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# C-O Bond Activation by Nickel-Palladium Hetero-Bimetallic Nano-Particles for Suzuki-Miyaura Reaction of Bioactive Heterocycle-Tethered Sterically Hindered Aryl Carbonates

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**ABSTRACT:** The Ni-Pd binary nanoclusters is reported for activation of C-O bond for Suzuki-Miyaura cross-coupling of bioactive heterocycle-tethered sterically hindered aryl carbonates with aryl boronic acids. The reaction does not take place in the presence of either the Pd or Ni salts/complexes or the individual Pd or Ni nanoparticles indicating ensembling cooperativity between the Pd and Ni nanoparticles in activating the C-O bond.

KEYWORDS: C-O bond activation, Suzuki-Miyaura coupling, aryl carbonates, sterically hindered, bioactive heterocycles, boronic acids, Ni-Pd nano-clusters, ensembling cooperativity.

#### INTRODUCTION

The Suzuki-Miyaura cross-coupling<sup>1</sup> is the most important synthetic transformations developed in the 20th century and the most powerful tool in modern synthetic organic chemistry to form biaryls that are present in 40% of the biologically active compounds with sp<sup>2</sup>-sp<sup>2</sup> linkage.<sup>2</sup> The biaryl framework is important structural motif for various therapeutic agents such as the selective inhibitor of the enzyme cyclooxygenase-2 flurbiprofen used as non-steroidal anti-inflammatory drug for the treatment of rheumatoid arthritis,<sup>3</sup> the angiotensin II (AT-II) receptor antagonists represented by the sartan family of drugs used for the treatment of blood pressure (hypertensiion),<sup>4</sup> and the antibiotic natural product vancomycin.<sup>5</sup> Aryl halides are the most commonly used electrophilic partner during the Suzuki-Miyaura cross-coupling reaction. The presence of phenolic hydroxyl group in pharmaceuticals<sup>6</sup> make them potential electrophilic partner for Suzuki-Miyaura reaction through C-O bond activation for late functionalization of such bioactive molecules to expand the chemical space in finding new therapeutic leads.<sup>7</sup> The diverse pharmaceutical applications of 2-substituted benzazoles (Figure 1)<sup>8</sup> make them attractive coupling partners for Suzuki-Miyaura reaction via C-O bond activation.



Figure 1. Representative examples of bioactive benzoxazoles.

The exploration of C-O electrophiles in cross coupling<sup>9</sup> is an active area of research to synthetic organic/medicinal. However, benzoxazole-tethered C-O electrophile that represents *o*-heterocycle-tethered sterically hindered phenol-based electrophile is yet to be explored.<sup>10</sup>

Herein we report Ni-Pd binary metallic nanoclusters (NCs), as effective catalyst system for C-O bond activation for Suzuki-Miyaura cross-coupling reaction of *o*-benzoxazole-tethered aryl ester, silyl ether, sulfonate, carbamate, and carbonate as the electrophilic coupling partners.

#### **RESULTS AND DISCUSSION**

The study began with the treatment of 2-(benzo[d] oxazol-2-yl) phenyl methyl carbonate **1a** with 4-methoxyphenylboronic acid (**2b**) to from 2-(4'-methoxy-biphenyl-2-yl)-benzo[d] oxazole (**3b**) under various conditions of Suzuki-Miyaura reaction (Scheme 1).<sup>11</sup>



Scheme 1. Suzuki-Miyaura reaction of 1a with 2b to form 3b.

In view of the literature reports on Pd-catalysed Suzuki-Miyaura reaction involving aryl esters as the coupling partner<sup>12</sup> various Pd(II) catalysts were used for the reaction of **1a** with **2b** but the desired product **3b** was formed in poor yields (10-35%) (ESI: Table S1).<sup>11</sup> The Suzuki-Miyaura reaction of aryl esters involves two competitive C-O bond activation processes (i) Ar-OAc bond and (ii) ArO-Ac bond with the corresponding C-O bond energies of 106 and 80 kcal/mol, respectively,<sup>13</sup> making the cleavage of the relatively inert Ar-OAc bond difficult. The Ni-derived catalysts are better activators of the C-OAc bond compared to the Pd-derived catalysts as the oxidative addition involving the Ni-catalysts usually have lower energy barrier compared to that of the Pd-catalysed process<sup>13</sup> and has been reflected in the use of Ni-catalysts for the Suzuki-Miyaura reaction via C-O activation.<sup>14</sup> However, the use of Ni-catalysts e.g., NiCl<sub>2</sub>·6H<sub>2</sub>O, [NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>], and [NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>] for the reaction of **1a** with **2b** afforded **3b** in poor yields (14-35%) (ESI: Table S2).<sup>11</sup>

As palladium nanoparticles (Pd NPs) exhibit better catalytic potential for the Suzuki-Miyaura reaction<sup>15</sup> the effect of the *in* situ formed Pd NPs was next assessed for the reaction of 1a with 2b under various conditions that led to the formation of 3b up to 50% yield (ESI: Table S3).<sup>11</sup> The use of *in situ* generated nickel nanoparticles NiNPs<sup>16</sup> also did not improve the yield (maximum up to 55%) of **3b** (ESI: Table S4).<sup>11</sup> The moderate yields (50-55%) obtained with the individually formed Pd and Ni NPs led us to explore the potential of hetero bimetallic NPs (ESI: Table S5).<sup>17</sup> Various combinations of Ni and Pd salts/complexes were tried in the presence of varying amounts of  $K_2CO_3$  or  $K_3PO_4$  as the base for the reaction of **1a** with 2b (1.2 to 2 equiv) in DMF at 100 °C in the presence of TBAF (10 mol%) as the stabilizer. The desired product 3b was obtained in 75 and 76% yields using 4 equiv of K<sub>2</sub>CO<sub>3</sub> and  $K_3PO_4$ , respectively, by treating **1a** with 2 equiv of **2b** in the presence of NiCl<sub>2</sub>·6H<sub>2</sub>O (2.5 mol%), PdCl<sub>2</sub> (2.5 mol%), TBAF (10 mol%) in dry DMF on addition of 1 equiv of water. Comparable yield was obtained in using  $Cs_2CO_3$  (4 equiv) as the base. This reflected the cooperative catalytic effect of the binary Ni-Pd NCs. Reduction of the amount base to 3 equiv revealed that the best result (76% yield) could be obtained with K<sub>3</sub>PO<sub>4</sub> while the other bases afforded inferior yields. Increase of the amount of either NiCl<sub>2</sub>·6H<sub>2</sub>O or PdCl<sub>2</sub> or both to 5 mol% did not increase the yield of 3b but the yield decreased significantly in reducing the catalyst loading to 1 mol%. These reflect that the threshold concentration of the Ni/Pd NPs is up to 2.5 mol% and at higher concentration aggregation of the NPs occur resulting in decreased catalytic activity.<sup>16d</sup> The presence of an optimal amount (1 molar equiv) of water is essential as the yield decreased in the presence of higher/lower amounts of water or in the absence of water (ESI: Table S5).<sup>15b,d</sup> This suggests that water plays important role in the catalytic cycle for which an optimal amount is necessary. However, the detrimental effect of increase of the amount of water beyond this critical amount could be due to catalyst inactivation through formation of nickel hydroxides/oxides.<sup>1</sup>

The replacement of NiCl<sub>2</sub>·6H<sub>2</sub>O by other Ni-compounds while using PdCl<sub>2</sub> (2.5 mol%) as the other pre-catalyst gave inferior yields (15-25%) (ESI: Table S6). Similarly the replacement of PdCl<sub>2</sub> by other Pd-compounds while using NiCl<sub>2</sub>·6H<sub>2</sub>O (2.5 mol%) as the other pre-catalyst also gave lesser yield (20-35%) (ESI: Table S6).<sup>11</sup> This indicated/reflected the effect of the precursor counter anion.<sup>19</sup> While the exact role of the precursor counter anion is not clear it could be due to the reason that the small amount of crystalline water present in the NiCl<sub>2</sub>·6H<sub>2</sub>O is critical to form the homogeneous Ni/Pd NPs.<sup>19a</sup> Further, the precursor counter-anion stabilises the primary NPs during the growth<sup>20</sup> and in case of NiCl<sub>2</sub>·6H<sub>2</sub>O and PdCl<sub>2</sub> as the chloride counter anion remains in the close vicinity of the incipiently formed Ni and Pd NPs it might prevent the irreversible agglomerisation<sup>20a</sup> of the Ni/Pd NPs.

The catalytic influence of different binary metal nano clusters (MNCs) for the cross-coupling of **1a** with **2b** was also assessed in using other metal salts as the pre-catalyst so as to form Pd-Cu, Pd-Co, Pd-Fe, Pd-In, Pd-Ag, Pd-Au, Ni-Cu, Ni-Co, Ni-Fe, Ni-In, Ni-Ag, and Ni-Au binary NCs (ESI: Table S7).<sup>11</sup> However, these catalytic protocols were found to be either totally ineffective or afforded **3b** in poor yields (10-20%). The poor reactivity in replacing NiCl<sub>2</sub>/PdCl<sub>2</sub> by other precursor is due to the fact that Pd and Ni compounds have the proven catalytic potential to catalyze the Suzuki-Miyaura reaction due to the favourable redox behavior of the Pd and Ni compounds for the respective oxidative insertion to the C-Br/C-O bonds and the subsequent reductive elimination. The Pd and Ni are elements of the same group with 4d<sup>10</sup>5s<sup>0</sup> and 3d<sup>8</sup>4s<sup>2</sup> outer electronic configuration, respectively.<sup>21</sup> This is conducive for their cooperative interaction resulting an inherent synergistic effect.<sup>17b,c,22</sup>

The role of other reaction parameters such as the stabilizing agent for the *in situ* formed MNPs and solvent was next determined. The TBAF (10 mol%) was found to be the most effective stabilizer as inferior yield of **3b** was obtained in using TBACl, TBAB, TBAI, SDS, and SDOSS (ESI: Table S8). Among the various aprotic, protic, weakly polar, and nonpolar solvents used (ESI: Table S9), DMF afforded the best result<sup>11</sup> that could be due to its beneficial effect in the formation of the MNPs.<sup>23</sup>

The formation of the Ni-Pd binary NCs was confirmed by HRTEM image (ESI: Figure S1) of the reaction mixture after 10 min of mixing of all the components that showed the presence of 10–12 nm particles identified by EDAX (ESI: Figure S2).<sup>11</sup> The Ni-Pd binary NCs could be recovered and reused (72, 73, 72, and 70% yields for fourth consecutive recycles) (ESI: Table S10). The yield decreased to 64% on the fifth recycle as the size of the recovered Pd-Ni binary NCs increased to 90-100 nm.<sup>11</sup> The HRTEM spectra of the freshly prepared and recovered Ni-Pd bimetallic catalyst showed high particle uniformity. This and the powder XRD and surface-sensitive X-ray photoelectron spectra (XPS) confirmed the formation of Ni-Pd NPs.

The HAADF-STEM (high angle annular dark field scanning transmission electron microscopy) images and line-scan EDAX spectra (ESI: Figures S3-S9) confirmed the formation of Ni-Pd NCs and not the core shell NPs as Ni is scattered in the continuous matrix of palladium.

The high resolution XPS spectra of the Ni-Pd bimetallic NCs gave the binding energy peaks for Pd 3d at 336.2 and 341.5 eV corresponding to Pd(+2)  $3d_{5/2}$  and Pd(+2)  $3d_{3/2}$ , respectively,<sup>24</sup> (ESI: Figures S10-S11). On the other hand, the binding energy peaks for Ni 2p were at 852, 854, and 872.5 eV indicating Ni(0)  $2p_{3/2}$ , Ni(+2)  $2p_{3/2}$ , and Ni(+2)  $2p_{1/2}$  states, respectively, along with the satellite peak at 860 eV of Ni(+2) suggesting nickel to be present in both 0 and +2 oxidation states<sup>25</sup> (ESI: Figures S10-S11).

To ascertain whether the catalytic effect is due to the heterogeneous Ni-Pd bimetallic NCs or any Ni and/or Pd species that might have leached out of the heterogeneous bimetallic NP surface the Hg(0) poisoning experiment was performed as it is well known heterogeneous-catalyst poison.<sup>26</sup> Cessation of the catalytic activity was observed on addition of Hg metal to the reaction of **1a** with **2b** performed in the presence of the in situ formed Ni-Pd bimetallic NCs and the catalytic activity could not be regenerated upon spiking with NiCl<sub>2</sub>·6H<sub>2</sub>O and PdCl<sub>2</sub><sup>26c</sup> (ESI: Scheme S5). This demonstrates that the Ni-Pd bimetallic NCs are the active catalytic agent. 1

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To explore the synthetic potential of the Ni-Pd binary NCscatalysed C-O activation process, **1a** was treated with various arylboronic acids 2 to form 3 (Table 1). The reaction works well with arylboronic acids bearing electron releasing and withdrawing groups affording the desired biaryls in 55-76% yields (Table 1). The reactions with aryl boronic acids containing electron withdrawing group required longer time (10-11 h). In a few selected cases wherein the yield was less than 70% the yield could be increased to some extent in recycling the recovered 1a after the first/fresh use. The sterically hindered boronic acids (entries 13 and 14) also required longer reaction time (12 h) and afforded lesser yields (52-58%) that could be increased (63-67%) after recycling 1a. The reactions with 2-naphthyl and 2-benzofuryl boronic acids represent the rare examples of Suzuki-Miyaura coupling reaction involving sterically hindered coupling partners (C-O electrophile and the boronic acid).

**Table 1.** The Suzuki-Miyaura cross-coupling of **1a** with various arylboronic acids **2** catalysed by the Ni-Pd binary NCs.<sup>a,b</sup>

|               | $HO_2B$<br>$HO_2B$<br>$R^2$<br>$R^2$  | $\rightarrow$   |  |
|---------------|---|-----------------|--|
| <b>D</b> atas |   | <b>T</b> : (h.) | $R^2$                                  |
| Entry         | Borollic acid (2)   | Time (n)        | r leid (%)                             |
| 1             | $\mathbf{R}^1 = \mathbf{R}^2 = \mathbf{H}$  | 6               | 75                                     |
| 2             | $\mathbf{R}^1 = \mathbf{OMe}; \mathbf{R}^2 = \mathbf{H}$                                | 6               | 76 (76) <sup>d</sup>                   |
| 3             | $\mathbf{R}^1 = \mathbf{R}^2 = \mathbf{OMe}$  | 6               | 75                                     |
| 4             | $R^1 = SMe; R^2 = H$  | 6               | 71                                     |
| 5             | $\mathbf{R}^1 = \mathbf{OCF}_3; \mathbf{R}^2 = \mathbf{H}$                              | 8               | 70                                     |
| 6             | $R^1 = OCH_2Ph, R^2 = Cl$   | 8               | 67                                     |
| 7             | $\mathbf{R}^1 = \mathbf{O}\mathbf{P}\mathbf{r}^i,  \mathbf{R}^2 = \mathbf{C}\mathbf{l}$ | 8               | 68 (72) <sup>e</sup>                   |
| 8             | $\mathbf{R}^1 = \mathbf{B}\mathbf{u}^t$ ; $\mathbf{R}^2 = \mathbf{H}$                   | 6               | 72                                     |
| 9             | $\mathbf{R}^1 = \mathbf{Cl};  \mathbf{R}^2 = \mathbf{H},$                               | 8               | 71 <sup>f</sup>                        |
| 10            | $\mathbf{R}^1 = \mathbf{COMe}; \mathbf{R}^2 = \mathbf{H}$                               | 10              | $60^{g}(74)^{h}(75)^{e}$               |
| 11            | $\mathbf{R}^1 = \mathbf{H},  \mathbf{R}^2 = \mathbf{NO}_2$                              | 11              | $68 (72)^{h} (70)^{e}$                 |
| 12            | $\mathbf{R}^1 = \mathbf{C}\mathbf{F}_3; \mathbf{R}^2 = \mathbf{H}$                      | 8               | 72                                     |
| 13            | B(OH) <sub>2</sub>  | 12              | $60(68)^{h}(71)^{e}$                   |
| 14            | B(OH)2  | 12              | 55 (67) <sup>h</sup> (70) <sup>e</sup> |

<sup>a</sup>Method A: 1a (1.0 mmol) in dry DMF (2 mL) was treated with 2 (2 mmol, 2 equiv) in the presence of NiCl<sub>2</sub>·6H<sub>2</sub>O (2.5 mol%), PdCl<sub>2</sub> (2.5 mol%), K<sub>3</sub>PO<sub>4</sub> (3 mmol, 3 equiv), TBAF (10 mol%), and water (1 equiv) at 100 °C under open air. Method B: 1a (1.0 mmol) in dry DMF (2 mL) was treated with 2 (1.5 mmol, 1.5 equiv) in the presence of NiCl<sub>2</sub>·6H<sub>2</sub>O (2.5 mol%), PdCl<sub>2</sub> (2.5 mol%), K<sub>3</sub>PO<sub>4</sub> (1.5 mmol, 1.5 equiv), TBAF (10 mol%), and water (1 equiv) at 100 °C under O<sub>2</sub> bubbling. <sup>b</sup>Unless otherwise mentioned the reaction was performed under Method A. <sup>c</sup>Isolated yield of 3. <sup>d</sup>The figure in the parenthesis is the yield after 1 and 6 h under Method B. <sup>c</sup>The figure in the parenthesis is the yield after 6 h. <sup>b</sup>The figure in the parenthesis is the combined isolated yield of 3 after one recycling of the recovered 1a.

The generality of the Ni-Pd binary NCs-catalysed C-O activation process with respect to structural variation of the oheterocycle-tethered aryl methyl carbonate **1** (prepared through aromatic hydroxylation of the corresponding 2arylbenzoxazoles<sup>27</sup> followed by *O*-carbomethoxylation of the resultant phenol<sup>28</sup>),<sup>11</sup> as the electrophilic coupling partner, was demonstrated for the reaction with **2b** resulting in the formation of the corresponding biaryls **3** in 68-80% yields (Table 2).

To assess the influence of the leaving group of the C-O electrophilic partner, the benzoate, pivalate, OTMS, OTs, OMs, carbonate, and carbamate derivatives of 2-(2-hydroxyphenyl)benzoxazole were used as the *o*-heterocycle-tethered electrophilic partner for reaction with **2b** catalysed by the Ni-Pd binary NCs (Table 3).

**Table 2.** The Ni-Pd binary NC-catalysed Suzuki-Miyaura cross-coupling of different variation of the *o*-heterocycle-tethered aryl methyl carbonates **1** with **2b** to from **3**.<sup>a</sup>

| R <sup>1</sup> | N<br>N<br>R <sup>3</sup><br>(HO) <sub>2</sub> B<br>O<br>O<br>O<br>Me<br>2b                     | $R^1$    | P <sup>3</sup><br>PR <sup>2</sup> |
|----------------|--|----------|-----------------------------------|
| Entry          | 1  | Time (h) | Yield                             |
|                |  | (h)      | (%) <sup>b</sup>                  |
| 1              | <b>1a</b> : $R^1 = R^2 = R^3 = H$  | 6        | 75                                |
| 2              | <b>1b</b> : $\mathbf{R}^1 = \mathbf{R}^3 = \mathbf{H};  \mathbf{R}^2 = \mathbf{C}\mathbf{H}_3$ | 6        | 72                                |
| 3              | <b>1c</b> : $\mathbf{R}^1 = \mathbf{R}^2 = \mathbf{H},  \mathbf{R}^3 = \mathbf{C}\mathbf{H}_3$ | 6        | 71                                |
| 4              | <b>1d</b> : $R^1 = Cl; R^2 = R^3 = H$  | 5        | 78                                |
| 5              | <b>1f</b> : $R^1 = OMe$ ; $R^2 = H$ , $R^3 = H$  | 6        | 80                                |
|                |  |          |                                   |
| 6              | 1g of OMe  | 8        | 65                                |

<sup>a</sup>**1** (1.0 mmol) in DMF (2 mL) was treated with **2b** (2 mmol, 2 equiv) in the presence of NiCl<sub>2</sub>·6H<sub>2</sub>O (2.5 mol%), PdCl<sub>2</sub> (2.5 mol%), K<sub>3</sub>PO<sub>4</sub> (3 equiv), TBAF (10 mol%), and water (1 equiv) at 100 °C under open air (Method A). <sup>b</sup>Isolated yield of **3**.

In case of acetate, benzoate, and pivalate (11-n) competitive debenzoylation/depivalation took place.<sup>29</sup> The silyl ether underwent desilylation to some extent by the TBAF used to stabilized the NPs. No side reaction was observed with sulfonates, carbamates, and methyl/ethyl/benzyl carbonates demonstrating chemoselectivity. The very good results obtained with methyl/ethyl carbonates represent significant advancement in Suzuki-Miyaura cross-coupling reaction as it would provide access to bioactive coupling partner due to the presence of the phenolic moiety in drugs and bioactive natural products, ease of their formation from phenols,<sup>26</sup> and waste free conversion (CO<sub>2</sub> and MeOH are the byproducts) to the biaryls.

**Table 3.** The Ni-Pd binary NC-catalysed Suzuki-Miyaura cross-coupling of *o*-heterocycle-tethered phenol-based electrophiles **1** with **2b**.<sup>a,b</sup>



| Entry | Phenol-based electrophile (1                                | l) Time (h) | Yield (%) <sup>c</sup>                 |
|-------|---|-------------|--|
| 1     | <b>1a:</b> $X = C(O)OMe$                                    | 6           | 75                                     |
| 2     | <b>1h:</b> X = C(O)OEt                                      | 6           | 65 <sup>d</sup>                        |
| 3     | <b>1i:</b> $X = C(O)OCH_2Ph$                                | 8           | 51 <sup>e</sup>                        |
| 4     | <b>1j:</b> $X = C(O)OBu^t$                                  | 8           | $00^{\rm f}  (68)^{\rm g}$             |
| 5     | <b>1k:</b> $X = C(O)NEt_2$                                  | 8           | 50                                     |
| 6     | <b>11:</b> $X = C(O)Me$                                     | 6           | $00^{f}(68)^{h}(68)^{i}$               |
| 7     | <b>1m:</b> $X = C(O)Ph$                                     | 8           | 40 (30) <sup>j</sup> (70) <sup>g</sup> |
| 8     | <b>1n:</b> $X = C(O)Bu^t$                                   | 8           | 38 (31) <sup>j</sup> (74) <sup>g</sup> |
| 9     | <b>10:</b> $X = S(O)_2 Me$                                  | 8           | 68 (74) <sup>g</sup>                   |
| 10    | <b>1p:</b> $X = S(O)_2$ -4-Me-C <sub>6</sub> H <sub>4</sub> | 8           | 65 (70) <sup>g</sup>                   |
| 11    | $1q: X = SiMe_3$  | 10          | 50 (20) <sup>j</sup>                   |
|       |   |             |  |

<sup>a</sup>Method A: 1a (1.0 mmol) in dry DMF (2 mL) was treated with 2 (2 mmol, 2 equiv) in the presence of NiCl<sub>2</sub>·6H<sub>2</sub>O (2.5 mol%), PdCl<sub>2</sub> (2.5 mol%), K<sub>3</sub>PO<sub>4</sub> (3 mmol, 3 equiv), TBAF (10 mol%), and water (1 equiv) at 100 °C under open air. Method B: 1a (1.0 mmol) in dry DMF (2 mL) was treated with 2 (1.5 mmol, 1.5 equiv) in the presence of NiCl<sub>2</sub>·6H<sub>2</sub>O (2.5 mol%), PdCl<sub>2</sub> (2.5 mol%), K<sub>3</sub>PO<sub>4</sub> (1.5 mmol, 1.5 equiv), TBAF (10 mol%), and water (1 equiv) at 100 °C under O<sub>2</sub> bubbling. <sup>b</sup>Unless otherwise mentioned the yield refers to reaction was performed under Method A. <sup>c</sup>Isolated yield of 3b. <sup>d</sup>66% yield after 12 h. <sup>e</sup>51% yield after 12 h. <sup>f</sup>The parent phenol was obtained. <sup>g</sup>The figure in the parenthesis is the yield after 1 and 6 h under Method B. <sup>h</sup>The figure in the parenthesis is the yield after 6 h under Method B. <sup>j</sup>The figure in the parenthesis is the yield of the parent phenol.

No significant amount of the Suzuki cross-coupling product was obtained<sup>11</sup> when **1a**, **1k**, **1m**, **1n**, and **1o** were treated with **2b** using (i) Buchwald's catalyst system,<sup>30</sup> (ii) Fu's catalyst system,<sup>12a</sup> and (iii) using NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>-PCy<sub>3</sub> mimicking Garg's<sup>14a</sup> and Shi's<sup>14b</sup> conditions that clearly establish that the newly discovered catalyst system the Ni-Pd binary NCs is by far the best catalyst for Suzuki cross-coupling of *o*heterocycle-tethered sterically hindered substrates (ESI Schemes S1-S4).<sup>11</sup> Further, the reported procedures for C-O activation of the phenol-based electrophilic partner require large excess of the aryl boronic acids or aryl boroxines at high temperature 130-150 °C for prolonged period (around 20 h). Contrary to these the Ni-Pd NCs induce the C-O activation more effectively so that the reaction takes lesser time and lower temperature.

Mechanistically the reaction proceeds through three distinct stages: (i) oxidative addition of the M(0) to the C-O bond, (ii) transmetallation of the aryl moiety of arylboronic acid to the complex formed through oxidative addition to the C-O bond, and (iii) reductive elimination to form the biaryl product and regenerate the M(0) as the active catalytic species [M = Ni or Pd centre in the Ni-Pd NCs].<sup>10,13</sup> The possible role of the Ni-Pd binary NCs for C-O activation is depicted in Scheme 2. The Ni site of the Ni-Pd binary NCs is involved in coordination with the N atom of the oxazoline moiety of 1 with concurrent coordination of the Pd site with the carbonyl oxygen atom of the methyl carbonate [X = C(O)OMe] to form Ia. This makes the Ni centre electron rich (more nucleophilic) to activate the C-O bond through oxidative addition to form the metallacycle I wherein the carbonyl group acts as the directing group.<sup>10</sup> The alternate mode of Pd-center assisted C-O activation seems unlikely due the higher energy barrier of the Pdmediated oxidative addition compared to that of the Nimediated process.<sup>13</sup> Trans-metallation of the aryl moiety of the arylboronic acid 2 (through its anion) with I forms the complex II through ligand (XO<sup>-</sup> anion) exchange/dissociation. The biaryl end product 3 is formed via reductive elimination from II along with regeneration of the catalyst (Ni-Pd NCs) that reenters the catalytic cycle.



Scheme 2. Probable mechanism for the Ni-Pd binary NCcatalysed Suzuki cross coupling reaction of 1 with 2.

The role of water can be visualised in its assistance to form the MNPs,<sup>31</sup> for removal of the leaving group in the transmetallation step, and proteolytic removal of the ligand for regeneration of the Ni-Pd NCs during the reductive elimination from II. However, the use of the first recycled Ni-Pd binary NCs for a fresh batch of reactions of 1a with 2b afforded 3b in 75 and 58% yields in dry DMF in the presnece and absence of water (1 equiv), respectively, (ESI: Table S10). This indicated the critical role of water in the catalytic cycle rather than the assistance in the formation of the MNPs. The Pd also plays important role in activating Ni as the noble metals serve as electron carrier during the formation of transition metal NPs thus establishing the synergistic effect of Ni and Pd NPs.<sup>17b,c,22,32</sup> Further role of Pd may also be during the reductive elimination stage due to the ease of transfer of electron from Pd to Ni in the heterogeneous surface of the Ni-Pd NCs.<sup>17c,33</sup> The presence of Pd+2 in the XPS spectra of the Ni-Pd bimetallic NPs is indicative of this.

The lack of significant amount of product formation in the absence of the base indicates its indispensable role in activating the boronic acid through proton abstraction to increase the nucleophilicity of the corresponding aryl moiety.

We realised that the oxidative addition of the Ar-O bond to Ni(0) site of the Ni-Pd NCs should be facilitated by air/O<sub>2</sub>. As a matter of fact, the yield of **3b** decreased to 20% when the Ni-Pd NCs-catalysed reaction of **1a** with **2b** was performed in degassed DMF using degassed water (1 equiv) (ESI Scheme S6). On the contrary, **3b** was formed in 76% yield in 1 h by passing/bubbling O<sub>2</sub> gas to the reaction mixture (ESI Scheme S7). The passing/bubbling O<sub>2</sub> gas also reduced the amount of the boronic acid and  $K_3PO_4$  to 1.5 equiv to afford the best result (ESI Table S12-13).

The better catalytic efficiency in performing the reaction under  $O_2$  bubbling led us to further utilise the advantage of the faster oxidative addition to the Ar-O bond for substrates (Table 3) that led to decreased product yield due to the competitive hydrolytic cleavage. Thus, the corresponding acetate, pivalate, benzoate, and the 'butyl carbonate analogs of **1a** effi1

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59 60 ciently underwent C-O activation to form the desired biaryl **3** on treatment with **2b**.

#### CONCLUSIONS

This work describes the ensembling catalysis by Ni-Pd binary NCs for C-O bond activation for Suzuki-Miyaura crosscoupling of *o*-heterocycle-tethered sterically hindered aryl ester, silyl ether, sulfonates, carbamate, and carbonates with aryl boronic acids. The catalyst system comprising of Ni-Pd binary NCs is distinctly superior to the various Pd/Ni compounds/complexes reported for Suzuki-Miyaura crosscoupling reaction involving phenol-based electrophilic coupling partner. The inability of the individual Ni and Pd NPs to promote the Suzuki-Miyaura cross-coupling of the *o*heterocycle-tethered electrophilic coupling partners imply a co-operative effect of the Ni and Pd NPs in the Ni-Pd NCs.

## ASSOCIATED CONTENT

**Supporting Information**. Experimental procedures, spectral data, and scanned spectra available free of charge via the Internet at http://pubs.acs.org.

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#### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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#### **ACS Catalysis**

## Table of Contents



Ensembling catalysis by Ni-Pd binary NCs is reported for C-O bond activation for Suzuki-Miayura cross-coupling reaction of *o*-heterocycle-tethered sterically hindered aryl ester, silyl ether, sulfonate, carbamate, and carbonate that are otherwise unreactive under the catalytic influence of the individual Pd or Ni salts/complexes (used under conventional Suzuki-Miayura reaction conditions) or the individual Pd or Ni nanoparticles.