Cyclopalladated complexes of 2-phenylaniline and their catalytic activity in Suzuki and Heck reactions under mild conditions

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A B S T R A C T

A series of palladium complexes bearing monodentate and bidentate ligands were applied in the Suzuki reaction of aryl halides and the Heck reaction of styrene with phenylboronic acid. The complexes were found to be effective catalysts for these reactions affording the cross-coupled products in moderate to excellent yields.

The palladium-catalyzed Suzuki cross-coupling is a very useful and convenient method, especially for the synthesis of various biaryl compounds1–6 that are found as important structural units in pharmaceuticals and natural products.7–10 The mild reaction conditions and the commercial availability of various boronic acids make this reaction preferable over other Pd-catalyzed cross-coupling reactions.1–3,11–16 Besides using aryl bromides, there is great interest in developing catalysts that use aryl chlorides in Suzuki reactions.1,17,18 Since the bond strengths of C–Cl and C–Br are stronger than C–I, the reactivity of aryl bromides and chlorides is reduced compared with the more active iodides. Thus, despite being cheaper, more available and practical, aryl bromides and chlorides often do not react efficiently.19 Furthermore, the Heck reaction and related chemistry has numerous applications in organic synthesis,20–25 polymers, dendrimers, fine chemicals and pharmaceutical intermediates.26–30 Many catalyst systems can be used to catalyze various frequently used cross-coupling reactions. In this regard, palladacycles have played an important role due to their versatility and non-toxicity. Besides phosphorus-containing complexes, a substantial amount of research has been undertaken on NC-based complexes. Cyclopalladated complexes with nitrogen donor atoms have been widely studied due to their novel and outstanding applications in a vast range of fields such as organic synthesis,31 insertion reactions,32 as anti-tumor drugs33 and in catalysis.34 The related benzylamine,35 ary urea,36 sulfilmine37 and benzodiazepine38 based palladacycles have also shown good activity with aryl bromides in C–C coupling reactions.

We have reported the synthesis and characterization of thermal, oxygen and moisture stable palladium complexes containing a 2-phenylaniline cyclopalladated unit that conveniently formed six-membered NC palladacycles39 (Fig. 1). Complex 4 was further studied by X-ray crystallography.39 In this Letter, we report the application of the palladacycles in Suzuki and Heck reactions. During our research40,41 we have used aryl bromides and chlorides with phenylboronic acid in the Suzuki reactions and aryl bromides with styrene in the Heck reaction.

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The reaction conditions such as the solvent and base, reaction temperature and time were optimized. Initially, the effectiveness of different solvents such as MeOH, THF, acetone and benzene were tested with palladacycles in the presence of K$_2$CO$_3$, Na$_2$CO$_3$, and K$_3$PO$_4$ as base, 1 h, 65 °C. The deactivated electron-rich aryl chlorides, 4-chlorotoluene and 2-bromobenzaldehyde, in order to optimize the base (Tables 3 and 4). Among the bases employed, K$_2$CO$_3$, K$_3$PO$_4$, Na$_2$CO$_3$ and Na$_3$CO$_3$ (Table 2) and K$_3$PO$_4$, Na$_2$CO$_3$ (Tables 3 and 4) were found to be the best. The third factor to be optimized was the reaction time. A shorter reaction time had a positive effect on the reaction of 4-bromoanisole with phenylboronic acid (Table 3, entry 3) which may be due to the prevention of homocoupling. In contrast, two reactions were negatively affected by this change and the catalytic activity decreased (Tables 2 and 4, entry 3). Decreasing the temperature of the reactions, led to different catalytic activity. As the temperature was lowered, there was no decrease in the reaction yield for the reaction of bromobenzene with phenylboronic acid (Table 2, entry 4). Moreover, utilizing Na$_2$CO$_3$ instead of K$_2$CO$_3$ showed no effect on the reaction, as the anion, CO$_3^{2-}$, which contributes to the catalytic cycle, is the same. The catalytic activity in two other reactions (Tables 3 and 4, entry 4) was reduced, however. The optimized conditions for the reaction of bromobenzene with phenylboronic acid were Na$_2$CO$_3$ as base, MeOH as solvent, 1 h as the reaction time, and room temperature. The study was pursued to test catalysts 2, 4–8 using these conditions which resulted in diverse yields. The catalysts with monodentate ligands (2–4) were the best in all reactions and exhibited better catalytic reactivity than complexes with bidentate ligands (5–8). Also, the catalytic activity of 6 was lower than that of 7 in all the reactions in this work. This may be due to the fact that Pd(II) in palladacycles with five-membered rings is difficult to reduce to Pd(0). The best conditions for the reactions of 4-bromoanisole and 2-bromobenzaldehydes with phenylboronic acid were the same as those for the reaction of bromobenzene with phenylboronic acid, except for differences in the reaction times, which are shown in Tables 3 and 4.

Using the optimized reaction conditions, complex 4 was applied to a representative range of aryl chlorides (Table 5). The activated electron-deficient substrate, 4-chlorobenzaldehyde coupled with phenylboronic acid to give a relatively high yield of product (entry 1). Unexpectedly, the reaction of 4-nitrochlorobenzene failed to give a high yield (entry 2). Chlorobenzene was also coupled with phenylboronic acid to afford a high yield of biphenyl (entry 3). The deactivated electron-rich aryl chlorides, 4-chlorotoluene and 4-chloroaniline were poor substrates (entries 4 and 5). It can be inferred that the electronic effects of the substituents on the aryl chlorides had significant influence on the reaction and electron-withdrawing substituents were more appropriate for the coupling.

In all the reactions of aryl bromides and chlorides, particularly when complexes 2–4 were applied, the suspension color turned

### Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<tr>
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<td>MeOH</td>
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<td>2</td>
<td>3</td>
<td>THF</td>
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</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Acetone</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Benzene</td>
<td>3</td>
</tr>
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<td>5</td>
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<td>6</td>
<td>THF</td>
<td>3</td>
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<tr>
<td>7</td>
<td>6</td>
<td>Acetone</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>Benzene</td>
<td>0</td>
</tr>
</tbody>
</table>

* Reaction conditions: bromobenzene (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.01 mmol), base (1.5 mmol), solvent (6 mL), 1 h, 65 °C.

### Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Temp/time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>K$_2$CO$_3$</td>
<td>65 °C/1 h</td>
<td>100</td>
</tr>
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<td>2</td>
<td>3</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>65 °C/1 h</td>
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<td>3</td>
<td>Na$_2$CO$_3$</td>
<td>65 °C/30 min</td>
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</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Na$_2$CO$_3$</td>
<td>rt/1 h</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
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<td>rt/1 h</td>
<td>100</td>
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<td>6</td>
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<td>Na$_2$CO$_3$</td>
<td>rt/1 h</td>
<td>100</td>
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<td>7</td>
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<td>rt/1 h</td>
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<td>10</td>
<td>8</td>
<td>Na$_2$CO$_3$</td>
<td>rt/1 h</td>
<td>55</td>
</tr>
</tbody>
</table>

* Reaction conditions: bromobenzene (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.01 mmol), base (1.5 mmol), MeOH (6 mL).

### Table 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Temp/time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>K$_2$CO$_3$</td>
<td>65 °C/1 h</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>65 °C/1 h</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>65 °C/30 min</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>rt/30 min</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>65 °C/30 min</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>65 °C/30 min</td>
<td>98</td>
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<tr>
<td>7</td>
<td>5</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>65 °C/30 min</td>
<td>31</td>
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<td>8</td>
<td>6</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>65 °C/30 min</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>65 °C/30 min</td>
<td>71</td>
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<td>10</td>
<td>8</td>
<td>K$_3$PO$_4$ 3H$_2$O</td>
<td>65 °C/30 min</td>
<td>35</td>
</tr>
</tbody>
</table>

* Reaction conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.01 mmol), base (1.5 mmol), MeOH (6 mL).
black at the beginning of the reactions. Thus, it can be inferred that the reaction mechanism starts with a pre-dissociation and/or reduction step in which the Pd(II) source is converted into the more active and coordinatively unsaturated Pd(0) catalyst.43 This is followed by oxidative addition of the aryl halide which is often the rate determining step in cross-coupling catalytic cycles.44 The high C–Cl bond strength compared with C–Br disfavors oxidative addition and makes the coupling of such substrates far more challenging.45 The catalytic cycle is completed by transmetallation, aryl group transfers from boron to palladium, and a final reduction–elimination to release the product. Therefore, the relative contribution of steric and electronic effects is very important, particularly for less reactive aryl halides.36–48

In comparison with PdCl2, complex 4 showed higher catalytic activity in the reactions of bromo- and chlorobenzene with phenylboronic acid (Table 5, entries 6 and 7). The rate of coupling for each of these reactions was lower than that when complex 4 was used (Table 2, entry 6 and Table 5, entry 3).

The catalytic activity of the palladacycles was also studied in the Heck reaction of aryl bromides with styrene. The catalytic activity of 2, 3, and 4 with the optimal conditions obtained from the Suzuki reaction of aryl bromides with phenylboronic acid were examined in the Heck reaction of bromobenzene, 4-bromoanisole, and 2-bromobenzaldehyde with styrene. The results are summarized in Table 6.

### Table 4
Effect of base, catalyst, temperature and time on the Suzuki reaction of 2-bromobenzaldehyde with phenylboronic acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Temp/time</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>K3PO4</td>
<td>Na2CO3</td>
<td>rt/1 h</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>K3PO4</td>
<td>Na2CO3</td>
<td>65 °C/1 h</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>K3PO4</td>
<td>Na2CO3</td>
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<tr>
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<td>K3PO4</td>
<td>Na2CO3</td>
<td>65 °C/1 h</td>
<td>96</td>
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<tr>
<td>6</td>
<td>K3PO4</td>
<td>Na2CO3</td>
<td>65 °C/1 h</td>
<td>88</td>
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<tr>
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<td>65 °C/1 h</td>
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<td>K3PO4</td>
<td>Na2CO3</td>
<td>65 °C/1 h</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>K3PO4</td>
<td>Na2CO3</td>
<td>65 °C/1 h</td>
<td>54</td>
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</table>

### Table 5
Use of the optimized conditions for the Suzuki reaction of aryl chlorides with phenylboronic acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Catalyst</th>
<th>Base</th>
<th>Temp/time</th>
<th>Yield (%)</th>
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<td>2</td>
<td>p-NO2</td>
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<td>K3PO4</td>
<td>65 °C/1 h</td>
<td>35</td>
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<tr>
<td>3</td>
<td>H</td>
<td>4</td>
<td>Na2CO3</td>
<td>rt/1 h</td>
<td>74</td>
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<tr>
<td>4</td>
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<tr>
<td>6</td>
<td>H</td>
<td>PdCl2</td>
<td>Na2CO3</td>
<td>rt/1 h</td>
<td>20</td>
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<td>Na2CO3</td>
<td>rt/1 h</td>
<td>42</td>
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### Table 6
The catalytic activity in the Heck reaction of aryl bromides with styrene using the optimized Suzuki reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R = H (%)</th>
<th>R = p-OMe (%)</th>
<th>R = p-CHO (%)</th>
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<td>7</td>
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</tr>
</tbody>
</table>

### Table 7
Optimization of the Heck reaction of aryl bromides with styrene

<table>
<thead>
<tr>
<th>Entry</th>
<th>R = H (%)</th>
<th>R = p-OMe (%)</th>
<th>R = p-CHO (%)</th>
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<td>10</td>
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</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
entry 2) were both increased. Even after changing the reaction time to 3 h, some reactions showed no catalytic activity. In other reactions, low to moderate yields were obtained. Moreover, the lower yields of the reaction 2-bromobenzaldehyde with styrene can be ascribed to the steric effect of the –CHO group. The results are summarized up in Table 7.

In conclusion, we have developed a new combination of palladacycles with 2-phenylaniline, monodentate and bidentate ligands, which proved to be efficient for the Suzuki reactions of various aryl bromides and chlorides with phenylboronic acid. However, these palladacycles did not work as efficiently in the Heck reaction.

Acknowledgment

We gratefully thank the Iran National Science Foundation (INSF) for financial support.

References and notes

42. General protocol for the Suzuki reaction: A round bottom flask was charged with aryl bromide (0.5 mmol), phenylboronic acid (0.75 mmol), base (1.5 mmol), catalyst (0.01 mmol) and solvent (6 mL). The mixture was heated for the time and at the temperature given in Tables 3–5 using the base and catalyst there indicated. The products were characterized by GC.
49. General protocol for the Heck reaction: A round bottom flask was charged with aryl bromide (0.5 mmol), styrene (0.75 mmol), base (1.5 mmol), catalyst (0.01 mmol) and MeOH (6 mL). The mixture was heated for the time and at the temperature given in Tables 6 and 7 using the base and catalyst there indicated. All the products were characterized by GC.