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Direct *ortho*-arylation of 2-arylbenzoxazoles via C–H activation

Fan Yang, Yangjie Wu *, Zhiwu Zhu, Junli Zhang, Yanan Li

Department of Chemistry, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou 450052, PR China

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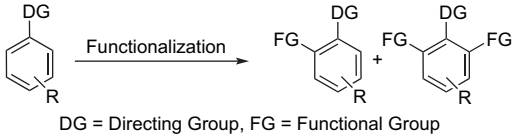
ABSTRACT

A new and highly regioselective arylation of 2-arylbenzoxazoles based on C–H activation has been developed. The results represent the first examples of palladium-catalyzed direct *ortho*-arylation of 2-arylbenzoxazoles and also provide a facile route for the synthesis of complicated structures containing arylated benzoxazoles moieties.

1. Introduction

Palladium-catalyzed C–C cross-coupling of aryl halides with a nucleophilic compound is increasingly becoming a preferred method in synthetic applications.[1] The method typically requires a highly reactive organometallic reagent (e.g., $RSnR'_3$, Stille; $RB(OH)_2$, Suzuki–Miyaura; RMgX, Kumada; and RZnX, Negishi) as the nucleophilic compound.[2] However, preparation of preactivated reagents often is a multi-step therefore time-consuming and economically inefficient process. An attractive alternative to this approach is to treat the aryl C–H bond as a functional group, subsequently achieving direct and selective replacement of C–H bonds with new bonds (such as C–C, C–O, and C–N) thereby yielding the desired products. This alternative would represent an ideal and environmentally friendly method for the construction of complicated structures.[3]

During the last few years, transition-metal-catalyzed direct arylation of the aryl C–H bond has emerged as a fascinating area rich in challenges and opportunities, and lately been realized in many arenes with or without a directing group.[4,5] With a directing group such as pyridine, imine, acetamine, carboxylic acid, or oxazoline, *ortho*-C–H bond can be highly regioselectively functionalized under palladium, ruthenium, or rhodium catalysis (Scheme 1).[4] In particular, palladium-promoted functionalization of C–H bond has shown its unique advantages. Notably, the arylation of 2-arylpyridines and other nitrogen heterocycles with diphenyliodonium salts under Pd(II) catalysis has been studied by Sanford et al.[4a] However, the scope of the reactions involving the various directing groups is still relatively limited and should be extended and investigated further.



Scheme 1. Functionalization of *ortho*-C–H bond via C–H activation.

Arylated benzoxazoles are the important biaryl pharmacophore and with lower toxicities, which have exhibited a variety of biological activities, including anti-HIV, antiinflammatory, antimicrobial, antibiotic, and antitumor properties.[6] Further extension and branching functional substituents on them would have valuable significance for the synthesis of pharmaceutical intermediates. In this work, we report for the first time successful direct arylation of 2-arylbenzoxazoles through *ortho*-C–H activation by coupling with aryl iodides.

2. Results and discussion

Reaction conditions were screened with respect to the additive and solvent using 2-phenylbenzoxazole (**1a**) and iodobenzene (**2a**) as the substrates (Table 1). After various additives such as $Cu(OAc)_2 \cdot H_2O$, BQ, $K_2S_2O_8$, and AgOAc were examined, AgOAc gave the best result with a yield of 66% (entries 1–7). When the loading

* Corresponding author. Tel./fax: +86 371 67766667.
E-mail address: wyj@zzu.edu.cn (Y. Wu).

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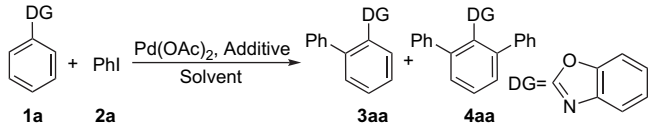
Table 1
ortho-Arylation of 2-phenylbenzoxazole via C–H activation under different conditions[a]



1a 2a 3aa 4aa

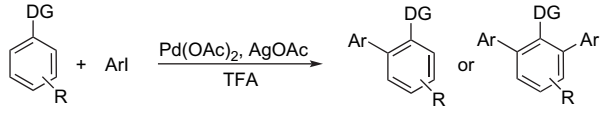
Entry	Additive (equiv)	Solvent	Yield[b] (%)	Ratio (**3aa**/**4aa**)
1	$Cu(OAc)_2 \cdot H_2O$ (2.4)	TFA	<5	100:0
2	BQ (2.4)	TFA	<5	100:0
3	$K_2S_2O_8$ (2.4)	TFA	6	100:0
4	$Cu(OAc)_2 \cdot H_2O$/BQ (1.2/1.2)	TFA	11	14:86
5	AgOAc/BQ (1.2/1.2)	TFA	16	75:25
6	AgOAc/$Cu(OAc)_2 \cdot H_2O$ (1.2/1.2)	TFA	13	70:30
7	AgOAc (2.4)	TFA	66	55:45
8	*AgOAc (4.8)*	*TFA*	*88*	*35:65*
9	AgOAc (4.8)	HOAc	18	100:0
10	AgOAc (4.8)	1,4-Dioxane	<5	100:0
11	AgOAc (4.8)	DMA	<5	20:80

[a] All the reactions were carried out in the presence of 0.25 mmol **1a**, 1.0 mmol **2a**, and 5 mol % $Pd(OAc)_2$ in 0.6 mL solvent under reflux for 72 h.
[b] Yields are given for isolated products of **3aa** and **4aa**.

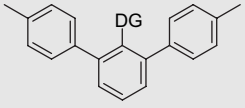
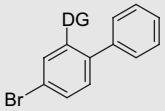
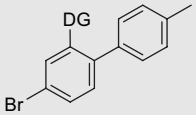
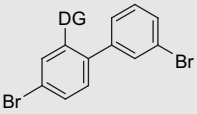
of AgOAc was increased to 4.8 equiv, the reaction rate was enhanced and 88% total yield of monophenylated product **3aa** and diphenylated product **4aa** was obtained with a **3aa**/**4aa** ratio of 35:65 (entry 8). However, when the solvent was changed to HOAc, the reaction proceeded very slowly (entry 9). Aprotic polar solvents, for example, 1,4-dioxane and DMA, examined in combination with $Pd(OAc)_2$ and AgOAc, did not exhibit comparably favorable results (entries 10 and 11).

Under above optimized conditions, the scope of the substrates was also surveyed (Table 2). The reaction was compatible with bromo substituent on the aryl iodides (entries 4, 7, 10, and 16) and bromo or chloro substituents on 2-arylbenzoxazoles (entries 2–7). These characteristics would permit construction of scaffolds that

Table 2
ortho-Arylation of 2-arylbenzoxazoles via C–H activation[a]

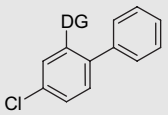
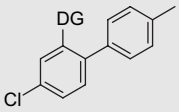
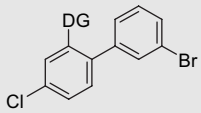
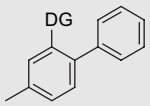
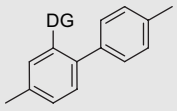
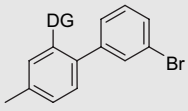
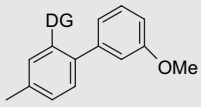
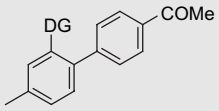
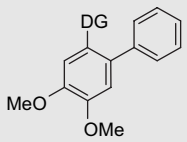
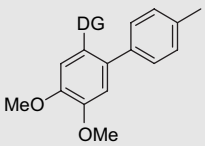
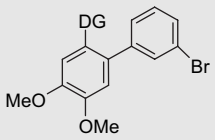


1 2 3 4

Entry	R	**2**	Product	Time (h)	Yield[b] (%)
1[c]	H (**1a**)	4-Me-C_6H_4I (**2b**)		72	70 (**4ab**)
2	3-Br (**1b**)	C_6H_5I (**2a**)		72	92 (**3ba**)
3	**1b**	**2b**		100	95 (**3bb**)
4	**1b**	3-Br-C_6H_4I (**2c**)		175	80 (**3bc**)

(*continued*)

Table 2 (*continued*)

Entry	R	**2**	Product	Time (h)	Yield[b] (%)
5	3-Cl (**1c**)	**2a**		83	76 (**3ca**)
6	**1c**	**2b**		72	85 (**3cb**)
7	**1c**	**2c**		161	50 (**3cc**)
8	3-Me (**1d**)	**2a**		43	93 (**3da**)
9	**1d**	**2b**		40	90 (**3db**)
10	**1d**	**2c**		96	82 (**3dc**)
11	**1d**	3-MeO-C_6H_4I (**2d**)		58	75 (**3dd**)
12	**1d**	4-MeCO-C_6H_4I (**2e**)		142	34 (**3de**)
13	**1d**	2-Cl-C_6H_5I (**2f**)	—	—	—
14	3,4-MeO (**1e**)	**2a**		86	80 (**3ea**)
15	**1e**	**2b**		74	84 (**3eb**)
16	**1e**	**2c**		170	60 (**3ec**)
17	2,4-Cl (**1f**)	**2a**	—	—	—

[a] All the reactions were carried out in the presence of 0.25 mmol **1**, 1.0 mmol **2**, 1.2 mmol AgOAc, and 5 mol % $Pd(OAc)_2$ in 0.6 mL TFA under reflux.
[b] Yields are given for isolated products.
[c] Approximately 12% of **3ab** was also obtained.

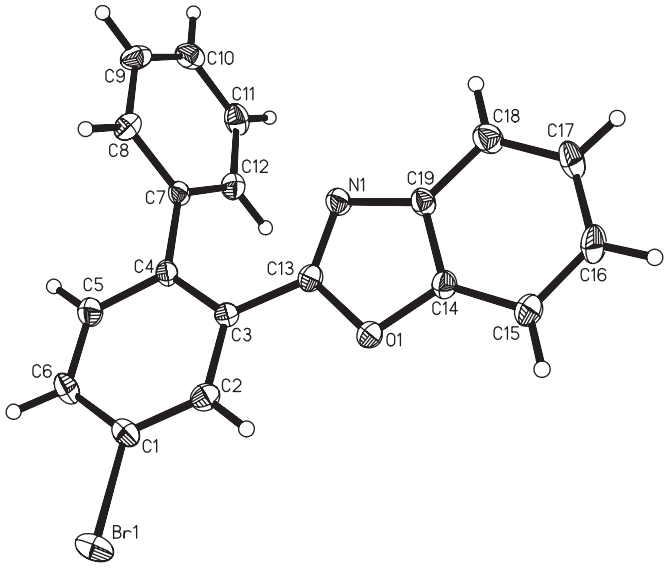
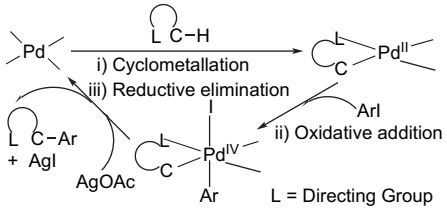


Figure 1. Molecular structure of **3ba**.

could be functionalized through conventional Pd(0)/Pd(II) coupling processes. Electronic factors had a critical effect on the reactivity of the substrate and electron-donating substituents on either 2-arylbenzoxazoles or aryl iodides would speed up the arylation, and vice versa. The reaction of iodides containing electron-neutral, electron-donating (CH_3), or moderately electron-withdrawing (Br) substituents proceeded well and moderate-to-good yields were obtained. However, in the case of iodides containing strongly electron-withdrawing groups (CH_3CO), the reactions were much slower and gave a yield of 34% (entry 12). And the arylated product of 2-arylbenzoxazole with aryl iodide containing a chloro group was not detected (entry 13). Similarly, the arylation of 2-arylbenzoxazoles containing two moderately electron-withdrawing (Cl) substituents with iodobenzene (**2a**) could not proceed and no product was observed (entry 17). Generally, for 2-arylbenzoxazoles containing a *meta*-substituent, high regioselectivity was observed for arylation of the less sterically hindered *ortho*-C–H bond. In case there is more than one possible substitution, the diarylation product could be obtained as the major product after a prolonged time (entry 1). The molecular structure of **3ba** was unambiguously determined by the single crystal X-ray diffraction study (Fig. 1).[7]

A possible reaction mechanism for the arylation of 2-arylbenzoxazole is outlined in Scheme 2. As an electrophilic C–H activation process, the reactions are faster when either 2-arylbenzoxazoles or aryl iodides possess the electron-donating substituents. Step (i) is cyclopalladation of 2-arylbenzoxazoles via C–H activation to afford a cyclopalladated intermediate. The *ortho*-alkylation of 2-aryloxazolines through the reaction of their cyclopalladated complexes with alkyl iodides provides the strong support for this proposed step.[8] We have found that reactions of aryl iodides containing electron-donating groups proceeded much faster than those of aryl iodides containing electron-withdrawing groups. The finding sets the current process apart from the conventional Pd(0)/Pd(II) catalytic cycle.[9] Step (ii) is proposed to be an oxidative addition of Pd(II) to unstable Pd(IV) species. And the final step (iii) is a reductive elimination process, which results in the desired product.[10]



Scheme 2. Proposed catalytic cycle.

3. Conclusion

In summary, we have developed a highly regioselective method for arylation of 2-arylbenzoxazoles based on C–H activation. The reaction could tolerate various functional groups, and allows bromo or chloro substituents on 2-arylbenzoxazoles and bromo substituent on aryl iodides. The arylation exhibits high regioselectivity for 2-arylbenzoxazoles containing a *meta*-substituent and the arylated product of the less sterically hindered *ortho*-C–H bond was observed as the major product. Current studies are focused on further exploration of the substrate scope and synthetic utility of this methodology.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer with $CDCl_3$ as the solvent and TMS as an internal standard. Melting points were measured using a WC-1 microscopic apparatus and are uncorrected. GC analysis was performed on Agilent 4890D gas chromatograph. Mass spectra were measured on an LC-MSD-Trap-XCT instrument. High-resolution mass spectra were measured on a Waters Q-Tof MicroTM spectrometer. 2-Arylbenzoxazoles and AgOAc were synthesized according to the literatures.[6c,11] DMA and 1,4-dioxane were purified by the standard methods. CH_2Cl_2 (analytical grade) was stored over molecular sieves and used without further purification. Ethyl acetate and hexane (reagent grade) were used for column chromatography without purification. The other chemicals were bought from commercial sources and used as-received unless otherwise noted.

4.2. General procedure for synthesis of 2-arylbenzoxazoles

To a solution of 2-aminophenol (0.109 g, 1.0 mmol) in MeOH (15 mL), aldehyde (1.0 mmol) was added. The resulting mixture was heated at 45 °C for 12 h. After concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 (25 mL) and Ag_2O (1.1 mmol) was then added. After stirring at room temperature for 5 h, the insoluble material was filtered off. The filtrate was evaporated and the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired product.

*4.2.1. 2-Phenylbenzoxazole (**1a**)*[11a]

White solid, mp 79–80 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.40 (m, 2H), 7.40–7.60 (m, 4H), 7.72–7.80 (m, 1H), 8.26 (t, J=2.40 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.60, 120.03, 124.58, 125.11, 127.18, 127.63, 128.92, 131.53, 142.11, 150.77, 163.05; MS, m/z (%): 196.1 (100) [M^++H].

*4.2.2. 2-(3-Bromo phenyl) benzoxazole (**1b**)*[12]

White solid, mp 128–130 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.44 (m, 3H), 7.56–7.65 (m, 1H), 7.65–7.69 (m, 1H), 7.76–7.81 (m, 1H), 8.20 (d, J=8.02 Hz, 1H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.74, 120.22, 123.04, 124.87, 125.60, 126.12, 129.02, 130.49, 130.54, 134.46, 141.80, 150.78, 161.50; MS, m/z (%): 274.4 (100) [M^++H].

*4.2.3. 2-(3-Chloro phenyl) benzoxazole (**1c**)*[12]

White solid, mp 124–125 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.40 (m, 2H), 7.44–7.53 (m, 2H), 7.58–7.62 (m, 1H), 7.77–7.79 (m, 1H), 8.15 (dt, J=7.60, 1.40 Hz, 1H), 8.27 (d, J=1.60 Hz, 1H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 110.74, 120.19, 124.87, 125.60, 125.67, 127.63, 128.75, 130.27, 131.56, 135.08, 141.74, 150.74, 161.64; MS, *m*/*z* (%): 230.4 (100) [M^++H].

*4.2.4. 2-(3-Methyl phenyl) benzoxazole (**1d**)*[13]

White solid, mp 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.24–7.79 (m, 3H), 7.37–7.42 (m, 1H), 7.56–7.60 (m, 1H), 7.75–7.80 (m, 1H), 8.05 (d, *J*=7.80 Hz, 1H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.36, 110.57, 119.92, 124.57, 124.76, 125.06, 126.92, 128.20, 128.83, 132.42, 138.76, 141.97, 150.69, 163.24; MS, *m*/*z* (%): 232.2 (100) [M^++H].

*4.2.5. 2-(3,4-Dimethoxyl phenyl) benzoxazole (**1e**)*[12]

White solid, mp 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.02 (s, 3H), 6.98 (d, *J*=0.88 Hz, 1H), 7.25–7.36 (m, 2H), 7.54–7.58 (m, 1H), 7.73–7.78 (m, 2H), 7.86 (d, *J*=8.40 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.05, 56.14, 109.99, 110.41, 110.98, 119.58, 119.67, 121.21, 124.52, 124.74, 142.07, 149.21, 150.65, 151.99, 163.13; MS, *m*/*z* (%): 256.3 (100) [M^++H].

*4.2.6. 2-(2,4-Dichloro phenyl) benzoxazole (**1f**)*[14]

White solid, mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.44 (m, 3H), 7.58–7.65 (m, 2H), 7.83–7.87 (m, 1H), 8.13 (d, *J*=8.40 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.77, 120.56, 124.72, 124.82, 125.80, 127.44, 131.30, 132.52, 134.23, 137.54, 141.58, 150.50, 160.07; MS, *m*/*z* (%): 264.5 (100) [M^++H].

4.3. General procedure for arylation of 2-arylbenzoxazoles

2-Arylbenzoxazole (0.25 mmol), aryl iodide (1.0 mmol), palladium acetate (5 mol%), and silver acetate (1.2 mmol) were dissolved in trifluoroacetic acid (0.6 mL) in a 5 mL vial under atmospheric air and heated under reflux. The reaction process was monitored by GC analysis. During this time, a yellow precipitate was formed. After the reaction was complete, the mixture was diluted with CH_2Cl_2 (10 mL), filtered through a pad of Celite, and washed multiple times with CH_2Cl_2. The combined organic solutions were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the pure product.

*4.3.1. 2-(2-Phenyl phenyl) benzoxazole (**3aa**)*

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15–7.35 (m, 8H), 7.45–7.51 (m, 2H), 7.51–7.59 (m, 1H), 7.70 (d, *J*=7.60 Hz, 1H), 8.11 (dd, *J*=7.30, 1.80 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.58, 120.13, 124.37, 124.97, 126.33, 127.32, 127.59, 128.18, 128.86, 131.04, 131.20, 141.02, 141.74, 142.50, 150.77, 163.91; HRMS (positive ESI) calcd for $C_{19}H_{13}NO$ (MH^+): 272.1075, found: 272.1075.

*4.3.2. 2-(2,6-Diphenyl phenyl) benzoxazole (**4aa**)*

White solid, mp 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.25 (m, 13H), 7.35–7.75 (m, 3H), 7.61 (t, *J*=7.60 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.35, 120.16, 123.98, 124.75, 126.35, 127.21, 128.17, 128.53, 129.22, 130.50, 140.49, 141.13, 143.80, 150.16, 162.16; HRMS (positive ESI) calcd for $C_{25}H_{17}NO$ (MH^+): 348.1388, found: 348.1392.

*4.3.3. 2-[2-(4-Methyl phenyl) phenyl] benzoxazole (**3ab**)*

Light yellow solid, mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 7.12 (d, *J*=8.00 Hz, 2H), 7.17 (d, *J*=8.00 Hz, 2H), 7.24–7.34 (m, 3H), 7.40–7.52 (m, 2H), 7.52–7.60 (m, 1H), 7.70–7.75 (m, 1H), 8.03–8.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.17, 110.57, 120.06, 124.25, 124.84, 126.24, 127.27, 128.63, 128.86, 130.96, 131.04, 131.14, 136.96, 137.93, 141.71, 142.40, 150.74, 164.02; HRMS (positive ESI) calcd for $C_{20}H_{15}NO$ (MH^+): 286.1232, found: 286.1230.

*4.3.4. 2-[2,6-Di(4-methyl phenyl) phenyl] benzoxazole (**4ab**)*

White solid, mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 6H), 6.96 (d, *J*=8.00 Hz, 4H), 7.11 (d, *J*=8.00 Hz, 4H), 7.15–7.23 (m, 2H), 7.23–7.31 (m, 1H), 7.45 (d, *J*=7.72 Hz, 2H), 7.51–7.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.97, 110.35, 120.11, 123.79, 124.55, 126.13, 128.30, 128.83, 128.97, 130.35, 136.75, 137.53, 141.19, 143.66, 150.13, 162.34; HRMS (positive ESI) calcd for $C_{27}H_{21}NO$ (MH^+): 376.1701, found: 376.1699.

*4.3.5. 2-(2-Phenyl-5-bromo phenyl) benzoxazole (**3ba**)*

White solid, mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.29 (m, 4H), 7.29–7.38 (m, 5H) 7.67–7.74 (m, 2H), 8.29 (d, *J*=2.04 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.59, 120.23, 121.45, 124.51, 125.28, 127.59, 127.89, 128.21, 128.65, 132.69, 133.53, 133.87, 139.84, 141.26, 141.45, 150.68, 162.26; HRMS (positive ESI) calcd for $C_{19}H_{12}BrNO$ (MH^+): 350.0181, found: 350.0196.

*4.3.6. 2-[2-(4-Methyl phenyl)-5-bromo phenyl] benzoxazole (**3bb**)*

White solid, mp 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 7.08–7.15 (m, 4H), 7.26–7.35 (m, 4H), 7.67 (dd, *J*=8.00, 2.04 Hz, 1H), 7.70–7.75 (m, 1H), 8.25 (d, *J*=2.08 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.20, 110.65, 120.23, 121.16, 124.49, 125.24, 127.82, 128.51, 128.97, 132.71, 133.61, 133.88, 136.81, 137.40, 141.27, 141.45, 150.70, 162.44; HRMS (positive ESI) calcd for $C_{20}H_{14}BrNO$ (MH^+): 364.0337, found: 364.0334.

*4.3.7. 2-[2-(3-Bromo phenyl)-5-bromo phenyl] benzoxazole (**3bc**)*

White solid, mp 102–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05–7.13 (m, 1H), 7.13–7.18 (m, 1H), 7.26–7.34 (m, 4H), 7.45–7.51 (m, 2H), 7.60–7.73 (m, 2H), 8.32 (d, *J*=2.08 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.61, 120.31, 122.09, 122.18, 124.65, 125.49, 127.54, 127.74, 129.55, 130.64, 131.63, 132.61, 133.51, 133.93, 139.53, 141.37, 141.91, 150.62, 161.60; HRMS (positive ESI) calcd for $C_{19}H_{11}Br_2NO$ (MH^+): 429.9265, found: 429.9261.

*4.3.8. 2-(2-Phenyl-5-chloro phenyl) benzoxazole (**3ca**)*

White solid, mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.28 (m, 4H), 7.28–7.35 (m, 4H), 7.39–7.43 (m, 1H), 7.54 (dd, *J*=8.00, 2.16 Hz, 1H), 7.71 (d, *J*=7.32 Hz, 1H), 8.14 (d, *J*=2.16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.59, 120.23, 124.52, 125.28, 127.57, 127.61, 128.19, 128.72, 130.66, 130.94, 132.49, 133.62, 139.83, 140.82, 141.43, 150.68, 162.39; HRMS (positive ESI) calcd for $C_{19}H_{12}ClNO$ (MH^+): 306.0685, found: 306.0661.

*4.3.9. 2-[2-(4-Methyl phenyl)-5-chloro phenyl] benzoxazole (**3cb**)*

White solid, mp 112–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 7.11–7.15 (m, 4H), 7.27–7.35 (m, 3H), 7.38–7.43 (m, 1H), 7.53 (dd, *J*=8.00, 2.24 Hz, 1H), 7.72 (m, 1H), 8.10 (d, *J*=2.24 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.21, 110.67, 120.26, 124.49, 125.24, 127.59, 128.59, 128.97, 130.75, 130.94, 132.52, 133.35, 136.82, 137.38, 140.83, 141.51, 150.72, 162.59; HRMS (positive ESI) calcd for $C_{20}H_{14}ClNO$ (MH^+): 320.0842, found: 320.0853.

*4.3.10. 2-[2-(3-Bromo phenyl)-5-chloro phenyl] benzoxazole (**3cc**)*

White solid, mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.20 (m, 2H), 7.28–7.36 (m, 3H), 7.38 (d, *J*=8.00 Hz, 1H), 7.46–7.52 (m, 2H), 7.54 (dd, *J*=8.00, 2.24 Hz, 1H), 7.68–7.73 (m, 1H), 8.19 (d, *J*=2.24 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.62, 120.31, 122.17, 124.66, 125.49, 127.51, 127.61, 129.54, 130.64, 131.00, 131.71, 132.44, 134.24, 139.10, 141.37, 141.90, 150.63, 161.75; HRMS (positive ESI) calcd for $C_{19}H_{11}BrClNO$ (MH^+): 383.9791, found: 383.9799.

*4.3.11. 2-(2-Phenyl-5-methyl phenyl) benzoxazole (**3da**)*

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.22–7.31 (m, 8H), 7.36–7.38 (m, 2H), 7.71 (d, *J*=8.00 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.88, 109.49, 118.90, 123.29,

123.85, 124.80, 126.03, 127.03, 127.78, 130.07, 130.39, 130.85, 136.41, 138.61, 139.84, 140.45, 149.63, 163.11; HRMS (positive ESI) calcd for $C_{20}H_{15}NO$ (MH^+): 286.1232, found: 286.1235.

*4.3.12. 2-[2-(4-Methyl phenyl)-5-methyl phenyl] benzoxazole (**3db**)*

White solid, mp 111–114 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.45 (s, 3H), 7.07–7.12 (m, 2H), 7.12–7.18 (m, 2H), 7.20–7.31 (m, 3H), 7.31–7.37 (m, 2H), 7.68–7.74 (m, 1H), 7.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.95, 21.22, 110.61, 120.04, 124.29, 124.84, 125.95, 128.72, 128.87, 131.17, 131.56, 131.88, 136.76, 137.21, 137.95, 139.64, 141.73, 150.78, 164.32; HRMS (positive ESI) calcd for $C_{21}H_{17}NO$ (MH^+): 300.1388, found: 300.1389.

*4.3.13. 2-[2-(3-Bromo phenyl)-5-methyl phenyl] benzoxazole (**3dc**)*

Light yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.08–7.15 (m, 2H), 7.23–7.31 (m, 4H), 7.35–7.40 (m, 1H), 7.40–7.46 (m, 1H), 7.49–7.53 (m, 1H), 7.67–7.73 (m, 1H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.01, 110.56, 120.10, 122.09, 124.45, 125.08, 125.84, 127.77, 129.43, 130.13, 131.08, 131.44, 131.84, 131.93, 138.00, 138.11, 141.60, 143.09, 150.68, 163.50; HRMS (positive ESI) calcd for $C_{20}H_{14}BrNO$ (MH^+): 364.0337, found: 364.0327.

*4.3.14. 2-[2-(3-Methoxyl phenyl)-5-methyl phenyl] benzoxazole (**3dd**)*

White solid, mp 111–113 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.66 (s, 3H), 6.80–6.91 (m, 3H), 7.14–7.23 (m, 1H), 7.23–7.32 (m, 3H), 7.35–7.40 (m, 2H), 7.16 (dd, J=7.60, 1.84 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.97, 55.17, 110.58, 113.05, 114.16, 120.00, 121.46, 124.33, 124.92, 126.04, 129.08, 130.97, 131.44, 131.85, 137.57, 139.46, 141.66, 142.28, 150.78, 159.35, 164.12; HRMS (positive ESI) calcd for $C_{21}H_{17}NO_2$ (MH^+): 316.1338, found: 316.1340.

*4.3.15. 2-[2-(4-Acetyl phenyl)-5-methyl phenyl] benzoxazole (**3de**)*

White solid, mp 169–172 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 2.61 (s, 3H), 7.26–7.32 (m, 3H), 7.32–7.39 (m, 3H), 7.39–7.44 (m, 1H), 7.70 (d, J=7.80 Hz, 1H), 7.91 (d, J=7.80 Hz, 2H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.98, 26.64, 110.54, 120.09, 124.44, 125.07, 125.84, 128.18, 129.13, 130.92, 131.52, 131.92, 135.68, 138.31, 138.36, 141.54, 145.97, 150.62, 163.45, 197.88; HRMS (positive ESI) calcd for $C_{22}H_{17}NO_2$ (MH^+): 328.1338, found: 328.1341.

*4.3.16. 2-[2-Phenyl-4,5-dimethoxyl phenyl] benzoxazole (**3ea**)*

White solid, mp 129–132 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.02 (s, 3H), 6.93 (s, 1H), 7.20–7.24 (m, 2H), 7.27–7.31 (m, 3H), 7.32–7.36 (m, 3H), 7.67 (s, 1H), 7.68–7.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.09, 56.25, 110.39, 113.01, 113.83, 118.13, 119.66, 124.25, 124.61, 127.12, 128.04, 128.94, 136.20, 141.09, 141.58, 148.24, 150.59, 150.92, 163.90; HRMS (positive ESI) calcd for $C_{21}H_{17}NO_3$ (MH^+): 332.1286, found: 332.1276.

*4.3.17. 2-[2-(4-Methyl phenyl)-4,5-dimethoxyl phenyl] benzoxazole (**3eb**)*

White solid, mp 142–145 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 6.83 (s, 1H), 7.03–7.14 (m, 4H), 7.14–7.22 (m, 3H), 7.55 (s, 1H), 7.59–7.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.17, 56.04, 56.22, 110.43, 113.12, 113.89, 118.10, 119.68, 124.20, 124.55, 128.77, 136.18, 136.80, 138.10, 141.67, 148.10, 150.62, 150.91, 164.03; HRMS (positive ESI) calcd for $C_{22}H_{19}NO_3$ (MH^+): 346.1443, found: 346.1440.

*4.3.18. 2-[2-(3-Bromo phenyl)-4,5-dimethoxyl phenyl] benzoxazole (**3ec**)*

White solid, mp 167–170 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.03 (s, 3H), 6.87 (s, 1H), 7.14–7.19 (m, 2H), 7.23–7.30 (m, 3H), 7.45–7.50 (m, 1H), 7.52–7.56 (m, 1H), 7.66–7.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.15, 56.27, 110.39, 112.92, 113.68, 118.11, 119.73, 121.99, 124.37, 124.79, 127.92, 129.37, 130.15, 131.85, 134.43, 141.49, 143.17, 148.59, 150.54, 150.98, 163.29; HRMS (positive ESI) calcd for $C_{21}H_{16}BrNO_3$ (MH^+): 410.0392, found: 410.0388.

4.4. Crystal structure determination

Intensity data of **3ba** were measured on a Rigaku-Raxis-IV X-ray diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073 Å). The data were corrected for Lorentz and polarization factors. The structure was solved by direct methods,[15] expanded using Fourier techniques, and refined by full-matrix least-squares methods. All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation.

5. Supplementary material

CCDC 684234 contains the supplementary crystallographic data for **3ba**, which can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

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2222/2222 (R_{int}=0.0000), goodness-of-fit on F^2 1.077, final R indices [$I>2\sigma(I)$]R_1=0.0732, wR_2=0.1824.
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