Supporting Information

Palladium-Catalyzed Direct Arylation of Benzoxazoles with Unactivated Simple Arenes

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General Information

5-fluorobenzoxazole, 5-bromobenzoxazole, 5-phenylbenzoxazole, naphtha[1,2-d]oxazole, 5-acetylbenzoxazole, 6-methylbenzoxazole, benzoxazole-5-carboxylic acid methyl ester, 4-methylbenzoxazole, 5-tert-butylbenzoxazole, 5-methoxybenzoxazole, 5-nitrobenzisoxazole, 5-trifluoromethylbenzoxazole benzoxazole-6-carboxylic acid methyl ester and 2-deuterated 5-methylbenzoxazole were prepared according to the reported procedures. 1H and 13C spectra of known compounds were in accordance with those described in the literatures. All other reagents were purchased from TCI, Sigma-Aldrich, Alfa Aesar, Acros, and Meryer and used without further purification. DMA was distilled from CaH2 under nitrogen and stored under nitrogen. 1H NMR (400 MHz), 13C NMR (100 MHz) and 19F NMR (377 MHz) spectra were recorded in CDCl3 solutions using a Burker AVANCE 400 spectrometer. Elemental analysis was done on the CHNOS Elemental Analyzer (Vario MICRO). Analysis of crude reaction mixture was done on the Varian 4000 GC/MS and 1200LC.
### General Experimental Procedures

#### Table 1 Selected Results from the Optimization Studies for Palladium-Catalyzed Direct Arylation of Benzoxazole with Simple Benzene

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*a Reaction conditions: benzoxazole 1 (0.2 mmol), benzene 2 (4.0 mL), base (2.0 equiv), acid (3.0 equiv), oxidant (2 equiv), solvent (2.0 mL), O₂ (1 atm), 120 °C, 24 h. b GC yields. c isolated yield. d Reaction was carried out under air. e Reaction was carried out under nitrogen. f In the absence of palladium. g acetic acid (3.0 equiv). h tert-butylacetic acid (3.0 equiv). i Isobutyric acid (3.0 equiv). j in the absence of K₃PO₄. Note: BQ = benzoquinone.

**General Procedure of Palladium-Catalyzed Direct Arylation of Benzoxazoles with Simple Arenes:**

In a glove box, a 25 mL Schlenk tube equipped with a stir bar was charged with CuBr₂ (2 equiv), K₃PO₄ (2 equiv), PivOH (3 equiv), Pd(OAc)₂ (10 mol %). The tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. Under dioxygen, DMA (2 mL), arene (4 mL), and benzoxazoles (0.2 mmol) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced by a Teflon screwcap under a oxygen flow. The reaction mixture was stirred at 120 °C for 24 h. After cooling down, the reaction mixture was diluted with 10 mL of ethyl ether, filtered through a pad of silica gel, followed by washing the pad of the silica gel with the same solvent (20 mL). The filtrate was washed with water (3×15 mL). The organic phase was dried over Na₂SO₄, filtered, concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel to provide the corresponding product.
Characterization of Products in Details:

2-phenylbenzoxazole\(^3\)

![2-phenylbenzoxazole](image)

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (79\% yield). The \(^1\)H, \(^13\)C NMR spectra were in accordance with those described in the literature.

5-methyl-2-phenylbenzoxazole\(^3\)

![5-methyl-2-phenylbenzoxazole](image)

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (93\% yield). The \(^1\)H, \(^13\)C NMR spectra were in accordance with those described in the literature.

6-methyl-2-phenylbenzoxazole\(^3\)

![6-methyl-2-phenylbenzoxazole](image)

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (65\% yield). The \(^1\)H, \(^13\)C NMR spectra were in accordance with those described in the literature.

4-methyl-2-phenylbenzoxazole\(^3\)

![4-methyl-2-phenylbenzoxazole](image)

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a
white solid (69% yield). The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.

5-fluoro-2-phenylbenzoxazole$^4$

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (91% yield). The $^1$H, $^{13}$C, $^{19}$F NMR spectra were in accordance with those described in the literature.

5-chloro-2-phenylbenzoxazole$^4$

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (83% yield). The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.

5-bromo-2-phenylbenzoxazole$^4$

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (52% yield). The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.

5-methoxy-2-phenylbenzoxazole$^3$

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (91% yield). The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.
Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (74% yield). The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.

5-acetyl-2-phenylbenzoxazole

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (65% yield) in 48h. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.37 (d, $J=1.5$ Hz, 1 H), 8.27 - 8.25 (m, 2H), 8.05 (dd, $J=8.5$, 1.7 Hz, 1H), 7.63 (d, $J=8.5$ Hz, 1H), 7.58-7.53 (m, 3H), 2.69 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 197.1, 164.5, 153.7, 142.3, 134.4, 132.1, 129.0, 127.8, 126.6, 125.8, 120.9, 110.6, 26.8; Anal. Calcd. For C$_{13}$H$_{11}$NO$_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.88; H, 5.18; N, 5.61.

2-phenyl-benzoxazole-5-carboxylic acid methyl ester

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (77% yield) in 48h. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.4 (d, $J=1.4$ Hz, 1H), 8.25-8.23 (m, 2 H), 8.09 (dd, $J=8.5$, 1.6 Hz, 1H), 7.6(d, $J=8.5$ Hz, 1H), 7.55-7.49 (m, 3H), 3.95 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 166.7, 164.3, 153.6, 142.2, 131.9, 128.9, 127.8, 127.0, 126.6, 121.9, 110.3, 52.3; Anal. Calcd. For C$_{13}$H$_{11}$NO$_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.14; H, 4.57; N, 5.47.

5-nitro-2-phenylbenzoxazole

5
Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (63% yield) in 48h. The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.

5-trifluoromethyl-2-phenylbenzoxazole$^6$

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (66% yield) in 48h. The $^1$H, $^{13}$C, $^{19}$F NMR spectra were in accordance with those described in the literature.

2,5-diphenyl-benzoxazole$^7$

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (75% yield). The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.

2-phenyl-naphth[1,2-d]oxazole$^3$

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (86% yield). The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.
5-tert-butyl-2-phenylbenzoxazole

Following the general procedure, using 9:1 hexane-EtOAc as the eluant afforded a white solid (94% yield). The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.

2-phenylbenzothiazole

Follow the general procedures, 2.0 equiv Cu(OAc)$_2$ and 1.5 equiv PivOH was used at 130°C for 48h, using 9:1 hexane-EtOAc as the eluant afforded a white solid (52% yield). The $^1$H, $^{13}$C NMR spectra were in accordance with those described in the literature.

5-methyl-2-(o-fluorophenyl)benzoxazole, 5-methyl-2-(m-fluorophenyl)benzoxazole and 5-methyl-2-(p-fluorophenyl)benzoxazole

Following the general procedure for 48h, using hexane as the eluant afforded a white solid (80% yield) containing (1:1.2:4) isomers (determined by $^{19}$F NMR, for two isomers had the same retention time on GC).

Anal. Calcd. For C$_{14}$H$_{10}$FNO: C, 74.00; H, 4.44; N, 6.16. Found: C, 74.14; H, 4.47; N, 6.32.

Assignments of $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR respectively.

3q$^1$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.26-8.22 (m, 2H), 7.54 (s, 1H), 7.44 (d, $J$ =8.3Hz, 1H), 7.22-7.15 (m, 3H), 2.48 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 164.8 (d,
$J_F$=252.6Hz), 162.2, 149.0, 142.1, 134.6, 129.8 ($J_F$=8.9Hz), 128.9, 127.6, 126.3, 123.6 ($J_F$=3.1Hz), 119.9, 116.1 ($J_F$=22.3Hz), 110.0, 21.5; $^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$ -107.66 (s, 1F).

3q$^2$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.05 (dm, $J$=7.8 Hz, 1H), 7.94 (dm, $J$=9.5 Hz, 1H), 7.58 (s, 1H), 7.53-7.47 (m, 2H), 7.25-7.18 (m, 2H), 2.50 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 162.9 ($J_F$=246.7Hz), 161.8 ($J_F$=3.5Hz), 149.0, 142.0, 134.7, 130.5 ($J_F$=8.2Hz), 129.3 ($J_F$=8.6Hz), 126.7, 123.3 ($J_F$=3.2Hz), 120.0, 118.4 ($J_F$=21.3Hz), 114.4 ($J_F$=24.0Hz), 110.0, 21.5; $^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$ -111.9 (s, 1F).

3q$^3$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.22 (td, $J$=7.6, 1.8 Hz, 1H), 7.61-7.60 (m, 1H), 7.54-7.47 (m, 2H), 7.32-7.23 (m, 2H), 7.20-7.18 (m, 1H), 2.49 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 160.8 ($J_F$=258.4Hz), 159.9, 148.7, 141.9, 134.5, 133.0 ($J_F$=8.7Hz), 130.5 ($J_F$=1.3Hz), 126.7, 124.4 ($J_F$=3.9Hz), 120.2, 117.0 ($J_F$=21.7Hz), 115.7 ($J_F$=10.4Hz), 110.0, 21.5; $^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$ -110.2 (s, 1F).
Electronic Supplementary Material (ESI) for Chemical Communications
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Sample Information

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S13
2-(4-chloro-phenyl)-5-methylbenzoxazole and 2-(3-chloro-phenyl)-5-methylbenzoxazole

Following the general procedure and 1.8 equiv CuBr₂, 2.5 equiv K₃PO₄, 3.75 equiv PivOH was used for 48h, using hexane as the eluant afforded a white solid (68% yield) containing (1.4:1) isomers (determined by ¹H NMR, for they had the same retention time on GC).

Anal. Calcd. For C₁₄H₁₀ClNO: C, 69.00; H, 4.14; N, 5.75. Found: C, 69.47; H, 4.20; N, 5.80.

Assignments of ¹H NMR, ¹³C NMR respectively.

３r²

¹H NMR (400 MHz, CDCl₃): δ 8.21 (s, 1H), 8.10-8.08 (m, 1H), 7.54(s, 1H), 7.48-7.40(m, 3H), 7.16(d, J= 8.3 Hz, 1H), 2.47(s, 3H); ¹³C NMR (100MHz, CDCl₃): δ 161.6, 149.0, 142.1, 135.0, 134.7, 131.3, 130.2, 129.0, 127.5, 126.7, 125.5, 120.0, 110.0, 21.5

３r³

¹H NMR (400 MHz, CDCl₃): δ 8.19-8.16 (m, 2H), 7.55 (s, 1H), 7.50-7.48(m, 2H), 7.44(d, J= 8.3 Hz, 1H), 7.17(d, J= 8.3 Hz, 1H), 2.49(s, 3H); ¹³C NMR (100MHz, CDCl₃): δ 162.1, 149.0, 142.1, 137.7, 134.7, 129.3, 128.8, 126.5, 125.8, 120.0, 110.0, 21.5;
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PDA Multi 1 / 310nm-440nm

PDA Multi 1
2-(o-tolyl)-5-methyl-benzoxazole, 2-(m-tolyl)-5-methyl-benzoxazole and 2-(p-tolyl)-5-methyl-benzoxazole

Following the general procedure and 1.8 equiv CuBr$_2$ was used at 140 °C for 48h, using hexane as the eluant afforded a white solid (74% yield) containing (1:1.8:1.6) isomers (determined by GC).

Anal. Calcd. For C$_{15}$H$_{13}$NO: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.26; H, 5.91; N, 6.26.

Assignments of $^1$H NMR, $^{13}$C NMR respectively.

3s$^1$

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.16 (d, $J$= 7.4 Hz, 1H), 7.60 (s, 1H), 7.55 (s, 1H), 7.46 (d, $J$= 8.2 Hz, 1H), 7.42-7.32 (m, 3H), 7.17 (d, $J$= 8.2 Hz, 1H), 2.81 (s, 3H), 2.50 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 163.6, 148.6, 142.3, 138.8, 134.2, 131.8, 130.8, 129.9, 126.4, 126.1, 126.0, 120.1, 109.8, 22.2, 21.5.

3s$^2$

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.08 (s, 1H), 8.04 (d, $J$= 7.6 Hz, 1H), 7.55 (s, 1H), 7.45-7.38 (m, 2H), 7.33 (d, $J$= 7.5 Hz, 1H), 7.15 (d, $J$= 8.2 Hz, 1H), 2.49 (s, 3H), 2.45 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 163.3, 149.0, 142.3, 138.6, 134.2, 132.1, 128.7, 128.0, 127.2, 126.1, 124.7, 119.9, 109.9, 21.5, 21.3.

3s$^3$

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.14 (d, $J$= 8.2 Hz, 2H), 7.54 (s, 1H), 7.43 (d, $J$= 8.0 Hz, 1H), 7.32 (d, $J$= 8.0 Hz, 2H), 7.14 (d, $J$= 8.2 Hz, 1H), 2.48 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 163.4, 148.9, 142.1, 142.0, 134.4, 129.6, 127.6, 126.0, 124.4, 119.7, 109.9, 21.6, 21.5.
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Page 1/1
2-(2,5-difluorophenyl)-5-methylbenzoxazole

Following the general procedure for 48h, using hexane as the eluant afforded a white solid (76% yield)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.93 -7.89 (m, 1H), 7.61 (s, 1 H), 7.48(d, $J=8.3$ Hz, 1H), 7.24-7.16(m, 3H), 2.49(s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 158.5 (dd, $J_F=243.6$, 2.5 Hz), 158.3(dd, $J_F=6.0$, 2.7 Hz), 156.8(dd, $J_F=255.2$, 2.5 Hz), 148.7(d, $J_F=1.1$ Hz), 141.8, 134.8, 127.1, 120.4, 119.5(dd, $J_F=24.2$, 8.8Hz), 118.4(dd, $J_F=24.4$, 8.3Hz), 116.7(dd, $J_F=13.0$, 8.7Hz), 116.4(d, $J_F=2.1Hz$), 110.1, 21.5; $^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$ -117.7 (d, $J_F=17.7$ Hz, 1F), -116.1 (d, $J_F=17.7$ Hz, 1F); Anal.Calcd. For C$_{14}$H$_9$F$_2$NO: C, 68.57; H, 3.70; N, 5.71. Found: C, 68.74; H, 3.75; N, 6.03.

2-(3,4-difluorophenyl)-5-methylbenzoxazole and 2-(2,3-difluorophenyl)-5-methylbenzoxazole

Following the general procedure for 48h, using hexane as the eluant afforded 3u$_1$ and 3u$_2$ in 46% and 38% yield, respectively, they were both white solids.
Anal. Calcd. For C$_{14}$H$_9$F$_2$NO: C, 68.57; H, 3.70; N, 5.71. Found: C, 68.44; H, 3.97; N, 5.82.
Assignments of $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR respectively.

3u$_1$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.05 -7.95 (m, 2H), 7.52 (s, 1 H), 7.42(d, $J=8.3$ Hz, 1H), 7.31-7.25(m, 1H), 7.17-7.15(m, 1H), 2.47(s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 161.0, 152.4(dd, $J_F=254.6$, 12.8 Hz), 150.6(dd, $J_F=249.6$, 13.2 Hz), 149.0, 142.1, 134.7, 126.6, 124.4(dd, $J_F=6.7$, 3.8Hz), 119.5(dd, $J_F=7.0$, 3.8Hz), 120.0, 118.0(d, $J_F=18.1Hz$), 116.7(d, $J_F=19.8Hz$), 110.0, 21.5; $^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$
-132.4 (d, J_F= 21.5 Hz, 1 F), -136.1 (d, J_F= 20.6 Hz, 1 F).

3u^2

^1H NMR (400 MHz, CDCl₃): δ 7.97-7.94 (m, 1H), 7.59(s, 1 H), 7.46(d, J_F=8.3 Hz, 1H), 7.34-7.26(m, 1H), 7.23-7.18(m, 2H), 2.48(s, 3H); ^13C NMR (100MHz, CDCl₃): δ 158.5, 151.3(dd, J_F=248.0, 11.4 Hz), 149.2(dd, J_F=258.6, 11.5 Hz), 148.8, 141.8, 134.8, 127.0, 125.0(d, J_F=3.7Hz), 124.3(dd, J_F=6.5, 5.3Hz), 120.3, 119.8(d, J_F=17.3Hz), 117.7(d, J_F=7.3Hz), 110.1, 21.5; ^19F NMR (377 MHz, CDCl₃): δ -136.0 (d, J_F= 19.7 Hz, 1 F), -136.5 (d, J_F= 20.0Hz, 1 F).

2-(3,4-dichlorophenyl)-5-methylbenzoxazole and 2-(2,3-dichlorophenyl)-5-methylbenzoxazole

Following the general procedure and 1.8 equiv CuBr₂ was used at 140 °C for 48h, using hexane as the eluant afforded 3v¹ and 3v² in 52% and 17% yield, respectively, they were both white solids.

Anal. Calcd. For C₁₄H₉Cl₂NO: C, 60.46; H, 3.26; N, 5.04. Found: C, 60.89; H, 3.34; N, 5.07.

Assignments of ^1H NMR, ^13C NMR respectively.

3v¹

^1H NMR (400 MHz, CDCl₃): δ 8.28 (d, J= 2.0 Hz, 1H), 8.01 (dd, J=8.4, 2.0 Hz, 1H), 7.55(d, J= 8.4 Hz, 1H), 7.52(s, 1H), 7.41(d, J= 8.4 Hz, 1H), 7.18-7.15(m, 1H), 2.47(s, 3H); ^13C NMR (100MHz, CDCl₃): δ 160.8, 149.0, 142.0, 135.6, 134.8, 133.4, 131.0, 129.2, 127.1, 126.8, 126.4, 120.1, 110.0, 21.5.

3v²

^1H NMR (400 MHz, CDCl₃): δ 8.00 (dd, J= 7.9, 1.5 Hz, 1H), 7.62-7.60 (m, 2H), 7.48(d, J= 8.3 Hz, 1H), 7.33(t, J= 7.9 Hz, 1H), 7.22-7.20(m, 1H), 2.49(s, 3H); ^13C
NMR (100MHz, CDCl₃): δ 160.4, 148.9, 141.7, 135.0, 134.7, 132.6, 132.0, 130.1, 128.7, 127.3, 127.0, 120.4, 110.2, 21.5.

2-(3,4-dimethylphenyl)-5-methylbenzoxazole and 2-(2,3-dimethylphenyl)-5-methylbenzoxazole

Following the general procedure and 1.8 equiv CuBr₂ was used at 140°C for 48h, using hexane as the eluant afforded 3w¹ and 3w² in 55% and 10% yield, respectively, they were both white solids.

Anal. Calcd. For C₁₅H₁₃NO: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.11; H, 6.49; N, 5.77.

Assignments of ¹H NMR, ¹³C NMR respectively.

3w¹

¹H NMR (400 MHz, CDCl₃): δ 8.00 (s, 1H), 7.93 (d, J=7.8Hz, 1H), 7.52(s, 1H), 7.41-7.38(m, 1H), 7.25-7.23(m, 1H), 7.10(d, J=8.0Hz, 1H), 2.46(s, 3H), 2.33-2.29(m, 6H); ¹³C NMR (100MHz, CDCl₃): δ 163.5, 148.9, 142.3, 140.7, 137.3, 134.2, 130.0, 128.6, 125.9, 125.1, 124.8, 119.7, 109.8, 21.5, 19.9, 19.7.

3w²

¹H NMR (400 MHz, CDCl₃): δ 7.79 (d, J=7.7Hz, 1H), 7.48 (s, 1H), 7.33(d, J=8.3Hz, 1H), 7.18(d, J=7.3Hz, 1H), 7.11(t, J=7.8Hz, 1H), 7.05-7.03(m, 1H), 2.56(s, 3H), 2.38(s, 3H), 2.27(s, 3H); ¹³C NMR (100MHz, CDCl₃): δ 164.0, 148.6, 142.2, 138.1, 137.1, 134.0, 132.3, 128.0, 127.0, 126.0, 125.5, 120.0, 21.4, 20.7, 17.1.

2-(2-fluoro-5-methylphenyl)-5-methylbenzoxazole and 2-(5-fluoro-2-methylphenyl)-5-methylbenzoxazole

Electronic Supplementary Material (ESI) for Chemical Communications
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Following the general procedure for 48h, using hexane as the eluant afforded $3x^1$ and $3x^2$ in 64% and 10% yield, respectively, they were both light yellow solids.

Anal. Calcd. For C$_{15}$H$_{12}$FNO: C, 74.67; H, 5.01; N, 5.81. Found: C, 74.74; H, 5.32; N, 5.83.

Assignments of $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR respectively.

$3x^1$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.03 -8.00 (m, 1H), 7.60 (s, 1 H), 7.47(d, $J$=8.3 Hz, 1H), 7.30-7.26(m, 1H), 7.19-7.10(m, 2H), 2.48(s, 3H), 2.40(s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 159.8(d, $J_F$=5.2 Hz), 159.0(d, $J_F$=256.0Hz), 148.7(d, $J_F$=1.1Hz), 141.9, 134.5, 134.0(d, $J_F$=3.7Hz), 133.5(d, $J_F$=8.3Hz), 130.5(d, $J_F$=1.1Hz), 126.6, 120.1, 116.7(d, $J_F$=21.7Hz), 115.0(d, $J_F$=10.6Hz), 110.0, 21.5, 20.6; $^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$ -115.6 (s, 1F).

$3x^2$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.87 (dd, $J$ =9.7, 2.8Hz 1H), 7.59 (s, 1 H), 7.45(d, $J$ =8.3 Hz, 1H), 7.31-7.27(m, 1H), 7.19-7.17(m, 1H), 7.09(td, $J$=8.2, 2.8Hz , 1H)2.76(s, 3H), 2.49(s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 162.2(d, $J_F$=2.9 Hz), 160.9(d, $J_F$=244.1Hz), 148.5, 142.2, 134.4, 134.4, 133.2(d, $J_F$=7.7 Hz), 127.6(d, $J_F$=8.0 Hz), 126.5, 120.2, 117.6(d, $J_F$=20.8 Hz), 116.3(d, $J_F$=23.7 Hz), 110.0, 21.5, 21.5; $^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$ -117.0 (s, 1F).

5-methyl-2-(3,5-dimethylphenyl)benzoxazole$^{10}$ and 5-methyl-2(2,4-dimethylphenyl) benzoxazole$^{11}$
Following the general procedure and 1.8 equiv CuBr₂ was used at 140°C for 48h, using hexane as the eluant afforded 3y₁ and 3y₂ in 54% and 23% yield, respectively, they were both white solids.

Anal. Calcd. For C₁₆H₁₅NO: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.11; H, 6.49; N, 5.77.

Assignments of ¹H NMR, ¹³C NMR respectively.

The ¹H, ¹³C NMR spectra of 3y₁ in accordance with those described in the literature.¹¹ The ¹H, ¹³C NMR spectra of 3y₂ in accordance with those described in the literature.¹²

5-methyl-2-(3,5-dichlorophenyl)benzoxazole and 5-methyl-2-(2,4-dichlorophenyl)benzoxazole

Following the general procedure and 1.8 equiv CuBr₂ was used at 140°C for 48h, using hexane as the eluant mixture of regioisomers 3z₁:3z₂ (17:1) determined by GC and 78% yield separated by column chromatography. Due to the low yield of the 3z₂ isomer, it is not possible to report its spectroscopic data. The following data belongs to the major regioisomer.

Anal. Calcd. For C₁₄H₉Cl₂NO: C, 60.46; H, 3.26; N, 5.04. Found: C, 60.50; H, 3.42; N, 5.32.

Assignments of ¹H NMR, ¹³C NMR of 3z₁ major product.

¹H NMR (400 MHz, CDCl₃): δ 8.00 (s, 1H), 7.93 (d, J=7.8Hz, 1H), 7.52(s, 1H), 7.41-7.38(m, 1H), 7.25-7.23(m, 1H), 7.10(d, J=8.0Hz, 1H), 2.46(s, 3H), 2.33-2.29(m, 6H); ¹³C NMR (100MHz, CDCl₃): δ 163.5, 148.9, 142.3, 140.7, 137.3, 134.2, 130.0, 128.6, 125.9, 125.1, 124.8, 119.7, 109.8, 21.5, 19.9, 19.7.

2-(3-Methoxycarbonyl-phenyl) -5-methylbenzoxazole and 2-(4-Meth oxycar bony l-phenyl) -5-methylbenzoxazole
Following the general procedure and 1.8 equiv CuBr₂ was used at 140 °C for 48h, using hexane as the eluant afforded a white solid (73% yield) containing (2:1) isomers (determined by GC).


Assignments of ¹H NMR, ¹³C NMR respectively.

3aa¹

¹H NMR (400 MHz, CDCl₃): δ 8.26 (d, J=7.7Hz, 2H), 8.14 (d, J=7.7Hz, 2H), 7.54 (s, 1H), 7.43 (d, J=8.0Hz, 1H), 7.16 (d, J=8.0Hz, 1H), 3.94(s, 3H), 2.47(s, 3H); ¹³C NMR (100MHz, CDCl₃): δ 166.3, 161.9, 142.3, 149.1, 142.2, 134.7, 132.3, 131.1, 130.0, 126.9, 120.2, 110.1, 52.3, 21.5.

3aa²

¹H NMR (400 MHz, CDCl₃): δ 8.89 (s, 1H), 8.43 (d, J=7.8Hz, 1H), 8.20 (d, J=7.8Hz, 1H), 7.61 (t, J=7.8Hz, 1H), 7.58 (s, 1H), 7.47 (d, J=8.3Hz, 1H), 7.18 (d, J=8.3Hz, 1H), 3.98(s, 3H), 2.49(s, 3H); ¹³C NMR (100MHz, CDCl₃): δ 166.3, 162.1, 149.0, 142.1, 134.7, 132.3, 131.6, 131.1, 128.6, 127.7, 126.7, 120.0, 110.1, 52.4, 21.5.
2-(4-chloro-3,5-dimethylphenyl)-5-methylbenzoxazole

Following the general procedure and 1.8 equiv CuBr$_2$ was used at 140 °C for 48h, using hexane as the eluant afforded a white solid (52% yield). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.77 (d, $J$=8.0 Hz, 1H), 7.48 (s, 1H), 7.33 (d, $J$=8.3Hz, 1H), 7.11(d, $J$=8.0 Hz, 1H), 7.06(d, $J$=8.3 Hz, 1H), 2.75(s, 3H), 2.39(s, 3H), 2.36(s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 163.0, 148.6, 142.2, 139.5, 136.7, 136.5, 134.3, 128.1, 128.0, 126.3, 126.1, 120.1, 109.8, 21.5, 21.5, 18.5; Anal. Calcd. For C$_{15}$H$_{12}$ClNO: C, 69.91; H, 4.69; N, 5.43. Found: C, 70.05; H, 4.75; N, 5.50.

methyl 2-(3,5-dichlorophenyl) benzoxazole-6-carboxylate and methyl 2-(2,4-dichlorophenyl) benzoxazole-6-carboxylate

Following the general procedure and 1.8 equiv CuBr$_2$ was used at 140 °C for 48h, using hexane as the eluant mixture of regioisomers 3ac$^1$:3ac$^2$ (12:1) determined by GC and 43% yield seperated by column chromatography. Due to the low yield of the 3ac$^2$ isomer, it is not possible to report its spectroscopic data. The following data belongs to the major regioisomer.

Anal. Calcd. For C$_{15}$H$_{9}$Cl$_2$NO$_3$: C, 55.93; H, 2.82; N, 4.35. Found: C, 56.01; H, 2.91; N, 4.38.

Assignments of $^1$H NMR, $^{13}$C NMR of 3ac$^1$ major product.

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.28 (s, 1H), 8.12 (t, $J$=7.8Hz, 2H), 7.83(d, $J$=8.4Hz, 1H), 7.58(s, 1H), 7.41(d, $J$=8.4Hz, 1H), 3.96(s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$): δ 166.5, 162.6, 150.2, 145.4, 138.2, 134.6, 132.7, 131.5, 127.8, 127.6, 126.5, 124.2, 120.1, 112.5, 52.4.
Kinetic Isotope Effect Experiment:

Initially, the target product, 5-methyl-2-phenylbenzoxazole was used as a standard compound to make a curve involving the product concentration and peak area (external standard method, GC-MS). Then an intermolecular competition reaction between 5-methylbenzoxazole and deuterated 5-methylbenzoxazole was carried out.

In a glove box, two 25 mL of Schlenk tubes equipped with a stir bar were charged with 5-methylbenzoxazole (0.2 mmol), CuBr₂ (2 equiv), K₃PO₄ (2 equiv), PivOH (3 equiv), Pd(OAc)₂ (10 mol %). The tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. In one tube, under dioxygen, DMA (2 mL), and benzene (4 mL) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced by a Teflon screwcap under a oxygen flow. In another tube, under dioxygen, DMA (2 mL), benzene (4 mL), and deuterated 5-methylbenzoxazole (0.2 mmol) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced by a Teflon screwcap under a oxygen flow. The reaction mixture was stirred at 120 °C for 3 h (conversion approximately 20% yield) and when measuring the values of KIE, the reaction was quenched at (3 h, 6 h, 9 h and 12 h, no significant difference in the KIE value was observed for different reaction time). After cooling down, the reaction mixture was diluted with 10 mL of ethyl ether, filtered through a pad of silica gel, and the mixture was analyzed by GC, and the GC yield of the target product was calculated according to the pre-established curve. The ratio of the two target products represents the KIE value.
In a glove box, two 25 mL of Schlenk tubes equipped with a stir bar were charged with 5-methyleneoxazole (0.2 mmol), CuBr₂ (2 equiv), K₃PO₄ (2 equiv), PivOH (3 equiv), Pd(OAc)₂ (10 mol %). The tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. In one tube, under dioxygen, DMA (2 mL) and benzene (4 mL) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced by a Teflon screwcap under an oxygen flow. In another tube, under dioxygen, DMA (2 mL), benzene-d₆ (4 mL), and 5-methyleneoxazole (0.2 mmol) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced by a Teflon screwcap under an oxygen flow. The reaction mixture was stirred at 120 °C for 6 h, The reaction was then cooled and an aliquot was removed and analyzed by GC/MS.

In a glove box, a 25 mL of Schlenk tube equipped with a stir bar was charged with CuBr₂ (2 equiv), K₃PO₄ (2 equiv), 5-methyleneoxazole (0.2 mmol), the tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. In one tube, under dioxygen, DMA (2 mL) and CH₃CO₂D (3 equiv) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced by a Teflon screwcap under an oxygen flow. The reaction mixture was stirred at 120 °C for 6 h, The reaction was then cooled and an aliquot was removed and analyzed by LC/MS.

Note: no deuterium incorporation into the 5-methyleneoxazole substrate was observed in the presence or in the absence of Pd(OAc)₂ catalyst, or CuBr₂.
(2equiv) CH$_3$CO$_2$D (3equiv), O$_2$, DMA and in the absence of K$_3$PO$_4$ base as catalyst system, corresponding experiments results also analyzed by LC/MS.

**Competition investigation:**

In a glove box, a 25 mL of Schlenk tube equipped with a stir bar was charged with 5-methylbenzoxazole (0.2 mmol), CuBr$_2$ (2 equiv), K$_3$PO$_4$ (0.75 equiv), PivOH (3 equiv), Pd(OAc)$_2$(10 mol %). The tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. Under dioxygen, DMA (2 mL), benzene (2 mL), and fluorobenzene (2 mL) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced by a Teflon screwcap under a oxygen flow. The reaction mixture was stirred at 120 for 48 h. The solution was then extracted and analyzed by GC to determine the product distribution.

**Plausible Mechanism to Approach Oxidative Cross-Coupling of Benzoxazole**
with Arenes

On the basis of the data above and precedent literature, a plausible catalytic cycle is proposed. Taking the coupling of benzoxazole with benzene for example, the initial palladation of benzene afforded A via an intramolecular abstraction process (This hypothesis is supported by the fact that electron-rich arenes such as anisole failed to react, while benzene and methyl benzoate readily coupled with benzoxazole), followed by coordination of benzoxazole to Pd through N atom and subsequent via concerted metalation-deprotonation to form an ArPd(benzoxazole) intermediate, which underwent reductive elimination to generate the product, along with Pd(0) which is reoxidized by the excess Cu(II)/O2 regenerated the catalytically active Pd(II) species to complete the catalytic cycle.

References:


