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PAPER

Chlorination and *ortho*-acetoxylation of 2-arylbenzoxazoles†

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Efficient and facile catalytic protocols for chlorination and ligand-directed *ortho*-acetoxylation of 2-arylbenzoxazoles have been developed. The chlorination is not a ligand-directed *ortho*-functionalization, but an electrophilic substitution process in the benzo ring of the benzoxazole moiety. Meanwhile, the acetoxylation exhibited high regioselectivity for the substrates containing a *meta*-substituent and occurred at the less sterically hindered *ortho*-C–H bond of the directing group.

Introduction

Since the discovery of σ-chelation directed C–H bond cleavage, transition metal-catalyzed ligand-directed C–H bond functionalization has emerged as a reliable and powerful tool in the valuable conversion of arenes into new products, and numerous endeavours have been focused on the application of this useful transformation.[1,2,3] Recently, the combination of transition metals and directing groups has been shown to be a useful strategy to facilitate the cleavage of the C–H bond, affording transformations of a sp^2-hybridized C–H bond to C–O,[4] C–C,[5] C–N,[6] C–X,[7] and C–S[8] bonds. In this context, many arenes containing a directing group such as pyridine, ketone, ester, amide, oxazoline, imine, and nitrile can be regioselectively functionalized *via* cyclometalated intermediates under Pd,[9] Ru,[10] or Rh[11] catalysis. Among them, palladium-mediated C–H activation of arenes is one of the most attractive processes. Particularly, in the development of palladium-catalyzed halogenation and acetoxylation with the use of directing groups, significant progress has been achieved by several groups, such as those of Sanford, Daugulis, Yu, and others.[12]

Benzoxazoles are an important pharmacophore with low toxicities, which have exhibited a variety of biological activities.[13] Further extension and branching functional substituents on the benzoxazole skeleton would have great importance for the synthesis of pharmaceutical intermediates. In 2008, we described the direct arylation of 2-arylbenzoxazoles.[14] Inspired by the above-mentioned and our own reports, we began to explore palladium-catalyzed chlorination and acetoxylation using benzoxazole as the directing group. Herein, we would like to report our research results as follows: the ligand-directed acetoxylation indeed occurred at the *ortho*-position of the pendant aryl group, affording the desired products in moderate to good yields; while the chlorination of 2-arylbenzoxazoles was not a ligand-directed *ortho*-C–H activation process, but an electrophilic substitution at the *para*-position to the nitrogen atom in the benzo ring of the benzoxazole moiety.

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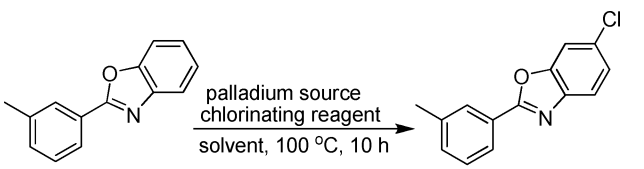
Table 1 Effects of chlorinating reagents, solvents and catalysts on the selective chlorination of 2-(3-methylphenyl)benzoxazole[a]



1a 2a

Entry	Chlorinating reagent	Palladium source	Solvent	Yield (%)[b]
1	*p*-$MeC_6H_4SO_2Cl$	$PdCl_2$	CH_3CN	32
2	NCS	$PdCl_2$	CH_3CN	59
3	NCS	$PdCl_2$	DCE	22
4	NCS	$PdCl_2$	Dioxane	<5
5	**NCS**	**$PdCl_2$**	**AcOH**	**92**
6	NCS	$Pd(OAc)_2$	AcOH	45
7[c]	NCS	$Pd_2(dba)_3$	AcOH	60
8	NCS	—	AcOH	24

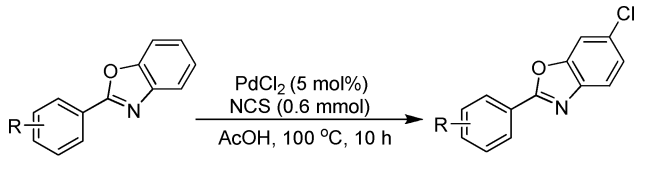
[a] Reaction conditions: **1a** (0.5 mmol), chlorinating reagent (0.6 mmol), catalyst (5.0 mol%), solvent (2.0 mL), 100 °C for 10 h. [b] Isolated yields. [c] With the catalyst loading of 2.5 mol%.

Results and discussion

Optimization of reaction conditions of the chlorination

In our initial study, we examined the effects of chlorinating reagents, solvents and various catalysts on the chlorination of 2-(3-methylphenyl)benzoxazole. The results are summarized in Table 1. The reaction of 2-(3-methylphenyl)benzoxazole with *p*-$MeC_6H_4SO_2Cl$ as the chlorinating reagent in CH_3CN only gave a low yield of 32% (Table 1, entry 1). When *N*-chlorosuccinimide (NCS) was used as the chlorinating reagent, the product with a higher yield of 59% was observed (Table 1, entry 2). Then, different

Table 2 The palladium-catalyzed selective chlorination of 2-arylbenzoxazoles with NCS[a]



1 2

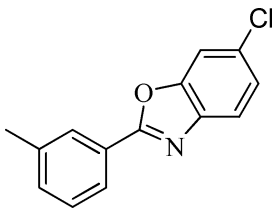
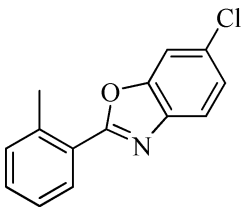
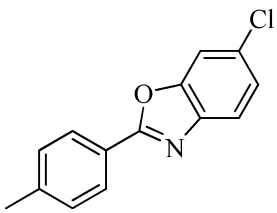
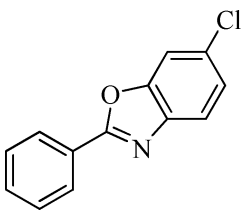
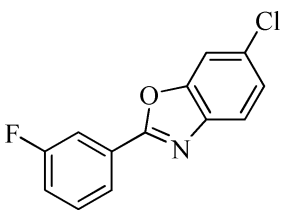
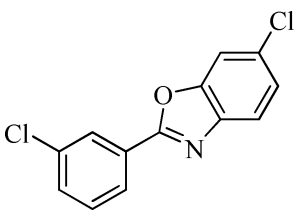
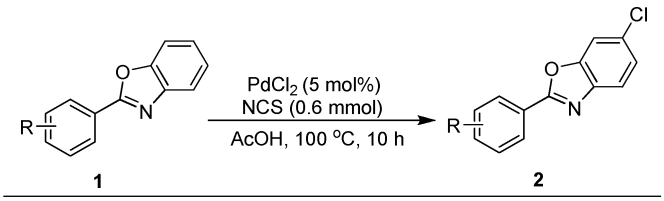
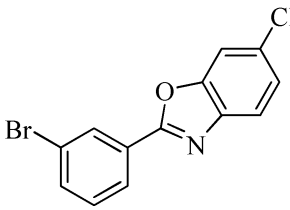
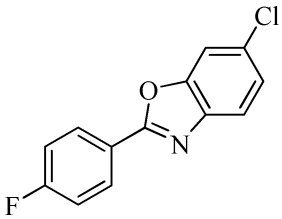
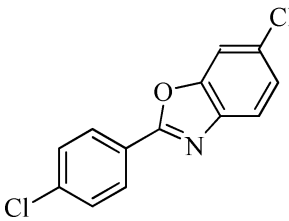
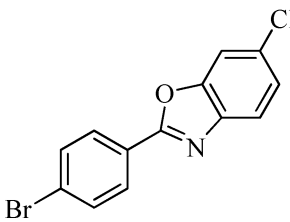
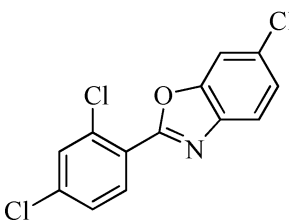
Entry	R	Product	Yield (%)[b]
1	*m*-Me (**1a**)		92 (**2a**)
2	*o*-Me (**1b**)		85 (**2b**)
3	*p*-Me (**1c**)		81 (**2c**)
4	H (**1d**)		87 (**2d**)
5	*m*-F (**1e**)		88 (**2e**)
6	*m*-Cl (**1f**)		82 (**2f**)

Table 2 *(Contd.)*



1 2

Entry	R	Product	Yield (%)[b]
7	*m*-Br (**1g**)		83 (**2g**)
8	*p*-F (**1h**)		82 (**2h**)
9	*p*-Cl (**1i**)		81 (**2i**)
10	*p*-Br (**1j**)		72 (**2j**)
11	*o*, *p*-Cl_2 (**1k**)		70 (**2k**)

[a] Reaction conditions: **1a–k** (0.5 mmol), NCS (0.6 mmol), $PdCl_2$ (5.0 mol%), AcOH (2.0 mL), 100 °C for 10 h. [b] Isolated yields.

other solvents were investigated, and AcOH could give the desired product in excellent yield of 92% using $PdCl_2$ as the catalyst (Table 1, entries 3–5). Finally, other palladium catalysts, such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ were examined and did not exhibit higher catalytic activity in this reaction (Table 1, entries 6–7). However, in the absence of palladium catalyst, the

yield of desired product was remarkably decreased (Table 1, entry 8).

Scope of substrates of the chlorination

Under the optimized conditions, the chlorination of diverse 2-arylbenzoxazoles was examined to explore the scope of the reaction (Table 2). Generally, the chlorination took place at the *para*-position to the nitrogen atom in the benzo ring of benzoxazole moiety owing to its higher electronic cloud density, and the electronic effect of the benzene ring has no significant influence on the reactions. For the benzene ring bearing electron-donating groups, the desired products were isolated in high yields (Table 2, entries 1–3). The chlorination of the electron-neutral substrate also worked well at the *para*-position to the nitrogen atom in the benzo ring of benzoxazole moiety (Table 2, entry 4). The reactions of the benzene ring containing electron-withdrawing groups also generated the products in satisfactory yields (Table 2, entries 5–11). It is noteworthy that this catalytic system could tolerate halogen atoms (F, Cl and Br) (Table 2, entries 5–11).

The determination of the structures of the chlorinated products by HMBC (^{1}H-detected heteronuclear multiple bond correlation) spectra

The HMBC spectral data of the two representative chlorinated products (**2a**, **2g**) were utilized to confirm that the chlorination took place at the *para*-position to the nitrogen atom in the benzo ring of the benzoxazole moiety (Fig. 1, 2).

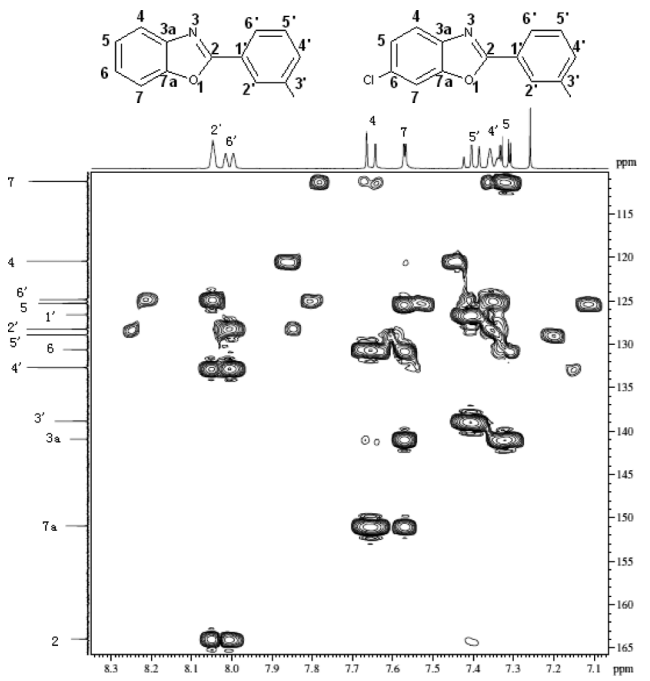


Fig. 1 HMBC spectrum of **2a**.

The HMBC spectral analysis of the 2-aryl benzoxazole containing a *meta*-substituent (**2a**) is outlined as Fig. 1. Initially, from ^{13}C NMR we could identify the position of the quaternary C**2** atom adjacent to N and O atoms with the lowest electronic cloud density, which is shifted to δ = 163.9 ppm at the lowest field. And the C**2** atom has two strong correlated H atoms (H**2′** and H**6′**), which indicates that both H**2′** and H**6′** atoms still exist in the benzene ring and the chlorination did not occur at the *ortho*-position of the directing group.

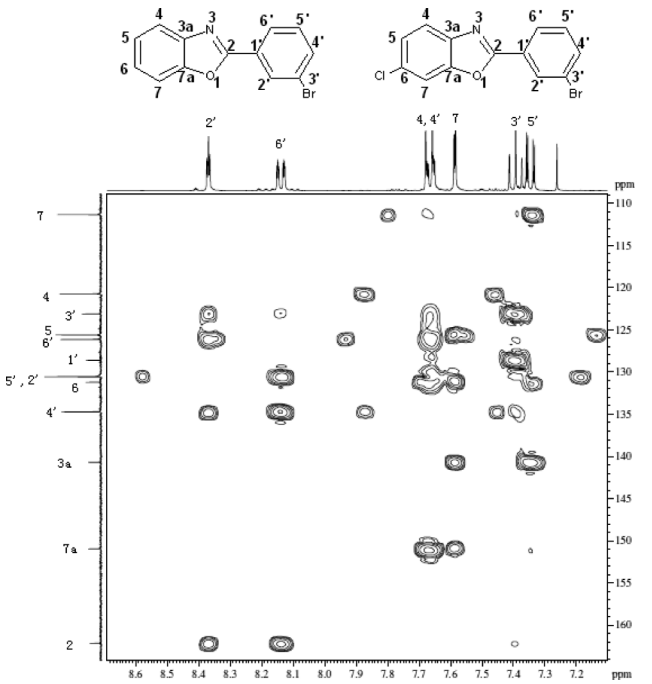


Fig. 2 HMBC spectrum of **2g**.

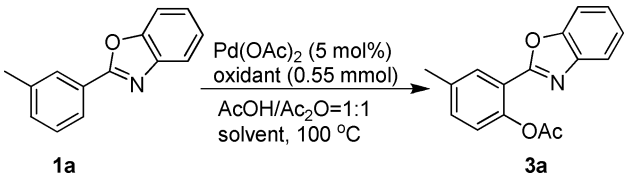
Then, from ^{13}C NMR we could also assign the position of the quaternary C**7a** atom bonded to the O atom and the quaternary C**3a** atom adjacent to the N atom, which are located at δ = 150.9 ppm at lower field and 140.8 ppm at slightly higher field, respectively. From HMBC spectra, the C**7a** atom has one strong correlated H atom (H**4**) and one weak correlated atom (H**7**), and the C**3a** atom has two strong correlated H atoms (H**5** and H**7**). Given this, we could assign the position of the H**7** atom at δ = 7.57 ppm in the ^{1}H NMR. The coupling constant of the H**7** atom is 2.00 Hz in the ^{1}H NMR spectrum, which indicates that there is no H atom at the *ortho*-position to the C**7**–H**7** bond. Thus, the chlorination should take place at the C**6**–H**6** bond.

In the same manner, the HMBC spectrum (Fig. 2) analysis of the chlorinated product (**2g**) could also confirm that the chlorination did not take place at the *ortho*-C–H bond to the directing group, but at the *para*-position to the nitrogen atom in the benzo ring of the benzoxazole moiety.

Optimization of reaction conditions of the acetoxylation

The effects on the direct acetoxylation of 2-arylbenzoxazoles were also explored (Table 3). The various oxidants (*e.g.*, $K_2S_2O_8$, oxone, $Cu(OTf)_2$, $Cu(OAc)_2$, O_2, AgOAc, H_2O_2 and $PhI(OAc)_2$) in the acetoxylation of 2-(3-methylphenyl)benzoxazole were firstly examined, and $PhI(OAc)_2$ turned out to be the best choice in the presence of $AcOH/Ac_2O$ as the solvent, affording the desired product with a high yield of 73% (Table 3, entries 1–8). However, other solvents, such as AcOH, Ac_2O, dioxane and toluene were also checked and did not give satisfactory results (Table 3, entries 9–12).

Table 3 Effects of oxidants and solvents on the selective acetoxylation of 2-(3-methylphenyl)benzoxazole[a]



1a 3a

Entry	Oxidant	Solvent	Yield (%)[b]
1	$K_2S_2O_8$	$AcOH/Ac_2O$ (1 : 1)	27
2	oxone	$AcOH/Ac_2O$ (1 : 1)	35
3	$Cu(OTf)_2$	$AcOH/Ac_2O$ (1 : 1)	14
4	$Cu(OAc)_2$	$AcOH/Ac_2O$ (1 : 1)	20
5	O_2	$AcOH/Ac_2O$ (1 : 1)	10
6	AgOAc	$AcOH/Ac_2O$ (1 : 1)	17
7	H_2O_2	$AcOH/Ac_2O$ (1 : 1)	15
8	**$PhI(OAc)_2$**	**$AcOH/Ac_2O$ (1 : 1)**	**73**
9	$PhI(OAc)_2$	Ac_2O	52
10	$PhI(OAc)_2$	AcOH	<5
11[c]	$PhI(OAc)_2$	dioxane	<5
12[c]	$PhI(OAc)_2$	Toluene	<5

[a] Reaction conditions: **1a** (0.5 mmol), $Pd(OAc)_2$ (5.0 mol%), oxidant (0.55 mmol), solvent (4 mL). [b] Isolated yields. [c] With the addition of AcOH (1.0 mmol) and Ac_2O (1.0 mmol).

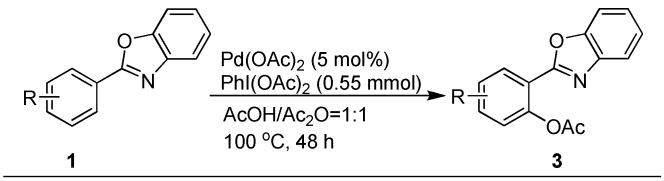
Scope of substrates of the acetoxylation

Under the optimized conditions, the scope of the palladium-catalyzed acetoxylation of an array of substituted 2-arylbenzoxazoles was investigated (Table 4). As expected, the reactions of various substrates worked well under the reaction conditions affording the products in mostly moderate to good yields. The electron-donating substituents on 2-arylbenzoxazoles would enhance the transformation (Table 4, entries 1, 3, 5, 6). Especially, when the 2-arylbenzoxazole possessed two electron-donating groups, the corresponding product was obtained in a higher yield of 84% (Table 4, entry 6). However, the electron-withdrawing substituent would decrease the reactivity of the substrate, and the desired product was nearly not observed (Table 4, entry 7). It is worthy to point out that the regioselectivity of the substrates containing a *meta*-substituent in this reaction was controlled by the steric effect and the acetoxylation occurred at the less sterically hindered *ortho*-C–H bond to the directing group (Table 4, entries 1, 5–7).

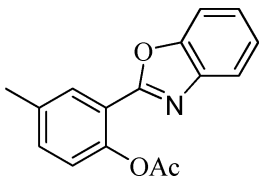
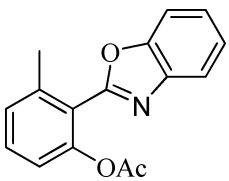
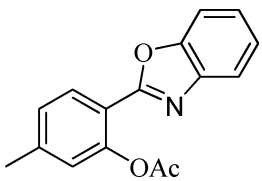
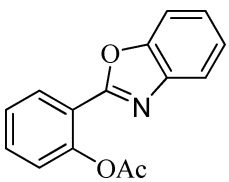
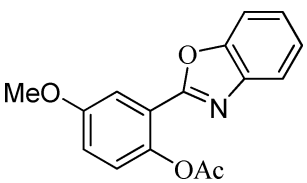
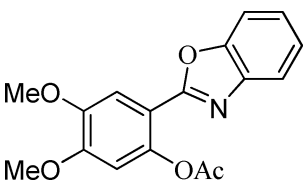
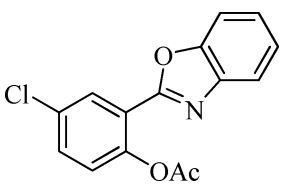
The determination of the structures of the acetoxylated products by HMBC (^{1}H-detected heteronuclear multiple bond correlation) spectra

The HMBC spectral data (**3a**) could unambiguously confirm the proposed structure of the acetoxylated products (Fig. 3). Initially, we could identify the position of the quaternary C**2** atom adjacent to N and O atoms at lowest electronic cloud density, which is shifted to δ = 160.1 ppm at the lowest field. The C**2** atom only has one strong correlated signal at δ = 8.10 ppm, and there is only one H atom at δ = 8.10 ppm in the ^{1}H NMR spectrum. This indicates that one of H**2′** and H**6′** atoms has been substituted by the OAc group. From the ^{1}H NMR spectrum, it could be seen that the coupling constant of the H atom (δ = 8.10 ppm) is 1.88 Hz,

Table 4 The palladium-catalyzed selective acetoxylation of 2-arylbenzoxazoles[a]



1 3

Entry	R	Product	Yield (%)[b]
1	*m*-Me (**1a**)		73 (**3a**)
2	*o*-Me (**1b**)		66 (**3b**)
3	*p*-Me (**1c**)		75 (**3c**)
4	H (**1d**)		62 (**3d**)
5	*p*-MeO (**1l**)		80 (**3e**)
6	*m*, *p*-$(MeO)_2$ (**1m**)		84 (**3f**)
7	*m*-Cl (**1f**)		<5 (**3g**)

[a] Reaction conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (5.0 mol%), $PhI(OAc)_2$ (0.55 mmol), AcOH (2.0 mL), Ac_2O (2.0 mL), 100 °C for 48 h. [b] Isolated yields.

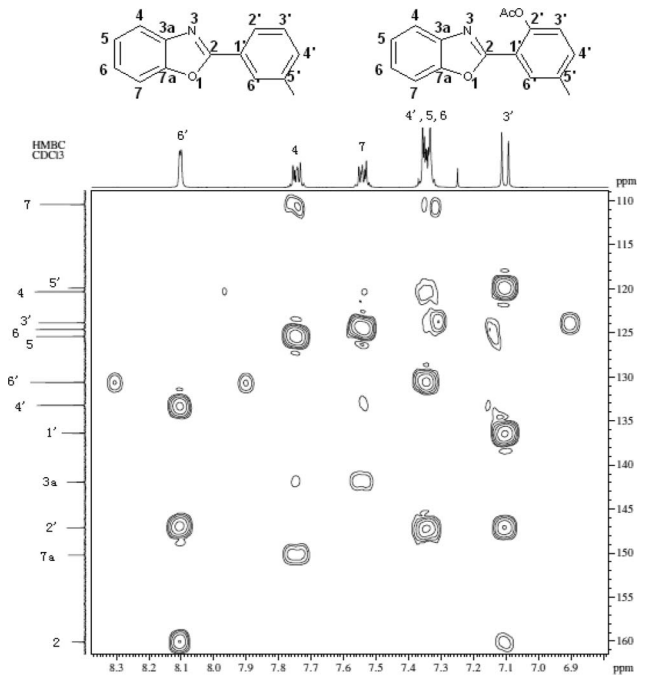
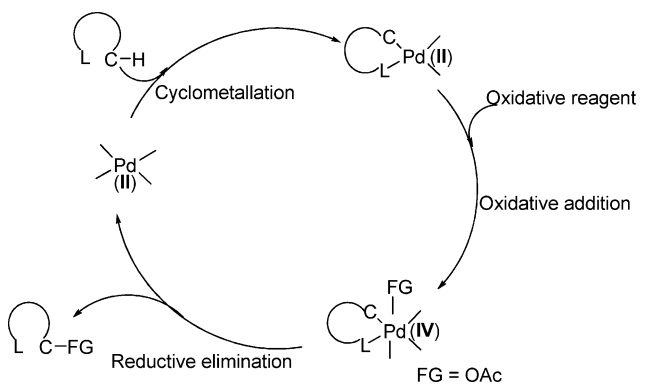


Fig. 3 HMBC spectrum of **3a**.

which indicates that there is no *ortho*-H atom to the H atom (δ = 8.10 ppm). Thus, this H atom (δ = 8.10 ppm) should be the H**6′** atom and the H**2′** atom was substituted by the OAc group. These spectral studies confirm that the acetoxylation occurred at the less sterically hindered *ortho*-C–H (C**2′**–H**2′**) bond of the directing group.

Proposed mechanism

The mechanism for the chlorination of 2-arylbenzoxazoles is the classical aromatic electrophilic substitution at the *para*-position to the nitrogen atom in the benzo ring of the benzoxazole moiety. In this chlorination, palladium would act as the Lewis acid catalyst. The proposed reaction mechanism for the ligand-directed *ortho*-acetoxylation of 2-arylbenzoxazoles is outlined in Scheme 1, which includes: (i) cyclopalladation of 2-arylbenzoxazoles *via* C–H activation, affording a cyclopalladated intermediate; (ii) oxidative addition of cyclopalladated intermediate with Ac_2O, leading to Pd(IV) species; (iii) elimination process, resulting in the desired product.



Scheme 1 A proposed mechanism of functionalization of 2-arylbenzoxazoles.

Conclusions

In summary, we have successfully developed chlorination, which is the classical aromatic electrophilic substitution, and ligand-directed *ortho*-acetoxylation of 2-arylbenzoxazole derivatives through palladium-catalyzed C–H bond activation. The acetoxylation showed high regioselectivity for 2-arylbenzoxazoles containing a *meta*-substituent. These protocols would be beneficial for the convenient, efficient and applicable synthesis of 2-arylbenzoxazoles derivatives. Further applications of these synthetic methodologies are currently underway.

Experimental section

General details

^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY NMR, ^{1}H–^{13}C HSQC NMR, ^{1}H–^{13}C HBMC 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 MALDI-FTMS. Elemental analyses were determined with a Carlo Erba elemental analyzer. IR spectra were recorded on a Bruker VECTOR 22 spectrophotometer. Dichloromethane, ethyl acetate and hexane (analytical grade) were used for column chromatography without further purification. Other solvents were purified according to the standard methods. Other chemicals were obtained from commercial sources and used as-received unless otherwise noted.

General procedure for synthesis of 2-arylbenzoxazoles

To a solution of 2-aminophenol (3.274 g, 30.0 mmol) in polyphosphoric acid (PPA, 30 mL), arylcarboxylic acid (30 mmol) was added. The resulting mixture was heated at 150 °C for 5 h. After the reaction was complete, the mixture was added into cold water and then the pH value was adjusted to 14 with an aqueous solution of sodium hydroxide. The mixture was extracted with ethyl acetate three times. The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (ethyl acetate/hexane) to afford the pure product.

2-(3-Methylphenyl)benzoxazole (1a)[15]

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 21.4, 110.6, 119.9, 124.6, 124.8, 125.1, 126.9, 128.2, 128.8, 132.4, 138.8, 142.0, 150.7, 163.2.

2-(2-Methylphenyl)benzoxazole (1b)[16]

White solid, mp 64–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.80 (s, 3H), 7.31–7.40 (m, 5H), 7.56–7.58 (m, 1H), 7.79–7.81 (m, 1H),

8.16–8.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 110.5, 120.1, 124.3, 125.0, 126.0, 126.2, 129.9, 130.9, 131.8, 138.8, 142.1, 150.2, 163.3.

2-(4-Methylphenyl)benzoxazole(1c)[17]

White solid, mp 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.30–7.34 (m, 4H), 7.55–7.57 (m, 1H), 7.75–7.77 (m, 1H), 8.13 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 110.5, 119.8, 124.4, 124.5, 124.8, 127.6, 129.6, 142.0, 142.1, 150.6, 163.3.

2-Phenylbenzoxazole (1d)[18]

White solid, mp 79–80 °C; ^{1}H 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 110.6, 120.0, 124.6, 125.1, 127.2, 127.6, 128.9, 131.5, 142.1, 150.8, 163.1.

2-(3-Fluorophenyl)benzoxazole (1e)[19]

White solid, mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.21 (m, 1H), 7.25–7.36 (m, 2H), 7.47–7.56 (m, 2H), 7.75–7.78 (m, 1H), 7.94–8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.7, 114.6 (d, J = 23.9 Hz), 118.5 (d, J = 21.2 Hz), 120.2, 123.3 (d, J = 3.1 Hz), 124.8, 125.5, 129.2 (d, J = 8.5 Hz), 130.6 (d, J = 8.1 Hz), 141.9, 150.7, 161.7 (d, J = 3.1 Hz), 162.9 (d, J = 245.4 Hz).

2-(3-Chlorophenyl)benzoxazole (1f)[19]

White solid, mp 124–125 °C; ^{1}H 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 110.7, 120.2, 124.9, 125.6, 125.7, 127.6, 128.8, 130.3, 131.6, 135.1, 141.7, 150.7, 161.6.

2-(3-Bromophenyl)benzoxazole (1g)[19]

White solid, mp 128–130 °C; ^{1}H 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 110.7, 120.2, 123.0, 124.9, 125.6, 126.1, 129.0, 130.5, 130.5, 134.5, 141.8, 150.8, 161.5.

2-(4-Fluorophenyl)benzoxazole (1h)[20]

White solid, mp 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.20 (m, 2H), 7.32–7.35 (m, 2H), 7.54–7.55 (m, 1H), 7.74–7.76 (m, 1H), 8.21–8.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.3, 115.6 (d, J = 22.1 Hz), 119.7, 123.2 (d, J = 2.9 Hz), 124.4, 124.8, 129.5 (d, J = 8.8 Hz), 141.7, 150.4, 161.8, 165.5 (d, J = 251.2 Hz).

2-(4-Chlorophenyl)benzoxazole (1i)[21]

white solid, mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.39 (m, 2H), 7.51–7.57 (m, 2H), 7.57–7.59 (m, 1H), 7.76–7.78 (m, 1H), 8.18–8.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.6, 120.0, 124.7, 125.5, 125.6, 128.8, 129.2, 137.7, 141.9, 150.7, 162.0.

2-(4-Bromophenyl)benzoxazole (1j)[22]

White solid, mp 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.38 (m, 2H), 7.57–7.58 (m, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.76–7.78 (m, 1H), 8.11 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.6, 120.1, 124.8, 125.4, 126.1, 126.2, 129.0, 132.2, 142.0, 150.7, 162.1.

2-(2,4-Dichlorophenyl)benzoxazole (1k)[23]

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 110.8, 120.6, 124.7, 124.8, 125.8, 127.4, 131.3, 132.5, 134.2, 137.5, 141.6, 150.5, 160.1.

2-(3-Methoxyphenyl)benzoxazole (1l)[19]

White solid, mp 71.3–73.8 °C; ^{1}H NMR (400 MHz, CDCl3): δ3.92 (s, 3H), 7.07–7.09 (m, 1H), 7.35–7.37 (m, 2H), 7.40–7.45 (m, 1H), 7.57–7.59 (m, 1H), 7.77–7.79 (m, 2H), 7.85 (d, J = 7.5 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 110.3, 111.5, 118.07, 119.7, 119.8, 124.3, 124.9, 128.0, 129.7, 141.7, 150.4, 159.2, 162.7.

2-(3,4-Dimethoxylphenyl)benzoxazole (1m)[19]

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 56.1, 56.1, 110.0, 110.4, 111.0, 119.6, 119.7, 121.2, 124.5, 124.7, 142.1, 149.2, 150.7, 152.0, 163.1.

General procedure for direct chlorination of 2-arylbenzoxazoles

Substrate **1** (0.5 mmol), chlorinating reagent (0.6 mmol) and $PdCl_2$ (5 mol%) were dissolved in AcOH (2 mL) in a 10 mL vial under air and heated at a specific temperature for 10 h. After the reaction was complete, the solvent was evaporated under reduced pressure. The residual was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the desired product.

6-Chloro-2-(3-methylphenyl)benzoxazole (2a)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.40; mp 99–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.26–7.43 (m, 3H), 7.57 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 111.2, 120.4, 124.8, 125.2, 126.5, 128.2, 128.9, 130.6, 132.7, 138.8, 140.9, 150.9, 163.9; IR (KBr): 3057, 1615, 1554, 1453, 1423, 1329,1261, 1052, 920, 864, 803, 714, 681, 593, 434 cm^{-1}; HRMS-ESI (m/z): calcd for $C_{14}H_{11}ClNO$ (M + H): 244.0529, found 244.0530.

6-Chloro-2-(2-methylphenyl)benzoxazole (2b)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.42; mp 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79 (s, 3H), 7.30–7.42 (m, 4H), 7.57 (s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 111.0, 120.5, 125.0, 125.60, 126.0, 129.8, 130.50, 131.1, 131.8, 138.9, 140.7, 150.3, 163.9; IR (KBr): 3065, 1606, 1542, 1485, 1432, 1389, 1245, 1208, 1084, 1027, 961, 913, 844, 774, 723, 673, 598,

456 cm^{-1}; HRMS-ESI (*m/z*): calcd for $C_{14}H_{11}ClNO$ (M + H): 244.0529, found 244.0525.

6-Chloro-2-(4-methylphenyl)benzoxazole (2c)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.41; mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.26–7.30 (m, 3H), 7.53 (s, 1H), 7.62 (d, J = 8.5 Hz, 1H), 8.12–8.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 111.1, 120.2, 123.9, 125.1, 127.6, 129.6, 130.3, 140.9, 142.3, 150.8, 163.9; IR (KBr): 3035, 2921, 1617, 1555, 1496, 1457, 1418, 1326, 1281, 1254, 1173, 1117, 1047, 1011, 917, 834, 807, 725, 699, 635, 595, 501 cm^{-1}; HRMS-ESI (*m/z*): calcd for $C_{14}H_{11}ClNO$ (M + H): 244.0529, found 244.0526.

6-Chloro-2-phenylbenzoxazole (2d)[24]

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.36; mp 59–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.32 (m, 1H), 7.48–7.56 (m, 4H), 7.64 (d, J = 8.5 Hz, 1H), 8.18–8.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.2, 120.4, 125.2, 126.6, 127.6, 128.9, 130.6, 131.7, 140.8, 150.8, 163.6; IR (KBr): 3057, 2924, 2854, 1618, 1552, 1483, 1451, 1426, 1331, 1263, 1121, 1052, 1022, 919, 876, 809, 693, 595, 487 cm^{-1}; Anal. Calcd for $C_{13}H_8ClNO$ (229.03): C 67.99, H 3.51, N 6.10, found: C 68.37, H 3.61, N 5.94.

6-Chloro-2-(3-fluorophenyl)benzoxazole (2e)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.38; mp 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.24 (m, 1H), 7.24–7.26 (m, 1H),7.32–7.35 (m, 1H) 7.48–7.50 (m, 1H), 7.58 (s, 1H), 7.65–7.68 (m, 1H), 8.00 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.3, 114.5 (d, J = 24.4 Hz), 118.8 (d, J = 21.2 Hz), 120.7, 123.3 (d, J = 3.1 Hz), 125.5, 129.9 (d, J = 8.9 Hz), 130.7 (d, J = 8.1 Hz), 130.7, 140.7, 150.9, 162.4 (d, J = 3.4 Hz), 162.9 (d, J = 245.8 Hz); IR (KBr): 3069, 1592, 1556, 1481, 1452, 1328, 1295, 1265, 1210, 1176, 1051, 881, 811, 787, 722, 673, 596, 516 cm^{-1}; Anal. Calcd for $C_{13}H_7ClFNO$ (247.02): C 63.05, H 2.85, N 5.66, found: C 63.16, H 2.98, N 5.46.

6-Chloro-2-(3-chlorophenyl)benzoxazole (2f)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.35; mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.33 (m, 1H), 7.43–7.48 (m, 2H), 7.55 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 7.7 Hz, 1H), 8.17 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 111.3, 120.6, 125.5, 125.6, 127.6, 128.3, 130.21, 131.1, 131.7, 135.1, 140.6, 150.8, 162.2; IR (KBr): 3065, 1611, 1550, 1472, 1428, 1330, 1259, 1102, 1051, 921, 862, 839, 805, 756, 718, 675, 595, 433 cm^{-1}; Anal. Calcd for $C_{13}H_7Cl_2NO$ (262.99): C 59.12, H 2.67, N 5.30, found: C 59.23, H 2.64, N 5.22.

6-Chloro-2-(3-bromophenyl)benzoxazole (2g)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.37; mp 141–143 °C;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.39 (m, 2H), 7.56 (s, 1H), 7.63–7.66 (m, 2H), 8.11 (d, J = 7.7 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.3, 120.6, 123.0, 125.5, 126.0, 128.5, 130.4, 131.1, 134.6, 140.6, 150.8, 162.0; IR (KBr): 3064, 1614, 1546, 1468, 1427, 1330, 1259, 1049, 860, 804, 715, 673, 594 cm^{-1}; Anal. Calcd for $C_{13}H_7BrClNO$ (306.94): C, 50.60; H, 2.29; N, 4.54, found: C, 50.76; H, 2.30; N, 4.24.

6-Chloro-2-(4-fluorophenyl)benzoxazole (2h)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.33; mp 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.21 (m, 2H), 7.30–7.32 (m, 1H), 7.54 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 8.17–8.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.2, 116.2 (d, J = 22.1 Hz), 120.4, 123.0 (d, J = 3.3 Hz), 125.3, 130.0 (d, J = 8.9 Hz), 130.7, 140.8, 150.9, 162.7, 164.9 (d, J = 251.8 Hz); Anal. Calcd for $C_{13}H_7ClFNO$ (247.02): C 63.05, H 2.85, N 5.66, found: C 63.22, H 2.87, N 5.59.

6-Chloro-2-(4-chlorophenyl)benzoxazole (2i)[25]

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.35; mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.35 (m, 1H), 7.48–7.51 (m, 2H), 7.57 (d, J = 1.8 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 8.13–8.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.3, 120.5, 125.2, 125.5, 128.9, 129.3, 130.9, 138.1, 140.8, 150.9, 162.7.

6-Chloro-2-(4-bromophenyl)benzoxazole (2j)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.38; mp 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.33 (m, 1H), 7.55 (s, 1H), 7.63–7.65 (m, 3H), 8.04–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.2, 120.5, 125.4, 125.6, 126.5, 129.0, 131.0, 132.3, 140.7, 150.8, 162.7; IR (KBr): 3078, 2924, 1612, 1584, 1457, 1427, 1394, 1327, 1256, 1233, 1066, 1046, 1003, 918, 837, 814, 723, 559, 499 cm^{-1}; Anal. Calcd for $C_{13}H_7BrClNO$ (306.94): C 50.60, H 2.29, N 4.54, found: C 50.78, H 2.24, N 4.34.

6-Chloro-2-(2,4-dichlorophenyl)benzoxazole (2k)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 30), provided the desired compound as a white solid; R_f 0.39; mp 140–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.40 (m, 2H), 7.57–7.61 (m, 2H), 7.73 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.4, 121.0, 124.2, 125.6, 127.5, 131.4, 131.5, 132.4, 134.3, 137.8, 140.3, 150.6, 160.6; IR (KBr): 3075, 1609, 1584, 1554, 1467, 1426, 1370, 1108, 1080, 1020, 919, 844, 805, 596 cm^{-1}; HRMS-ESI (*m/z*): calcd for $C_{13}H_6Cl_3NO$ (M + H): 297.9593, found 297.9602.

General procedure for direct acetoxylation of 2-arylbenzoxazoles

Substrate **1** (0.5 mmol), $PhI(OAc)_2$ (0.55 mmol), $Pd(OAc)_2$ (5 mol%) were dissolved in AcOH (2 mL) and Ac_2O (2 mL) in a

10 ml vial under air and heated at a specific temperature for 48 h. Upon completion, the solvent was evaporated to dryness *in vacuo*. The residual was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the desired product.

2-(Benzoxazol-2-yl)-4-methylphenyl acetate (3a)

Purification by flash chromatography over silica gel, eluting with ethyl acetate-hexane (1 : 10), provided the desired compound as a white solid; R_f 0.32; White solid; mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45–2.47 (s, 3H), 2.48 (s, 3H), 7.11 (d, J = 8.2 Hz, 1H), 7.34–7.38 (m, 3H), 7.54–7.55 (m, 1 H), 7.74–7.76 (m, 1H), 8.10–8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 21.4, 110.4, 119.8, 120.2, 123.8, 124.5, 125.3, 130.5, 133.2, 136.3, 141.8, 147.0 150.1, 160.0, 170.2; IR (KBr): 2919, 1752, 1612, 1548, 1479, 1448, 1222, 1191, 1007, 908, 841, 739, 637, 547 cm^{-1}; HRMS-ESI (m/z): calcd for $C_{16}H_{14}NO_3$ (M + H): 268.0973, found 268.0968.

2-(Benzoxazol-2-yl)-5-methylphenyl acetate (3b)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 10), provided the desired compound as a white solid; R_f 0.35; mp 79–80 °C; ^{1}H NMR (400 MHz, CDCl3): δ 2.45 (s, 3H), 2.49 (s, 3H), 7.04 (s, 1H), 7.21–7.35 (m, 3H), 7.53–7.55 (m, 1H), 7.72–7.74 (m, 1H), 8.17 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 21.4, 110.3, 117.5, 120.1, 124.4, 124.6, 125.2, 127.4, 130.0, 142.0, 143.6, 149.1, 150.0, 160.0, 170.0; IR (KBr): 2928, 1758, 1618, 1557, 1497, 1459, 1245, 1196, 1017, 910, 844, 740 cm^{-1}; HRMS-ESI (m/z): calcd for $C_{16}H_{14}NO_3$ (M + H): 268.0973, found 268.0967.

2-(Benzoxazol-2-yl)-3-methylphenyl acetate (3c)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 10), provided the desired compound as a white solid; R_f 0.35; mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.53 (s, 3H), 7.07–7.09 (m, 1H), 7.24–7.26 (m, 1H), 7.38–7.46 (m, 3H), 7.57–7.60 (m, 1H), 7.81–7.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 21.4, 110.5, 120.3, 120.80, 121.0, 124.4, 125.3, 128.6, 131.3, 140.6, 141.40, 150.0, 150.4, 159.6, 169.6; IR (KBr): 2932, 2847, 1765, 1616, 1510, 1453, 1365, 1247, 1190, 1148, 1011, 896, 846, 753 cm^{-1}; HRMS-ESI (m/z): calcd for $C_{16}H_{14}NO_3$ (M + H): 268.0973, found 268.0977.

2-(Benzoxazol-2-yl)-phenyl acetate (3d)[26]

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 10), provided the desired compound as a white solid; R_f 0.33; mp 75–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H), 7.23–7.24 (m, 1 H), 7.35–7.37 (m, 3 H), 7.42 (m, 2 H), 7.55–7.56 (m, 1H), 8.30 (dd, J = 7.9 Hz, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 110.4, 120.3, 120.4, 124.1, 124.6, 125.4, 126.5, 130.2, 132.4, 141.9, 149.2, 150.1, 159.8, 170.0; IR (KBr): 3070, 2920, 1754, 1612, 1547, 1480, 1446, 1367, 1185, 1032, 913, 737, 473 cm^{-1}.

2-(Benzoxazol-2-yl)-4-methoxyphenyl acetate (3e)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 6), provided the desired compound as a white solid; R_f 0.32; mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3 H), 3.89 (s, 3H), 7.05–7.14 (m, 2H), 7.34–7.36 (m, 2H), 7.53–7.54 (m, 1H), 7.74–7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 55.9, 110.4, 114.0, 118.7, 120.3, 120.7, 124.6, 125.0, 125.5, 141.8, 142.8, 150.2, 157.5, 159.8, 170.4; IR (KBr): 2937, 2838, 1763, 1597, 1552, 1499, 1453, 1365, 1326, 1242, 1180, 1033, 1006, 936, 876, 827, 755, 578, 516 cm^{-1}; HRMS-ESI (m/z): calcd for $C_{16}H_{14}NO_4$ (M + H): 284.0932, found 284.0931.

2-(Benzoxazol-2-yl)-4,5-dimethoxyphenyl acetate (3f)

Purification by flash chromatography over silica gel, eluting with ethyl acetate–hexane (1 : 4), provided the desired compound as a white solid; R_f 0.35; mp 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3 H), 3.95 (s, 3H), 4.01 (s, 3H), 6.71–6.72 (s, 1H), 7.27–7.35 (m, 2 H), 7.52–7.54 (m, 1H), 7.72–7.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 56.2, 56.4, 107.1, 110.2, 111.1, 111.8, 119.9, 124.5, 125.0, 141.9, 143.7, 147.0, 150.0, 152.1, 160.0, 170.3; IR (KBr): 2936, 2838, 1765, 1615, 1560, 1503, 1453, 1245, 1175, 1134, 1025, 939, 877, 744 cm^{-1}; HRMS-ESI (m/z): calcd for $C_{17}H_{16}NO_5$ (M + H): 314.1028, found 314.1038.

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