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Replacing Pd(OAc)$_2$ with supported palladium nanoparticles in ortho-directed CDC reaction of alkylbenzenes

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Supported palladium nanoparticles is used as an efficient catalyst for the synthesis of aromatic ketones via cross dehydrogenative coupling reactions of 2-arylpyridines with alkylbenzenes. The catalyst can be reused for five cycles without significantly losing activity. Mechanism research showed that alkylbenzene were oxidized to their corresponding aldehydes and subsequently coupled with 2-arylpyridines to generate aryl ketones through a Pd$^{0}$/Pd$^{IV}$ catalytic cycle.

**Introduction**

As significant materials and building blocks in the synthesis of fine chemicals, aromatic ketones have a wide range applications in many areas such as pharmaceuticals, agrochemicals, dyes and fragrances. The direct introduction of carbonyl functional groups onto the aromatic motifs via cross dehydrogenative coupling (CDC) reaction is a more environmentally-friendly, regioselective alternative over traditional methods in aryl ketone synthesis. Many successful strategies involve Pd-catalyzed ortho-coupling reactions using aldehydes as acylation reagents. Compared with aldehydes, alkylbenzenes have low toxicity and are stable, commercially available, and easy to handle and thus may potentially be used as ideal acylation reagents. It is now commonly accepted that alkylbenzene could be oxidized in situ to give benzaldehyde in the presence of peroxide and subsequently complete various reactions, such as copper-catalyzed esterifications and o-arylations, tetrabutylammonium iodide (TBAI) catalyzed synthesis of benzamides, iron-catalyzed synthesis of thioesters and palladium-catalyzed ortho-acylations (see Scheme 1).

In 2012, B. K. Patel et al. have reported Pd(OAc)$_2$ catalyzed synthesis of aromatic ketones using alkylbenzene as the aroyl moiety via directed aromatic C-H bond activation. The GC-MS analysis of the model reaction showed no presence of either benzaldehyde or benzyl alcohol which possibly form via a radical oxidation of toluene. They proposed that the reaction proceeded through the addition of benzyl radical to palladium substrates and the benzyl C-H bond cleavage. Whereafter, P. P. Sun et al. put forward another possible mechanism, that is, toluene was oxidized to benzaldehyde and subsequently coupled with 2-arylpyridines to give the corresponding aryl ketones. So the acylation mechanism proceeding via whether the oxidative dehydrogenation of benzyl intermediate or a consecutive process that toluene is oxidized to benzaldehyde and subsequently couples with 2-arylpyridines remains to be explored and verified.

Supported palladium nanoparticles (PdNPs) has been successfully applied in many catalysis synthesis field in recent years, such as Mizoroki-Heck cross coupling reaction, semihydrogenation of phenylacetylene, aerobic oxidation of alcohols, and directed C-H activation reactions. However, to the best of our knowledge, there has been no report on the supported PdNPs catalyzed ortho-directed CDC reaction using alkylbenzene as acyl donors. Based on our research on the supported PdNPs catalyzed ortho-directed C-C coupling reaction between 2-arylpyridines and aldehydes, we verify that supported PdNPs can be used to drive the ortho-directed CDC reaction of alkylbenzene. In a series of supported PdNPs, Pd/γ-Al$_2$O$_3$ catalyst with a PdNPs mean diameter of 3.21 nm exhibited the best catalytic activity and it could be used five times without significant loss in catalytic activity.

**Scheme 1. Various Reactions of Toluene through Being Oxidized to Benzaldehyde Route**

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activity. A relatively clear mechanism was proposed based on the experimental results and relative literatures.

**Experimental**

**Catalyst Preparation**

The PdNPs on γ-Al2O3 and other supports were prepared by an impregnation-reduction method using the preparation of Au/γ-Al2O3 as reference.28 For example, 3 wt% Pd/γ-Al2O3 catalyst was prepared by the following procedure: 0.97 g of γ-Al2O3 powder was dispersed in 50 mL of distilled water. The two kinds of aqueous solutions of PdCl2 (0.01 M, 28.2 mL) and L-Lysine (0.03 M, 1 mL) were then added to the mixture consecutively under vigorous stirring for 20 min. Subsequently, 0.1 M NaOH aqueous solution was added into the mixture to adjust the pH to 7. An aqueous solution of NaBH4 (0.35 M, 4.5 mL) was added gradually in about 10 min to the suspension. The mixture was left to stand for 24 h and the solid was separated, washed with distilled water (4 times) and ethanol (once), and dried at 80 °C. The dried solid was used directly in catalytic experiments.

**Catalyst characterization**

The TEM images were recorded on a JEM-2100 transmission electron microscope employing an accelerating voltage of 200 kV. The samples were suspended in ethanol and dried on holey carbon-coated Cu grids. The X-ray photoelectron spectroscopy (XPS) was recorded on a Kratos Amicus of British equipped with a hemispherical analyzer Mg Kα radiation. The C1s hydrocarbon peak at 284.60 eV of fresh catalyst and 284.60 eV was used as an internal standard for the correction of binding energies. The XPS results were compared with a database of known compounds were further corroborated by comparing their 1H NMR data with those of literature. This journal is © The Royal Society of Chemistry [year]

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**Results and discussion**

To have a good knowledge of the information for the catalyst, the fresh and used (recovered after 5th cycle) PdNPs on γ-Al2O3 catalysts were studied by X-ray photoelectron spectroscopy (XPS), X-ray diffraction (XRD), and transmission electron microscopy (TEM) and so on. In order to understand the state of PdNPs supported on γ-Al2O3, the catalysts before and after reaction were tested by XPS analysis. The XPS results of the catalysts confirm that palladium exists in the metallic state on γ-Al2O3 supports before and after reaction. As shown in Figure 1a, the binding energies of Pd 3d5/2 and Pd 3d3/2 electrons are 335.11 eV and 340.36 eV of fresh catalyst and 335.02 eV and 340.27 eV of used catalyst respectively, which are identical to the bulk of palladium metal. It is shown that Pd[0] as the active center completes the catalytic cycle.

Figure 1b depicts the XRD patterns of the fresh and used 3 wt% Pd/γ-Al2O3 catalysts. The XRD patterns of catalysts with different loadings (1 wt%, 5 wt%) are shown in Figure S1 (see ES1†). It is noted that no palladium peaks can be observed by XRD pattern of all samples, probably indicate that the loaded palladium did not form large particles, and was well dispersed in the support structure.

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![Figure 1](image-url)

**Figure 1.** (a) XPS spectra of fresh and used 3 wt% Pd/γ-Al2O3; (b) XRD patterns of fresh and used 3 wt% Pd/γ-Al2O3.
The transmission electron microscopic (TEM) analysis of the fresh and used catalysts are represented in Figure 2. The PdNPs are distributed evenly on the γ-Al₂O₃ surface, and the mean diameters of the PdNPs are 3.21 nm of fresh catalyst and 3.89 nm of used catalyst, respectively. It does not cause obvious increase in the average size of PdNPs after five runs. From the TEM images of 1 wt% and 5 wt% Pd/γ-Al₂O₃, PdNPs supported on γ-Al₂O₃ also exhibit small particles and narrow size distributions (Figure S2, see ESI†).

Figure 2. (a,b) TEM images of fresh 3 wt% Pd/γ-Al₂O₃ and used 3 wt% Pd/γ-Al₂O₃, respectively; (c, d) PdNPs size distributions of fresh and used catalysts, respectively.

The BET analyses were conducted and specific surface areas were given in Table 1. Comparing the γ-Al₂O₃ with the corresponding Pd/γ-Al₂O₃ catalysts, it can be found that the surface areas of all catalysts do not arise obvious change after loading PdNPs. The amounts of Pd loading of the catalysts were derived from atomic absorption spectrophotometer (AAS), and the Pd content of fresh catalyst is approximately 3 wt %. We did note a slight decrease in Pd content after being cycled 5 times (2.86%, Table 1), which can further decrease the catalytic activity on the basis of available Pd on the support surface.

Table 1. Characterization Results of BET, AAS of Catalysts

<table>
<thead>
<tr>
<th>Samples</th>
<th>S_{BET} (m²/g)</th>
<th>Pd loading (wt %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-Al₂O₃</td>
<td>101</td>
<td>-</td>
</tr>
<tr>
<td>3 wt% Pd/γ-Al₂O₃(fresh)</td>
<td>114</td>
<td>3.02</td>
</tr>
<tr>
<td>3 wt% Pd/γ-Al₂O₃(used)</td>
<td>108</td>
<td>2.86</td>
</tr>
</tbody>
</table>

Our initial attempt was executed toward sp² C-H bond arylation of 2-phenylpyridine 1a using toluene 2a as both the aryl reagent and solvent, 3 wt% Pd/γ-Al₂O₃ as the catalyst in the presence of different oxidants such as tert-butyl hydroperoxide (TBHP), cumene hydroperoxide (CHP) and tert-butyl peroxybenzoate (TBPB). To our delight, TBPB gave the best performance (entry 4): after 24 h of refluxing in the presence of 3 wt% Pd/γ-Al₂O₃, the conversion of 2-phenylpyridine was above to 84% and the TON of this entry was 17, which was nearly 3-fold of the acylation reaction in the presence of other oxidants (entries 1-3). Besides, PdNPs supported on other oxide powders, including CeO₂ and Sm₂O₃, were prepared by the impregnation-reduction method and applied to the CDC reaction of 2-phenylpyridine with toluene (entries 5 and 6). The PdNPs on CeO₂ and Sm₂O₃ exhibited much lower activity and selectivity. The higher activity of PdNPs on γ-Al₂O₃ was for the reason that γ-Al₂O₃ had a large surface area and open porosity which could enable a high dispersion of a PdNPs catalyst.²⁵ We also examined the effect of different Pd loadings on the reaction. It was found that the catalytic efficiency was significantly influenced by palladium loading and that the catalyst with 3 wt % Pd exhibited the best performance. Both a decrease and increase in the reaction temperature (100 °C and 120 °C) reduced the conversion of 2-phenylpyridine (entries 9 and 10). It can be explained that TBPB might decompose at high temperature.²⁶ Control experiment was carried out in the absence of TBPB and it failed to give the expected product 3aa, suggesting the importance of the oxidant (entry 11). The results for various trial reactions are summarized in Table 2.

Table 2. Optimization of reaction conditions²⁵

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>T (°C)</th>
<th>Conv. (%)</th>
<th>Sel. (%)</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 wt% Pd/γ-Al₂O₃</td>
<td>TBPB 70% in water</td>
<td>110</td>
<td>26</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>3 wt% Pd/γ-Al₂O₃</td>
<td>CHP</td>
<td>110</td>
<td>23</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>3 wt% Pd/γ-Al₂O₃</td>
<td>TBPB +5.5 M in decane</td>
<td>110</td>
<td>32</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>3 wt% Pd/γ-Al₂O₃</td>
<td>TBPB</td>
<td>110</td>
<td>84</td>
<td>97</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>3 wt% Pd/Al₂O₃</td>
<td>TBPB</td>
<td>110</td>
<td>46</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>3 wt% Pd/CeO₂</td>
<td>TBPB</td>
<td>110</td>
<td>69</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>1 wt% Pd/γ-Al₂O₃</td>
<td>TBPB</td>
<td>110</td>
<td>68</td>
<td>30</td>
<td>14²⁶</td>
</tr>
<tr>
<td>8</td>
<td>5 wt% Pd/γ-Al₂O₃</td>
<td>TBPB</td>
<td>110</td>
<td>56</td>
<td>56</td>
<td>11²⁶</td>
</tr>
<tr>
<td>9</td>
<td>3 wt% Pd/Sm₂O₃</td>
<td>TBPB</td>
<td>100</td>
<td>70</td>
<td>78</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>3 wt% Pd/γ-Al₂O₃</td>
<td>TBPB</td>
<td>120</td>
<td>36</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>11</td>
<td>3 wt% Pd/γ-Al₂O₃</td>
<td>-</td>
<td>110</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

²⁵ Reaction conditions: 1a (0.2 mmol), 2a (2 mL), catalyst (35 mg), indicated oxidant (0.7 mmol), air, 24 h. Conversion and selectivity are based on 1a, determined by GC. ²⁶ catalyst (105 mg), ³ catalyst (21 mg).

The directed arylation of 2-arylyphenyl with a set of substituted alkylbenzenes was performed under the optimized reaction conditions, and the results are presented in Table 3. The initial investigations were focused on the CDC reactions of 2-phenylpyridine 1a with various alkylbenzenes 2 (entries 1-9). Various functional groups including methyl, methoxy, chloro, bromo were compatible and the desired products were achieved in moderate to good yields. For example, 4-methoxytoluene 2e (which bears a strongly electron-donating group) afford the desired product (4-methoxyphenyl)(2-(pyridin-2-yl)phenyl)meth ane 3ae in a yield of 81% (entry 4). Gratifyingly, 4-bromotoluene 2i and 3-bromotoluene 2j were also reactive, even though only moderate yields of the acylation products 3ai and 3aj
Table 3. Substrate Scope for the Synthesis of Aromatic Ketones via C-H Functionalization

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Arylpyridine</th>
<th>Alkylbenzene</th>
<th>Product</th>
<th>Yield% (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2b</td>
<td>3ab</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2c</td>
<td>3ac</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2d</td>
<td>3ad</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2e</td>
<td>3ae</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>2f</td>
<td>3af</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>2g</td>
<td>3ag</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>2h</td>
<td>3ah</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>2i</td>
<td>3ai</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>2j</td>
<td>3aj</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>1a</td>
<td>2k</td>
<td>3aa</td>
<td>31</td>
</tr>
<tr>
<td>11</td>
<td>1a</td>
<td>2l</td>
<td>3aa</td>
<td>44</td>
</tr>
<tr>
<td>12</td>
<td>1b</td>
<td>2a</td>
<td>3ba</td>
<td>84</td>
</tr>
<tr>
<td>13</td>
<td>1c</td>
<td>2a</td>
<td>3ca</td>
<td>70</td>
</tr>
<tr>
<td>14</td>
<td>1d</td>
<td>2a</td>
<td>3da</td>
<td>81</td>
</tr>
<tr>
<td>15</td>
<td>1e</td>
<td>2a</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1 (0.2 mmol), 2 (2 mL), 3 wt% Pd/γ-Al2O3 (35 mg), TBPB (0.7 mmol), 110°C, 24 h. * isolated yield.

were obtained (entry 8 and 9). The notable results might be explained that the aryl bromide substrates are usually very reactive in PdO/Pd catalytic cycles, and the bromo-substituent products can undergo further modification facilely. Compared to its para or meta isomers, o-xylene 2c and o-chlorotoluene 2g delivered a lower yield, which resulted from the steric hindrance effect. Encouragingly, ethylbenzene and n-propylbenzene kept to perform this CDC reaction to give the same product as toluene respectively in 31% and 44% yields (entries 10-11). This indicated that the oxidation took place on the α-carbon of the ethylbenzene or n-propylbenzene and generated a small percentage of benzaldehyde. The directly formation of benzyl radical from ethylbenzene is almost impossible because C-C homolytic cleavage is involved in the process. Therefore, the acylation mechanism proceeding via the oxidative dehydrogenation of benzyl intermediate is not accurate. In addition, the optimized reaction conditions were implemented in the coupling reactions between various phenyl-N-heteroarene 1 and toluene 2a (entries 12-14). It is noted that this acylation reaction could be also applicable to heterocycle-substituted pyridines such as benzo[ h]quinolone, and the good yield (84%) of the product benzo[ h]quinolin-10-yl(phenyl)methanone 3ba was obtained. The superior yield is probably due to the planar structure of benzo[ h]quinolone. When 1-phenyl-1H-pyrazole 1c, five membered nitrogen containing heterocycles served as directing- group, was employed instead of 2-phenylpyridine, the acylation reaction also proceeded expeditely to afford (2-(1H-pyrazol-1-yl)phenyl) (phenyl)methanone 3ca in 70% yield. Unfortunately, the highly electron-deficient 2-(2,4-difluorophenyl)pyridine 1e failed to deliver our desired product under the present reaction conditions (entry 15). The acylation reaction might be blocked by the electrophilic attack of the Pd(0) center to the phenyl ring. It is important to point out that the reaction gave the monoacylation products selectively in all cases.

The recyclability of catalyst was examined in the reaction of 2-phenylpyridine 1a and toluene 2a as provided in the experimental section. As shown in Figure 3, the catalyst can be reused for five cycles with only 13% decline of activity after the 5th recycle. Interestingly, the average yield of five cycles of toluene was much higher than benzaldehyde in this heterogeneous catalyzed system. From the TEM image of the used 3 wt% Pd/γ-Al2O3 catalyst (Figure 2b), the PdNPs still distribute evenly on the γ-Al2O3 surface, no apparent agglomeration was observed. The decreased catalytic activity of the PdNPs may result from the slight increase in the average size of the particles recovered after 5th cycle (Figure 2d).

To gain mechanistic insight, a radical capture experiment was conducted. There was a great restraining of the reaction between 2-phenylpyridine 1a and toluene 2a in the presence of radical

![Graph showing the recyclability of catalyst.](image-url)
scavenger TEMPO (0.4 mmol) and no acylation product 3aa was detected, suggesting a possible radical approach. This result indicates that TBPB is potentially acting on both an oxidant and a radical initiator. A GC-MS analysis of the reaction solution of 2-phenylpyridine 1a and toluene 2a showed that both benzaldehyde and benzyl alcohol were detected which could possibly result from a radical oxidation of toluene 2a (see ESI†). In addition, the similar result was also obtained for the reaction between 2-phenylpyridine 1a and 4-methoxytoluene 2e (see ESII†).

Based on the previous reports35-41 and our own results, a tentative mechanism is illustrated in Scheme 2. First step involves the coordination of Pd0 with the nitrogen atom of the pyridine group of 2-phenylpyridine 1 and the further oxidation of Pd0 to PdII by air.42 Subsequently PdII activates the ortho C-H bond through chelate-directed effect to afford palladacycle intermediate A. Secondly, the reaction of TBPB with benzaldehyde which is resulted from the oxidation of toluene 2 provides a benzylic radical by releasing the tert-butyl alcohol (or benzonic acid). And intermediate A coordinated with benzylic radical and benzoate radical to form a PdIV complex B,43, 44 which fast releasing benzoic acid to form intermediate C. Finally, the final product 3 is generated through the reductive elimination of intermediate C and releases a Pd0 to continue catalytic cycle.

Scheme 2. Possible reaction mechanism

Conclusions

In summary, it is found for the first time that metallic state palladium, Pd0, can catalyze the ortho-directed CDC reaction of alkylenzences including methyl, ethyl and propyl benzene for the synthesis of aromatic ketones via a Pd0/PdII/PdIV catalytic cycle. Differed from B. K. Patel’s report, the acylation reaction might undergo through another possible mechanism, that is, the alkylenzences were oxidized to their corresponding aldehydes and subsequently coupled with 2-arylpindines to generate ary ketones. Using supported PdNPs as heterogeneous catalyst, TBPB as the oxidant, various methylearenes which bear both electron-withdrawing and electron-donating groups, can react with 2-arylpindine to synthesize the corresponding ketones in yields up to 84%. The catalyst can be readily recovered and reused for five cycles with only 13% decline of activity after the 5th recycle. The practicality of this study may inspire further studies on the heterogeneous catalyzed ortho-directed acylation reactions. With the advantages of easy separation, recycling of heterogeneous catalyst and high catalytic activity, the PdNPs catalyst would be an alternative to Pd(OAc)2 in more catalytic organic reaction.

Acknowledgements

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Notes and references

Pd(0) = Supported palladium nanoparticles

1 + \( \text{C}_x\text{H}_{2n+1} \) \( \xrightarrow{\text{Pd(0), TBPB, 110°C, 24 h}} \) 3

TEM images  XPS spectra  Recyclability of the Catalyst

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