N-Heterocyclic carbene–Pd(II) complex derived from proline for the Mizoroki–Heck reaction in water

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1. Introduction
Palladium-catalyzed Mizoroki–Heck coupling reaction, sharing the 2010 Nobel Prize, is a powerful and versatile method for arylation and vinylation of olefins. During the past decades, most efficient Mizoroki–Heck reactions reported were carried out in organic solvents with phosphate-based compounds as the ancillary ligand. In order to overcome the toxicity of organic solvents and the toxicity, air and/or moisture-sensitivity of phosphate-based ligands, many efforts have been made to find out alternative ligands and clean solvents. Compared to toxic and volatile organic solvents, water, as a non-toxic, non-flammable and the most environmentally friendly solvent, had attracted much attention in organic synthesis. On the other hand, in contrast to phosphate-based ligands, N-heterocyclic carbenes (NHCs), as excellent N-donors and weaker p-acceptors, can produce stable NHC–metal complexes with strong NHC–metal bonds, which usually exhibits higher stability in the solid state and even in solution than phosphate-based ligands. Although NHC–metal complexes have attracted much attention in the carbon–carbon and carbon–heteroatom bond formation reactions performed in routine organic solvents, their applications in pure water were rarely reported. Recently, we have developed some NHC–metal complexes derived from proline and found them to be efficient catalysts in carbon–carbon bond formations performed in water. For instance, NHC–Pd(II) complexes derived from N-benzyl proline were proved to be good catalysts in the room temperature Suzuki–Miyaura coupling reaction of aryl iodides and bromides carried out in pure water. These results prompted us to further investigate the applications of these complexes in other carbon–carbon bond formation reactions. In continuing research, we found that NHC–Pd(II) complex 1 (Fig. 1) derived from N-benzyl proline was also a favourable catalyst for the Mizoroki–Heck reaction of aryl iodides and bromides performed in pure water. Herein, we wish to report these results in detail.

2. Results and discussion
Initial examinations were carried out using bromobenzene 2a (1.0 mmol) and acrylic acid 3a (1.5 equiv) as the substrates, NHC–Pd(II) complex 1 (1.0 mol %) as the catalyst, H2O (2.0 mL) as
the solvent at 100 °C to find out the best base (Table 1, entries 1–9). As can be seen from Table 1, the best result was obtained with KOtBu as the base and the corresponding coupling product 3a can be achieved in 91% yield (entry 3). The yield can be further increased to 96% at elevated temperature (120 °C) (entry 10).

![Table 1
Optimization for the NHC–Pd(II) complex 1 catalyzed reaction of bromobenzene 2a with acrylic acid 3a](image)

<table>
<thead>
<tr>
<th>Entry*</th>
<th>Base</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaO[Bu]</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>KOH</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>KOtBu</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>NaOH</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>K2CO3</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>Na2CO3</td>
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<tr>
<td>7</td>
<td>KHCO3</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>KF 2H2O</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>K2PO4 3H2O</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>KOtBu</td>
<td>96</td>
</tr>
</tbody>
</table>

* Otherwise specified, all reactions were carried out using 2a (1.0 mmol), 3a (1.5 mmol), base (3.0 equiv), 1 (1.0 mol %) in H2O (2.0 mL) at 100 °C for 24 h.

b Isolated yields.

c The temperature is 120 °C.

It is conceivable that the base KOtBu will rapidly hydrolyze to KOH and tBuOH under the identical reaction conditions. Further studies showed that tBuOH was essential for the reactions with KOH as the base, which clearly illustrated the differences between the results using KOH and tBuOK as the base, respectively (Table 2).

To survey the generality of this NHC–Pd(II) complex 1 catalyzed reaction of bromobenzene 2a with acrylic acid 3a under the identical conditions (Table 3). As can be seen from Table 3, all reactions took place smoothly to give the coupling products 4 in good to excellent yields in most cases. Substituents on the aryl bromides have some effect on the reactions. For instance, it seems that aryl bromides with electron-donating groups, such as 4-MeO (2b), 4-Me (2c) and 3-MeO (2d) gave better yields (entries 1–3). On the contrary, aryl bromides with electron-poor groups, such as 4-Cl (2e) and 4-F (2f) gave inferior results (entries 4 and 5). Only moderate yield of product 4g was obtained when strongly electron-withdrawing group-substituted 4-nitrophenyl bromide 2g was used as the substrate (entry 6). Heteroaryl bromides, such as 2-bromothiophene 2h and 3-bromothiophene 2i were also proved to be suitable reaction partners to give the corresponding products 4h and 4i in reasonable yields, respectively (entries 10 and 11). In addition, aryl iodides showed better reactivity in these Mizoroki–Heck reactions to give products 4 in excellent yields, with no differences between the substituents on the aryl rings (entries 7–9).

The reactions of bromobenzene 2a with some acrylate esters, such as acrylate methyl ester 3b, ethyl ester 3c and n-butyl ester 3d were also investigated under the similar conditions. The reactions can be performed at 100 °C to give product 4a, the coupling-hydrolyzed product, in good to excellent yields in all cases (Table 4). Maybe the high solubility of product 4a in H2O accelerates the hydrolysis of the coupling products, the esters, resulting in cinnamic acid 4a as the sole product.
Furthermore, the reactions between aryl bromides 2 and a kind of styrenes were also carried out under the identical conditions. As can be seen from Table 5, all reactions can give the corresponding coupling products 6 in moderate to high yields, despite the electron-rich or poor, or sterically hindered substituents on the aryl rings of both of aryl bromides and styrenes. The reaction between 3-bromopyridine 2o and styrene 5a also works well to give product 6j in 84% yield (entry 10).

In further investigations, we found that NHC–Pd(II) complex 1 showed no catalytic activity towards aryl chlorides under the identical reaction conditions. In addition, we found that when enone, such as 1-phenyl-propenone was used as the substrate, the reaction became disordered and no desired product can be obtained.

3. Conclusion

In summary, NHC–Pd(II) complex 1 derived from proline showed good to excellent catalytic activities upon Mizoroki–Heck reaction performed in water, with aryl bromides and iodides as the electrophilic partners. We, for the first time, systematically investigated the NHC–Pd complex catalyzed Mizoroki–Heck reactions performed in pure water. The complex is air- and moisture stable and can be stored under air for several months.

4. Experimental section

4.1. General methods

1H and 13C NMR spectra were recorded on Bruker Avance-300 or 500 MHz spectrometer for solution in CDCl3 with tetramethylsilane (TMS) as an internal standard or in DMSO-d6; J-values are in hertz. Commercially obtained reagents were used without further purification. Flash column chromatography was carried out using Huanghai 300–400 mesh silica gel at increased pressure.

4.2. Experimental procedures

4.2.1. General procedure for the NHC–Pd(II) complex 1-catalyzed Mizoroki–Heck reaction. (If olefin is acrylate esters) Under N2 atmosphere, NHC–Pd(II) complex 1 (1.0 mol %) and KOBu (3.0 equiv) and H2O (2.0 mL) were added into a sealed tube, then acrylate esters 3 (1.5 mmol) and aryl bromides 2 (1.0 mmol) were added. The mixture was stirred vigorously at 100 °C for 24 h. After cooling to room temperature, the solvent was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4. The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (SiO2) to give the pure product.

Table 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>2 (R')</th>
<th>3 (R')</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (H)</td>
<td>5a (H)</td>
<td>6a, 90</td>
</tr>
<tr>
<td>2</td>
<td>2b (4-MeO)</td>
<td>5a</td>
<td>6b, 80</td>
</tr>
<tr>
<td>3</td>
<td>2c (4-Me)</td>
<td>5a</td>
<td>6c, 69</td>
</tr>
<tr>
<td>4</td>
<td>2d (3-MeO)</td>
<td>5a</td>
<td>6d, 88</td>
</tr>
<tr>
<td>5</td>
<td>2e (4-Cl)</td>
<td>5a</td>
<td>6e, 89</td>
</tr>
<tr>
<td>6</td>
<td>2f (4-F)</td>
<td>5a</td>
<td>6f, 86</td>
</tr>
<tr>
<td>7</td>
<td>2g (4-NO2)</td>
<td>5a</td>
<td>6g, 85</td>
</tr>
<tr>
<td>8</td>
<td>2h (2-Me)</td>
<td>5a</td>
<td>6h, 90</td>
</tr>
<tr>
<td>9</td>
<td>2i (4-Ac)</td>
<td>5a</td>
<td>6i, 81</td>
</tr>
<tr>
<td>10</td>
<td>2j Br</td>
<td>5a</td>
<td>6j, 84</td>
</tr>
</tbody>
</table>

a All reactions were carried out using 2 (1.0 mmol), 5 (1.5 mmol), KOBu (3.0 equiv), 1 (1.0 mol %) in H2O (2.0 mL) at 120 °C for 24 h.

b Isolated yields.
1H NMR (300 MHz, CDCl3, TMS) δ 0.27 (d, J = 15.6 Hz, 1H), 7.32−7.38 (m, 2H, Ar), 7.56 (d, J = 1.5 Hz, 1H, Ar), 7.77 (d, J = 15.6 Hz, 1H). 13C NMR (125 MHz, CDCl3) δ 115.9, 128.2, 131.6, 139.2, 139.3, 171.7.

1H NMR (300 MHz, CDCl3, TMS) δ 3.83 (s, 3H, OMe), 6.99 (d, J = 8.5 Hz, 2H, Ar), 6.98 (d, J = 16.0 Hz, 1H), 7.07 (d, J = 16.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H, Ar), 7.42 (t, J = 7.5 Hz, 1H, Ar), 7.34 (t, J = 7.5 Hz, 2H, Ar), 7.46−7.50 (m, 4H, Ar). 13C NMR (125 MHz, CDCl3) δ 55.3, 114.1, 126.2, 126.6, 127.2, 127.7, 128.2, 128.6, 130.2, 133.7, 159.3.

1H NMR (300 MHz, CDCl3, TMS) δ 3.85 (s, 3H, OMe), 6.82 (d, J = 7.5 Hz, 1H, Ar), 7.04−7.12 (m, 4H), 7.25−7.29 (m, 2H), 7.36 (t, J = 7.5 Hz, 2H, Ar), 7.51 (d, J = 7.5 Hz, 2H, Ar). 13C NMR (CDCl3, 125 MHz) δ 55.3, 111.8, 113.3, 119.3, 126.5, 127.7, 128.6, 129.7, 133.8, 135.8, 159.9.

1H NMR (300 MHz, CDCl3, TMS) δ 7.05−7.12 (m, 4H), 7.26−7.38 (m, 5H, Ar), 7.44 (d, J = 8.5 Hz, 2H, Ar), 7.51 (d, J = 7.0 Hz, 2H, Ar). 13C NMR (CDCl3, 125 MHz) δ 126.5, 127.4, 126.7, 129.6, 128.7, 128.9, 132.2, 133.5, 133.7. 19.9, 125.4, 126.2, 126.5, 126.7, 127.6, 128.7, 130.0, 130.4, 135.8, 136.4, 137.7.

1H NMR (CDCl3, 500 MHz, TMS) δ 2.61 (s, 3H, Me), 7.14 (d, J = 16.0 Hz, 1H), 7.23 (d, J = 16.0 Hz, 1H, 7.30 (t, J = 7.5 Hz, 1H, Ar), 7.38 (t, J = 7.5 Hz, 2H, Ar), 7.54 (d, J = 7.5 Hz, 2H, Ar), 7.59 (d, J = 8.0 Hz, 2H, Ar), 7.96 (d, J = 8.0 Hz, 2H, Ar). 13C NMR (CDCl3, 125 MHz) δ 26.6, 126.5, 126.8, 127.5, 128.3, 128.8, 128.9, 131.5, 136.0, 136.7, 142.0, 197.5.

1H NMR (300 MHz, CDCl3, TMS) δ 7.07 (d, J = 16.5 Hz, 1H), 7.18 (d, J = 16.5 Hz, 1H), 7.27−7.33 (m, 2H, Ar), 7.38 (t, J = 7.2 Hz, 2H, Ar), 7.53 (d, J = 7.2 Hz, 2H, Ar), 7.83 (d, J = 7.8 Hz, 1H, Ar), 8.49 (dd, J = 4.8, 1.5 Hz, 1H, Ar), 8.73 (d, J = 2.1 Hz, 1H, Ar). 13C NMR (125 MHz, CDCl3) δ 123.5, 124.9, 126.7, 128.2, 128.8, 130.8, 132.6, 133.0, 146.7.

1H NMR (300 MHz, CDCl3, TMS) δ 2.35 (s, 3H, Me), 3.83 (s, 3H, OMe), 6.89 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H, Ar), 7.15 (d, J = 7.8 Hz, 2H, Ar), 7.39 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H). 13C NMR (125 MHz, CDCl3) δ 21.2, 55.3, 114.1, 126.2, 126.6, 127.3, 127.6, 129.3, 130.4, 134.9, 137.0, 159.2.

1H NMR (300 MHz, CDCl3, TMS) δ 2.38 (s, 3H, Me), 7.09 (d, J = 16.5 Hz, 1H), 7.19−7.28 (m, 3H, Ar + C=CH), 7.45 (d, J = 7.8 Hz, 2H, Ar), 7.61 (d, J = 9.0 Hz, 2H, Ar), 8.21 (d, J = 9.0 Hz, 2H, Ar). 13C NMR (125 MHz, CDCl3) δ 213.4, 124.1, 125.3, 126.7, 127.0, 129.6, 133.3, 133.5, 139.0, 144.1, 146.6.

1H NMR (300 MHz, CDCl3, TMS) δ 8.18−8.93 (m, 3H, Ar + C=CH), 7.03 (d, J = 16.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H, Ar), 7.41 (d, J = 9.0 Hz, 2H, Ar), 7.44 (d, J = 9.0 Hz, 2H, Ar). 13C NMR (125 MHz, CDCl3) δ 55.3, 114.2, 125.3, 127.4, 127.8, 128.8, 129.8, 132.7, 136.2, 159.5.

1H NMR (300 MHz, CDCl3, TMS) δ 7.11 (d, J = 16.5 Hz, 1H), 7.17 (d, J = 16.5 Hz, 1H, 7.37 (d, J = 8.4 Hz, 2H, Ar), 7.48 (d, J = 8.4 Hz, 2H, Ar), 7.63 (d, J = 9.0 Hz, 2H, Ar). 8.23 (d, J = 9.0 Hz, 2H, Ar). 13C NMR (125 MHz, CDCl3) δ 124.2, 126.89, 128.3, 129.1, 131.9, 134.6, 143.5, 147.0.

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