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Direct arylation of benzoxazole C–H bonds with iodobenzene diacetates

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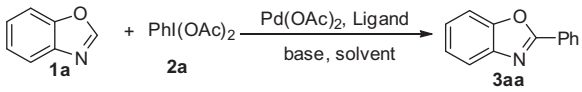
ABSTRACT

A Pd $(OAc)_2$-catalyzed direct arylation of benzoxazole C–H bonds has been achieved with iodobenzene diacetates as the arylation reagent in moderate to good yields. The procedure tolerates a series of functional groups, such as methoxy, nitro, cyano, chloro, and bromo groups.

Heteroaromatics are important structural units frequently found in natural products, pharmaceuticals, and other functional compounds.[1] Recently, direct functionalization of heteroarenes C–H bond represents an environmentally and economically attractive strategy, which is a potential alternative to traditional cross-coupling reactions because it avoids the extra introduction of functional groups at one of the coupling partners.[2] Among the direct arylation of C–H bonds,[3] much progress has been made on employing convenient electrophiles, such as ArX[4] (X = I, Br, Cl, OTf and OMs), $ArSO_2Cl$, $ArSO_2Na$,[5] and ArM (M = Mg, B, Si etc.).[6] Meanwhile, the employment of diaryliodonium salts (usually Ar_2IBF_4) as the arylation reagents in the C–H activation received great attentions.[7] For example, in 2006, Sanford developed Pd-catalyzed direct 2-arylation of indoles with Ar_2IBF_4.[8] Subsequently, Gaunt reported a site-selective Cu(II)-catalyzed C–H bond functionalization of indoles with Ar_2IBF_4 or Ar_2IOTf.[9] Recently, Liu described a Pd(II)-catalyzed *ortho* C–H arylation of phenol esters with Ph_2IOTf.[10] However, to our surprise, iodobenzene diacetate ($PhI(OAc)_2$) was not found to be arylating reagent for these C–H bond functionalizations. As we know, iodobenzene diacetates mainly served as oxidant[11] and acetoxylation reagent in the C–H bond functionalization.[12] Herein, we report our study in the direct arylation of benzoxazole with iodobenzene diacetate as the arylating reagent.

At the outset of the investigation, benzo[*d*]oxazole was employed as the substrate to react with $PhI(OAc)_2$ in the presence of $Pd(OAc)_2$, PPh_3, and Na_2CO_3 in DMSO at 150 °C under nitrogen. To our delight, 2-phenylbenzoxazole (**3aa**) was detected by GC–MS and isolated in 22% yield (Table 1, entry 1). The preliminary result encouraged us to optimize the reaction conditions. Among the bases tested, such as LiOH, *t*-BuOLi, NaOH, K_2CO_3, $K_3PO_4{\cdot}3H_2O$, and Cs_2CO_3, Cs_2CO_3 was the best (Table 1, entries 2–8). Next, a variety

Table 1
Selected results of screening the optimal conditions



Entry	Ligand	Base	Solvent	Yield[a] (%)
1	PPh_3	Na_2CO_3	DMSO	22
2	PPh_3	LiOH	DMSO	25
3	PPh_3	*t*-BuOLi	DMSO	<5
4	PPh_3	NaOH	DMSO	<5
5	PPh_3	K_2CO_3	DMSO	21
6	PPh_3	$K_3PO_4{\cdot}3H_2O$	DMSO	17
7	PPh_3	Cs_2CO_3	DMSO	53
8	dppb	Cs_2CO_3	DMSO	53
9	dppf	Cs_2CO_3	DMSO	<5
10	dppe	Cs_2CO_3	DMSO	54
11	dppp	Cs_2CO_3	DMSO	31
12	2,2′-Bipyridine	Cs_2CO_3	DMSO	57
13	2,2′-Biquinoline	Cs_2CO_3	DMSO	27
14	Phen	Cs_2CO_3	DMSO	84(46)[b](60)[c]
15	Phen	Cs_2CO_3	THF	26
16	Phen	Cs_2CO_3	DMF	52
17	Phen	Cs_2CO_3	Toluene	39
18	Phen	Cs_2CO_3	NMP	44
19	Phen	Cs_2CO_3	Acetonitrile	20
20	Phen	Cs_2CO_3	Dioxane	<5
21	Phen	*t*-BuOK	DMSO	38

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.25 mmol), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), base (0.2 mmol), dry solvent (2 mL), 150 °C, under N_2, 20 h, sealed tube. Isolated yield.
[b] Under air.
[c] 130 °C. Phen = 1,10-phenanthroline.

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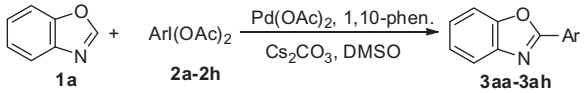
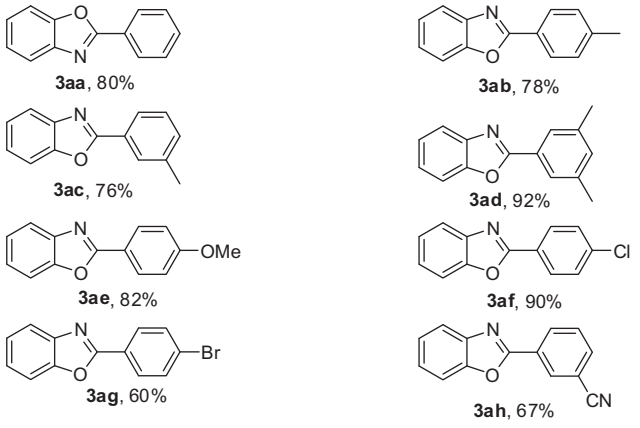
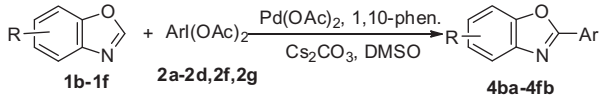
Table 2
Palladium-catalyzed arylation of benzoxazole derivatives with iodobenzene diacetates[a]

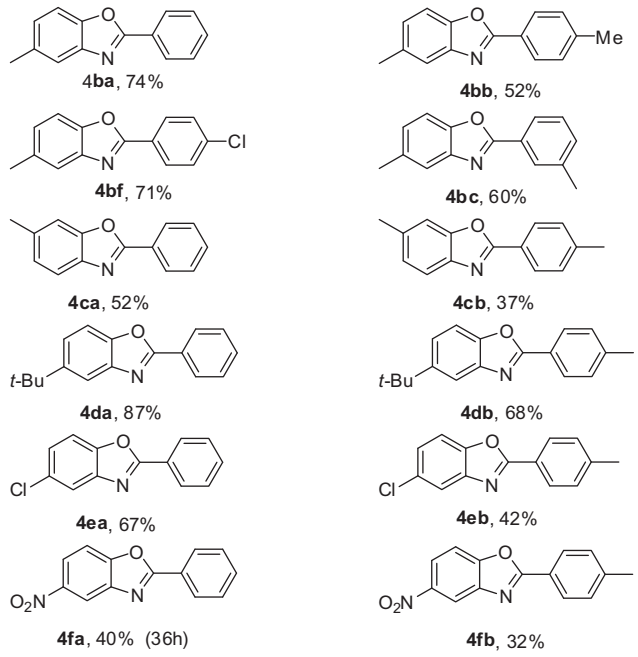




[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (5 mol %), Phen (10 mol %), Cs_2CO_3 (0.2 mmol), DMSO (2 mL), 150 °C, 20 h, under N_2, isolated yield.

Table 3
Palladium-catalyzed arylation of benzoxazole derivatives with iodobenzene diacetates[a]





[a] Reaction conditions: **1** (0.2 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (5 mol %), Phen (10 mol %), Cs_2CO_3 (0.2 mmol), DMSO (2 mL), 150 °C, 20 h, under N_2, isolated yield.

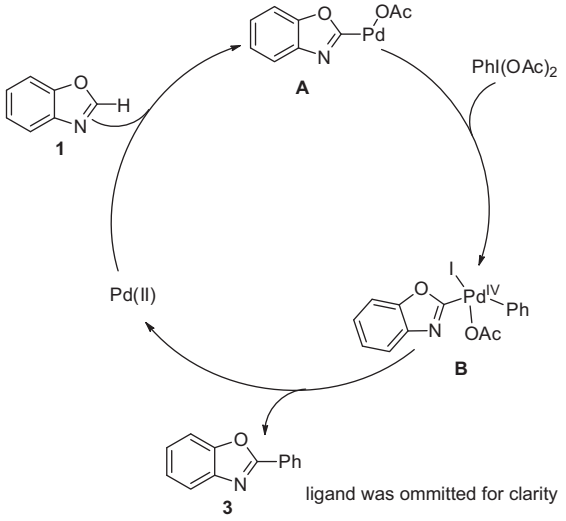
of bidentate phosphine and nitrogen ligands were screened, and 1,10-phenanthroline (Phen) gave the optimal result (Table 1, entry 14). The solvents were significant to this reaction and the initially used DMSO provided the optimal result (Table 1, entries 17–20). Only 60% yield was obtained when the temperature was decreased to 130 °C (Table 1, entry 14). Finally, we found that the combination of 5 mol % of $Pd(OAc)_2$, 10 mol % of Phen, and 1 equiv of Cs_2CO_3 in DMSO at 150 °C under nitrogen for 24 h served as the optimal conditions for this transformation.

With acceptable conditions in hand (Table 1, entry 14), we first tested the scope of this methodology for different iodobenzene diacetates, as shown in Table 2. As expected, a series of functional groups on the phenyl ring of iodobenzene diacetates, such as methoxy, bromo, chloro, and cyano groups, were compatible for the procedure, providing the arylated products in moderate to good yields (**3aa**–**3ah**, Table 2). Generally, the reaction was not sensitive to the electronic properties of the substituents on the phenyl ring of iodobenzene diacetates, as both electron-donating groups and electron-withdrawing groups were well-tolerated. Except **3af**, electron-donating groups gave slight higher yields than those electron-withdrawing groups analogs (**3aa** and **3ab** vs **3ag** and **3ah**, Table 2). Notably, 1-(diacetoxyiodo)-4-chlorobenzene gave the corresponding arylating products in excellent yields (**3af**, Table 2).

After a broad scope of electrophiles established, we were particularly interested in extending the direct arylation to benzo[*d*]oxazole derivatives (Table 3). 5-Methyl, 6-methyl, 5-*tert*-butyl, 5-chloro and 5-nitro analogs could be selectively arylated with an acceptable efficiency. However, the electron-withdrawing groups on the phenyl ring of benzo[*d*]oxazole slightly decreased the reaction efficiency.

When PhI instead of $PhI(OAc)_2$ was subjected to the procedure, only trace of arylation products was detected by GC–MS. This result ruled out the possibility of ArI as the intermediate in the reaction.

The mechanism of the arylation reaction may involve a Pd(II) insertion into the benzoxazole 2-C–H bond in the presence of base and subsequent oxidation of the Pd(II) complex **A** to a Pd(IV) intermediate **B** by $PhI(OAc)_2$ (Scheme 1).[8,10] Then, reductive



Scheme 1. Possible mechanism.

elimination from the Pd(IV) complex affords the desired product and regenerates the Pd(II) species.

In conclusion, we have developed a palladium-catalyzed arylation of benzo[*d*]oxazole C–H bond with iodobenzene diacetates.[13] The reaction provides a novel methodology allowing for a wide functional group tolerance. Further mechanistic studies of this process and its application to the synthesis of functional materials are currently underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.076.

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13. *Gerenal procedure*: Under N_2, a reaction tube was charged with benzoxazole (0.2 mmol), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol), $Pd(OAc)_2$ (2.2 mg, 5 mol %), 1,10-phenanthroline (7.9 mg, 10 mol %) and DMSO (2 mL). The mixture was stirred at 150 °C for 20 h. After the completion of the reaction, as monitored by TLC, 10 mL of ethyl acetate was added and the mixture was washed with water (3×5 mL). Then the organic layer was concentrated in vacuo and the residue was purified by flash column chromatography on a silica gel to give the desired product.