at 110 ºC in an oil bath. To elaborate the reaction, the mixture was diluted with water, and then extracted three times with ethyl acetate (5 mL each). The reaction mixture was analysed by GC and GC-MS, after being dried with anhydrous Na_2SO_4. Nitro compound **21** was isolated by crystallization from a water:acetone 5:1 mixture as a brown solid compound.

Catalytic hydrogenation of *N*-(4-chlorophenyl)-3-nitropyridin-2-amine (21) by PVP-Pd NPs: into a 25 mL bottom round flask equipped with a magnetic stirrer, nitro **21** (0.25 mmol) was dissolved in EtOH (0.5 mL) and 0.90 mL of colloidal dispersion of PVP-Pd NPs was added. After that, a solution of 2 mmol of $NaBH_4$ in H_2O (4 mL) was dropped. After 45 minutes under vigorous stirring, a decolouration occurred. The reaction was stirred for 2.5 h at room temperature. The mixture was finally diluted with water and then extracted three times with ethyl acetate (5 mL each). To isolate amine product **22**, column chromatography on silica gel eluting with pentane:ethyl acetate gradient (100:00→70:30), obtaining amine **22** as an orange solid.

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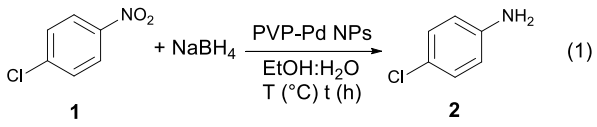
2.5 Catalyst reuse experiment in nitroaromatic hydrogenations by PVP-Pd NPs

In order to perform the reuse test of PVP-Pd nanocatalyst, after carried out the hydrogenation reaction following the procedure previously described in Section 2.1 with 0.2 mol % of Pd, the same reaction mixture was used by addition of fresh amounts of reactants. The experiment was performed five times by consecutive addition of a new batch of *p*-chloronitrobenzene (**1**, 0.25 mmol), $NaBH_4$ (1 mmol), EtOH (0.5 mL) and water (2 mL). The reaction mixture was stirred at room temperature for 1 h. After this time, the reaction was monitored by CG analyses and no *p*-chloronitrobenzene (**1**) was observed in the reaction mixture after each catalytic cycle.

Results and Discussions

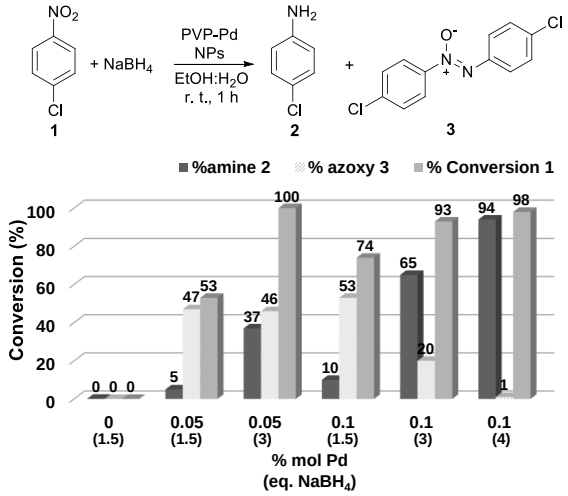
The PVP-Pd NPs were electrochemically synthesized as previously described, and used without further purification.[44,45] This electrochemical methodology allowed to obtain Pd NPs of mean diameter lower than 10 nm. Taking into account our previous reports on the catalytic activity of the PVP-Pd NPs, we decided to evaluate the nitroaromatic reduction in a mixture of EtOH:H_2O as solvent. The benchmark substrate, 4-cloronitrobenzene (**1**), was chosen as a model for the hydrogenation process (eq. 1),[47] since the presence of chlorine substituent allowed evaluating the selectivity of the process. The reducing agent selected was $NaBH_4$ as it is easy to handle and involves a safe source of hydrogen under low concentrations.[29,36,46]



Several reactions conditions were evaluated in the optimization process of this catalytic system, like: time, amount of reducing agent and catalyst loading. These assays were conducted at room temperature, under vigorous stirring for 1 hour in a mixture of EtOH:H_2O (1:6). The yields of aniline **2** and conversions for the reactions are presented in Scheme 1. In every case, GC and GC-MS were used to evaluate the reactions, in order to quantify yield of amine **2,** and detect formation of side products.

When the reaction was conducted in the presence of 1.5 equivalents of $NaBH_4$ but without PVP-Pd NPs, substrate **1** was fully recovered from the reaction media after 1 hour (Scheme 1). Moreover, the hydrogenation proceeded smoothly with the addition of 0.05 mol % of Pd (Scheme 1). As a general trend, the yield of amine **2** was raised as the amount of PVP-Pd NPs and $NaBH_4$ was increased. In these cases good conversions were observed. However, aside from amine **2**, other side products were identified and isolated from the reaction mixture. This

could be interpreted considering the mechanism proposed for this reaction (Scheme 2).[48]



Scheme 1. Selectivity and conversion observed in the reduction of 4-cloronitrobenzene (**1**).

It is generally accepted that the hydrogenation process follows a multistep mechanism that involves several intermediates (Scheme 2). The direct hydrogenation path involving the nitroso (**III**) and hydroxylamine (**IV**) derivatives (Scheme 2), are usually observed with Pd catalyst.[47,48] However, in the present work only traces of nitroso intermediate (**III**) was detected by GC-MS analysis. Conversely, the major by-product was azoxy (**VI**), and to a lesser extent, azo (**VII**) intermediate. Thus, the condensation route was preferentially followed (Scheme 2). It was proposed that under some reaction conditions the condensation path could be favored, as in the reactions performed under low concentration of H_2 or nitroaromatic compound.[49] Both Turáková, *et. al.* and Gelder, *et. al*. suggested that the formation of azoxy (**VI**) came from the condensation of two molecules of chemisorbed species Ar-N-O-H (**II**, Scheme 1), which are accumulated over the catalyst surface.[48,49] Furthermore, azoxy compound was obtained almost exclusively when the reaction was performed with 0.05 mol% of PVP-Pd NPs and 1.5 equivalents of $NaBH_4$ (Scheme 1). The combination of low Pd loading and low $NaBH_4$ addition allowed obtaining azoxy **3** in 47 % of yield and 88 % of selectivity (Scheme 1). The preparation of azoxy compounds like **3** finds important applications in dye and pigment production.[50] These azoxy adducts were usually prepared by hydrogenation of nitro compounds; yet, in general, special reaction conditions and catalysts are needed.[50] In the present study, azoxy **3** was obtained in moderate yield but with good selectivity just by changing the ratio between catalyst and reducing agent (Scheme 1).

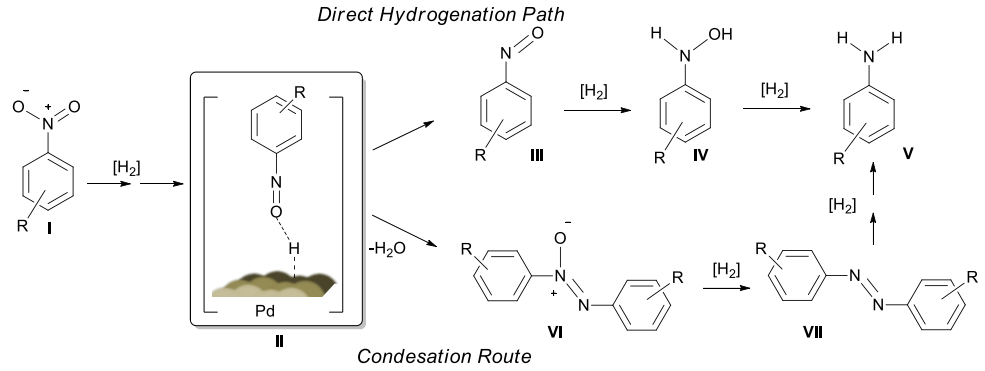
Likewise, full conversion of substrate **1** was achieved when 3 equivalents of $NaBH_4$ were combined with 0.05 mol % Pd (Scheme 1). This particularly low catalyst loading is a remarkable characteristic of these Pd nanocatalysts.

As expected, an increase in the amount of catalyst and reducing agent gradually led to the disappearance of intermediate products, raising the selectivity for amine **2** (Scheme 1). Accordingly, 94 % of yield of amine **2** could be reached after 1 hour with a combination of 0.1 mol% of PVP-Pd NPs and 4 equivalents of $NaBH_4$. Finally, when catalyst loading or $NaBH_4$ amount were further increased, the dehalogenated product aniline was detected.

Therefore, the catalytic system PVP-Pd NPs/$NaBH_4$ proved to be highly efficient under sustainable reaction conditions (aqueous medium, short reaction time, room temperature and moderate excess of reducing agent compared to other Pd NPs systems).[29,51] It also proceeded with an excellent conversion under low catalyst loading conditions. This is a notable feature since usually higher amounts of Pd are required to perform this kind of transformation.

Furthermore, when the reaction was performed in a higher scale using 1 mmol of *p*-chloronitrobenzene (**1**), the amine **2** was achieved in 92 % of yield with 93 % of selectivity.

To establish a reactivity order for the catalytic system PVP-Pd NPs/$NaBH_4$, this nanocatalyst was compared with some selected examples of *p*-chloronitrobenzene (**1**) hydrogenation (Table 1). The selection criteria was based on methodologies that use solvents recommended in guidelines elaborated by CHEM21 consortium project.[16] Both colloidal and supported nanocatalysts were analyzed, in combination with different reducing agents like H_2, siloxanes and $NaBH_4$.



Scheme 2. General mechanism for the nitroaromatic hydrogenation.

Table 1: Selected Pd catalyst for hydrogenations of *p*-chloronitrobenzene (**1**).[a]

Pd catalyst	Catal. load. (% mol)	Reaction medium	Temp (ºC)	Time (min)	[H]	TOF [b] (min^{-1})[ref]
PVP-Pd NPs	0.05	EtOH: H_2O	r. t.	60	$NaBH_4$ (3 eq.)	33 This work
Octyne- Pd NPs	0.04	THF	30	1560	H_2 (8 atm)	1 [52]
Pd@Fe_3O_4	0.20	EtOH	r. t.	60	H_2 (1 atm)	8 [53]
Pd/C (NF)	0.06	AcOEt	r. t.	120	H_2 (10 atm)	13 [54]
Pd-Si (foam)	0.5	AcOEt	r. t.	120	H_2 (1 atm)	2 [55]
Ps-Pd-MgO	2.0	H_2O	80	120	PMHS (4 eq.)	0.5 [27]
Pd-SS	2.0	MeOH:H_2O	50	60	$NaBH_4$ (3 eq.)	1 [29]

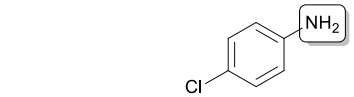
The data collected in Table 1 shows that the electrochemically prepared PVP-Pd NPs had a great catalytic activity in the nitroaromatic hydrogenation, exhibiting high TOF values compared to those of heterogeneous and colloidal catalysts. Besides these catalytic systems, very high TOF values under sustainable conditions were obtained by Göksu *et. al*. employing an heterogeneous catalyst consisted in Pd NPs supported over AlO(OH). The system proceed with TOF values close to 900 min^{-1} for several nitro compounds. [36] However, in this heterogeneous catalytic system the reaction with *p*-chloronitrobenzene (**1**) was not informed.

To further evaluate the scope of this methodology, several nitroaromatic substrates were hydrogenated under the optimized reaction conditions (Table 2). In general, all nitroaromatic compounds were efficiently reduced with high TOF values and excellent yields.

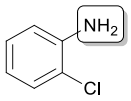
Both electron-donating and electron-withdrawing groups were tolerated, in different positions *o*-, *m*- and *p*- (Table 2). Chlorine substituent in *o*- or *p*- position was not reduced under the conditions employed. However, some steric hindrance was observed with chloro in *o*-position, since amine **4** was obtained in 79 % of yield (Table 2). Aniline (**5**) was obtained in excellent yield by reduction of nitrobenzene. Amines bearing amide or ester groups, **6** and **7** respectively, were efficiently obtained with high selectivity for nitro group hydrogenation (Table 2). Diamine **8**, a key product in polymer preparations, could be prepared by monohydrogenation of *p*-nitroaniline (**9**) or dehydrogenation of dinitrobenzene, both in good yields (Table 2). For the complete reduction of *p*-dinitrobenzene, 6 equivalents of $NaBH_4$ were needed in order to obtain the fully hydrogenated product **8** in 75 % of yield. When a lower excess of reducing agent was used, a mixture of *p*-nitroaniline (**9**) and diamine **8** products was achieved.

Several nitro compounds like nitrophenols are environmental pollutants, usually remediated by hydrogenation process.[56] In these cases, they were successfully converted to the corresponding amines **10** and **11** in short reaction times (Table 2).

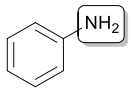
Table 2: Nitroaromatic hydrogenation by PVP-Pd NPs and $NaBH_4$ in aqueous medium.[a]



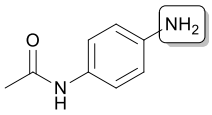
2 (94 %)[b] TOF: 16 min^{-1} (90 %)[c]



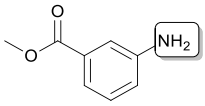
4 (76 %)[c] TOF: 13 min^{-1}



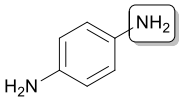
5 (97 %)[b] TOF: 16 min^{-1}



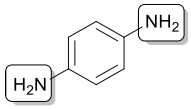
6 (93 %)[c] TOF: 16 min^{-1}



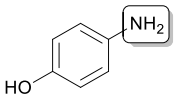
7 (99 %)[b] TOF: 17 min^{-1}



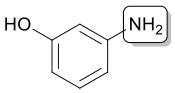
8 (92%[c]) TOF: 15 min^{-1}



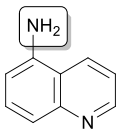
8 (75 %[c])[d, e] TOF: 13 min^{-1}



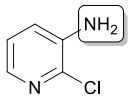
10 (100 %)[c] TOF: 17 min^{-1}



11 (100 %)[c] TOF: 17 min^{-1}



12 (75 %)[c] TOF: 25 min^{-1} (30 min)



13 (92 %)[b] TOF: 61 min^{-1} (15 min)

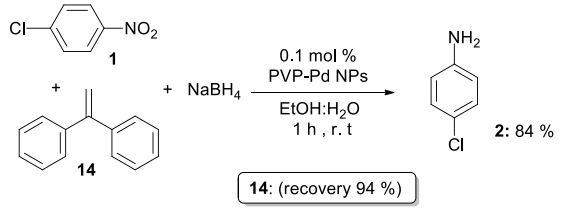
[a] Reaction conditions: 0.25 mmol of $ArNO_2$, 1 mmol de $NaBH_4$, 0.1 mol % PVP-Pd NPs, a mixture EtOH: H_2O 1:6 (final volume 3.5 mL), room temperature, 1 hour. [b] The reaction mixture was extracted with ethyl acetate and quantified by GC analysis with benzophenone as internal standard. [c] The reaction mixture was diluted with MeOH and quantified by HPLC analysis using external standard method. [d] 1.5 mmoles of $NaBH_4$ were used (6 equivalents). [e] 13 % of *p*-nitroaniline (**9**) was quantified.

Likewise, heteroaromatic amines **12** and **13** were also obtained in good yields employing this methodology (Table 2). These kinds of compound are important synthetic intermediates, and they are difficult to obtain by other methodologies.[33] In these examples, the reactions should not exceed the 30 minutes, since longer exposition to the reaction medium leads to decomposition of products, lowering the mass balance of the reaction.

The chemoselectivity of hydrogenation reaction over other susceptible functionalities, like alkenes and ketones, was also examined. The selectivity for nitro hydrogenation against the keto group reduction was corroborated using *p*-nitroacetophenone as a substrate. Several reaction conditions

were tested; yet, the keto group was unfortunately always hydrogenated before the nitro group, even under 0º C and with lower excess of reducing agent. In general, the nitro group could be selectively reduced over the keto group when reducing agents like hydrazine,[20] silicon derivatives[39] or H_2 were used.[34,38,37]

The selectivity over alkene functionalities was evaluated in competitive reactions. For these experiments, *p*-chloronitrobenzene (**1**) and the corresponding alkene were mixed with PVP-Pd NPs catalyst and $NaBH_4$ (Scheme 3).

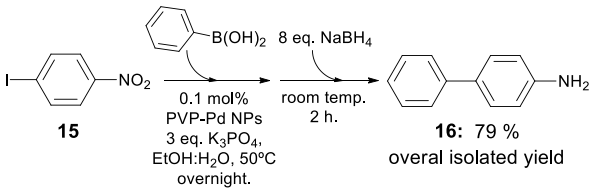


Scheme 3: Competitive reaction between nitroaromatic compound (**1**) and alkene (**14**) for hydrogenation process by $NaBH_4$ and PVP-Pd NPs.

With a hindered alkene, like 1,1-diphenylethylene (**14**, Scheme 3), the reaction proceeded efficiently over the nitro group giving amine **2** in 84 % of yield, leaving alkene **14** unchanged. By contrast, an opposite behavior was observed in the presence of mono substituted alkene styrene, since both alkene and nitro compound **1** were partially reduced. This could be explained on basis that the interactions of the alkene π system with the NPs surface were efficiently blocked by steric hindrance in the alkene **14**, avoiding the coordination and later hydrogenation of the double bond. Hence, PVP-Pd NPs were able to discriminate between the nitro groups from the bulky alkene system. When styrene was explored, due to its smaller size, the alkene coordinates efficiently to the catalyst surface, leading to reduction of both functional groups.[47]

Once the scope of the reaction was established, it was important to investigate the synthetic applicability of this green protocol in a tandem process. Hence, we analyzed the incorporation of nitro group hydrogenation by PVP-Pd NPs in one-pot consecutive reactions.

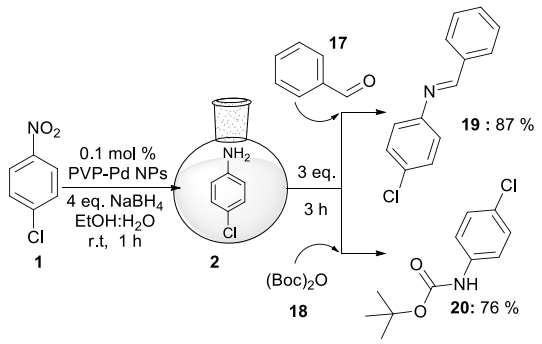
First, a Suzuki cross-coupling reaction/nitroaromatic hydrogenation reaction sequence was examined (Scheme 4), as an example of consecutive one-pot reactions catalyzed by PVP-Pd NPs.



Scheme 4: *One-pot* Suzuki/Hydrogenation reaction sequence catalyzed by PVP-Pd NPs to synthesize biphenyl amine **16**.

This one-pot procedure was accomplished considering the previously reported optimized conditions for the Suzuki cross-coupling reaction.[45] For that, a number of control experiments were performed to evaluate the cross-coupling process between *p*-iodonitrobenzene (**15**) and phenylboronic acid, in which time and temperature were optimized. Under the best condition (50 ºC, overnight), *p*-nitrobiphenyl was obtained with 83 % of isolated yield. Then, one-pot reaction was examined to obtain amine **16** directly from *p*-iodonitrobenzene (**15**). Thus, after performing Suzuki cross-coupling reaction, the mixture was cooled down and a water solution of 8 equivalents of $NaBH_4$ was added. The reaction was kept at room temperature for 2 hours. Accordingly, *p*-aminobiphenyl (**16**) was obtained in 79 % of isolated yield by this one-pot consecutive protocol.

It was important to evaluate the directly amino group protection after the catalytic hydrogenation in a tandem process. The synthesis of *N*-protected arylamines is a key step in the chemistry of amino compounds since, even though amines are important chemical products, their major drawback involves inherent reactivity. Thus, they often require protection to participate in multistep synthesis.[57] In general, there are a number of method to perform these protection reactions. The most used methods involve reactions in organic media or anhydrous conditions.[58,59] In order to avoid purification steps or change the reaction media, after performing the hydrogenation protocol with *p*-chloronitrobenzene (**1**), 3 equivalents of benzaldehyde (**17**) or di-*tert*-butyl dicarbonate (**18**) were added to the reaction media (Scheme 5).

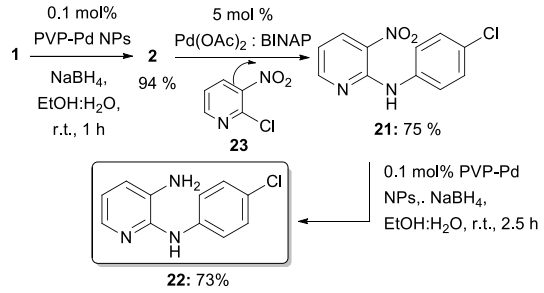


Scheme 5: One-pot strategy to obtain *N*-protected arylamines with benzaldehyde (**17**) or di-*tert*-butyl dicarbonate (**18**).

The reactions were stirred for 3 hours until ethyl acetate was added to extract the reaction mixture. As a result, amines derivatives **19** and **20** were obtained in good isolated yield for this one-pot procedure in a EtOH:H_2O mixture (Scheme 5). Therefore, without any purification or isolation steps, amine **2** was directly protected by only adding the protecting agent to the reaction mixture of the hydrogenation protocol.

The hydrogenation protocol was also employed to obtain 2,3-diaminopyridines **22** (Scheme 6). The great significance of this kind of functionalized 2,3-diaminopyridines lies in their use as precursors for the synthesis of ligands and biologically active molecules.[60–62] Some hydrogenation protocols for reduction nitro compounds like **21** were developed, since they were involved in API's production. These methodologies currently are protected by basic patents.[63] Taking into account the synthetic relevance of the 2,3-diaminopyridines derivatives, hydrogenation reaction by PVP-Pd NPs was chosen to perform

synthesis of amine **22**, and also to evaluate the sustainability of the process.



Scheme 6: Synthesis of 2,3-diaminopyridine **22** by sequential Pd-catalyzed reactions.

The synthetic path proposed for amine **22** consisted in three steps (Scheme 6). First, hydrogenation protocol was used to obtain amine **2** (Scheme 6). Then, nitropyridine **21** was synthesized by a Pd-catalyzed amination of 2-chloro-3-nitropyridine (**23**) with amine **2** in toluene, employing a mixture $Pd(OAc)_2$:BINAP as catalyst. Nitropyridine **21** was obtained in 75 % of isolated yield after 24 hours. Unfortunately, when amination reaction was performed in the presence of PVP-Pd NPs as catalyst, no conversion of 2-chloro-3-nitropyridine (**23**) was observed.

Reduction of nitropyridine **21** was performed under the previously optimized condition for hydrogenation reaction with PVP-Pd NPs. In this particular case, 8 equivalents of $NaBH_4$ and 2 hours of reaction were needed in order to obtain better yields of **22**.

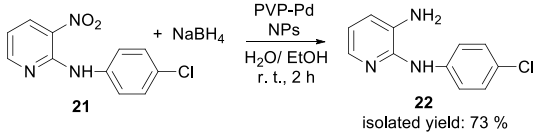
With the aim of determining whether the hydrogenation protocol by PVP-Pd NPs is a convenient tool in this synthetic path (providing improvements in term of sustainability), some considerations about the "greenness" of the reaction were examined. For that, some key parameter were evaluated (Table 3). Moreover, our protocol was compared with one of the few reports available for the synthesis of amine **22**. The procedure reported by Kamal, *et. al*., in which stoichiometric excess of $SnCl_2$ was used as a reducing agent in MeOH under reflux for 2 hours (Table 3).[60]

The "green metrics" analyzed in Table 3 were proposed by McElrond, *et. al*.[17] as an unified "green metrics toolkit" which facilitates monitoring, measuring, comparing and evaluating new methodologies in terms of their "green credentials".[17] This toolkit was classified into a number of levels that move from the discovery of a process towards commercialization of a product, and in each stage, some key parameters were analyzed. The analysis of these parameters allows scoring greenness with a flag system: green flag for "preferred", amber flag for "acceptable/some issues" and red flag denotes "undesirable".[17] In the present study the first stage of the toolkit, the discovery level or "zero pass", was chosen to perform the analysis.

Under the two protocols, amine **22** was obtained with high selectivity and in good isolated yields (73 % and 85 %, Table 3). The McElrond *et al*. toolkit establish that yields and selectivities higher than 89 % are assigned with a green flag; an amber flag corresponds to values between 89 % and 70 %; and a red flag for values lowers than 70 %.[17] Thus, in both cases for the yield parameter were assigned an amber flag, and a green flag for the reaction selectivity.

Table 3. Comparison of methodologies for reduction of nitro compound **21** by green metrics toolkit.[17]

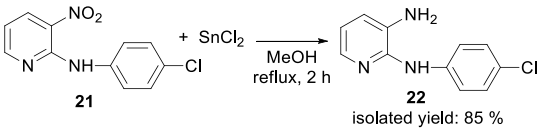
Reaction Conditions: This work



Green parameters

Yield	Sel.	AE[a]	RME[b]	Solv.	Crit. Elem.[c]	H&S[c]
		76	39			

Reaction Conditions: Kamal, *et. al*.



Green parameters

Yield	Sel.	AE[a]	RME[b]	Solv.	Crit. Elem.[c]	H&S[c]
		46	20			

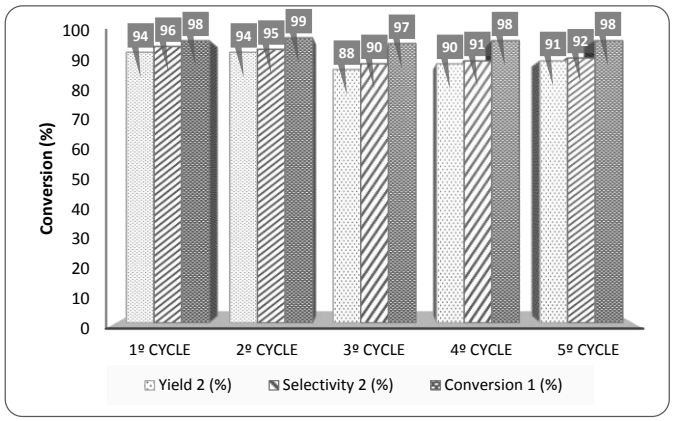
a- AE = (molecular weight product/total molecular weight of reactants)*100. b- RME = (mass of isolated product/total mass reactants)*100. c- ref.17 .

Nevertheless, when the Atom Economy parameter (AE) was calculated, a significant difference was observed. The AE is a useful parameter since it measured the reaction efficiency by the number of atoms in the reactants which appear in the final product. To determine AE parameter, the molecular weight of the product and all reactants was taken into account.[64] In that sense, the methodology using $SnCl_2$ as a stoichiometric reducing agent had a considerably lower value of AE, because of the large amounts of heavy metal tin (Table 3). Complementary to the AE parameter was defined the Reaction Mass Efficiency (RME) parameter. It provides a fuller picture of the utilization of reactants, since incorporates yield and stoichiometry of the reaction. For calculation of RME values, the ratio between mass of isolated product and the total mass of reactants was performed.[17,64] Similarly to the observed with AE, RME value was higher for the catalytic hydrogenation reaction by PVP-Pd NPs (Table 3). In addition, the use of tin reagent in the Kamal methodology also had an impact on other parameters like Health and Safety (H&S) and Critical Elements considerations. The H&S parameters is employed to determine if the reactants used in the synthesis had a severe hazard statement, based on the globally harmonized system of classification and labelling of chemicals (GHS).[65] Accordingly to the McElrond *et al*. toolkit, some Hazard statements (H-statement) results in the production of a red flag.[17] Since $SnCl_2$ has environmental

implications and high toxicity, a red flag and three amber flags were assigned in agreement with its H-statements. In the catalytic hydrogenation, H-statements for $NaBH_4$ lead to one red flag and one amber flag assignation (Table 3). In addition, an element was defined by the EU to be critical if it is of high economic value coupled with a high risk of supply.[66] This considerations were evaluated in both hydrogenation reactions with the Critical Element parameter (Table 3).[17] A red flag was given to the Kamal methodology, since Sn have a high risk to depletion within the next 5-50 years. In the case of catalytic hydrogenation methodology an amber flag was generated, due Pd and B are considered more available in the next 50-500.[17] Solvent choice was also examined, and in both cases a green flag was given, since MeOH and a water: EtOH mixture are recommend.[17]

Metrics analysis demonstrated that our process provided improvements in terms of sustainability for be used in organic synthesis; and confirmed that replacing stoichiometric hydrogenation method by catalytic hydrogenation with PVP-Pd NPs is appropriate for the synthesis of compounds like **22**.

An important feature of any catalytic system is their ability of reutilization. Thus, recyclability test for this catalytic system was evaluated. Due to the high stability of the PVP-Pd NPs in water,[44,45] separated them from the aqueous reaction media is a difficult task. Any attempt to separate the nanocatalyst from reaction media by centrifugation, precipitation or organic extraction eventually lead to a dramatic drop of the catalytic activity. Thus, for reuse experiments, repeated runs on the same batch were performed; reusing the aqueous reaction mixture with the PVP-Pd nanocatalyst. The benchmark substrate *p*-chloronitrobenzene (**1**) was employed in these experiments. Once the reduction was completed, a new batch of nitrocompound **1**, $NaBH_4$ and mixture of $EtOH:H_2O$ was reintroduced. The yield, selectivity and conversion of five successive runs are showed in Scheme 7.



Scheme 7: Recyclability test for the PVP-Pd NPs in the hydrogenation of *p*-chloronitrobenzene (**1**) with $NaBH_4$.

The PVP-Pd NPs exhibited a great catalytic activity after five cycles of hydrogenation reaction, without any significant loss of activity/selectivity in aqueous medium. This is another factor to assigned high "greenness" to the PVP-Pd NPs catalytic system.

This reusing outcome of the PVP-Pd NPs clearly points out the robust nature of this nanocatalyst.

In order to analyses the possible modification of the catalyst during the reaction the TEM micrograph of PVP-Pd NPs before and after one catalytic cycle was performed. For that, nanocatalyst was separate from the reaction mixture performing a physical separation of NPs by centrifugation. Considering that, the physical manipulation of the NPs might generate changes in size or morphology of the nanocatalyst, and in order to compare NPs being process in the same way, the original colloidal dispersion of PVP-Pd NPs was centrifuged before the TEM achievement (Figures S1 and S2, Supporting information). The comparison between NPs mean diameter reveal that the original small size PVP-Pd NPs (7 ± 5) nm clump to larger aggregates after the catalytic cycle, providing NPs with a mean diameter of (20 ± 10) nm with high dispersion in size (Figures S1 y S2, Supporting information). Despite of the coalescence of small size NPs by action of the chemical reaction, the bigger NPs were still active as catalysts, as was demonstrated by the successful recycling. The morphology of the NPs appear not to be modified, and always look like a "blackberry". Probably, this particular structure leave expose enough surface available to efficiently perform the catalytic reaction.

Conclusion

The electrochemically prepared PVP-Pd NPs exhibited an outstanding catalytic activity on hydrogenation process for nitroaromatic reduction, in addition to the already proved homeopathic activity in coupling reactions for C-C bond formation.[44,45]

Anilines were obtained in very good or excellent yields and with high TOF values, even better than those with reported colloidal and supported Pd nanocatalysts. Several functional groups were tolerated under the reaction conditions employed, such as chlorine, ester, amide, amine, hydroxyl, hindered alkenes and heterocyclic compounds. Moreover, selectivity could be modulated, obtaining the azoxy derivative in moderate yield by only changing the ratio between Pd and reducing agent.

Furthermore, this green protocol was compatible to one-pot process for the synthesis of amines derivatives, and applicable to the synthesis of complex molecules in consecutive reactions, key synthones in preparation of biologically active compounds.

Most importantly, the methodology developed was simple, fast and easily handled, via which the use of harmful solvents or reagents was avoided. Reducing agent $NaBH_4$ was employed under relative low excess, and the reactions were performed in aqueous medium, under mild reactions conditions. Recyclability test of the reaction mixture showed that PVP-Pd NPs maintain their outstanding catalytic activity even after five reuse cycle.

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Table of Contents:

Towards an efficient, mild and sustainable approach for nitroarene hydrogenation by Pd nanoparticles in aqueous medium.