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Direct arylation of oxazole and benzoxazole with aryl or heteroaryl halides using a palladium–diphosphine catalyst

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Abstract

Through the use of PdCl(dppb)(C_3H_5) as a catalyst, a range of aryl bromides and chlorides undergoes coupling *via* C–H bond activation/functionalization reaction with oxazole or benzoxazole in good yields. This air-stable catalyst can be used at low loadings with several substrates. Surprisingly, better results in terms of substrate/catalyst ratio were obtained in several cases using electron-excessive aryl bromides than with the electron-deficient ones. This seems to be mainly due to the relatively low thermal stability of some of the 2-arylbenzoxazoles formed with electron-deficient aryl halides. With these substrates, in order to obtain higher yields of product, the reactions had to be performed at a lower temperature (100–120 °C) using a larger amount of catalyst. On the other hand, in the presence of the most stable products, the reactions were performed at 150 °C using as little as 0.2 mol% catalyst. Arylation of benzoxazole with heteroaryl bromides also gave the coupling products in moderate to high yields using 0.2–5 mol% catalyst. With this catalyst, electron-deficient aryl chloride such as 4-chlorobenzonitrile, 4-chloroacetophenone or 2-chloronitrobenzene have also been used successfully.

Keywords: Aryl bromides; Catalysis; C–H activation; Oxazole; Palladium

1. Introduction

Aryloxazoles are very useful compounds due to their biological or physical properties [1]. The palladium-catalyzed Negishi [2], Stille [3] or Suzuki [4] cross-coupling reactions are powerful method for the preparation of such compounds (Scheme 1) [5]. However, these methods are not very convenient due to the limited access to halooxazoles or to organometallic derivatives of oxazoles. Moreover these reactions provides an organometallic or salt (MX) as by product.

Since a few years, very interesting results for the direct coupling of aryl halides with oxazole derivatives *via* C–H activation have been reported [6]. This reaction provides only HX as by-product and therefore is very interesting both in terms of atom-economy and inert wastes (Scheme 2). So far, most of the results were described using relatively large amounts (in general 5 mol%) of simple palladium salts or Pd associated with monodentate ligands [7–9]. The first direct arylations of oxazole and benzoxazole were reported by Ohta and coworkers in 1992 [7a]. They observed the selective 2-arylation of benzoxazole using three chloropyrazines in the presence of 5% $Pd(PPh_3)_4$ as catalyst and KOAc as base. A few years after, Miura also explored the arylation of benzoxazole with aryl halides [7b]. The reaction of benzoxazole with bromo- and iodobenzene using Cs_2CO_3 or K_2CO_3 as bases in DMF using 5 mol% $Pd(OAc)_2$ associated with PPh_3 gave the 2-arylated product in 58% and 95% yields, respectively. Tamagnan et al. reported that benzoxazole reacts with bromoanilines or 2,4-dimethoxybromobenzene using 5 mol% $Pd(OAc)_2$ associated to the electron-rich and sterically hindered ligand P(tBu)$_3$ as catalyst to provide after 1 h at 150 °C

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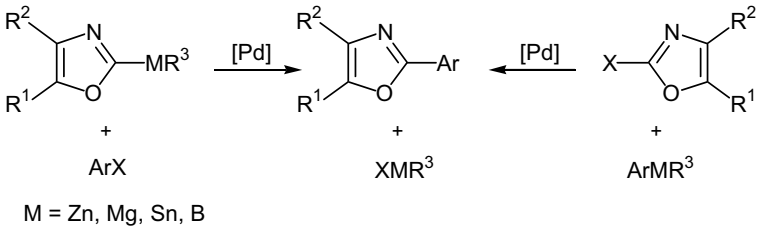
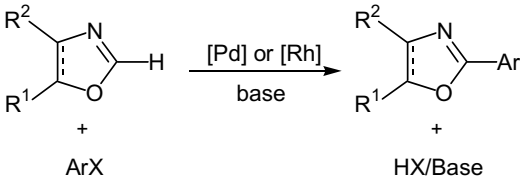


Scheme 1.



Scheme 2.

the desired 2-arylbenzoxazoles in good yields [8a] An other bulky electron-rich phosphine, butyldi-1-adamantylphosphine (10 mol%) associated to 5 mol% $Pd(OAc)_2$ was employed for the coupling of a few aryl chlorides with benzoxazole [8c]. The arylation of an oxazolopyridine at low temperature has been reported recently. They observed that 72% yield for the addition of iodobenzene to the oxazolopyridine derivative could be obtained at 30 °C using $Pd(OAc)_2$ (5%)/PPh_3. (20%), Cs_2CO_3 and acetone as reaction conditions. A good yield of 76% was also obtained for this reaction using $Pd(PPh_3)_4$ as catalyst. Sterically constrained dppf led to a lower yield of 52% while the use of bulky ligands PCy_3 or P(*o*Tol)$_3$ gave no product [8b]. The arylation of benzoxazole in moderate to high yields with aryl iodides using 5 mol% $[RhCl(cyclooctene)]_2$ associated to 40 mol% of PCy_3 has also been reported recently [9]. Even if several other methods for the preparation of 2-aryloxazoles have been reported [1,10,11], the direct coupling of oxazole derivatives with aryl halides is a very promising process for the preparation of such compounds.

If monophosphine ligands such as PPh_3 or the air-sensitive PCy_3, P*t*Bu$_3$ or butyldi-1-adamantylphosphine have been successfully used for the direct coupling of oxazole derivatives with aryl halides, the efficiency of bidentate phosphine ligands for such couplings has not been demonstrated [8b]. Moreover, it should be noted that, so far, relatively few aryl chlorides [8c] or electron-deficient aryl bromides have been employed for this reaction. Therefore, an effective and selective method using an air-stable catalyst for the direct coupling of both electron-excessive and electron-deficient aryl bromides or chlorides with these challenging substrates using high substrate/catalyst ratios is still subject to significant improvement.

Most of the coupling reactions of heteroaryl derivatives with aryl bromides *via* C–H activation were performed at elevated temperature (140–150 °C) [6–8]. A few reaction with aryl iodides were performed at 30 °C due to their easy oxidative addition to palladium [8c], however, these substrates are generally expensive. The use of bromides or chlorides is more attractive in terms of atom-economy, environment, available substrates and cost, but their activation requires more elevated reaction temperature. At elevated temperatures a fast decomposition of the palladium complexes associated to monophosphines generally occurs. In order to find more efficient palladium catalysts for this coupling reaction, we have prepared the $PdCl(C_3H_5)$(dppb) complex [12]. The idea was that intermediate Pd(0) species have to be protected by internal ligation against decomposition pathways through underligation and subsequent colloid and "Pd black" formation. The presence of the bidentate ligand dppb on palladium might also reduce the poisoning of the catalyst due to the presence of heteroaromatics. We have already reported some results for the direct coupling of furans with aryl bromides at low catalyst loadings using a tetraphosphine ligand [13,14]. These results demonstrated that polydentate ligands associated to palladium are useful catalysts for the direct arylation of heteroaromatics. Herein, we report that the catalyst $PdCl(C_3H_5)$(dppb) provides a powerful system for the cross-coupling of oxazole derivatives, such as benzoxazole or oxazole with a wide variety of electronically and sterically diverse aryl bromides and chlorides and also for heteroaryl halides.

2. Experimental

2.1. General remarks

All reactions were run under argon in Schlenk tubes using vacuum lines. DMF analytical grade was not distilled before use. Cesium carbonate (99+) was used. Commercial aryl halides and oxazole derivatives were used without purification. ^1H and ^{13}C spectrum were recorded with a Bruker 200 MHz spectrometer in $CDCl_3$ solutions. Chemical shift are reported in ppm relative to $CDCl_3$ (7.25 for ^1H NMR and 77.0 for ^{13}C NMR). Flash chromatography were performed on silica gel (230–400 mesh). GC and NMR yields in the tables are conversions of the aryl halides into the product calculated with GC and ^1H NMR spectrum of the crude mixtures.

2.2. Preparation of the $PdCl(dppb)(C_3H_5)$ catalyst [12]

An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was

charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (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. ^{31}P NMR (81 MHz, $CDCl_3$) $\delta = 19.3$ (s).

2.3. General procedure for coupling reactions

In a typical experiment, the aryl halide (1 mmol), oxazole derivative (2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and $PdCl(C_3H_5)$(dppb) (see Tables 1–4) were dissolved in DMF (5 mL) under an argon atmosphere. The reaction mixture was stirred at 100–150 °C (see Tables 1–4) for 20 h. The solution was diluted with an H_2O/KOH solution 1 M (20 ml), then the product was extracted three times with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography.

2.4. 1-(4-Benzooxazol-2-ylphenyl)-ethanone (*1*) (Table 1, entry 1)

From 4-bromoacetophenone (0.199 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **1** was obtained in 61% (0.145 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.38 (d, $J = 8.5$ Hz, 2H), 8.12 (d, $J = 8.5$ Hz, 2H), 7.83 (m, 1H), 7.64 (m, 1H), 7.40 (m, 2H), 2.70 (s, 3H).

2.5. 1-(4-Benzooxazol-2-ylphenyl)-propan-1-one (*2*) (Table 1, entry 3)

From 4-bromopropiophenone (0.213 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **2** was obtained in 75% (0.189 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.32 (d, $J = 8.5$ Hz, 2H), 8.08 (d, $J = 8.5$ Hz, 2H), 7.76 (m, 1H), 7.56 (m, 1H), 7.36 (m, 2H), 3.01 (q, $J = 7.5$ Hz, 2H), 1.22 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 200.0, 162.3, 151.3, 142.4, 139.2, 131.2, 128.8, 128.1, 126.1, 125.3, 120.7, 111.2, 32.4, 8.5.

Anal. calc. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. Found: C, 76.80; H, 5.25%.

2.6. 2-(4-Trifluoromethylphenyl)-benzooxazole (*3*) (Table 1, entry 5)

From 4-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **3** was obtained in 84% (0.221 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.36 (d, $J = 8.2$ Hz, 2H), 7.81 (m, 1H), 7.80 (d, $J = 8.2$ Hz, 2H), 7.59 (m, 1H), 7.39 (m, 2H).

2.7. 4-Benzooxazol-2-yl-benzonitrile (*4*) (Table 1, entry 9)

From 4-bromobenzonitrile (0.182 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **4** was obtained in 79% (0.174 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.30 (d, $J = 8.2$ Hz, 2H), 7.75 (m, 1H), 7.58 (m, 3H), 7.40 (m, 2H).

2.8. 2-(4-Nitrophenyl)-benzooxazole (*5*) (Table 1, entry 10)

From 4-bromonitrobenzene (0.202 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **5** was obtained in 69% (0.166 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.45 (d, $J = 8.2$ Hz, 2H), 8.40 (d, $J = 8.2$ Hz, 2H), 7.85 (m, 1H), 7.61 (m, 1H), 7.42 (m, 2H).

2.9. 2-(3,5-Bistrifluoromethylphenyl)-benzooxazole (*6*) (Table 1, entry 11)

From 3,5-bistrifluoromethylbromobenzene (0.293 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **6** was obtained in 82% (0.272 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.69 (s, 2H), 8.03 (s, 1H), 7.80 (m, 1H), 7.61 (m, 1H), 7.39 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 159.8, 150.8, 141.6, 132.6 (q, $J = 35.2$ Hz), 129.2, 127.4, 126.3, 125.2, 124.5 (q, $J = 3.7$ Hz), 121.5 (q, $J = 273.0$ Hz), 120.2, 110.9.

Anal. calc. for $C_{15}H_7F_6NO$: C, 54.39; H, 2.13. Found: C, 54.27; H, 2.41%.

2.10. 2-(4-Fluorophenyl)-benzooxazole (*7*) (Table 1, entry 15)

From 4-fluorobromobenzene (0.175 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **7** was obtained in 78% (0.166 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.28 (dd, $J = 8.2$, 5.5 Hz, 2H), 7.78 (m, 1H), 7.59 (m, 1H), 7.39 (m, 2H), 7.23 (t, $J = 7.6$ Hz, 2H).

2.11. 2-(4-tert-Butylphenyl)-benzooxazole (*8*) (Table 1, entry 16)

From 4-*t*-butylbromobenzene (0.213 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **8** was obtained in 80% (0.201 g) yield.

^1H NMR (200 MHz, $CDCl_3$) δ 8.21 (d, $J = 8.2$ Hz, 2H), 7.78 (m, 1H), 7.59 (m, 1H), 7.56 (d, $J = 8.2$ Hz, 2H), 7.39 (m, 2H), 1.40 (s, 9H).

2.12. 2-p-Tolylbenzooxazole (**9**) (Table 1, entry 18)

From 4-bromotoluene (0.171 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **9** was obtained in 61% (0.128 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.17 (d, $J = 8.2$ Hz, 2H), 7.78 (m, 1H), 7.59 (m, 1H), 7.39 (m, 2H), 7.36 (d, $J = 8.2$ Hz, 2H), 2.46 (s, 3H).

2.13. 2-(4-Methoxyphenyl)-benzooxazole (**10**) (Table 1, entry 19)

From 4-bromoanisole (0.187 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **10** was obtained in 85% (0.191 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18 (d, $J = 8.2$ Hz, 2H), 7.80 (m, 1H), 7.59 (m, 1H), 7.50 (d, $J = 8.2$ Hz, 2H), 7.39 (m, 2H), 4.08 (s, 3H).

2.14. (4-Benzooxazol-2-ylphenyl)-dimethylamine (**11**) (Table 1, entry 21)

From 4-bromo-*N*,*N*-dimethylaniline (0.200 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **11** was obtained in 87% (0.207 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.13 (d, $J = 8.2$ Hz, 2H), 7.71 (m, 1H), 7.53 (m, 1H), 7.28 (m, 2H), 7.79 (d, $J = 8.2$ Hz, 2H), 3.10 (s, 6H).

2.15. 2-Naphthalen-2-ylbenzooxazole (**12**) (Table 1, entry 23)

From 2-bromonaphthalene (0.207 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **12** was obtained in 88% (0.216 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.35 (d, $J = 8.2$ Hz, 1H), 7.98 (m, 2H), 7.83 (m, 2H), 7.58 (m, 3H), 7.35 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 163.1, 150.8, 142.1, 134.7, 132.9, 128.9, 128.7, 128.0, 127.8, 127.7, 126.8, 125.1, 124.6, 124.3, 123.9, 119.9, 110.5.

2.16. 2-Phenylbenzooxazole (**13**) (Table 1, entry 25)

From iodobenzene (0.204 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **13** was obtained in 82% (0.160 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (m, 2H), 7.83 (m, 1H), 7.70–7.32 (m, 6H).

2.17. 3-Benzooxazol-2-yl-benzonitrile (**14**) (Table 2, entry 1)

From 3-bromobenzonitrile (0.182 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **14** was obtained in 81% (0.178 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.48 (d, $J = 8.2$ Hz, 1H), 7.80 (m, 2H), 7.61 (m, 2H), 7.42 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 160.5, 150.7, 141.6, 134.3, 131.3, 130.9, 129.8, 128.4, 125.9, 125.0, 120.3, 117.8, 113.4, 110.8.

Anal. calc. for $C_{14}H_8N_2O$: C, 76.35; H, 3.66. Found: C, 76.20; H, 3.87%.

2.18. 2-(3-Nitrophenyl)-benzooxazole (**15**) (Table 2, entry 3)

From 3-bromonitrobenzene (0.202 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **15** was obtained in 64% (0.154 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.59 (d, $J = 8.2$ Hz, 1H), 8.37 (d, $J = 8.2$ Hz, 1H), 7.85–7.43 (m, 3H), 7.42 (m, 2H).

2.19. 2-Benzooxazol-2-yl-benzoic acid methyl ester (**16**) (Table 2, entry 4)

From methyl 2-bromobenzoate (0.215 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **16** was obtained in 79% (0.200 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, $J = 8.2$ Hz, 1H), 7.80 (m, 2H), 7.60 (m, 3H), 7.40 (m, 2H), 3.87 (s, 3H).

2.20. 2-Benzooxazol-2-ylbenzonitrile (**17**) (Table 2, entry 5)

From 2-bromobenzonitrile (0.182 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **17** was obtained in 79% (0.174 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.44 (d, $J = 8.2$ Hz, 1H), 7.95–7.50 (m, 5 H), 7.42 (m, 2H).

2.21. 2-(2,4-Difluorophenyl)-benzooxazole (**18**) (Table 2, entry 6)

From 2,4-difluorobromobenzene (0.193 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **18** was obtained in 82% (0.190 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.22 (q, $J = 7.5$ Hz, 1H), 7.83 (m, 1H), 7.58 (m, 1H), 7.39 (m, 2H), 6.99 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 165.1 (dd, $J = 168.7$, 11.6 Hz), 160.5 (dd, $J = 175.0$, 12.2 Hz), 158.0, 150.2,

141.5, 131.7 (m), 125.4, 124.6, 120.2, 112.1 (dd, $J = 21.9$, 3.8 Hz), 112.0, 110.5, 105.3 (t, $J = 25.4$ Hz).

Anal. calc. for $C_{13}H_7F_2NO$: C, 67.53; H, 3.05. Found: C, 67.47; H, 3.17%.

2.22. 2-(2-Fluorophenyl)-benzooxazole (**19**) (Table 2, entry 7)

From 2-fluorobromobenzene (0.175 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **19** was obtained in 72% (0.154 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.26 (t, $J = 7.7$ Hz, 1 H), 7.83 (m, 1H), 7.65 (m, 1H), 7.53 (t, $J = 7.7$ Hz, 1H), 7.45–7.20 (m, 4H).

2.23. 2-Naphthalen-1-yl-benzooxazole (**20**) (Table 2, entry 8)

From 1-bromonaphthalene (0.207 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **20** was obtained in 78% (0.191 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.47 (d, $J = 8.2$ Hz, 1 H), 8.43 (d, $J = 8.2$ Hz, 1 H), 8.03 (d, $J = 8.2$ Hz, 1H), 7.94 (d, $J = 8.2$ Hz, 1H), 7.88 (m, 1H), 7.75–7.50 (m, 4 H), 7.40 (m, 2H).

2.24. 2-o-Tolylbenzooxazole (**21**) (Table 2, entry 9)

From 2-bromotoluene (0.171 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **21** was obtained in 79% (0.165 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.19 (d, $J = 8.2$ Hz, 1H), 7.78 (m, 1H), 7.58 (m, 1H), 7.35 (m, 5 H), 2.84 (s, 3H).

2.25. 2-(2-Methoxyphenyl)-benzooxazole (**22**) (Table 2, entry 10)

From 2-bromoanisole (0.187 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **22** was obtained in 61% (0.138 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16 (d, $J = 8.2$ Hz, 1H), 7.81 (m, 1H), 7.58 (m, 1H), 7.48 (d, $J = 8.2$ Hz, 1H), 7.38 (m, 2H), 7.10 (m, 2H).

2.26. 2-Thiophen-2-yl-benzooxazole (**23**) (Table 3, entry 1)

From 2-bromothiophene (0.163 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **23** was obtained in 73% (0.147 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (d, $J = 3.6$ Hz, 1 H), 7.75 (m, 1H), 7.55 (m, 2H), 7.37 (m, 2H), 7.18 (t, $J = 4.1$ Hz, 1H).

2.27. 2-Thiophen-3-yl-benzooxazole (**24**) (Table 3, entry 3)

From 3-bromothiophene (0.163 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **24** was obtained in 79% (0.159 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.17 (d, $J = 2.9$ Hz, 1H), 7.78 (d, $J = 5.2$ Hz, 1H), 7.73 (m, 1H), 7.53 (m, 1H), 7.42 (dd, $J = 5.2$, 2.9 Hz, 1H), 7.32 (m, 2H).

2.28. 2,5-Di(benzooxazole)thiophene (**25**) (Table 3, entry 5)

From 2,5-dibromothiophene (0.242 g, 1 mmol), benzoxazole (0.476 g, 4 mmol), Cs_2CO_3 (1.300 g, 4 mmol) and Pd complex (0.05 mmol), product **25** was obtained in 51% (0.162 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.80 (m, 2H), 7.60 (m, 2H), 7.42 (m, 4 H).

2.29. 2-(6-Methylpyridin-2-yl)-benzooxazole (**26**) (Table 3, entry 6)

From 2-methyl-5-bromopyridine (0.172 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **26** was obtained in 78% (0.164 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.14 (d, $J = 8.0$ Hz, 1 H), 7.80 (m, 1H), 7.73 (t, $J = 8.0$ Hz, 1H), 7.64 (m, 1H), 7.37 (m, 2H), 7.10 (d, $J = 8.0$ Hz, 1H), 2.70 (s, 3H).

2.30. 2-Pyridin-3-yl-benzooxazole (**27**) (Table 3, entry 7)

From 3-bromopyridine (0.158 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **27** was obtained in 84% (0.165 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.48 (d, $J = 1.5$ Hz, 1H), 8.78 (dd, $J = 4.9$, 1.5 Hz, 1H), 8.54 (dt, $J = 8.1$, 1.8 Hz, 1H), 7.82 (m, 1H), 7.64 (m, 1H), 7.49 (dd, $J = 4.9$, 8.1 Hz, 1H), 7.42 (m, 2H).

2.31. 2-Pyridin-4-ylbenzooxazole (**28**) (Table 3, entry 9)

From 4-bromopyridine (0.158 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **28** was obtained in 82% (0.161 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.82 (d, $J = 7.0$ Hz, 2H), 8.07 (d, $J = 7.0$ Hz, 2H), 7.81 (m, 1H), 7.61 (m, 1H), 7.40 (m, 2H).

2.32. 2-Pyrimidin-5-ylbenzooxazole (**29**) (Table 3, entry 11)

From 5-bromopyrimidine (0.159 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd

complex (0.05 mmol), product **29** was obtained in 82% (0.162 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.51 (s, 2H), 9.35 (s, 1H), 7.82 (m, 1H), 7.61 (m, 1H), 7.40 (m, 2H).

2.33. 3-Benzooxazol-2-ylquinoline (*30*) (Table 3, entry 12)

From 3-bromoquinoline (0.208 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.01 mmol), product **30** was obtained in 78% (0.192 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.98 (s, 1H), 8.16 (d, $J = 8.6$ Hz, 1H), 7.96 (d, $J = 8.6$ Hz, 1H), 7.81 (m, 2H), 7.63 (m, 2H), 7.41 (m, 2H).

2.34. 4-Benzooxazol-2-yl-benzoic acid methyl ester (*31*) (Table 4, entry 4)

From methyl 4-chlorobenzoate (0.171 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **31** was obtained in 70% (0.177 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.32 (d, $J = 8.4$ Hz, 2H), 8.18 (d, $J = 8.4$ Hz, 2H), 7.82 (m, 1H), 7.62 (m, 1H), 7.40 (m, 2H), 3.97 (s, 3H).

2.35. 2-(2-Nitrophenyl)-benzooxazole (*32*) (Table 4, entry 5)

From 2-chloronitrobenzene (0.158 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **32** was obtained in 55% (0.132 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.13 (d, $J = 8.4$ Hz, 1 H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.80 (m, 1H), 7.72 (m, 2H), 7.56 (m, 1H), 7.41 (m, 2H).

2.36. 2-Pyrimidin-2-yl-benzooxazole (*33*) (Table 4, entry 9)

From 2-chloropyrimidine (0.115 g, 1 mmol), benzoxazole (0.238 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **33** was obtained in 74% (0.146 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.91 (d, $J = 4.9$ Hz, 2H), 7.82 (m, 1H), 7.63 (m, 1H), 7.39 (t, $J = 4.9$ Hz, 1H), 7.37 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 160.0, 158.5, 155.7, 151.6, 142.1, 127.4, 125.7, 122.4, 122.0, 111.9.

Anal. calc. for $C_{11}H_7N_3O$: C, 67.00; H, 3.58. Found: C, 67.18; H, 3.41%.

2.37. 2-(4-tert-Butylphenyl)-oxazole (*34*) [16] (Scheme 5)

Reaction performed in an autoclave. From 4-*t*-butylbromobenzene (0.213 g, 1 mmol), oxazole (0.138 g, 2 mmol), Cs_2CO_3 (0.650 g, 2 mmol) and Pd complex (0.05 mmol), product **34** was obtained in 69% (0.139 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (d, $J = 8.5$ Hz, 2H), 7.68 (s, 1H), 7.47 (d, $J = 8.5$ Hz, 2H), 7.21 (s, 1H), 1.34 (s, 9H).

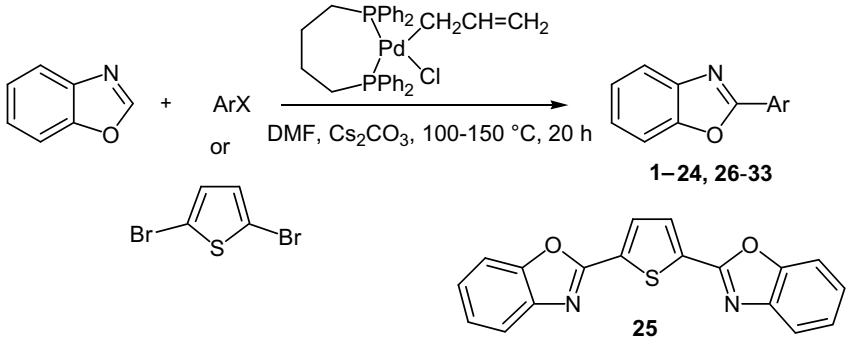
2.38. CAS Registry No.

1 37069-08-2; **3**, 478247-76-6; **4**, 838-33-5; **5**, 840-58-4; **7**, 397-54-6; **8**, 5998-50-5; **9**, 835-71-2; **10**, 838-34-6; **11**, 840-57-3; **12**, 14625-56-0; **13**, 833-50-1; **15**, 840-56-2; **16**, 92533-24-9; **17**, 54175-73-4; **19**, 212758-52-6; **20**, 3164-18-9; **21**, 32959-60-7; **22**, 13459-17-1; **23**, 23999-63-5; **24**, 638213-72-6; **25**, 2866-43-5; **26**, 64819-72-3; **27**, 2295-42-3; **28**, 2295-47-8; **29**, 39116-33-1; **30**, 72435-72-4; **31**, 20000-53-7; **32**, 840-37-9; **34**, 126773-86-2.

3. Results and discussion

First, we tested several reaction conditions for the coupling of 4-*t*butylbromobenzene with benzoxazole in the presence of 1 mol% PdCl(dppb)(C_3H_5) [12] as catalyst. The reaction using KOAc as base in DMF or DMAc at 150 °C gave no coupling product. Using similar reaction conditions, K_2CO_3 led to a very low conversion and yield. On the other hand, using Cs_2CO_3 as base in DMF, the product **8** was obtained in 80% yield with complete conversion of the aryl bromide. Moreover, the reaction was very selective in **8**. Therefore, for this study, DMF was chosen as the solvent and caesium carbonate as the base. In order to obtain high substrate/catalyst ratios, we generally performed the reactions at relatively elevated temperatures: 100–150 °C.

To determine the electronic and steric influence of the substituents on the aryl bromides on this coupling reaction, we studied the reactivity of several *para*- *meta*- an *ortho*-substituted aryl bromides with benzoxazole (Scheme 3, Tables 1 and 2). Using the *para*-substituted electron-deficient aryl bromides such as 4-bromoacetophenone, 4-bromopropiophenone, 4-trifluoromethylbromobenzene or 4-bromobenzonitrile, the reactions could be performed using as little as 0.2–1 mol% catalyst (Table 1, entries 3, 5–8). However, if the coupling reaction proceeds nicely at 150 °C, the stability of some coupling products appears to be quite limited and the formation of side-products due to partial degradation of **2**–**4** was observed in some cases. Using a lower reaction temperature, the reactions were generally cleaner, but the presence of 1–5 mol% catalyst had to be used in order to obtain high yields of products **1**, **2**, **4** and **5** (Table 1, entries 1, 2, 4, 9, 10). Surprisingly, 4-fluorobromobenzene was found to give only traces of coupling product when the reaction was performed at 150 °C. On the other hand, using lower temperatures of 100 and 120 °C, the expected product **7** was obtained in 37% and 78% isolated yields, respectively (Table 1, entries 11–14). The thermal stability of the products formed with electron-rich aryl bromides seems to be higher and with 4-*t*butylbromobenzene, 4-bromoanisole or 4-*N*,*N*-dimethylaminobromobenzene, the reaction could



Scheme 3.

Table 1
Palladium-catalyzed arylation of benzoxazole using *para*-substituted aryl bromides (Scheme 3)

Entry	Aryl bromide	Ratio substrate/catalyst	Temperature (°C)	Product	Yield (%)[a]
1	4-Bromoacetophenone	20	100	**1**	100 (78)[b]
2	4-Bromoacetophenone	100	100	**1**	88
3	4-Bromopropiophenone	100	150	**2**	100 (61)
4	4-Bromopropiophenone	20	100	**2**	76
5	4-Trifluoromethylbromobenzene	100	150	**3**	100 (84)
6	4-Trifluoromethylbromobenzene	500	150	**3**	62
7	4-Bromobenzonitrile	100	150	**4**	60 (45)
8	4-Bromobenzonitrile	500	150	**4**	24
9	4-Bromobenzonitrile	20	100	**4**	88 (79)
10	4-Bromonitrobenzene	20	100	**5**	100 (69)
11	3,5-Bis(trifluoromethyl)bromobenzene	20	100	**6**	100 (82)
12	4-Fluorobromobenzene	20	150	**7**	Traces
13	4-Fluorobromobenzene	100	150	**7**	Traces
14	4-Fluorobromobenzene	20	100	**7**	42 (37)
15	4-Fluorobromobenzene	20	120	**7**	100 (78)
16	4-*t*Butylbromobenzene	100	150	**8**	100 (80)[c]
17	4-*t*Butylbromobenzene	500	150	**8**	44
18	4-Bromotoluene	100	150	**9**	67 (61)
19	4-Bromoanisole	100	150	**10**	100 (85)
20	4-Bromoanisole	500	150	**10**	72
21	4-*N*,*N*-dimethylaminobromobenzene	100	150	**11**	96 (87)
22	4-*N*,*N*-dimethylaminobromobenzene	500	150	**11**	15
23	2-Bromonaphthalene	100	150	**12**	100 (88)
24	2-Bromonaphthalene	500	150	**12**	12
25	Iodobenzene	100	150	**13**	100 (82)

[a] Conditions: catalyst: $PdCl(C_3H_5)(dppb)$, aryl halide (1 mmol), benzoxazole (2 mmol), Cs_2CO_3 (2 mmol), DMF, 20 h, yields are GC and NMR conversions, yields in parenthesis are isolated.
[b] This reaction performed using $PdCl(C_3H_5)(dppe)$ instead of $PdCl(C_3H_5)(dppb)$ as catalyst led to **1** in 100% conversion and 74% yield.
[c] This reaction performed using $PdCl(C_3H_5)(dppe)$ instead of $PdCl(C_3H_5)(dppb)$ as catalyst led to **8** in 100% conversion and 71% yield.

be performed at 150 °C without formation of side products (Table 1, entries 15–21). Moreover, with these substrates, high turnover numbers (TONs) of 220, 360 and 96 have been obtained (Table 1, entries 16, 19 and 20). 2-bromonaphthalene or iodobenzene also gave the expected products in good yield using 1 mol% catalyst (Table 1, entries 22–24). In the presence of $PdCl(dppe)(C_3H_5)$ instead of $PdCl(dppb)(C_3H_5)$ as catalyst, the coupling of 4-bromobenzophenone or 4-*t*butylbromobenzene gave products **1** and **8** in similar yields (Table 1, entries 1 and 16). It should be noted that, in the literature, the rare examples of palladium-catalyzed couplings with benzoxazole were described with electron-rich aryl bromides [8a] or aryl iodides [7].

Then, we examined the reactivity of *meta*- and *ortho*-substituted aryl bromides with benzoxazole (Table 2). Coupling reaction with 3-bromobenzonitrile or 3-bromonitrobenzene gave **14** and **15** in 81% and 64% yield, respectively, using 5 mol% catalyst (Table 2, entries 1–3). Sterically congested aryl bromides are also suitable substrates for this reaction. *ortho*-Substituted electron-poor methyl 2-bromobenzoate, 2-bromobenzonitrile, 2-fluorobromobenzene or 2,4-difluorobromobenzene gave the coupling products using 5 mol% catalyst at 100 °C (Table 2, entries 4–7). In the presence of the electron-rich aryl bromides, 2-bromotoluene, 2-bromoanisole or 1-bromonaphthalene, **20**–**22** were obtained selectively. Moreover, no

Table 2
Palladium-catalyzed arylation of benzoxazole using *meta*- or *ortho*-substituted aryl bromides (Scheme 3)

Entry	Aryl bromide	Ratio substrate/catalyst	Temperature (°C)	Product	Yield (%)[a]
1	3-Bromobenzonitrile	20	100	**14**	100 (81)
2	3-Bromonitrobenzene	20	100	**15**	95
3	3-Bromonitrobenzene	20	150	**15**	100 (64)
4	Methyl 2-bromobenzoate	20	100	**16**	100 (79)
5	2-Bromobenzonitrile	20	100	**17**	100 (79)
6	2,4-Difluorobromobenzene	20	100	**18**	100 (82)
7	2-Fluorobromobenzene	20	100	**19**	77 (72)
8	1-Bromonaphthalene	100	150	**20**	100 (78)
9	2-Bromotoluene	100	150	**21**	100 (79)
10	2-Bromoanisole	100	150	**22**	100 (61)

[a] Conditions: catalyst: $PdCl(C_3H_5)(dppb)$, aryl bromide (1 mmol), benzoxazole (2 mmol), Cs_2CO_3 (2 mmol), DMF, 20 h, yields are GC and NMR conversions, yields in parenthesis are isolated.

formation of side-products was observed at 150 °C, and the reactions could be performed with only 1 mol% catalyst.

Palladium chemistry involving heterocycles has its unique characteristics stemming from the heterocycles' inherently different structural and electronic properties in comparison to the corresponding carbocyclic aryl compounds [5]. Thiophene are π-electron excessive and pyridines are π-electron deficient heterocycles. However, we observed with 2-bromothiophene, 3-bromothiophene, 3-bromopyridine or 4-bromopyridine high reactivities and high yields of coupling products **23**, **24**, **27** and **28** in all cases in the presence of 1 mol% catalyst. With 3- or 4-bromopyridines satisfactory yields were also obtained using as little as 0.2 mol% catalyst (Table 3, entries 1–4 and 7–10). A very similar reactivity was observed with 3-bromoquinoline (Table 3, entry 11). On the other hand, using 5-bromopyrimidine, the reaction performed at 150 °C gave only traces of product **29**. Again, using a lower reaction temperature (100 °C), the selective formation of the expected product **29** was observed (Table 3, entry 11). Using 2,5-dibromothiophene and 4 eq. of benzoxazole, the diarylated thiophene derivative **25** was obtained in 51% yield (Table 3, entry 5). Due to their coordination or fluorescent properties the direct formation of such compounds should be very useful.

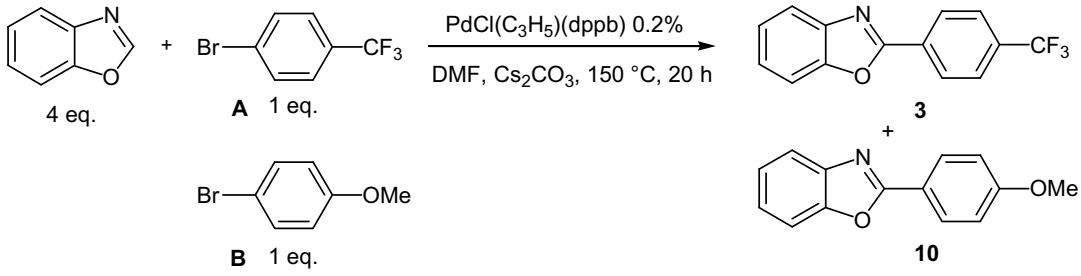
These results seem to indicate that, for this reaction, the oxidative addition of the aryl bromide to palladium is probably not the rate-limiting step of the reaction. In order to have more insight of the reaction mechanism, we performed a reaction using a mixture of 4-bromoanisole and 4-trifluoromethylbromobenzene in the presence of benzoxazole (Scheme 4). We observed after 1 h of reaction, the formation of a mixture of **3** and **10** in a ratio 95:5 indicating a faster oxidative addition of 4-trifluoromethylbromobenzene to palladium. After 6 h, all the 4-trifluoromethylbromobenzene and 37% of the 4-bromoanisole were consumed and the ratio or products **3**:**10** was 80:20. However, we had observed in Tables 1–3 that relatively similar TONs could be obtained with electron-deficient and electron-excessive aryl bromides. Therefore, the rate limiting step of this reaction with aryl bromides might be the insertion of palladium in the C–H bond of oxazole or the reductive elimination to form the product. When a mixture of aryl bromides is employed, the most reactive aryl bromide: 4-trifluoromethylbromobenzene reacts more rapidly with palladium than 4-bromoanisole, but the electronic

Table 3
Palladium-catalyzed arylation of benzoxazole with heteroaryl bromides (Scheme 3)

Entry	Aryl bromide	Ratio substrate/catalyst	Temperature (°C)	Product	Yield (%)[a]
1	2-Bromothiophene	100	150	**23**	100 (73)
2	2-Bromothiophene	500	150	**23**	17
3	3-Bromothiophene	100	150	**24**	100 (79)
4	3-Bromothiophene	500	150	**24**	15
5	2,5-Dibromothiophene	20	150	**25**	100 (51)[b]
6	2-Bromo-6-methylpyridine	20	150	**26**	100 (78)
7	3-Bromopyridine	100	150	**27**	100 (84)
8	3-Bromopyridine	500	150	**27**	61
9	4-Bromopyridine	100	150	**28**	100 (82)
10	4-Bromopyridine	500	150	**28**	62
11	5-Bromopyrimidine	20	100	**29**	100 (82)
12	3-Bromoquinoline	100	150	**30**	92 (78)

[a] Conditions: catalyst: $PdCl(C_3H_5)(dppb)$, aryl bromide (1 mmol), benzoxazole (2 mmol), Cs_2CO_3 (2 mmol.), DMF, 20 h, yields are GC and NMR conversions, yields in parenthesis are isolated.

[b] Benzoxazole (4 mmol.), Cs_2CO_3 (4 mmol.), the formation of the monoarylated product was also observed in low yield.



Reaction time (h)	Ratio **3**:**10**	Conversion of **A** (%)	Conversion of **B** (%)
2	95:5	73	4
6	75:25	100	37
20	72:28	100	40

Scheme 4.

properties of these aryl bromides does not accelerates the other steps of the catalytic cycle.

Then, we examined the reactivity of aryl chlorides for the coupling with benzoxazole (Table 4). The generalisation of the use of chloride substrates for cross-couplings, both at the laboratory scale and in the industry, would be a considerable advantage for sustainable development because of their lower cost, lower mass, and the wider diversity of available compounds, as well as for the treatment of the relatively inert chloride waste. Very few examples of couplings of aryl chlorides with benzoxazoles have been reported in the literature. They were performed using heteroaryl chlorides [7a] or with the bulky electron-rich phosphine butyldi-1-adamantylphosphine, which is not air-stable [8c]. As expected, the electronic properties of the aryl chloride have an important effect on the reaction rates. Using PdCl(dppb)(C_3H_5), the electron-deficient aryl chlorides 4-trifluoromethylchlorobenzene, 3- or 4-chlorobenzonitrile, 4-chloroacetophenone, methyl 4-chlorobenzoate or 2-chloronitrobenzene the products **1**, **3**, **4**, **14**, **31** and **32** were obtained in good yields together with a few side-products (Table 4, entries 1–6). On the other hand, 2-chlorobenzonitrile or 3-chloropyridine led to **17** and **26** in low yields (Table 4, entries 7 and 8). From 2-chloropyrimidine, **33** was obtained in high yield (Table 4, entry 9).

Table 4
Palladium-catalyzed arylation of benzoxazole with aryl chlorides (Scheme 3)

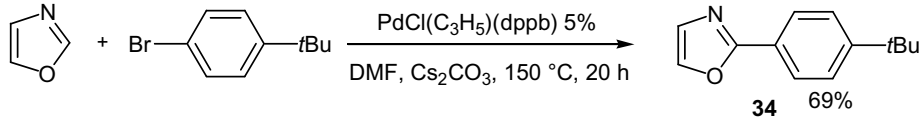
Entry	Aryl chloride	Temperature (°C)	Product	Yield (%)[a]
1	4-Trifluoromethylchlorobenzene	150	**3**	100 (71)
2	4-Chlorobenzonitrile	150	**4**	100 (77)
3	4-Chloroacetophenone	120	**1**	100 (74)
4	Methyl 4-chlorobenzoate	120	**31**	88 (70)
5	2-Chloronitrobenzene	120	**32**	83 (55)
6	3-Chlorobenzonitrile	120	**14**	100 (62)
7	2-Chlorobenzonitrile	150	**17**	12
8	3-Chloropyridine	150	**26**	18
9	2-Chloropyrimidine	120	**33**	100 (74)

[a] Conditions: catalyst: PdCl(C_3H_5)(dppb) (0.05 mmol), aryl chloride (1 mmol), benzoxazole (2 mmol), Cs_2CO_3 (2 mmol), DMF, 20 h, yields are GC and NMR conversions, yields in parenthesis are isolated.

In the presence of oxazole, a selective 2-arylation with 4-*t*butylbromobenzene to give **34** in 69% yield was observed using this catalytic system (Scheme 5). Under these reaction conditions, the 5-arylation or the diarylation products were not observed. Such selective 2-arylation of oxazole derivative has already been observed but was limited to reactive aryl iodides. With 4-iodoanisole under base-free and ligandless conditions or iodobenzene using P(*o*tol)$_3$ as ligand the 2-arylated oxazoles had been obtained in 23% and 89% yields, respectively [15].

4. Conclusion

In summary, we have established that the PdCl(dppb)-(C_3H_5) system provides an efficient catalyst for the coupling of oxazole derivatives with electron-deficient or electron-excessive aryl bromides and also with electron-deficient aryl chlorides. To the best of our knowledge, this work represents one of the most wide-ranging study reported so far for the preparation of 2-aryloxazoles via C–H activation/functionalization. In general, better results were obtained for the coupling with electron-rich aryl bromides than with the electron-poor ones. If the electronic properties of aryl bromides appear to have a minor influence on the reactions rates, they seem to have a larger



Scheme 5.

influence on the stability of some products. With this Pd-diphosphine catalyst, several reactions could be performed with as little as 0.2% catalyst without further optimisation of the reaction conditions. An other advantage of this reaction is the remarkable functional group tolerance; substituents such as fluoro, trifluoromethyl, acetyl, methoxy, amino, carboxylate, nitro or nitrile on the aryl halide have been used. Several heteroaromatics were also employed successfully. Moreover, the air-stability of this catalyst makes this procedure very convenient. This methodology should allow the synthesis in one step of several biologically active compounds or polydentate ligands useful in organometallic chemistry.

Acknowledgements

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