Carbonates: eco-friendly solvents for palladium-catalysed direct arylation of heteroaromatics†

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Received 18th June 2010, Accepted 22nd September 2010
DOI: 10.1039/c0gc00229a

The palladium-catalysed direct 2-, 4- or 5-arylation of a wide range of heteroaromatics with aryl halides proceed in moderate to good yields using the eco-friendly solvents carbonates. The best yields were obtained using benzoazoxole or thiazole derivatives. The arylation of furan, thiophene, pyrrole, imidazole or isoxazole derivatives was found to require a more elevated reaction temperature.

The direct arylation of heteroaromatics is an important field for research in organic synthesis due to the biological or physical properties of the aryl-heteroaryl derivatives.1 Ohta and co-workers reported in 1985–1992 that the direct 2- or 5-arylation of several heteroaromatics with aryl halides proceed in moderate to good yields using Pd(PPh3)4 as the catalyst and DMAc as the solvent.2 Since these exciting results, the palladium-catalysed direct arylation of heteroaryl derivatives with aryl halides or triflates has proved to be a very powerful method for the synthesis of a wide variety of arylated heterocycles.3-10 This reaction provides a cost-effective and environmentally attractive access for the preparation of such compounds. Indeed, the major by-products of the reaction are a base associated to HX, instead of metallic salts produced under classical cross-coupling procedures such as Suzuki, Negishi or Stille reactions. Moreover, the method avoids the preliminary preparation of a requisite organometallic reducing then the number of steps to prepare these compounds. However, these reactions were currently performed in most cases using relatively toxic solvents such as DMF, DMAc, NMP or dioxane. A few palladium-catalysed direct arylations of heteroaromatics have also been performed using toluene, xylene or mesitylene.3 The direct arylation of oxazoles, thiazoles or indazoles using water11 as the solvent has been reported by Greaney. René and Fagnou have developed biphasic conditions using a mixture of water and EtOAc for the direct arylation of thiophenes.12 Recently, polyethylene glycol (PEG 20000) has been found to be a useful solvent for the direct arylation of triazoles.13

Carbonates, such as diethylcarbonate or propylene carbonate, are polar, aprotic, nontoxic, and biodegradable solvents.14 Based on these properties, such carbonates should offer an environmentally friendly alternative to standard polar solvents. Since a few years ago, carbonates have been employed successfully for some classical metal-catalysed reactions such as enantioselective hydrogenation, alkene metathesis, carbonylation, oxidation, hydroxylation, Sonogashira coupling, Heck vinylation or allylic alkylation.14 The ruthenium-catalysed direct arylation of 2-arylpyridines has also been reported recently by Fischmeister, Dixneuf and co-workers.16 However, to our knowledge, so far, carbonates have not been employed as the solvents for palladium-catalysed direct arylation. The use of this family of solvent would provide a cost-effective and environmentally attractive procedure for the preparation of arylated heteroarenes. Herein, we wish to report on the use of diethycarbonate and propylene carbonate for palladium-catalysed direct 2-, or 5-arylation of a wide range of heteroaromatic derivatives.

In order to determine the suitability of these solvents for palladium-catalysed direct arylations, a first set of direct arylation reactions of several heteroarenes with 4-bromoaethophenone was carried out under previously reported reaction conditions but using diethycarbonate as the solvent.16,56c,9o Employing the 2-n-butylthiophene, 2-n-butyliuran or 2-formyl-N-methylpyrrole and 4-bromoaethophenone as coupling partners, at 130 °C during 17 h, the corresponding 5-arylation products were obtained in low yields. On the other hand, at this temperature, the direct arylation of benzoazoxo proceeded nicely using only 1 mol% of PdCl2(C6H5)(dppb) as the catalyst to provide 1 in 85% isolated yield (Scheme 1, Table 1, entries 1 and 2). Interestingly, this latter reaction performed in diethycarbonate was found to be more selective than in DMF,9o DMAc, NMP or dioxane since using this solvent, fewer traces of unidentified side-products were detected (Table 1, entries 3–6).

![Scheme 1](https://example.com/scheme1.png)

**Scheme 1** Coupling of benzoazoxole with 4-bromoaethophenone.

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† Electronic supplementary information (ESI) available: NMR data of new compounds. See DOI: 10.1039/c0gc00229a

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2 Electronic supplementary information (ESI) available: NMR data of new compounds. See DOI: 10.1039/c0gc00229a

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Then, we studied the scope and limitations of this procedure, using other aryl bromides (Scheme 2, Tables 2–4). 4-Bromobenzaldehyde, 4-bromopropiophenone or 4-trifluoromethylbromobenzene reacted with benzoxazole gave the expected products 2, 3 and 5 in 77–92% yields (Table 2, entries 1, 2 and 4). Slower reactions were observed using 4-bromobenzonitrile or methyl 4-bromobenzoate. However, using longer reaction time (72 h), very high conversions of these aryl bromides and high yields of coupling products 4 and 6 were obtained (Table 2, entries 3 and 5). A lower yield of 25% of 7 was obtained using 4-bromonitrobenzene, due to a moderate conversion of this aryl bromide (Table 2, entry 6). This is probably due to a partial poisoning of the palladium catalyst. Using the electron-rich aryl bromides, 4-bromotoluene or 4-bromoanisole, the products 9 and 10 were obtained in 83% and 62% yields, respectively (Table 2, entries 8 and 9). With these two reactants, long reaction times (72 h) had to be employed in order to obtain high conversions. 4-N,N-Dimethylaminobromobenzene led to a moderate yield of 11 (Table 2, entry 10). This is certainly due to a slow oxidative addition of this strongly deactivated aryl bromide to palladium. With this catalyst, the oxidative addition of the aryl bromides to palladium appears to be the rate-limiting step of the catalytic cycle. For all these reactions, a very high selectivity in favour of the formation of 2–11 was observed. Moreover, the stability of these products seems to be higher than in DMF, and very limited amount of side-products due to partial degradation was detected."

Scheme 2 Coupling of benzoxazole with aryl bromides.

Then, the reactivity of three meta-substituted aryl bromides was examined (Table 3). As expected, similar results than in the presence of para-substituted aryl bromides were obtained. 3-Bromobenzaldehyde, 3-bromobenzonitrile or 3,5-bis(trifluoromethyl)bromobenzene gave 12–14 in 85–88% yields (Table 3, entries 1–3).

Ortho-substituents on aryl bromides generally have a more important influence on the yields of palladium-catalysed reactions, due to their steric or coordination properties. Ortho-substituted 2-bromobenzaldehyde, 2-bromobenzonitrile, 2-bromobenzotrifluoride or 2-fluorobromobenzene reacted with benzoxazole gave 15–18 in 62–90% yields (Table 2, entries 4–6). Remarkably, the reaction was also successfully realized with the congested and slightly deactivated aryl bromide, 2-bromotoluene to give 19, albeit in moderate 50% yield (Table 2, entry 8).

Next, we explored the reactivity of benzoxazole with heteroaryl bromides. The results depicted in Table 4 also revealed clearly the good performance of the novel friendly protocol in direct coupling with benzoxazole. Selective reactions were observed using 2-, 3- or 4-bromopyridines, 3-bromoquinoline, 4-bromoquinolinone or 5-bromopyrimidine. With these substrates the target products 20–25 were obtained in 64–91% yields. The reaction in the presence of 4-bromoquinolinone was found to be quite slow. However, a high yield of 24 was obtained after 48 h (Table 4, entry 5).

It should be noted that the direct coupling of benzoxazole with 4-bromoaacetophenone using propylene carbonate as the

Table 1 Influence of the reaction conditions for palladium catalysed direct coupling of benzoxazole with 4-bromoacetophenone (Scheme 1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂</td>
<td>diethyl carbonate</td>
<td>11</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>PdCl(C₆H₅)(dppb)</td>
<td>diethyl carbonate</td>
<td>91 (85)</td>
<td>77</td>
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<tr>
<td>3</td>
<td>PdCl(C₆H₅)(dppb)</td>
<td>DMF</td>
<td>(78)</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>PdCl(C₆H₅)(dppb)</td>
<td>DMF</td>
<td>31</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>PdCl(C₆H₅)(dppb)</td>
<td>NMP</td>
<td>79 (51)</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>PdCl(C₆H₅)(dppb)</td>
<td>dioxane</td>
<td>88 (73)</td>
<td>83</td>
</tr>
</tbody>
</table>

* Conditions: Pd (0.01 eq.), benzoxazole (2 eq.), 4-bromoacetophenone (1 eq.), Cs₂CO₃ (2 eq.), 17 h, 130 °C, conversion of 4-bromoacetophenone, yield in parenthesis is isolated. °Pd (0.05 eq.), 100 °C.

Table 2 Palladium-catalysed coupling of benzoxazole with para-substituted aryl bromides (Scheme 2)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br-H</td>
<td>H</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Br-H</td>
<td>H</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>Br-H</td>
<td>H</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>Br-H</td>
<td>H</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>Br-H</td>
<td>H</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>Br-H</td>
<td>H</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>Br-H</td>
<td>H</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>Br-H</td>
<td>H</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>Br-H</td>
<td>H</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>Br-H</td>
<td>H</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>Br-H</td>
<td>H</td>
<td>72</td>
</tr>
</tbody>
</table>

* Conditions: PdCl(C₆H₅)(dppb) (0.01 eq.), benzoxazole (2 eq.), aryl bromide (1 eq.), Cs₂CO₃ (2 eq.), diethyl carbonate, 130 °C, 17 h, isolated yields. °Reaction time 48 h. ºReaction time 24 h. †Reaction time 72 h.
Table 3 Palladium-catalysed coupling of benzoxazole with meta- or ortho-substituted aryl bromides (Scheme 2)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br-</td>
<td>O-H</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Br-</td>
<td>CN</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Br-</td>
<td>CF3</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>H-</td>
<td>O-H</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>N-</td>
<td>NC</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>F-</td>
<td>Cl</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>Br-</td>
<td>F-</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>Me-</td>
<td>Me</td>
<td>50</td>
</tr>
</tbody>
</table>

*Conditions: PdCl(C3H5)(dppb) (0.01 eq.), benzoxazole (2 eq.), aryl bromide (1 eq.), Cs2CO3 (2 eq.), diethylcarbonate, 130 °C, 17 h, isolated yields.

Scheme 3 Coupling of benzoxazole with 4-bromoacetophenone using propylene carbonate as the solvent.

Table 4 Palladium-catalysed coupling of benzoxazole with heteroaryl bromides (Scheme 2)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heteroaryl bromide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br-N</td>
<td>N-N</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>Br-N</td>
<td>N-N</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Br-N</td>
<td>N-HCl</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>Br-N</td>
<td>N</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>Br-N</td>
<td>N</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Br-N</td>
<td>N</td>
<td>90</td>
</tr>
</tbody>
</table>

* Conditions: PdCl(C3H5)(dppb) (0.01 eq.), benzoxazole (2 eq.), heteroaryl bromide (1 eq.), Cs2CO3 (2 eq.), diethylcarbonate, 130 °C, 24 h, isolated yields.

Scheme 4 Coupling of ethyl oxazole-4-carboxylate with aryl halides.

As a practical and valuable functionalised oxazole substrate, ethyl oxazole-4-carboxylate was recently successfully evaluated in palladium-catalyzed regioselective 2-(hetero)arylation with a broad variety of iodo, bromo and chloro(hetero)aromatics (Scheme 4). Pleasingly, a preliminary assay of direct coupling of ethyl oxazole-4-carboxylate with 4-bromoacetophenone under previously designed conditions Pd(OAc)2/P(oTol)3 in diethylcarbonate as the solvent, gave the expected 2-arylated oxazole in 56% yield (Table 5, entry 1). It should be noted that the use of PdCl(C3H5)(dppb) as the catalyst proved to be less effective, leading to a poor conversion of starting material (<20%) within 48 h. Under the same experimental conditions, the direct arylation of ethyl oxazole-4-carboxylate with several iodo and bromo(hetero)aromatics bearing electron-attractive as well as electron-donating groups were successfully achieved to afford 2-arylated oxazoles in good yields (Table 5, entries 2, 4–6). Notably, the novel friendly catalyst system preserve the regiochemical outcome of the direct arylation at the 2-position and proved to be as efficient as the previously designed system. Indeed, in the course of this reaction, complete conversion of starting material was observed and the 5-arylated and 2,5-diarylated oxazole-4-carboxylates were isolated in very low yields (<10%). Interestingly, under the same conditions, activated chloro(hetero)aromatics (Table 5, entry 3) appeared to be also useful coupling partners to give selectively the...
Table 5  Palladium-catalysed coupling of ethyl oxazole-4-carboxylate derivatives with aryl halides (Scheme 4)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>69</td>
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<td>3</td>
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<td>4</td>
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<td>93</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>72</td>
</tr>
</tbody>
</table>

* Conditions: Pd(OAc)₂ (0.05 eq.), P(oTol)₃ (0.1 eq.), ethyl oxazole-4-carboxylate (2 eq.), aryl halide (1 eq.), Cs₂CO₃ (2 eq.), diethylcarbonate, 110 °C, 18 h, isolated yields. *S-Arylation and 2,5-diarylation products were also isolated (<10%). *2,5-Diarylation product was also isolated (<10%). *Oxazole derivative: 1 eq.

2-(hetero)arylated oxazole-4-carboxylates 27 and 31 in good yields.

Moreover, the 5-arylated and heteroarylated oxazoles* showed also a good reactivity in the same experimental conditions providing the 2,5-di(hetero)arylated oxazole-4-carboxylates 32–34 (Table 5, entries 8–10).

Then, we examined the reactivity of thiazole derivatives for the direct arylation in diethylcarbonate (Table 6). Using the quite similar reaction conditions PdCl₂(C₂H₅)₂(dppe), 130 °C and KOAc instead of Cs₂CO₃, 2-n-propylthiazole was successfully regioselectively arylation on carbon 5. The reaction was found to be
Table 6 (Contd.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Product</th>
<th>Yield (%)†</th>
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<tr>
<td>17</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>70†</td>
</tr>
<tr>
<td>18</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>83†</td>
</tr>
</tbody>
</table>

† Conditions: PdCl(C₅H₅)(dppb) (0.01 eq.), thiazole derivative (2 eq.), aryl halide (1 eq.), KOAc (2 eq.), diethylcarbonate, 130 °C, 24 h, isolated yields. * 24 h. † 67 h. † 140 °C. ‡ Pd(OAc), (0.05 eq.), P(oTol), (0.1 eq.), Cs₂CO₃ (2 eq.), 110 °C, 18 h. ‡ 2.5-Diphenylatedthiazole was isolated in 23% yield. ‡ Pd(OAc), (0.05 eq.), P(oTol), (0.1 eq.), iodobenzene (2 eq.), thiazole derivative (1 eq.), Cs₂CO₃ (2 eq.), 130 °C, 18 h.

slower than in DMAC,™ however, very high yields of compound 35–42 were obtained (Table 6, entries 1–8). As expected, the use of 2-ethyl-4-methylthiazole also allowed the synthesis of the 5-arylated thiazoles 43–45 in high yields (Table 6, entries 1–8). However, under the same conditions but by allowing the reaction to proceed at 140 °C, 23% yield. *

Nevertheless, under the same conditions but by allowing the reaction temperature of 140 °C, a moderate yield of 52% yield.

Table 7 Palladium-catalysed coupling of 2-n-butylfuran with aryl bromides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Product</th>
<th>Yield (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>70†</td>
</tr>
<tr>
<td>2</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>56†</td>
</tr>
<tr>
<td>3</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>61†</td>
</tr>
<tr>
<td>4</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>62†</td>
</tr>
<tr>
<td>5</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>84†</td>
</tr>
<tr>
<td>6</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>85†</td>
</tr>
</tbody>
</table>

† Conditions: PdCl(C₅H₅)(dppb) (0.01 eq.), furan derivative (2 eq.), aryl bromide (1 eq.), KOAc (2 eq.), diethylcarbonate, 140 °C, 23 h, isolated yields. * 72 h. † 43 h.

product 48 was obtained (Scheme 5). Using these reaction conditions, the coupling with 2-bromobenzonitrile gave 49 in 52% yield.

Scheme 5 Coupling of benzothiazole with 4-bromobenzaldehyde.

The direct use of furan derivatives is an important field for research in green chemistry, since some of them can be obtained from agricultural wastes rich in pentosan polymers. Our first attempts to arylate 2-n-butylfuran with 4-bromoacetoephene using 130 °C as the reaction temperature gave very low yields of 55. On the other hand, we observed that using a more elevated reaction temperature of 140 °C, a moderate yield of 55 could be obtained after 23 h. As the catalyst appears to be quite stable in this solvent, the use of longer reaction times (43 or 72 h) allowed to obtain the 5-arylated furans in good yields (Table 7). For example, after 43 or 72 h, the reaction of 2-n-butylfuran with 2-bromobenzonitrile or 4-bromoacetoephene gave 59 and 55 in 84% and 70% yields, respectively. In all cases, the reaction was very regioselective in favour of the 5-arylation product.

The reactivity of 2-n-butyliophene was found to be similar to 2-n-butylfuran (Table 8). When we employed 140 °C as the reaction temperature, a high yield of 89% of the 2-arylated benzothiazole was isolated as the major product in 53% yield (Table 6, entry 16).
reaction temperature, a variety of aryl bromides was coupled to give 61–66 in moderate to good yields. Again, the arylation was highly regioselective in favour of the 5-arylation. The moderate yields obtained in the presence of methyl 4-bromobenzoate or 3,5-bis(trifluoromethyl)bromobenzene are due to partial conversions of these aryl bromides.

Then, three arylated isoxazoles have been prepared via the direct 4-arylation of 3,5-dimethylisoxazole (Table 9). The yields strongly depend on the nature of the aryl bromides. A good yield of 71% of 67 was obtained in the presence of 4-bromoacetophenone; whereas, the use of 2-bromobenzonitrile gave 69 in only 23% yield.

1-Methyl-2-formylpyrrole has a poor reactivity for direct arylation in diethylcarbonate (Table 10). Much slower reactions than in DMAc were observed, and low to moderate yields were obtained. For example the coupling of 4-bromobenzonitrile with this reactant gave the 5-arylated pyrrole 71 in only 33% yield.

We have already reported the direct 5-arylation of a range of imidazole derivatives in DMAc. Again, the arylation were found to be slower in diethylcarbonate than in DMAc, however, the reactions were very clean using a range of aryl bromides (Table 11). High conversions of 4-bromocetophenone, 4-bromobenzonitrile or 3-bromopyridine were observed, and 73, 74 and 76 were obtained in high yields. On the other hand, only a partial conversion of 4-trifluoromethylybromobenzene was observed leading to a moderate yield of 75.

In conclusion, these results demonstrate that carbonates, which are considered to be “green solvents”, can be advantageously employed as an alternative to the solvents usually used for the direct arylation of several heteroaromatic derivatives. In the presence of diethylcarbonate or propylene carbonate and 1 mol% PdCl(C₅H₅)(dppb) as the catalyst precursor at 130 °C, the direct 2-arylation of benzoazole, ethyl oxazole-4-carboxylate or the 5-arylation of thiazoles using aryl bromides as coupling partners proceeds in moderate to high yields. The direct arylation of furan, thiophene, pyrrole, imidazole or isoxazole derivatives was found to require a more elevated reaction temperature (140 °C) to give high yields of coupling products. It should be noted that a wide range of functions such as acetyl, propionyl, formyl, ester, nitrile, trifluoromethyl, fluoro or methoxy on the aryl halide is tolerated. The major by-product of these couplings is CsX or KX/AcOH instead of metallic salts with more classical coupling procedures. For these reasons, this novel process should give an economically viable and environmentally attractive access to arylated heteroaromatics.
Table 11  Palladium-catalysed coupling of 1,2-dimethylimidazole with aryl bromides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
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*Conditions: PdCl(C₃H₅)(dpbb) (0.01 eq.), 1,2-dimethylimidazole (2 eq.), aryl bromide (1 eq.), KOAc (2 eq.), diethyl carbonate, 140 °C, 72 h, isolated yields.*

Experimental

Diethyl carbonate was purchased from Acros Organics and was not purified before use. Heteroarenes, propylene carbonate, KOAc and Cs₂CO₃ were purchased from Alfa Aesar and were not purified before use. Ethyl oxazole-4-carboxylate was prepared from ethyl isocyanoacetate according to Schöllkopf procedure.

Preparation of the PdCl(C₃H₅)(dpbb) catalyst:

An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with [Pd(C₃H₅)Cl] (182 mg, 0.5 mmol) and dpbb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ³¹P NMR (81 MHz, CDCl₃) δ = 19.3 (s).

Typical experiment for coupling reactions

The reaction of the aryl halide (1 mmol), heteroaromatic (2 mmol) and Cs₂CO₃ (0.651 g, 2 mmol) or KOAc (0.196, 2 mmol) (see Tables) at 130–140 °C (see Tables and Schemes) in diethyl carbonate (5 mL) in the presence of PdCl(C₃H₅)(dpbb) (6.1 mg, 0.01 mmol) or Pd(OAc)₂ (0.05 eq.)/P(oTol)₃ (0.1 eq.), (see Tables and Schemes) under argon affords the corresponding product after evaporation and filtration on silica gel (pentane/ether).

2-(4-Formylphenyl)-benzoxazole (2)*

4-Bromobenzaldehyde (0.184 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 2 in 92% (0.205 g) yield.

2-(4-Propionylphenyl)-benzoxazole (3)*

4-Bromopropiophenone (0.213 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 3 in 77% (0.193 g) yield.

Methyl 4-benzozazol-2-yl-benzoate (4)*

Methyl 4-bromobenzoate (0.215 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 4 in 87% (0.220 g) yield.

2-(4-Trifluoromethylphenyl)-benzoxazole (5)*

4-Trifluoromethylbromobenzene (0.225 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 5 in 90% (0.237 g) yield.

4-Benzoxazol-2-yl-benzonitrile (6)*

4-Bromobenzonitrile (0.182 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 6 in 87% (0.192 g) yield.

2-(4-Nitrophenyl)-benzoxazole (7)*

4-Bromonitrobenzene (0.182 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 7 in 25% (0.060 g) yield.

2-(4-Fluorophenyl)-benzoxazole (8)*

4-Bromofluorobenzene (0.175 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 8 in 85% (0.181 g) yield.

2-(4-Methylphenyl)-benzoxazole (9)*

4-Bromotoluene (0.171 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 9 in 83% (0.119 g) yield.

2-(4-Methoxyphenyl)-benzoxazole (10)*

4-Bromoanisole (0.187 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 10 in 62% (0.140 g) yield.

2-(4-Dimethylaminophenyl)-benzoxazole (11)*

(4-Bromophenyl)-dimethylamine (0.200 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 11 in 50% (0.119 g) yield.

2-(3-Formylphenyl)-benzoxazole (12)*

3-Bromobenzaldehyde (0.184 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 12 in 88% (0.194 g) yield.

2-(3,5-Bistrifluoromethylphenyl)-benzoxazole (14)*

3,5-Bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 14 in 86% (0.285 g) yield.
2-(2-Formylphenyl)-benzoxazole (15)

2-Bromobenzaldehyde (0.184 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 15 in 62% (0.138 g) yield.

2-Benzoxazol-2-yl-benzonitrile (16)

2-Bromobenzonitrile (0.182 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 16 in 84% (0.185 g) yield.

2-(2-Trifluoromethylphenyl)-benzoxazole (17)

2-Trifluoromethylbromobenzene (0.225 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 17 in 90% (0.237 g) yield.

2-(2-Fluorophenyl)-benzoxazole (18)

2-Bromofluorobenzene (0.175 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 18 in 78% (0.166 g) yield.

2-(2-Methylphenyl)-benzoxazole (19)

2-Bromotoluene (0.171 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 19 in 50% (0.105 g) yield.

2-Pyridin-2-yl-benzoxazole (20)

2-Bromopyridine (0.158 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 20 in 71% (0.139 g) yield.

2-Pyridin-3-yl-benzoxazole (21)

3-Bromopyridine (0.158 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 21 in 88% (0.173 g) yield.

2-Pyridin-4-yl-benzoxazole (22)

4-Bromopyridine hydrochloride (0.194 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 22 in 64% (0.126 g) yield.

3-Benzoxazol-2-ylquinoline (23)

3-Bromoquinoline (0.208 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 23 in 91% (0.224 g) yield.

4-Benzoxazol-2-ylisoquinoline (24)

4-Bromoisoquinoline (0.208 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 24 in 80% (0.197 g) yield.

2-Pyrimidin-5-ylbenzoxazole (25)

5-Bromopyrimidine (0.159 g, 1 mmol) and benzoxazole (0.238 g, 2 mmol) affords 25 in 90% (0.177 g) yield.

Ethyl 2-(4-acetylphenyl)-oxazole-4-carboxylate (26)

4-Bromoacetophenone (0.199 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords 26 in 56% (0.145 g) yield.

Ethyl 2-(4-cyanophenyl)-oxazole-4-carboxylate (27)

4-Iodobenzonitrile (0.229 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords 27 in 69% (0.167 g) yield.

Ethyl 2-phenyloxazole-4-carboxylate (28)

Iodobenzene (0.204 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords 28 in 74% (0.161 g) yield.

Ethyl 2-(4-Methoxyphenyl)-oxazole-4-carboxylate (29)

Iodoanisole (0.234 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords 29 in 80% (0.214 g) yield.

Ethyl 2-pyridin-2-yl-oxazole-4-carboxylate (31)

2-Chloropyridine (0.113 g, 1 mmol) and ethyloxazole-4-carboxylate (0.282 g, 2 mmol) affords 31 in 82% (0.214 g) yield.

5-(4-Cyanophenyl)-2-(4-methoxyphenyl)-oxazole-4-carboxylic acid ethyl ester (32)

4-Bromoanisole (0.065 g, 0.35 mmol) and ethyl 5-(4-cyanophenyl)oxazole-4-carboxylate (0.085 g, 0.35 mmol) affords 32 in 82% (0.100 g) yield.

2-(4-Methoxyphenyl)-5-pyridin-4-yl-oxazole-4-carboxylic acid ethyl ester (34)

4-Bromoanisole (0.065 g, 0.35 mmol) and ethyl 5-(pyridin-4-yl)oxazole-4-carboxylate (0.076 g, 0.35 mmol) affords 34 in 72% (0.082 g) yield.

4-(2-Propylthiazol-5-yl)acetophenone (35)

4-Bromoacetophenone (0.199 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords 35 in 82% (0.201 g) yield.

5-(4-Cyanophenyl)-2-(4-methoxyphenyl)-oxazole-4-carboxylic acid ethyl ester (36)

4-Trifluoromethylbromobenzene (0.225 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords 36 in 74% (0.201 g) yield.

3-(2-Propylthiazol-5-yl)benzaldehyde (37)

3-Bromobenzaldehyde (0.184 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords 37 in 83% (0.192 g) yield.

2-(2-Propylthiazol-5-yl)benzonitrile (38)

2-Bromobenzonitrile (0.182 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords 38 in 76% (0.173 g) yield.
5-Naphthalen-2-yl-2-propylthiazole (39)

2-Bromonaphthalene (0.207 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords 39 in 78% (0.197 g) yield.

3-(2-Propylthiazol-5-yl)pyridine (40)

3-Bromopyridine (0.158 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords 40 in 84% (0.171 g) yield.

4-(2-Propylthiazol-5-yl)pyridine (41)

4-Bromopyridine hydrochloride (0.194 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords 41 in 85% (0.174 g) yield.

2-(2-Propylthiazol-5-yl)quinoline (42)

2-Bromonaphthalene (0.207 g, 1 mmol) and 2-n-propylthiazole (0.254 g, 2 mmol) affords 42 in 86% (0.219 g) yield.

4-(2-Ethyl-4-methylthiazol-5-yl)benzaldehyde (43)

4-Bromobenzaldehyde (0.184 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol) affords 43 in 80% (0.185 g) yield.

2-(2-Ethyl-4-methylthiazol-5-yl)benzonitrile (44)

2-Bromobenzonitrile (0.182 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol) affords 44 in 87% (0.199 g) yield.

4-(2-Ethyl-4-methylthiazol-5-yl)-pyridine (45)

4-Bromopyridine hydrochloride (0.194 g, 1 mmol) and 2-ethyl-4-methylthiazole (0.254 g, 2 mmol) affords 45 in 78% (0.159 g) yield.

4-(4-Methylthiazol-5-yl)acetophenone (46)

4-Bromacetophenone (0.199 g, 1 mmol) and 4-methylthiazole (0.198 g, 2 mmol) affords 46 in 80% (0.174 g) yield.

4-(4-Methylthiazol-5-yl)benzonitrile (47)

4-Bromobenzonitrile (0.182 g, 1 mmol) and 4-methylthiazole (0.198 g, 2 mmol) affords 47 in 81% (0.162 g) yield.

3-(4-Methylthiazol-5-yl)acetophenone (48)

3-Bromacetophenone (0.199 g, 1 mmol) and 4-methylthiazole (0.198 g, 2 mmol) affords 48 in 73% (0.159 g) yield.

3-(4-Methylthiazol-5-yl)-quinoline (49)

3-Bromquinoline (0.208 g, 1 mmol) and 4-methylthiazole (0.198 g, 2 mmol) affords 49 in 76% (0.172 g) yield.

terr-Butyl 5-phenylthiazole-4-carboxylate (50)

Iodobenzene (0.055 g, 0.35 mmol) and terr-butylthiazole-4-carboxylate 50 in 53% (0.037 g) yield.
Methyl 4-(5-n-butyliphen-2-yl)-benzoate (63)\textsuperscript{c}

Methyl 4-bromobenzoate (0.215 g, 1 mmol) and 2-n-butyliphen (0.280 g, 2 mmol) affords 63 in 46% (0.126 g) yield.

2-3,5-Bis(trifluoromethyl)phenyl-5-n-butyliphen (64)\textsuperscript{d}

3,5-Bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol) and 2-n-butyliphen (0.280 g, 2 mmol) affords 64 in 53% (0.187 g) yield.

2-(5-Butyliphen-2-yl)benzonitrile (65)\textsuperscript{d}

2-Bromobenzonitrile (0.182 g, 1 mmol) and 2-n-butyliphen (0.280 g, 2 mmol) affords 65 in 81% (0.195 g) yield.

3-(5-n-Butyliphen-2-yl)pyridine (66)\textsuperscript{c}

3-Bromopyridine (0.158 g, 1 mmol) and 2-n-butyliphen (0.280 g, 2 mmol) affords 66 in 71% (0.154 g) yield.

4-(3,5-Dimethylisoxazol-4-yl)-acetophenone (67)\textsuperscript{a}

4-Bromoacetophenone (0.199 g, 1 mmol) and 3,5-dimethylisoxazol (0.192 g, 2 mmol) affords 67 in 71% (0.153 g) yield.

4-(3,5-Dimethylisoxazol-4-yl)-benzonitrile (68)\textsuperscript{d}

4-Bromobenzonitrile (0.182 g, 1 mmol) and 3,5-dimethylisoxazol (0.192 g, 2 mmol) affords 68 in 47% (0.093 g) yield.

2-(3,5-Dimethylisoxazol-4-yl)-benzonitrile (69)\textsuperscript{a}

2-Bromobenzonitrile (0.182 g, 1 mmol) and 3,5-dimethylisoxazol (0.192 g, 2 mmol) affords 69 in 23% (0.046 g) yield.

5-(4-Acetylphenyl)-1-methyl-2-formylpyrrole (70)\textsuperscript{d}

4-Bromoacetophenone (0.199 g, 1 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2 mmol) affords 70 in 61% (0.139 g) yield.

5-(4-Formyl-1-methylpyrrol-2-yl)-benzonitrile (71)\textsuperscript{a}

4-Bromobenzonitrile (0.182 g, 1 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2 mmol) affords 71 in 33% (0.069 g) yield.

5-(4-Formylphenyl)-1-methyl-2-formylpyrrole (72)\textsuperscript{d}

4-Bromobenzaldehyde (0.184 g, 1 mmol) and 1-methyl-2-formylpyrrole (0.219 g, 2 mmol) affords 72 in 35% (0.075 g) yield.

5-(4-Acetylphenyl)-1,2-dimethylimidazole (73)\textsuperscript{b}

4-Bromoacetophenone (0.199 g, 1 mmol) and 1,2-dimethylimidazole (0.192 g, 2 mmol) affords 73 in 85% (0.182 g) yield.

4-(2,3-Dimethylimidazol-4-yl)-benzonitrile (74)\textsuperscript{d}

4-Bromobenzonitrile (0.182 g, 1 mmol) and 1,2-dimethylimidazol (0.192 g, 2 mmol) affords 74 in 81% (0.160 g) yield.

5-(4-Trifluoromethylphenyl)-1,2-dimethylimidazole (75)\textsuperscript{d}

4-Trifluoromethylbromobenzene (0.225 g, 1 mmol) and 1,2-dimethylimidazol (0.192 g, 2 mmol) affords 75 in 48% (0.115 g) yield.

5-(3-Pyridyl)-1,2-dimethylimidazole (76)\textsuperscript{d}

3-Bromopyridine (0.158 g, 1 mmol) and 1,2-dimethylimidazol (0.192 g, 2 mmol) affords 76 in 65% (0.112 g) yield.

Acknowledgements

J. R. is grateful to “Ministère de la Recherche” for a grant. We thank the CNRS and “Rennes Metropole” for providing financial support and C. Fischmeister for helpful discussions.

References


8 For recent examples of direct 2- or 5-arylations of thiazoles: (a) O. René and K. Fagnou, Org. Lett., 2010, 12, 2116.


