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### **Graphical Abstract**

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1	Palladium catalyzed ortho-C-H-benzoxylation of 2-arylpyridines using
2	iodobenzene dibenzoates
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9	
10	Abstract
11	A palladium-catalyzed ortho-C-H-benzoxylation of 2-arylpyridines using iodobenzene dibenzoates has been
12	developed. The reaction employed the stable and easily accessible hypervalent iodine reagents as both benzoxylate
13	source and oxidant which made the protocol simple and facile. It showed high regioselectivity and good functional
14	group tolerance, and gave the mono-benzoxylation products in moderate to excellent yields.
15	
16	Keywords
17	Palladium catalysis; C-H benzoxylation; Hypervalent iodine reagent
18	
19	1. Introduction
20	Transition-metal-catalyzed C-H bond functionalization has become one of the most efficient and facile tools in
21	organic synthesis, which avoids prefunctionalization of substrates and shows great atom economy. <sup>1</sup> Notable progress
22	has been made predominantly with Pd, Cu, Ru, Rh and Ir for transforming C-H bond to C-C or C-heteroatom
23	bonds. <sup>2</sup> Among them, C-O bond formation especially acyloxylation has attracted considerable attention as the
24	important role of ester functionality in natural products, pharmaceuticals, and functional materials. <sup>3</sup>
25	In 2006, Yu and co-workers reported Cu(II) catalyzed acetoxylation of arene C-H bond in HOAc/Ac <sub>2</sub> O using
26	oxygen as oxidant. <sup>4</sup> Later Sanford, Kwong, Pelcman, Chen, Liang and Li et al. described the sp <sup>2</sup> C-H acetoxylation
27	of different aromatic substances by using PhI(OAc) <sub>2</sub> as acyloxylate source and/or oxidant (Scheme 1, (a)). <sup>5</sup> However,
28	most reports on C-H bond acyloxylation is limited to acetoxylation, the benzoxylation of C-H bond is less

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developed.<sup>6</sup> Aryl benzoates are important as them have been found as key structures of some natural products. A 1 Rh-catalyzed ortho-benzoxylation of sp<sup>2</sup> C-H bond was introduced by Cheng and co-workers in 2009 with benzoic 2 acids.<sup>7</sup> Then, significant efforts have been made towards such *ortho*-benzoxylation by the groups of Cheng, Patel, 3 4 Ackermann and others, employing benzoic acids/salts, benzoyl chlorides, anhydrides, alkylbenzene, benzyl amines, 5 aryl alkenes or alkynes as benzoxy surrogates and  $O_2$ ,  $K_2S_2O_8$ , TBHP or  $Ag_2CO_3$  as oxidants (Scheme 1, (b)).<sup>8</sup> In 6 general, most of the methods employed independent acyloxylate source and oxidant, which would lead the reaction 7 condition sophisticated. Otherwise, chemoselectivity remained a problem in these transformations as the mono- and di-acyloxylation products were usually obtained simultaneously with a non-ignorable ratio. Therefore, it's highly 8 9 desirable to develop simpler and more facile protocols for highly selective C-H bond acyloxylation. In 2013, Wu and 10 coworkers developed a Pd-catalyzed ortho-benzoxylation of 2-arylpyridines using aryl acylperoxides without external oxidant.<sup>9</sup> Herein, we report the Pd-catalyzed ortho-benzoxylation of 2-arylpyridines using iodobenzene 11 12 dibenzoates, a stable hypervalent iodine reagent which was easily accessible from the reaction of PhI(OAc)<sub>2</sub> and benzoic acids,<sup>10</sup> as both benzoxylate source and oxidant. 13

14

#### 15 Scheme 1. Transition-metal-catalyzed ortho-C-H-acyloxylation



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### 18 **2. Results and discussion**

Initial investigation was carried out between 2-phenylpyridine (1a) and iodobenzene dibenzoate (2a) with Pd(OAc)<sub>2</sub> as the catalyst (Table 1). Solvents were first examined. The reaction hardly proceeded in chlorobenzene, DME and 1,4-dixoane while a mixture of mono- (3a) and di-benzoxylation (4a) products were obtained in CH<sub>3</sub>CN, toluene and DCE (Table 1, entries 1–6). The results showed that DCE should be the superior solvent for the reactivity

but toluene was beneficial for the selectivity. Delighting result was obtained with a mixed solvent of DCE/toluene 1 2 (4:1), which greatly promoted the isolated yield ratio of **3a**: **4a** to 77:9 (Table 1, entry 7). The substrate ratio of 3 2-phenylpyridine (1a) to iodobenzene dibenzoate (2a) was also essential to the chemoselectivity. With the changing of substrate ratio from 1:1.3 to 1:1.05, the ratio of 3a: 4a was increased from 77:9 to 85:1 (Table 1, entries 7-10). 4 5 Treating the reaction under air caused a slightly decrease of the isolated yield (Table 1, entry 11). Prolonging the 6 reaction time from 8 h to 12 h didn't improve the yield of **3a** but lead to more conversion to **4a** (Table 1, entry 12). 7 The reaction gave poor yield with lower loading of palladium catalyst and didn't proceed without catalyst (Table 1, 8 entry 13, 14). Other palladium catalysts such as  $PdCl_2$  and  $Pd_2(dba)_3$  were not so efficient as  $Pd(OAc)_2$  (Table 1, entry 15 and 16). The product yield dramatically decreased under lower temperature (Table 1, entries 17, 18).<sup>11</sup> 9

10

11 **Table 1.** Optimization of the reaction conditions<sup>a</sup>

			+ Phl(OCO	Ph) <sub>2</sub> Pd(II) solvent, 8 h		Ph O +	O Ph
12		1a	2a		3a	4a	
	Entry	Pd(II)	1a:2a	Solvent	T (°C)	Yield	(%) <sup>b</sup>
				· ·		3a	4a
	1	$Pd(OAc)_2$	1:1.3	chlorobenzene	130	<5	-
	2	$Pd(OAc)_2$	1:1.3	DME	85	<5	-
	3	$Pd(OAc)_2$	1:1.3	1,4-dioxane	100	<5	-
	4	Pd(OAc) <sub>2</sub>	1:1.3	CH <sub>3</sub> CN	85	50	22
	5	$Pd(OAc)_2$	1:1.3	toluene	110	52	7
	6	Pd(OAc) <sub>2</sub>	1:1.3	DCE	85	72	15
	7	Pd(OAc) <sub>2</sub>	1:1.3	DCE/toluene (4:1)	85	77	9
	8	Pd(OAc) <sub>2</sub>	1:1.2	DCE/toluene (4:1)	85	76	5
	9	$Pd(OAc)_2$	1:1.1	DCE/toluene (4:1)	85	80	4
	10	Pd(OAc) <sub>2</sub>	1:1.05	DCE/toluene (4:1)	85	85	<1
	11 <sup>c</sup>	$Pd(OAc)_2$	1:1.05	DCE/toluene (4:1)	85	80	10
	12 <sup>d</sup>	$Pd(OAc)_2$	1:1.05	DCE/toluene (4:1)	85	79	<1
	13 <sup>e</sup>	$Pd(OAc)_2$	1:1.05	DCE/toluene (4:1)	85	38	2
	14	-	1:1.05	DCE/toluene (4:1)	85	n.d.	-
	15	PdCl <sub>2</sub>	1:1.05	DCE/toluene (4:1)	85	78	2
	16	$Pd_2(dba)_3$	1:1.05	DCE/toluene (4:1)	85	80	4
	17	$Pd(OAc)_2$	1:1.05	DCE/toluene (4:1)	65	60	<1
	18	Pd(OAc) <sub>2</sub>	1:1.05	DCE/toluene (4:1)	45	<5	_

<sup>13</sup> 

14 15 <sup>a</sup>Reaction conditions: 2-phenyl pyridine (**1a**) (0.3 mmol), iodobenzene dibenzoate (**2a**), palladium catalyst (5 mol%) in solvent (2.0 mL) stirring under  $N_2$  for 8 h. <sup>b</sup>Isolated yield. <sup>c</sup>Reacted for 12 h. <sup>d</sup>Under air. <sup>e</sup>With 2.5 mol% Pd(OAc)<sub>2</sub>.

2 Under the optimized conditions, the benzoxylation of a series of 2-arylpyridine (1) with iodobenzene dibenzoate 3 (2a) were examined as shown in Table 2. Generally, the reaction could tolerate various functional groups such as Me, 4 OMe, Cl, Br, F, and OCOMe, giving the desired products in good to excellent yields. The 2-arylpyridines which 5 possessed electron-donating functional groups on the benzene ring gave higher yields than those bearing 6 electron-withdrawing groups (Table 2, entry 2-7 and 8-14). Especially, isolated product yields of the substrates possessed an ortho-CH<sub>3</sub> or meta-CH<sub>3</sub> substituent were up to 99% (Table 2, entry 5–7). Remarkably, the reaction 7 8 showed highly regioselectivity when the benzene ring contained a *meta*-substituted group, in which the benzoxylation 9 occurred at the sterically less hindered ortho-C-H bond (Table 2, entry 3, 4, 6 and 7). Furthemore, this benzoxylation 10 could be applied to heteroaryl substrates such as 2-thienyl pyridines, which gave the 3-benzoxylated thiophenes in 11 good yields (Table 2, entry 15, 16).

12

13 **Table 2.** The palladium-catalyzed benzoxylation of 2-arylpyridines<sup>a,b</sup>

14		+ Phl(OCOPh) <sub>2</sub> 2a	Pd(OAc) <sub>2</sub> (5 mol%) DCE/toluene 85 °C, 8 h	$R^{1}$
	Entry	Substrate	Product	Yield (%) <sup>b</sup>
	1 [	(1b)	Ph O N (3b)	68
	2 MeC	(1c)	Ph O N MeO (3c)	82
	3	Me (1d)	Ph O N OMe (3d)	78



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The benzoxylation of 2-(3-methyl)phenylpyridine (**1g**) with various iodobenzene dibenzoate derivatives (**2**) were also investigated as shown in Table 3. Good functional group compatibility on the benzoyl group such as Me, OMe, F and Cl was demonstrated, affording the corresponding desired products in moderate to excellent yields (Table 3, entry 1-4). It was worth noting that the method was also suitable for aliphatic acetoxylation with iodobenzene diacetate derivetives such as iodobenzene dipivalate, which gave the desired product in 82% yield (Table 3, entry 5).

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8 reacted with iodobenzene dibenzoate (2a) to generate the oxidative addition product intermediate B, which might be a
9 Pd(IV) or bimetallic Pd(III)-Pd(III) complex.<sup>6a, 12</sup> Finally, reductive elimination of intermediate B afforded the desired

10 product **3a** and regenerated the palladium(II) species to complete the catalytic cycle.<sup>6c, 13</sup>

11

12 Scheme 3. Plausible mechanism of the *o*-benzoxylation

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1 2

A control experiment of 2-phenylpyridine with both PhI(OAc)<sub>2</sub> and PhI(OBz)<sub>2</sub> was also carried out to illustrate the reaction mechanism (Scheme 4). The result indicated that *ortho*-benzoxylation was more favored than *ortho*-acetoxylation under the standard conditions.

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7 Scheme 4. Control reaction of *o*-benzoxylation *vs o*-acetoxylation



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9

#### 10 **3. Conclusions**

In summary, a palladium-catalyzed *ortho*-C–H-benzoxylation of 2-arylpyridines using iodobenzene dibenzoates has been developed, in which the stable and easily accessible hypervalent iodine reagents served as both benzoxylate source and oxidant. This process showed high regioselectivity and good functional group tolerance, and gave the mono-benzoxylation products in moderate to excellent yields. It provides a simple and facile synthetically strategy for the construction of benzoic ester functionalities. Further application of this synthetic methodology is currently underway in our laboratory.

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#### 1

#### 2 Supplementary data

- 3 Supplementary data associated with this article can be found, in the online version, at doi:
- 4

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