Effect of Substrates on Catalytic Activity of Biogenic Palladium Nanoparticles in C–C Cross-Coupling Reactions

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ABSTRACT: This work describes a practical methodology for C–C bond formation reactions with the aid of biogenic palladium nanoparticles, which are synthesized by using phytochemicals extracted from two common plant species. Comparative studies have been done on the activity of two plant species (Ocimum sanctum and Aloe vera) in generation of palladium nanoparticles via ex situ and in situ methods. The structural and morphological characteristics of the nanoparticles are examined by UV/visible spectroscopy, powder X-ray diffraction, X-ray photoelectron spectroscopy, Fourier transform infrared spectroscopy, and transmission electron microscopy analyses. We have observed a significant influence of the substrates on the catalytic activity of the palladium nanoparticles in Sonogashira and Suzuki cross-coupling reactions.

1. INTRODUCTION

In recent years, metal nanoparticles (NPs) have been widely applied in different areas ranging from catalysis to biomedical diagnostics on account of their unique size, shape, and composition. These materials are susceptible to various chemical and physical modifications and can conjugate with varying antibodies, ligands, and drugs providing a wide range of applications.1–4 Various chemical, biological, and physical methods have been explored for synthesis of metal NPs.5,6 The characteristic feature in the synthesis of NPs is that the nanosystems should be stable, biocompatible, and selective in their action. Catalytic activity of metal NPs finds wide application in organic synthesis and the “NP-catalyzed organic synthesis enhancement” (NOSE) approach is considered as an effective route for organic synthesis.7,8 The catalytic activity of metal NPs is specifically related to their size and distribution. However, smaller NPs in some cases agglomerate to minimize their surface area due to their excess surface free energy, resulting in a remarkable decrease in their catalytic activities. As such there requires additional stabilizers or supports for the enhanced catalytic activity of the metal NPs. In situ-generated NPs (NPs\textsubscript{in\,situ}) on account of their one-pot condition does not demand additional stabilizers because it remains under the influence of the reactant species. Another advantage of NPs\textsubscript{in\,situ} is that it avoids the laborious preparative and isolation processes.

Considering the positive aspects of NPs\textsubscript{in\,situ} researchers now tend to utilize transition-metal NPs\textsubscript{in\,situ} in different fields of catalysis and organic synthesis. Various approaches for generation of in situ NPs of Au, Ag, Cu, and Pd have been reported.9–14 Chemical methods for generation of NPs are associated with toxic byproducts and uneconomical issues. From the green chemistry point of view, environmentally benevolent alternative reducing agents for the synthesis of NPs are in great demand. In this regard, the introduction of microorganisms and plant resources provides an environmentally benign and a cost-effective alternative route for the synthesis of metal NPs.15–17 There are various methodologies in which the specific pure compound of plant origin is used in NP preparation, for example, ascorbic acid and gallic acid which are plant polyphenols and act as great stabilizing agents in synthesis of NPs.18–20 Plant extracts possess various biologically active phytochemicals (e.g., alkaloids, terpenoids, and polyphenolic compounds) which themselves serve as a reducing/stabilizing agent for bulk transition metals to nanodimensional particles.21 The plant-based approaches of synthesis of metal NPs not only provides a faster rate of reduction of metal ions to zero valent metal but nucleate/cap them into stable and controlled morphology. As such
biogenic reduction of metal ions in the absence of chemical reagents is an interesting approach on account of the environmental sustainability.

The C–C framework in organic synthesis is an indispensable tool for synthesis of numerous structural functionalities which are indeed building blocks of natural products, agrochemicals, medicinally important compounds, and so forth. The simplest and of course the most imperative synthetic transformations are based on Csp2–Csp2 and Csp2–Csp bonds commonly known as Suzuki and Sonogashira cross-coupling reactions, respectively. These transformations turn up as a pioneer for synthesis of various biologically active compounds and construction of pharmaceuticals, fine chemicals, and smart engineering materials, including conducting polymers and molecular wires.22 Of all transition metals, Pd contributes an impressive ability to construct C–C bonds between diversely functionalized substrates.27 Very recently, we have reported the synthesis of Pd NPs using papaya peel extract and subsequently evaluated the catalytic efficiencies toward Suzuki and Sonogashira cross-coupling reactions.28 Motivated by the remarkable results, we herein explore the tandem synthesis of Pd NPs and C–C cross-coupling reaction in a one-pot reaction process using two different plant extracts [Ocimum sanctum (OS) and Aloe vera (AV)]. Interestingly, we found a significant difference in the catalytic behavior of the two Pd NPs (PdAV NPs and PdOS NPs). PdAV NPs were found to be more effective for Suzuki coupling reaction, whereas PdOS NPs were more proficient for Sonogashira coupling reaction.

2. RESULTS AND DISCUSSION

2.1. Characterization of Pd NPs. The Pd NPs were characterized by transmission electron microscopy (TEM), powder X-ray diffraction (XRD), UV/visible spectroscopy, X-ray photoelectron spectroscopy (XPS), and Fourier transform infrared spectroscopy (FTIR) spectroscopy and investigated the catalytic activity in C–C coupling reactions and annulation via C–X functionalization.

During the preparation of Pd NPs, it was noticed that both the extract and the Pd(OAc)2 mixture undergoes reduction of Pd(II) to Pd(0) in different time intervals (Figure 1).

The mixture of OS leaf extract (Ext OS) and Pd(OAc)2 shows a gradual change in color from light brown to black after 1 h (Figure 1a). The change in color of Pd(OAc)2 on addition of AV extract (Ext AV) was observed after 5 h (Figure 1b). This variation of reducing potential of the extracts with time may be due to the presence of different concentrations of phytochemicals present in the two plant species.

It was found from the existing literature that various quantitative analyses have been carried out to reveal the chemical compositions of OS and AV. From the comparative study of both the plant species, it was found that OS leaves possess a greater amount of reducing sugar and ascorbic acid, although different amounts were reported by Hassan et al. and Kashif et al. (Table 1).29−32 It is seen in various

| parameters       | A. vera | O. sanctum |
|------------------|---------|------------|
| ascorbic acid    | 1.90 ± 1.90 | (65.41 ± 0.76) ± 37 (0.24 ± 0.91)27 |
| (mg/100 g)       |         |            |
| reducing sugar (%)| 0.36 ± 0.36 | (35.8 ± 0.14)30 (26.52 ± 1.54)30 |

literature reports that ascorbic acid and different reducing sugars are used in generation of NPs.33−35 As such these phytochemicals in the respective plant species helps in the reduction of the Pd(II) ion. However, the presence of a greater amount of these chemical constituents in OS as compared to AV reveals its greater reducing potential. Additionally, other phytochemicals such as flavanoids, essential oils, and phenolic contents are also present which may also assist in the reduction/stabilization of metal NPs.36−41

Initially, we have performed powder XRD to understand the formation of the Pd NPs using both plant extracts. Figure 2a shows the powder XRD pattern of the PdOS NP, which matches well with standard JCPDS card no. 89-4987. The diffraction peaks at a 2θ value of 40.5°, 46.3°, and 67.8° corresponding to crystallographic planes (111), (200), and (220), respectively, suggest the formation of the face-centered cubic (fcc) lattice system of PdOS NPs. Again, Figure 2b shows the powder XRD pattern of PdAV NPs, which shows the formation of the fcc lattice system (JCPDS card no. 89-4987) with an additional tetragonal system for the PdO nanostructure (JCPDS card no. 75-0200). The observed peaks at a 2θ value of 39.9°, 46.1°, and 68.3° correspond to planes (111), (200), and (220), respectively, with two additional diffraction peaks of PdO at a 2θ value of 18.1 and 30.6 for (001) and (100) reflections, respectively. The formation of Pd/PdO in the case of PdAV NPs may be due to longer time requirement for reduction of Pd(II) which as a result leads to aerial oxidation of Pd(0).
Further, we have characterized by X-ray photoelectron spectroscopy (XPS) analysis in order to confirm the oxidation state of Pd NPs in PdOS NPs and PdAV NPs. Figure 3a shows the survey scan spectrum of PdOS NPs, indicating the presence of Pd. The high-resolution peak fitting spectrum of PdOS NPs comprises two peaks at 335.05 and 340.20 eV attributed to the Pd 3d_{3/2} and Pd 3d_{5/2} spin-orbit peaks of Pd(0) as shown in Figure 3b. From the XPS analysis of PdOS NPs, it is evident that Pd NPs present in the zero (0) oxidation state.

On the other hand, the survey scan XPS of PdAV NPs signifies the occurrence of Pd and O as shown in Figure 3c.
The high-resolution peak fitting Pd 3d spectrum for PdAV NPs reveals the presence of four peaks at 334.66, 337, 338.93, and 342.30 eV, which belongs to Pd(0), Pd(II), Pd(0), and Pd(II), respectively (Figure 3d). Therefore, the formation of Pd/PdO NPs is confirmed from the high-resolution XPS spectrum. Further, the high-resolution O 1s spectrum as shown in Figure 3e also confirmed the presence of PdO in PdAV NPs.

FTIR of the PdOS NPs and PdAV NPs was recorded by comparing with the precursor Pd(OAc)2 as shown in Figure 4. The shifting/disappearance of characteristic peaks of Pd(OAc)2 reveals the formation of metallic Pd(0) particles. Figure 4a shows the vibrational peaks at 1604 and 1332 cm\(^{-1}\), which is due to the respective asymmetric and symmetric stretching of C=O.\(^{42}\) The sharp peak at 1408 cm\(^{-1}\) is due to the ionized carboxylate group. The shifting of these vibrational modes after the addition of Ext OS and Ext AV to Pd(OAc)2 confirms the reduction of the Pd(II) ion (Figure 4b). Additionally, the disappearance of peak at 691 cm\(^{-1}\) due to Pd–O further validates the formation of the Pd(0) nanostructure using Ext OS.\(^{43}\) Further, the peak in region 781 and 597 cm\(^{-1}\) signifies the presence of PdO along with Pd(0) particles.

Next, the potential of Ext OS and Ext AV was examined in case of in situ generation of NPs considering C–C cross-coupling as the model reaction. The formation of Pd NPs was further confirmed by the UV/visible spectroscopic experiment and TEM analyses.

Figure 5a–c shows the UV/visible absorption spectra of the in situ-generated colloidal suspension of PdOS NPs. A weak band at 279 nm was observed in Figure 5a, which corresponds to Ext OS.\(^{44,45}\) After the addition of Pd(OAc)\(_2\), an additional peak centered near 400 nm was observed which is a characteristic of the Pd(II) ion Figure 5b.\(^{46}\) Subsequent bioreduction of the precursor Pd(OAc)\(_2\) solution results in the disappearance of the corresponding peak at 400 nm (Figure 5c), indicating the complete reduction of the Pd(II) salts to nanosized Pd(0). Figure 5d shows a distinctive UV absorption peak at 260 nm due to Pd(OAc)\(_2\) and Ext AV solutions. On addition of subsequent reagents of C–C coupling, the peak at 260 nm disappeared which signifies the complete reduction of Pd(II) (Figure 5e). However, a very broad UV absorption peak centered near 260 nm was observed for pre-prepared PdAV NPs (Figure 5f) which shows that the Pd(II) ion in this condition does not undergo complete reduction to Pd(0) even after prolonged stirring.
Figure 7. (a–c) are the TEM and HRTEM images and (d) is the SAED pattern of PdAV NPs_{ex situ}.

2.2. Catalytic Activity of Pd NPs. The catalytic activities of both PdAV and PdOS NPs were investigated for the Suzuki–Miyaura cross-coupling reaction. Initially, the catalytic activity was examined for the pre-prepared Pd NPs using 4-bromonitrobenzene and phenylboronic acid as the model substrate. The reaction affords only 30 and 10% of isolated yields of the cross-coupling product with both ex situ-generated PdAV and PdOS NPs. In the case of PdOS NPs, a significant amount of the homocoupling product of arylboronic acid was observed (Table 2, entries 1 & 2). We next opt to study the in situ catalytic effects of the aqueous plant extracts on the reaction progress. On using Ext AV, we were able to isolate 50% of the desired product using 1 mol % Pd(OAc)_{2} in biphasic solvent medium (Table 2, entry 3). On increasing the amount of Ext AV, a gradual increase in reaction yield was observed (Table 2, entries 4 & 5). Enhanced catalytic activity was observed using 2 mL of Ext AV (Table 2, entry 6). However, on performing the reaction using Ext OS, relatively lower yield of the cross-coupling product was obtained (Table 2, entries 6 & 7). Because the phytochemical constituents in both the plant extracts (Ext OS & Ext AV) vary in nature and composition (Table 1), the catalytic efficiency in the coupling reaction seems to differ. Interestingly, during the synthesis of Pd NPs using both the plant extracts, we have observed that Ext OS was more effective than Ext AV, and PdOS NPs_{ex situ} is formed quickly compared to PdAV NPs_{ex situ} (Figure 1). On the contrary, during the in situ experiments, Ext OS was found to be less effective compared to Ext AV in Suzuki reaction. The cause of poorer conversion in case of Ext OS might be due to the presence of arylboronic acid. Liu et al. in 2008 described the role of arylboronic acid in the formation of NPs. They had performed a controlled experiment for in situ generation of NPs, and established that arylboronic acid acts as an associate reducing agent in the formation of NPs. A similar case was observed in the present protocol in the generation of in situ PdAV NPs. As we have seen that in the synthesis of PdAV NPs_{ex situ} it requires a longer time for the conversion of Pd(II) to Pd(0) nano without any chemical reducing agent. However, in the in situ catalytic approaches, after addition of arylboronic acid, the Pd(II) ions immediately changes to black color indicating the

Table 2. Optimization of Reaction Conditions for Suzuki–Miyaura Reaction

| entry | R     | Pd catalyst (mol%) | (Ext.) (mL) | solvent (mL) | base (mmol) | time (min) | yield (%) |
|-------|-------|--------------------|-------------|--------------|-------------|------------|-----------|
| 1     | NO_{2} | Pd_{ex situ} (1)   |             | EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 6 h       | 30        |
| 2     | NO_{2} | Pd_{ex situ} (1)   |             | EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 6 h       | 10        |
| 3     | NO_{2} | Pd(OAc)_{2} (1)    | Ext AV (0.5) | EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 1 h       | 50        |
| 4     | NO_{2} | Pd(OAc)_{2} (1)    | Ext AV (1)  | EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 15        | 70        |
| 5     | NO_{2} | Pd(OAc)_{2} (1)    | Ext AV (2)  | EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 15        | 90        |
| 6     | NO_{2} | Pd(OAc)_{2} (1)    | Ext OS (0.5)| EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 1 h       | 40        |
| 7     | NO_{2} | Pd(OAc)_{2} (1)    | Ext OS (2)  | EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 1 h       | 40        |
| 8     | NO_{2} | Pd(OAc)_{2} (1)    |              | EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 1 h       | 50        |
| 9     | NO_{2} | Pd(OAc)_{2} (0.5)  | Ext AV (2)  | EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 15        | 40        |
| 10    | NO_{2} | Pd(OAc)_{2} (1)    | Ext AV (2)  | H_{2}O         | K_{2}CO_{3} (1.5) | 15        | 60        |
| 11    | OMe   | Pd(OAc)_{2} (1)    | Ext AV (2)  | EtOH/H_{2}O (1:1) | K_{2}CO_{3} (1.5) | 15        | 95        |
| 12    | OMe   | Pd(OAc)_{2} (0.5)  | Ext AV (2)  | H_{2}O         | K_{2}CO_{3} (1.5) | 15        | 92        |
| 13    | OMe   | Pd(OAc)_{2} (0.5)  | Ext AV (2)  | H_{2}O         | NaOH (1.5)      | 15        | 78        |
| 14    | OMe   | Pd(OAc)_{2} (0.5)  | Ext AV (2)  | H_{2}O         | Na_{2}CO_{3} (1.5) | 15        | 80        |
| 15    | OMe   | Pd(OAc)_{2} (0.5)  | Ext AV (2)  | H_{2}O         | Na_{2}PO_{4} (1.5) | 15        | 85        |

Reaction conditions: arylbromide (1 mmol), phenylboronic acid (1.2 mmol), solvent (2 mL). Isolated yields.
quickered formation of Pd NPs. UV/vis spectra have also revealed the difference in reduction of the Pd(II) ion. Moreover, arylboronic acids act as a stabilizer for NPs and serve as a capping agent to keep them constant in size. This may sometimes lead to limitation of catalytic activity of NPs, which was observed in the case of PdOS NPs in situ. Because the Ext OS act a great reducing stabilizer in the generation of NPs, the additional stabilizing effect of arylboronic acid capped most of the free surface active site for catalysis resulting in the weaker catalytic activity of PdOS NPs in situ. As such according to the adsorption theory, activation of 4-bromonitrobenzene was diminished because of adsorption/capping of arylboronic acid particulates in the catalyst surface, resulting in poor reaction yield. Again, it is seen that in the absence of either of the extracts, the reaction does not proceed efficiently, which reveal the significance of the plant extract in the reaction medium (Table 2, entry 8).

Considering the higher activity of Pd AV NPs in situ in this Suzuki–Miyaura coupling, further optimization was carried out using Ext AV. The catalytic activity of Pd AV NPs in situ was examined by lowering the amount of Pd(OAc)$_2$. However, a significant decrease in reaction yield was observed (Table 2, entry 9). The catalytic efficiency was checked using water as the reaction medium. However, no appreciable result was obtained (Table 2, entry 10). This may be due to insolubility of the reactant species in water resulting in weaker coordination with the catalyst. Next, we have performed the reaction considering 4-bromoanisole and phenylboronic acid as the coupling partners. In this case, the reaction seems to proceed efficiently in water as the reaction medium along with lower catalyst loading (Table 2, entries 11 & 12). This is evidence of the solubility and coordination issue of the reactant species with the reaction medium and the catalyst. Then, the effect of different bases such as NaOH, Na$_2$CO$_3$, and Na$_2$PO$_4$ has been studied, but superior catalytic activity was achieved only with K$_2$CO$_3$ (Table 2, entries 13–15 vs 12).

The catalytic system was studied for electronically diverse arylbromides and arylboronic acid. The reaction efficiency for both the methods using Ext OS and Ext AV was shown in Table 3. As already discussed, method A (with Ext OS) does not show diverse substrate compatibility. Method B (Ext AV) delivers an excellent yield of the cross-coupling product with an electron donating substituent with lower catalyst loading in pure water as solvent (Table 3, 3a, 3e, 3k–o). The aryl halide-bearing hydroxyl group, on the other hand, demands greater catalyst loading with EtOH as cosolvent. The reaction was also compatible for electron withdrawing substituents according excellent conversion in biphasic medium. However, a slightly greater amount of the catalyst was required in comparison to electron-donating arylbromides (Table 3, 3b–d, 3g–i). From Table 3, it is observed that electronically varied arylboronic acid does not affect the reaction yield. The t-Bu substituent on phenylboronic acid requires a biphasic condition for effective coupling. This may be due to a solubility issue of the substrate in water (Table 3, 3j). The effectiveness of method B was examined for heteroaryl halide, and moderate yield of the cross-coupling product was achieved although greater reaction time was required (Table 3, 3p).

Table 3. Substrate Scope for Suzuki–Miyaura Cross-Coupling Reaction$^a$

| Method A | Method B |
|----------|----------|
| OHC | O$_2$N |
| 3a, 60 min, 30% | 3b, 60 min, 40% |

$^a$Reaction conditions: arylbromides (0.5 mmol), arylboronic acid (0.6 mmol), Pd(OAc)$_2$ (0.5 mol %), Ext (2 mL), and H$_2$O (2 mL).$^6$EtOH/H$_2$O (2 mL, 1:1).$^7$1 mol % Pd(OAc)$_2$. | |
Because the recyclability of the catalyst is one of the most important factors in a reaction protocol, we have investigated the recyclability of the catalytic species using 4-bromoanisole and phenylboronic acid as the coupling partners. After the first catalytic cycle, the reaction mixture was extracted with ethyl acetate followed by centrifugation. The clearly separated organic fraction was removed and evaporated to get the crude product and purified to obtain 92% isolated yield. The residue catalyst was washed with ethanol and then directly reused for the next catalytic run with the addition of fresh reactants, base, and solvent. The reaction affords similar reactivity till the third cycle (Figure 8). However, a slight decrease in catalytic activity was observed with 80% yield in the fourth cycle with a slightly longer reaction time.

The morphology of Pd\textsubscript{AV} NPs\textsubscript{in situ} after the second catalytic cycle was studied by TEM and HRTEM analysis (Figure S57, Supporting Information). The TEM and HRTEM images show spherical NPs of Pd/PdO for Pd\textsubscript{AV} NPs\textsubscript{in situ}. Most of the Pd/PdO NPs were agglomerated during the reaction course. Therefore, the size of the NPs after the second catalytic cycle is not clearly determinable. However, the lattice fringes are visible in the HRTEM image (Figure S57d). The lattice fringe distance was found to be 0.22 nm corresponding to the Pd(111) crystallographic plane.

Next, we have studied the catalytic activity of the ex situ and in situ-generated Pd NPs in Sonogashira cross-coupling of arylhalides and terminal alkynes. Considering our previous work on Sonogashira coupling\textsuperscript{49} we have performed the reaction using 4-iodonitrobenzene and phenylacetylene as our screening substrates in EtOH and \( \text{K}_2\text{CO}_3 \) as a base at 40 °C. The results are summarized in Table 4.

Initially, we have studied the catalytic activity of both Pd NPs\textsubscript{ex situ} for Sonogashira coupling. We have noticed a significant difference in reactivity in comparison to the Suzuki–Miyaura cross-coupling reaction. Superior catalytic activity was observed using Pd\textsubscript{OS} NPs with 95% of the cross-coupling product (Table 4, entry 1). A comparatively lower conversion was observed for Pd\textsubscript{AV} NPs with extended reaction time (Table 4, entry 2). Similar observation was achieved in the case of the in situ approach with Ext OS (Pd\textsubscript{OS} NPs\textsubscript{in situ}) being more competent than Ext AV (Pd\textsubscript{AV} NPs\textsubscript{in situ}) (Table 4, entries 3 & 4). Moreover, Pd\textsubscript{OS} NPs\textsubscript{in situ} affords greater yield within shorter reaction time, which may be due to the greater reducing and stabilizing effect of the extract in the reaction medium (Table 4, entry 1 vs entry 3). Considering the enhanced catalytic activity of Pd\textsubscript{OS} NPs\textsubscript{in situ}, further screening of the reaction was performed using these conditions.

The difference in reaction yield on varying the amount of extract (Table 4 entries 3 vs 6) may be due to greater capping of

### Table 4. Screening the Catalytic Effect on Sonogashira Coupling

| entry | catalyst (mol %) | extract (mL) | solvent (mL) | base (mmol) | time (h) | yield (%)  |
|-------|-----------------|--------------|--------------|-------------|----------|------------|
| 1     | Pd\textsubscript{AV} NPs\textsubscript{ex situ} (1) |             | EtOH         | \( \text{K}_2\text{CO}_3 \) | 3        | 95         |
| 2     | Pd\textsubscript{AV} NPs\textsubscript{ex situ} (1) |             | EtOH         | \( \text{K}_2\text{CO}_3 \) | 10       | 78         |
| 3     | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | EtOH         | \( \text{K}_2\text{CO}_3 \) | 2        | 97         |
| 4     | Pd(OAc)\textsubscript{2} (1) | Ext AV (2)   | EtOH         | \( \text{K}_2\text{CO}_3 \) | 8        | 88         |
| 5     | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | EtOH         | \( \text{K}_2\text{CO}_3 \) | 3        | 82\textsuperscript{c} |
| 6     | Pd(OAc)\textsubscript{2} (1) | Ext OS (1)   | EtOH         | \( \text{K}_2\text{CO}_3 \) | 2        | 95         |
| 7     | Pd(OAc)\textsubscript{2} (1) | Ext OS (1)   | EtOH         | \( \text{K}_2\text{CO}_3 \) | 4        | 60         |
| 8     | Pd(OAc)\textsubscript{2} (0.5) | Ext OS (0.5) | EtOH         | \( \text{K}_2\text{CO}_3 \) | 6        | 50         |
| 9     | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | EtOH         | \( \text{Cs}_2\text{CO}_3 \) | 2        | 97\textsuperscript{d} |
| 10    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | EtOH         | \( \text{Na}_2\text{CO}_3 \) | 6        | 60         |
| 11    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | EtOH         | \( \text{NaHCO}_3 \) | 6        | 20         |
| 12    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | EtOH         | \( \text{NaOAc} \) | 12       | 70         |
| 13    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | EtOH         | \( \text{NaOH} \) | 3        | 80         |
| 14    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | \( \text{H}_2\text{O} \) | \( \text{K}_2\text{CO}_3 \) | 24       | 40         |
| 15    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | \( \text{EtOH/H}_2\text{O} \) | \( \text{K}_2\text{CO}_3 \) | 12       | 40         |
| 16    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | 2-MeTHF      | \( \text{K}_2\text{CO}_3 \) | 24       | nr         |
| 17    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | 2-MeTHF/H\textsubscript{2}O | \( \text{K}_2\text{CO}_3 \) | 24       | 20         |
| 18    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | THF          | \( \text{K}_2\text{CO}_3 \) | 12       | 30         |
| 19    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | EtOH         | \( \text{K}_2\text{CO}_3 \) | 4        | 85         |
| 20    | Pd(OAc)\textsubscript{2} (1) | Ext OS (0.5) | EtOH         | \( \text{K}_2\text{CO}_3 \) | 3        | 85\textsuperscript{e} |

\textsuperscript{a}Reaction conditions: 4-iodonitrobenzene (0.5 mmol), phenylacetylene (0.6 mmol), base (1.5 mmol), solvent (4 mL) at 40 °C. \textsuperscript{b}Isolated yield. \textsuperscript{c}RT. \textsuperscript{d}\( \text{Cs}_2\text{CO}_3 \) (1 mmol). \textsuperscript{e}4-Iodonitrobenzene (0.5 mmol), phenylacetylene (0.5 mmol).
free Pd surface sites by the plant extract, which as a result lowers the accessibility of the Pd NP particle at the surface for catalysis.\(^50,51\) Moreover, in the absence of Ext OS, the reaction bears very minimum conversion, which signifies their role and importance for the present cross-coupling reaction (Table 4, entry 7). On lowering the amount of Pd(OAc)\(_2\), the reaction efficiency decreases (Table 4, entry 8). Next, we have screened the Sonogashira cross-coupling for different bases. The activity of various inorganic bases such as Cs\(_2\)CO\(_3\), Na\(_2\)CO\(_3\), NaHCO\(_3\), NaOAc, and NaOH was studied (Table 4, entries 9−13). However, greater efficiency was achieved only in the case of K\(_2\)CO\(_3\) and Cs\(_2\)CO\(_3\) (Table 4, entries 3 & 9). However considering the cost and hygroscopic nature of Cs\(_2\)CO\(_3\), we opt for the readily available and low-cost K\(_2\)CO\(_3\) for our reaction protocol. Again, the efficiency of the catalyst was checked using varying solvent systems. Use of pure water or biphasic medium such as EtOH−H\(_2\)O (1:1) significantly decreases the yield of the product (Table 4, entries 14 & 15). Other solvents such as 2-MeTHF, 2-MeTHF/H\(_2\)O (1:1), and tetrahydrofuran (THF) do not meet to our expectation in terms of isolated yield (Table 4, entries 16−18). Later, considering the optimized reaction condition, the coupling reaction was also tested for different palladium sources such as PdCl\(_2\). But, lower conversion of the desired product was noticed (Table 4, entry 19). This lower activity of PdCl\(_2\) in the present reaction system may be due to difference in coordination of the anion (Cl\(^−\) < OAc\(^−\)) to the NP surface. Thus, lower efficacy of the Cl\(^−\) anion toward stabilization of the nanostructure may hamper the catalytic performance.\(^52,53\) We have carried out our reaction using 1:1 ratio of the substrates (Table 4, entry 20). However, a significant decrease in reaction efficiency was observed.

Electronically different substrates were examined to verify the catalytic activity of method A and method B for Sonogashira coupling (Table 5). Method B, as already discussed provides lower efficiency in terms of yield and time (Table 5, 6a, b & c). Method A provides efficient cross-coupling for diverse range of substrates (Table 5, 6d−6u). It is compatible for aliphatic alkynes which in general is low reactive in nature (Table 5, 6q−6u).\(^54,55\) Aryl iodides-bearing electron withdrawing groups in p- and m-positions proceed to completion of reaction with excellent yield of the cross-coupling product (Table 5, 6d, 6f, 6g, 6l−p). However, electron-donating aryl iodides are less competent in comparison to the later (Table 5, entry 6h & 6i). The variation in reaction efficiency may be due to the electronic effect of the substituents. Because the presence of the electron-donating group increases, the electron density over sp\(^2\) carbon and halide bond causes difficulty in C−X bond breaking for the oxidative addition step.\(^56,57\) Again, the steric

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**Table 5. Substrate Scope for Sonogashira Cross-Coupling Reaction**

| Compound | Method | Reaction conditions: | Isolated yield (%) |
|----------|--------|----------------------|-------------------|
| 6(a) | Method A | Aryl halide (0.5 mmol), acetylene (0.6 mmol), Pd(OAc)\(_2\) (1 mol %), Ext OS (0.5 mL), Ext AV (2 mL), K\(_2\)CO\(_3\) (1.5 mmol), EtOH (4 mL) at 40 °C. | 95% |
| 6(b) | Method A | Aryl halide (0.5 mmol), acetylene (0.6 mmol), Pd(OAc)\(_2\) (1 mol %), Ext OS (0.5 mL), Ext AV (2 mL), K\(_2\)CO\(_3\) (1.5 mmol), EtOH (4 mL) at 40 °C. | 95% |

\(^\text{a}\)Isolated yield.
effect as in case of 2-iodonitrobenzene results in low yield of the product (Table 5, 6f). Next, the effect of different aromatic and aliphatic alkynes was investigated. The catalytic system delivers similar conversion in the case of different substituted aromatic alkynes (Table 5, 6k–6p). A slightly longer reaction time is required for aliphatic alkynes; nevertheless, in all cases, modest to good yield of the desired product was achieved (Table 5, 6q–6u). However, a difference in reactivity of 1-hexyne was observed with 4-iodonitrobenzene and 4-iodotoluene (Table 5, 6t and 6u). Iodobenzene in all cases offers comparable catalytic performance in terms of both reaction yield and time (Table 5, 6e, 6k, and 6q).

The catalytic activity of both the ex situ- and in situ-generated Pd NPs was examined. The results are shown in Table 6. However, the yield of the desired product was not satisfactory. A comparatively better activity was observed in comparison to C−Br activation of substituted arylbromides. Because C−Br activation is difficult in comparison to C−I, coupling of substituted arylbromides was found to be difficult. Only 50−65% of isolated yield was achieved for p-NO2 and p-CH3 substituents of arylbromide (Table 5, 6d and 6h). Bromobenzene, on the other hand, delivers a good yield of the desired cross-coupled product in shorter reaction time (Table 5, 6e). However, the reaction did not proceed with aryl chlorides. Moreover, we have tried to investigate the catalytic activity of the present protocol in the synthesis of indole derivatives via intramolecular cyclization of 2-iodoaniline and arylalkynes. The catalytic activity of both the ex situ- and in situ-generated Pd NPs was examined. The results are shown in Table 6. However, the yield of the desired product was not as such prevents the Pd NPs to dissociate into smaller aggregates.

3. CONCLUSIONS

The present system highlights the different reducing characteristics of two naturally abundant herbs found over worldwide. This protocol provides a platform for the study of different catalytic influences of Pd NPs in C−C cross-coupling reactions with a wide range of substrate scope under mild reaction conditions. The significant influence of the substrates on the catalytic activity of the biogenic palladium NPs has been observed in Sonogashira and Suzuki cross-coupling reactions. Moreover, the present work focuses on one-pot biogenic generation of Pd NPs under aerobic conditions without the use of any additional chemical reducing agent. The process appears as an excellent alternative for many ligand-assisted systems for C−C coupling and elegantly follows the green chemistry principles of a safer reaction strategy.

4. EXPERIMENTAL SECTION

4.1. General Information and Characterization Techniques. In this work, the chemicals were used without further drying or purification. Plant species were collected from the Tezpur University Campus, India. The UV/visible spectra were recorded in a UV/visible spectrophotometer (Shimadzu Corporation, UV-2550). Infrared spectra were recorded using an FTIR spectrophotometer (PerkinElmer Frontier MIR FIR). Measurements are performed by pelletizing the samples with KBr in the midinfrared region. The X-ray diffraction study of the samples was carried out in a Rigaku MultiFlex instrument using a nickel-filtered Cu Kα (0.15418 nm) as the radiation source. The morphology and particle size distribution were studied by TEM analysis with JEOL JEM 2100 (200 kV). H and 13C spectra were recorded in CDCl3 using tetramethylsilane as an internal standard on a JEOL JNM ECS NMR spectrometer operating at 400 MHz. X-ray photoelectron spectroscopy (XPS) measurements were performed by the ESCALAB Xi+ spectrometer (Thermo Fisher Scientific Pvt. Ltd. UK) having a monochromatic Al Kα X-ray source (1486.6 eV).

4.2. Isolation of Plant Extracts. 4.2.1. Preparation of Ext OS. Fresh leaves of OS (1 g) were collected and washed thoroughly with distilled water and grounded in a mortar. The pastes so obtained were boiled in 10 mL distilled water for 5 min. The mixture was then centrifuged, and the filtrate was collected for further use. As an additional assessment, to identify the catalytic nature of both the Pd NPs (Pd2(OS)Pd2(OS)Pd2(OS)Pd2(OS)) in the reaction medium, we have performed the hot filtration test for both the cross-coupling reactions. Leaching of Pd particles was not observed because the reaction did not proceed further after the filtration of the catalytic species from the reaction mixture. Hence, the in situ-generated Pd NPs are heterogeneous in nature. As per the recyclability of Pd2(OS)Pd2(OS)Pd2(OS)Pd2(OS) in Sonogashira coupling reaction, the catalyst could not be recovered after the workup, which may be due to smaller particle sizes of Pd2(OS)Pd2(OS)Pd2(OS)Pd2(OS). However, in Suzuki coupling, boronic acid stabilized and capped the Pd NPs and further drying or puriﬁcation or techniques.

### Table 6. Annulation of 2-Iodoaniline with Phenylacetylene

| entry | Pd catalyst (mol %) | extract (mL) | yield (%) |
|-------|---------------------|--------------|-----------|
| 1     | Pd2(NP)ex situ (5)  | Ext AV (2)   | 40 (10)   |
| 2     | Pd2(NP)ex situ (5)  | Ext AV (2)   | 40 (10)   |
| 3     | Pd2(OAc)ex situ (5) | Ext AV (2)   | 40 (10)   |
| 4     | Pd2(OAc)ex situ (5) | Ext AV (2)   | 40 (10)   |

Reaction conditions: 2-iodoaniline (0.5 mmol), phenylacetylene (0.6 mmol), Pd(OAc)2 (1 mol%), Ext OS (0.5 mL), Ext AV (2 mL), K2CO3 (1.5 mmol), dimethylformamide (DMF) (4 mL) at 90 °C, 24 h. Isolated yield. Sonogashira cross-coupling yield.
in 5 h and subsequently to black after 12 h (Figure 1b). The resulting Pd NPs were separated through centrifugation, and the pastes were dried under vacuum for further analysis.

4.4. General Information about Catalytic Experiments. Cross-coupling and annihilation reactions were carried out under aerobic conditions. The progress of the reactions was monitored by aluminum-coated TLC plates (Merck silica gel 60F254) and visualized under a UV lamp. The desired products were purified and isolated by the column chromatographic technique using a silica gel (60–120 mesh) and n-hexane. The desired isolated products were identified by comparing their 1H and 13C NMR spectra as presented in the Supporting Information.

4.5. Experimental Procedure for the Catalytic Reactions. 4.5.1. Typical Procedure for in Situ-Catalyzed Suzuki–Miyaura Reaction. A mixture of aryl halide (0.5 mmol), aryloboronic acid (0.6 mmol), K2CO3 (1.5 mmol), Pd(OAc)2 (1 mol %), required amount of extract, and (1:1) EtOH/H2O was taken in a 25 mL round-bottom flask. The reactants were allowed to stir at room temperature. After completion (vide TLC), the catalyst was separated from the reaction mixture by centrifugation, and the crude reaction mixture was extracted with ethyl acetate (3 × 10 mL). The resultant organic fraction was separated and washed with brine (2 × 10 mL) and dried over anhydrous Na2SO4 and evaporated under reduced pressure. The desired product was isolated by column chromatography using ethyl acetate and hexane as an eluant and purity was confirmed by 1H and 13C NMR spectroscopy analyses.

4.5.2. Typical Procedure for in Situ-Catalyzed Sonogashira Coupling Reaction. In a 50 mL round-bottom flask, 1 mol % (0.001 g) Pd(OAc)2 and the required amount of extract was mixed. To the resulting mixture, 0.5 mmol (1 equiv) aryl halide and 0.6 mmol (1.2 equiv) terminal alkyne were added followed by addition of 4 mL EtOH and K2CO3 (1.5 mmol). The mixture was then stirred at 40 °C, and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with H2O and extracted with ethyl acetate (3 × 10 mL), dried over Na2SO4, and concentrated in vacuum. The residue was purified by column chromatography on silica gel using hexane as an eluant to obtain the pure product (functionalized alkyne).

4.5.3. Catalytic Procedure Using Pd NPsex situ Prepared from Respective Ext Os (PDex OS NP) and Ext AV (PDex AV NP). Pd NPs (1 mol %) were mixed with 0.5 mmol aryl halide, 0.6 mmol of aryloboronic acid, and phenylacetylene with 1.5 mmol K2CO3 with the required amount of solvent. The progress of both the Suzuki–Miyaura and Sonogashira coupling reactions was monitored via TLC, and the desired product was isolated by the column chromatographic technique.

4.5.4. Typical Procedure for Annulation Reaction of 2-Iodoaniline and Phenylacetylene. Pd(OAc)2 (5 mol %), a specific amount of extract, 0.5 mmol 2-iodoaniline, 0.6 mmol phenylacetylene, and 1.5 mmol K2CO3 in DMF were mixed in a 50 mL round-bottom flask. The mixture was then allowed to stir at 90 °C, and the progress was monitored via TLC. The reaction mixture was then extracted with ethyl acetate and water, and the organic fraction was dried over Na2SO4 and concentrated in vacuum. The desired product was isolated by column chromatography and characterized by 1H and 13C NMR spectroscopy. Again considering the same substrate ratio, the reaction was performed using 5 mol % of both the ex situ Pd NPs, and the comparative conversion of each reaction was monitored via TLC. Later, the reaction mixture was extracted with ethyl acetate, dried over Na2SO4, and concentrated in vacuum. The desired product was then isolated by the column chromatographic technique and analyzed by NMR spectroscopy.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02697.

1H NMR and 13C NMR spectra of isolated products and TEM images of reused PdAV NPin situ are enclosed in this section (PDF).

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#### Notes

The authors declare no competing financial interest.

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