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Novel Methodology for the Efficient Synthesis of 3-Aryloxindoles: [1,2]-Phospha-Brook Rearrangement–Palladium-Catalyzed Cross-Coupling Sequence

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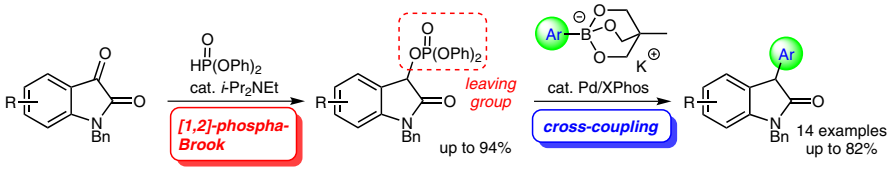

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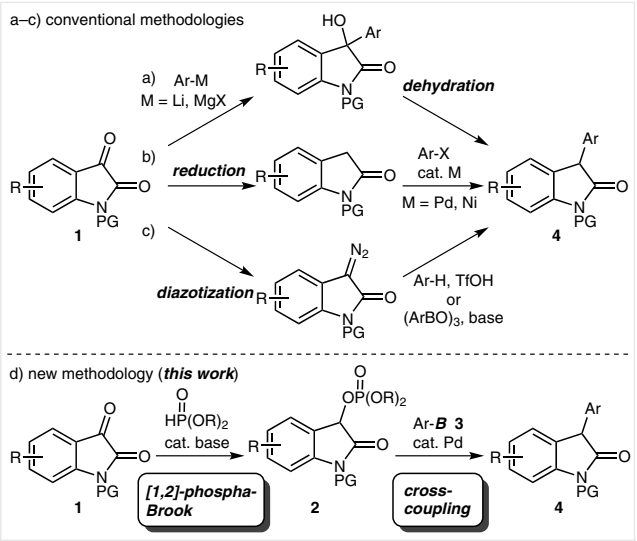
Abstract A novel methodology for the efficient synthesis of 3-aryloxindoles from isatin derivatives was developed. The methodology involves the formation of an oxindole having a phosphate moiety at the C-3 position via the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis followed by palladium-catalyzed cross-coupling with aryl boron reagents. The one-pot synthesis of 3-aryloxindoles from isatin derivatives is also described.

Key words oxindole derivatives, phospha-Brook rearrangement, Brønsted base catalysis, cross-coupling, palladium catalyst

Oxindole derivatives with C-3 functionalities are common motifs in biologically active natural products and pharmaceuticals.[1] 3-Aryloxindoles are particularly important because they not only belong to one of the privileged subclasses but also serve as valuable building blocks in organic synthesis. For instance, these compounds are widely employed as substrates in various catalytic asymmetric reactions to provide 3,3-disubstituted oxindoles possessing quaternary stereogenic centers.[2] Many methodologies for the synthesis of 3-aryloxindoles have been developed over the past decades. They can be divided into two types of approaches. The first is the intramolecular cyclizations of α-aryl acetanilide derivatives, including acid-promoted Friedel–Crafts cyclization,[3] base-promoted cyclization,[4] or photoinduced cyclization.[5] Palladium-catalyzed intramolecular α-arylation of amides, developed in recent years, is also categorized as this approach.[6] The reaction efficiently provides 3-aryloxindoles; however, this approach requires multistep syntheses of each precursor for the cyclization, which is not suitable for divergent syntheses. The second approach, which is more commonly utilized, is based on transformations starting from isatin derivatives. The most general methodology involves arylation of isatin derivatives using arylating agents, such as aryl lithium and aryl Grignard reagents, followed by dehydration (Scheme 1, a).[7] An alternative methodology is C-3 selective arylation of C-3 unsubstituted oxindoles, which are accessible by the reduction of the corresponding isatin derivatives, catalyzed by transition-metal complexes, such as a palladium and a nickel complex (Scheme 1, b).[8] Although both methodologies are highly reliable, they require the use of reactive arylating agents and/or harsh reductive conditions, so that there remains the issue of functional-group tolerance. Recently, the arylation of 3-diazooxindoles has also been reported (Scheme 1, c).[9] While the reaction proceeds under mild reaction conditions, the introducible aryl group is rather limited. Therefore, a new methodology that allows the efficient synthesis of 3-aryloxindoles from isatin derivatives under mild reaction conditions would be highly valuable.

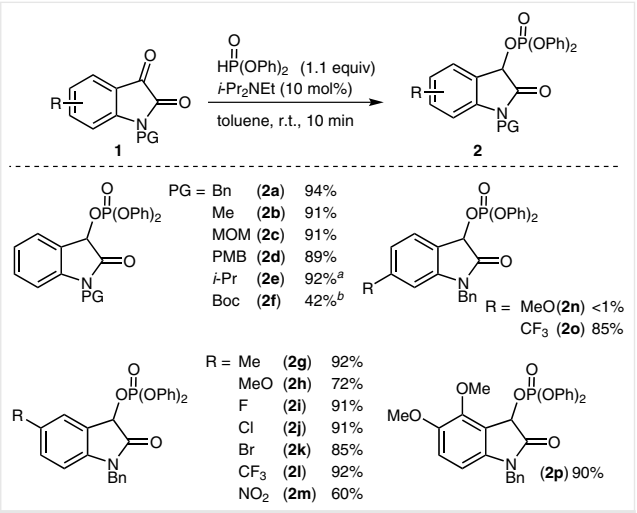
In this context, we envisioned a new methodology based on the two-step sequence strategy shown in Scheme 1 (d). The first step of our designed methodology is the direct conversion of a keto moiety at the C-3 position of isatin derivatives into a phosphate moiety via the [1,2]-phospha-Brook rearrangement.[10,11] Treatment of isatin derivatives **1** with a secondary phosphite in the presence of a catalytic amount of Brønsted base would result in the addition of phosphite to a keto moiety followed by the migration of the dialkoxyphosphoryl moiety from carbon to oxygen, that is, the [1,2]-phospha-Brook rearrangement, to provide corresponding phosphate **2**. This transformation of ketones is known to take place under mild reaction conditions, especially in the case of α-keto carbonyl compounds including isatin derivatives. The second step is the introduction of an aryl group by palladium-catalyzed cross-coupling reaction with aryl boron reagents utilizing the phosphate moiety of **2** as a leaving group. Although the coupling reaction of oxindole derivatives having a leaving group at the C-3 posi-



Scheme 1 Synthetic methodologies for 3-aryloxindoles from isatin derivatives

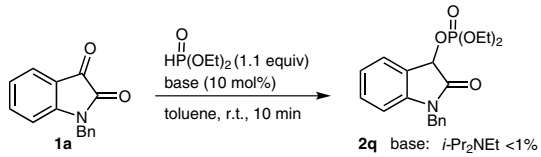
tion has never been studied, we expected that the cross-coupling would be possible because the phosphate moiety is located at the benzylic position as well as at the position α to an amide group.[12] Herein, we report a new synthesis of 3-aryloxindoles from isatin derivatives using the [1,2]-phospha-Brook rearrangement–cross-coupling sequence strategy. We also describe the one-pot synthesis of 3-aryloxindoles from isatin derivatives.

The investigation began by exploring the conditions for the direct conversion of a keto moiety at the C-3 position of the isatin derivatives into a phosphate moiety via the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis. *N*-Benzyl-protected isatin **1a** was chosen as the initial substrate, and the reaction with diphenyl phosphite was attempted. As a result, the reaction reached completion within 10 minutes by using *N*,*N*-diisopropylethylamine as a catalyst and corresponding oxindole **2a** having a phosphate moiety at the C-3 position was obtained in high yield (Scheme 2).[13] These conditions were applicable to a wide range of isatin derivatives having different protective groups, including MOM, PMB, and Boc groups, and a variety of substituents on the benzene ring to afford the corresponding oxindole derivatives in good to high yields except for isatin **1n** having a methoxy group at the C-6 position.



Scheme 2 Synthesis of oxindole derivatives having a phosphate moiety at the C-3 position via the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis. Yields are isolated yields. [a] Reaction was carried out for 40 min. [b] Reaction was carried out for 1 h.

The reaction with diethyl phosphite instead of diphenyl phosphite did not proceed under the reaction conditions with *N*,*N*-diisopropylethylamine as a catalyst. In this case, DBU was found to be a suitable catalyst and corresponding product **2q** was quantitatively obtained (Equation 1).

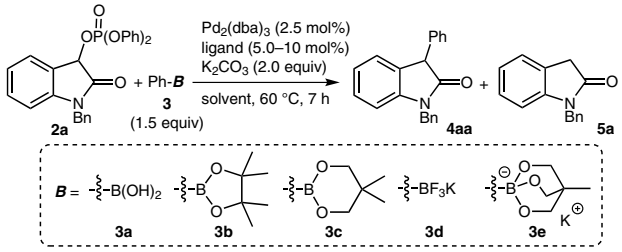


Equation 1 The reaction of **1a** with diethyl phosphite

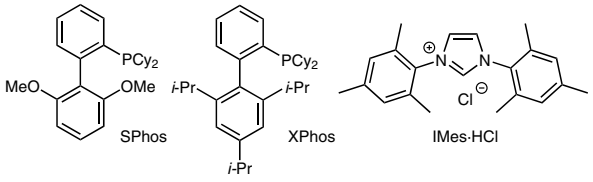
Next, the investigation of the cross-coupling reaction of oxindole derivatives thus synthesized with aryl boron reagents was undertaken. Initially, the reaction of **2a** and phenyl boronic acid (**3a**) was examined by treatment with a catalytic amount of $Pd_2(dba)_3$ and various types of ligands in the presence of 2.0 equivalents of K_2CO_3 in toluene at 60 °C for seven hours (Table 1, entries 1–7). As a result, XPhos was found to be a prominent ligand for this transformation, and the desired product was obtained in moderate yield along with the formation of **5a** as a byproduct (Table 1, entry 5). Other phosphine ligands and the NHC ligand did not provide the desired product **4aa** except for SPhos (albeit only in 3% yield), and **5a** was obtained as a major product in many cases.[14] Screening of the solvent revealed that, in addition to toluene, ethereal solvents, such as THF and methyl *tert*-butyl ether (MTBE), could be used, and **4aa** was obtained in moderate yields (Table 1, entries 8 and 9). Furthermore, addition of H_2O to toluene or MTBE as a co-solvent improved the yield (Table 1, entries 10 and 12). At this stage, other aryl boron reagents were tested (Table 1, entries 13–16). While phenyl boronic acid pinacol ester (**3b**) and potassium phenyltrifluoroborate (**3d**) provided **4aa** only in low yield (Table 1, entries 13 and 15), phenyl boronic acid neopentyl glycol ester (**3c**) afforded the product in comparable yield to that of phenyl boronic acid (**3a**, Table 1, entry 14). In addition, the reaction with phenyl cyclic-triolborate potassium salt **3e**[15] proceeded without using K_2CO_3 to provide the product in moderate yield (Table 1, entry 16).

Further optimization of the reaction conditions was conducted by using **3e** as the arylating agent (Table 1, entries 17 and 18). Finally, the yield was improved to 80% by performing the reaction in a 2:1 mixture of toluene and H_2O using $NaHCO_3$ as an additive (Table 1, entry 18).[16,17]

Table 1 Screening of Reaction Conditions for Cross-Coupling Reaction of Oxindole Derivatives **2** and Aryl Boron Reagents **3**

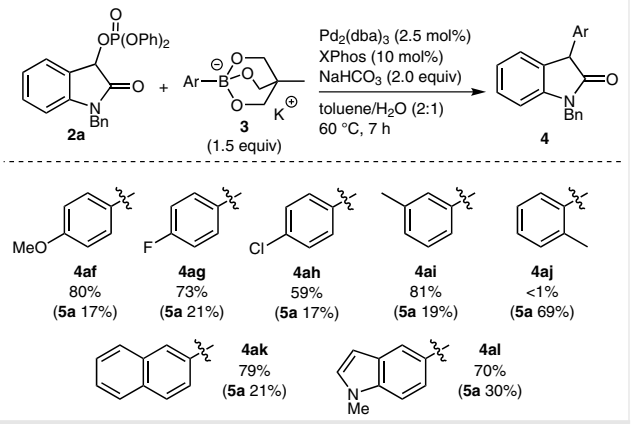


Entry	3	Ligand (mol%)	Solvent	Yield of **4aa** (%)[a]	Yield of **5a** (%)[a]
1	**3a**	Ph_3P (10)	toluene	<1	53
2	**3a**	PCy_3 (10)	toluene	<1	32
3	**3a**	P*t*-Bu_3 (10)	toluene	<1	<1
4	**3a**	SPhos (10)	toluene	3	29
5	**3a**	XPhos (10)	toluene	41	36
6	**3a**	dppf (5)	toluene	<1	64
7	**3a**	IMes·HCl (10)	toluene	<1	5
8	**3a**	XPhos (10)	THF	59	21
9	**3a**	XPhos (10)	MTBE	35	36
10	**3a**	XPhos (10)	toluene–H_2O (2:1)	56	29
11	**3a**	XPhos (10)	THF–H_2O (2:1)	34	16
12	**3a**	XPhos (10)	MTBE–H_2O (2:1)	62	21
13	**3b**	XPhos (10)	MTBE–H_2O (2:1)	28	11
14	**3c**	XPhos (10)	MTBE–H_2O (2:1)	52	25
15	**3d**	XPhos (10)	MTBE–H_2O (2:1)	25	10
16[b]	**3e**	XPhos (10)	MTBE–H_2O (2:1)	52	26
17[b]	**3e**	XPhos (10)	toluene–H_2O (2:1)	73	16
18[b,c]	**3e**	XPhos (10)	toluene–H_2O (2:1)	(80)	17



[a] Yields are based on ^1H NMR analysis of the crude reaction mixture by using 1,1,2,2-tetrabromoethane as the internal standard. Isolated yield is given in parentheses.
[b] Reaction was conducted without K_2CO_3.
[c] Reaction was conducted with 2.0 equivalents of $NaHCO_3$ as an additive.

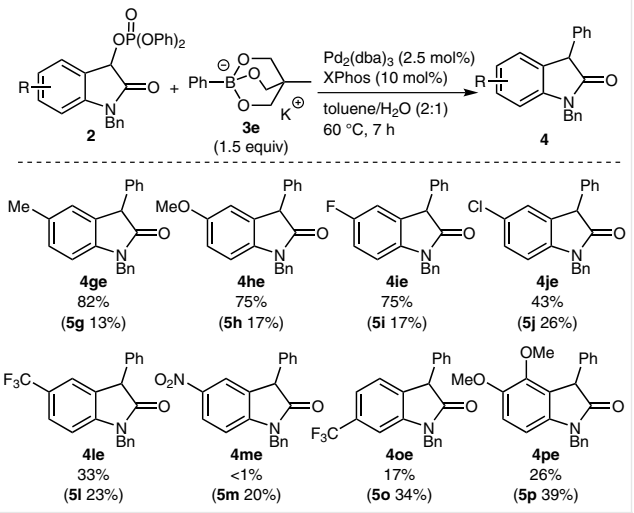
With the optimum conditions in hand, the scope of oxindole derivatives **2** and aryl boron reagents **3** was investigated. First, the scope of aryl boron reagents **3** was examined (Scheme 3). Aryl boron reagents having substituents at the *para* position, such as methoxy, fluoro, or chloro groups, provided the corresponding products **4af**, **4ag**, and **4ah**, respectively, in moderate to good yields. The *meta*-tolyl boron reagent **3i** also underwent the reaction without any problem, and **4ai** was obtained in good yield. In contrast, *ortho*-tolyl boron reagent **3j** only provided the reduced product **5a** in 69% yield. 2-Naphthyl boron reagent **3k** and 5-indolyl boron reagent **3l** were applicable to this reaction to afford the corresponding products **4ak** and **4al**, respectively, in good yields. Heteroaryl boron reagents, such as 2-pyridyl and 2-thienyl boron reagents, were also tried; however, the corresponding products were not obtained, and the reduced product **5a** and the remaining **2a** were observed in the crude reaction mixture.



Scheme 3 Scope of aryl cyclic-triolborate potassium salts **3**. Yields are based on ^1H NMR analysis of the crude reaction mixture by using 1,1,2,2-tetrabromoethane as the internal standard.

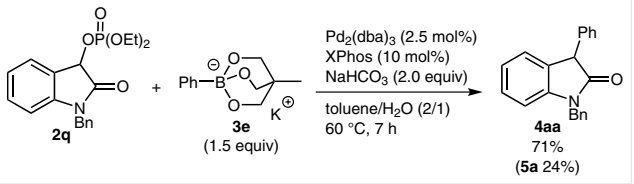
Next, the scope of oxindole derivatives **2** was examined (Scheme 4). The substrates having an electron-donating group at the C-5 position, such as a methyl or methoxy group, underwent the reaction smoothly to provide the corresponding products **4ge** and **4he** in good yields. In regard to a halogen moiety at the C-5 position, fluoro and chloro groups were compatible under the reaction conditions, and the coupling products **4ie** and **4je**, respectively, were obtained in moderate yields, although a bromo group was not tolerated. In contrast, introducing a strong electron-withdrawing group to the C-5 or C-6 position, such as a trifluoromethyl or nitro group, detrimentally affected the reaction. The reaction with the substrates **2l** and **2o** having a trifluoromethyl group at the C-5 and C-6 positions, respectively, provided the corresponding products **4le** and **4oe** in modest yields. The reaction of the substrate having a nitro group at the C-5 position did not provide the desired product **4me**. In these cases, very poor mass balance was observed, indicating that decomposition of electron-deficient **2** might occur under the reaction conditions. The re-

action of the substrate having two methoxy groups at the C-4 and C-5 positions provided the product **4pe** in low yield along with a significant amount of reduced product **5p**.



Scheme 4 Scope of 3-oxindoles **2**.[18] Yields are based on ^{1}H NMR analysis of the crude reaction mixture by using 1,1,2,2-tetrabromoethane as the internal standard.

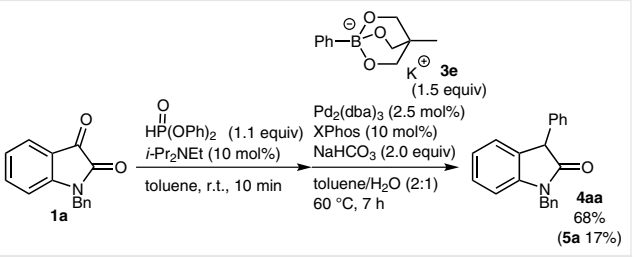
The reaction with **2q** having a diethoxyphosphoryloxy group at the C-3 position instead of a diphenoxyphosphoryloxy group was also tested under the optimum reaction conditions (Equation 2). The reaction with this substrate also proceeded; however, the yield of **4aa** was slightly lower than that obtained with **2a**, and the amount of byproduct **5a** was increased.



Equation 2 Reaction of oxindole **2q** with **3e**

Finally, the one-pot synthesis of 3-aryloxindoles from isatin derivatives was attempted (Scheme 5). Isatin derivative **1a** and diphenyl phosphite were treated with a catalytic amount of *i*-Pr_2NEt in toluene for 10 minutes. A stock solution of the mixture of $Pd_2(dba)_3$ and XPhos, additional toluene, $NaHCO_3$, **3e**, and H_2O were added sequentially, and the resulting mixture was stirred for seven hours at 60 °C.[19] The desired 3-aryloxindole **4aa** was successfully obtained in good yield. This result demonstrated the benefit of the newly developed methodology.

In conclusion, a novel methodology for the efficient synthesis of 3-aryloxindoles from isatin derivatives was developed. The methodology involves the formation of an oxindole having a phosphate moiety at the C-3 position via the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis and the subsequent palladium-catalyzed cross-coupling reaction with aryl boron reagents. The benefit of the newly developed methodology was proven by conducting the one-pot synthesis of 3-aryloxindole derivatives from isatin derivatives. Further application of the methodology, that is, the combination of the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis and a transformation of the resulting phosphate under transition-metal catalysis, is in progress.



Scheme 5 One-pot synthesis of 3-aryloxindole **4aa** from isatin derivative **1a**

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561859.

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(13) **Typical Procedure for the Synthesis of Oxindole Derivatives 2**
Synthesis of **2a** is representative. To a solution of **1a** (1.0 g, 4.3 mmol) and diphenyl phosphite (0.92 mL, 4.8 mmol) in toluene (8.7 mL) was added *i*-Pr_2NEt (75 µL, 0.43 mmol). The resulting mixture was stirred at room temperature for 10 min. The reaction was quenched with sat. aq NH_4Cl, and the product was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (hexane–EtOAc, 2:1) to provide **2a** (1.9 g, 4.1 mmol, 94%) as a colorless oil.
Compound **2a**: ^1H NMR (600 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.2 Hz, 3 H), 3.63–3.95 (m, 2 H), 7.24–7.27 (m, 5 H), 7.28–7.31 (m, 1 H), 7.36–7.40 (m, 2 H), 7.52 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.54 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1 H), 7.59–7.62 (m, 1 H), 7.66 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1 H), 7.94 (dd, *J* = 7.8, 0.60 Hz, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.7, 62.0, 88.1, 93.6, 122.9, 123.2, 128.0, 128.16 (2 C), 128.23, 128.3, 130.0, 130.6, 131.2, 131.4, 132.2, 132.5, 134.7, 141.4, 141.7, 163.0, 188.5. ^{31}P NMR (243 MHz, $CDCl_3$): δ = –10.8. IR (ATR): 3061, 2984, 1748, 1731, 1691, 1597, 1496, 1442, 1197, 1020 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{24}H_{18}O_3$ $[M + Na]^+$: 377.1148; found: 377.1148.

(14) The reduction of α-halocarbonyl compounds and α-halosulfoxides, which is related to the formation of byproduct **5**, was discussed in the literature, see: (a) Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525. (b) Rodoríguez, N.; Cuenca, A.; de Arellano, C. R.; Medio-Simón, M.; Asensio, G. *Org. Lett.* **2003**, *5*, 1705. (c) Rodoríguez, N.; Cuenca, A.; de Arellano, C. R.; Medio-Simón, M.; Peine, D.; Asensio, G. *J. Org. Chem.* **2004**, *69*, 8070. (d) Zhao, Y.; Wang, H.; Hou, X.; Hu, Y.; Lei, A.; Zhang, H.; Zhu, L. *J. Am. Chem. Soc.* **2006**, *128*, 15048. (e) Peng, Z.-Y.; Wang, J.-P.; Cheng, J.; Xie, X.-M.; Zhang, Z. *Tetrahedron* **2010**, *66*, 8238.

(15) Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 928.

(16) **Typical Procedure for the Synthesis of 3-Aryloxindoles 4**
The reaction of **2a** and **3e** is representative (Table 1, entry 18). $Pd_2(dba)_3$ (6.8 mg, 7.5 µmol) and XPhos (14 mg, 30 µmol) were dissolved in toluene (0.60 mL), and the solution was stirred for 15 min. Compound **2a** (0.14 g, 0.30 mmol) in toluene (2.4 mL), $NaHCO_3$ (50 mg, 0.60 mmol), **3e** (0.11 g, 0.45 mmol), and H_2O (1.5 mL) were sequentially added, and the resulting mixture was then warmed to 60 °C. After stirred for 7 h, the reaction was quenched with sat. aq NH_4Cl, and the product was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and evaporated. The crude mixture was purified by column chromatography (hexane–EtOAc, 4:1) to afford **4aa** (72 mg, 0.24 mmol, 80%) as a white solid.
Compound **4aa**: ^1H NMR (400 MHz, $CDCl_3$): δ = 4.74 (s, 1 H), 4.90 (d, *J* = 15.6 Hz, 1 H), 5.00 (d, *J* = 15.6 Hz, 1 H), 6.79 (d, *J* = 7.8 Hz, 1 H), 7.02 (dd, *J* = 7.2, 7.2 Hz, 1 H), 7.14–7.18 (m, 1 H), 7.18–7.24 (m, 3 H), 7.24–7.37 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.9, 52.0, 109.2, 122.7, 125.1, 127.3, 127.59, 127.62, 128.3, 128.4, 128.8, 128.89, 128.92, 135.9, 136.7, 143.6, 176.1.

(17) The exploratory investigation for reaction conditions are summarized in the Supporting Information.

(18) With these substrates **2**, the reaction without $NaHCO_3$ provided almost the same or slightly better yields than those obtained with $NaHCO_3$.

(19) **Procedure for the One-Pot Synthesis of 3-Aryloxindoles**
To a solution of **1a** (50 mg, 0.21 mmol) and diphenyl phosphite (45 µL, 0.23 mmol) in toluene (0.42 mL) was added *i*-Pr_2NEt (3.6 µL, 21 µmol). The resulting mixture was then stirred at room temperature for 10 min. A stock solution of $Pd_2(dba)_3$ (4.8 mg, 5.3 µmol) and XPhos (10 mg, 21 µmol) in toluene (0.42 mL), toluene (3.4 mL), $NaHCO_3$ (35 mg, 0.42 mmol), **3e** (77 mg, 0.31

mmol), and H_2O (2.1 mL) were added sequentially, and the resulting mixture was then warmed to 60 °C. After stirred for 7 h, the reaction was quenched with sat. aq NH_4Cl, and the product was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (hexane–EtOAc, 4:1) to provide **4aa** (43 mg, 0.14 mmol, 68%) as a white solid.