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BF_3·OEt_2 Mediated Regioselective Reaction of Electron-Rich Arenes with 3-Ylidene Oxindoles

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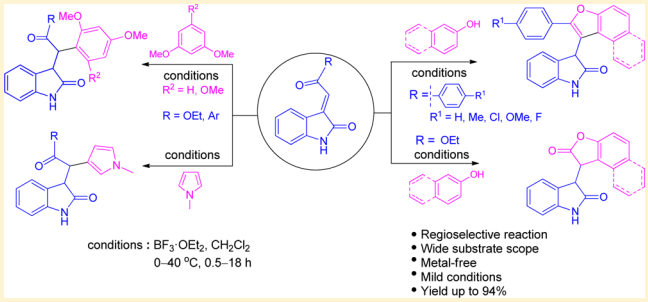
Supporting Information

ABSTRACT: A BF_3·OEt_2 mediated novel and regioselective protocol for the construction of a C−C bond between 3-ylidene oxindoles and electron-rich arenes has been successfully accomplished. The reaction was compatible with a wide variety of electron-rich arenes. A cascade reaction of 3-ylidene oxindoles with phenols and β-naphthol resulted in 2,3-difunctionalized benzofuran and lactone bearing indoline-2-one scaffolds under same conditions.



INTRODUCTION

Oxindole and 2,3-disubstituted benzofuran cores are privileged heterocyclic scaffolds that are frequently present in numerous biologically and pharmacologically active molecules and exhibit many properties including anticancer, anticonvulsant, antidepressant, antibacterial, antifungal, antioxidant, and antiviral activities (Figure 1).[1−7] Hence, efforts have been directed toward the development of productive methods for the synthesis of compounds having such scaffolds as core structures.[8,9] The Friedel−Crafts (F−C) reaction[10−13] was considered as a major tool to construct C−C bond in many bioactive molecules. F−C reactions of arenes and heteroarenes with isatin and its derivatives[14−18] have attracted significant attention in recent years. A literature survey reveals that 3-ylidene oxindoles act as potent precursors for the synthesis of compounds having biological profiles.[19−22] However, to the best of our knowledge, F−C reactions of electron-rich arenes with 3-ylidene oxindoles were not known. In continuation of our interest in F−C reactions of arenes,[12,23] we envisaged that 3-ylidene oxindoles would add regioselectively onto electron-rich arenes under acidic conditions to give α-aryl oxindoles. Also, the synthesis of 2,3-difunctionalized benzofuran embraced products from the former electrophile and resorcinol was deliberated (Figure 2). On the basis of the above hypothesis, herein we report the acid mediated F−C reaction of electron-rich arenes with 3-ylidene oxindoles for synthesizing α-aryl oxindoles.

RESULTS AND DISCUSSION

We commenced our work with 3-ylidine oxindole **1** and 1,3-dimethoxybenzene (**7**) in a model reaction. The F−C reaction of **7** was carried out with **1** at 40 °C in the presence of BF_3·OEt_2 in CH_2Cl_2, and with continued stirring of the reaction contents for 18 h, the desired product **13** was afforded in 42% yield after column chromatography (Table 1, entry 1). Inspired by the result obtained, we optimized the reaction conditions to improve the yield of desired product **13**. For this purpose, a series of Lewis acids such as I_2, $ZrCl_4$, $ZnCl_2$, $FeCl_3$, $SnCl_4$, and BF_3·OEt_2 were screened (Table 1). We investigated the catalytic activity of $ZrCl_4$, $ZnCl_2$, and $SnCl_4$ in acetonitrile as well as in halogenated solvents; oxindole derivative **13** was obtained in 20%, 18%, and 24% yield (entries 2−4). Molecular iodine facilitated the desired product **13** in 30% yield in 20 h (entry 5), and when its amount was raised from 0.5 equiv to 1.0 equiv, the product yield of **13** improved to 52%; the reaction was slow and did not show complete conversion even after 20 h (entry 6). Brønsted acid TFA was also tested for the transformation, but no reaction was observed and the starting materials were recovered (entry 7). Among the tested Lewis acids, $FeCl_3$ and BF_3·OEt_2 afforded product **13** in an acceptable yield (entries 8 and 9), but with BF_3·OEt_2 the reaction was more facile and benign in comparison to $FeCl_3$. We tested many solvents such as methanol, toluene, CH_3CN, $CHCl_3$, CH_2Cl_2, hexane, THF, and 1,2-dichloroethane for the transformation. Solvents like methanol and hexane were not found to be suitable for the reaction; only traces of product **13** were obtained (entries 10 and 11). The reaction in toluene afforded product **13** in 38% yield (entry 12). Shifting the solvent to acetonitrile and halogenated solvents furnished the product **13** in 62% yield (entries 13 and 14). Among all the solvents studied, CH_2Cl_2 was found to be the optimal medium in terms of yield and reaction efficiency (entry 9). We proceeded further to optimize the reaction with BF_3·OEt_2. Subsequently, by increasing the amount of BF_3·OEt_2 from 1.0 to 1.5 equiv in the reaction, product **13** was obtained in an improved yield of 74% in 15 h (entry 15). On lowering the temperature to 0 °C with addition of BF_3·OEt_2 and then raising the temperature of the

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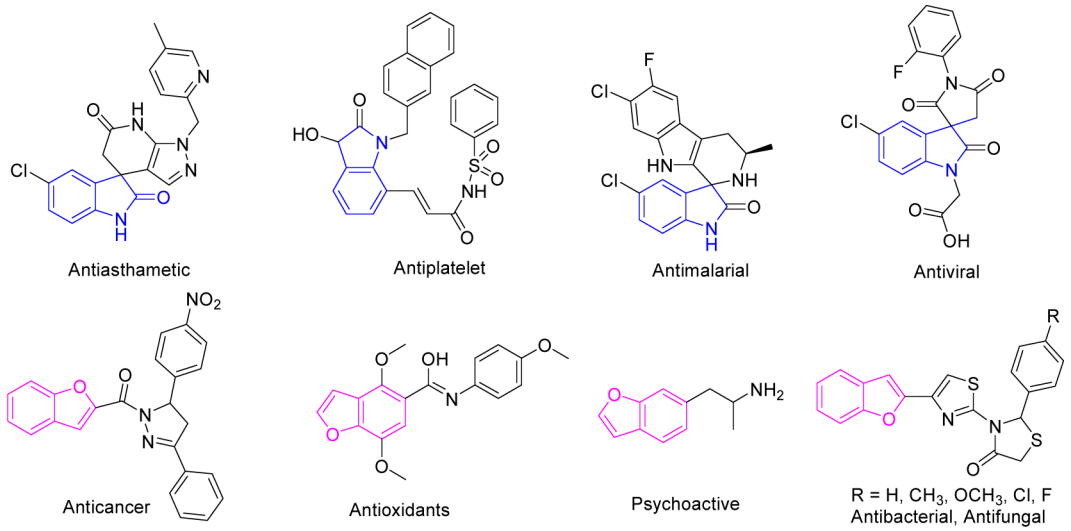


Figure 1. Oxindole/benzofuran containing bioactive compounds.

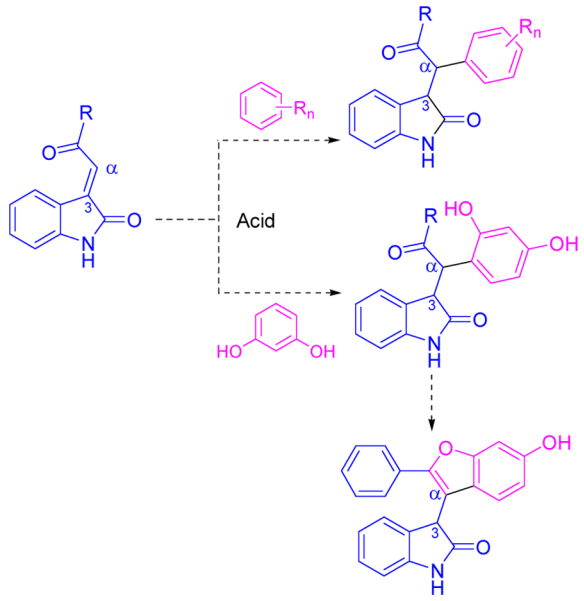
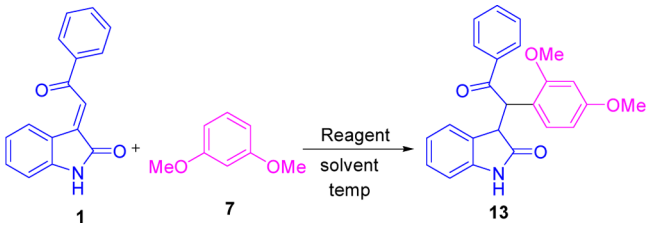


Figure 2. Working hypothesis for the synthesis of α-aryl oxindoles.

reaction to 40 °C, the yield of **13** increased to 80% (entry 16). Further, when the amount of $BF_3{\cdot}OEt_2$ was increased from 1.5 to 1.75 equiv, the yield of product **13** improved to 87% in 12 h (entry 17).

The reaction of **1** with **7** displayed low diastereoselectivity. We screened various solvents, temperature conditions, Lewis acids, and $BF_3{\cdot}OEt_2$ concentrations to improve the diastereoselectivity of the reaction, but all attempts to increase the diastereoselectivity of **13** failed to give any significant enhancement (Table 1, entries 18–20). The low diastereoselectivity of reactions of oxindoles was documented in literature.[24,25] The reaction proceeded with complete regioselectivity which was confirmed by ^{1}H NMR analysis of the product. From the ^{1}H NMR spectra of **13**, the coupling constants for the aliphatic protons show vicinal coupling and J values are found to be nearly 6.5 Hz which indicates that F–C reaction occurs exclusively on the α-position of the oxindole **1** (for details, see Supporting Information).

Table 1. Optimization of the Reaction Conditions[a]



entry	reagent (equiv)	solvent	temp (°C)	time (h)	% yield[b] (dr[c])
1	$BF_3{\cdot}OEt_2$ (0.5)	CH_2Cl_2	40	18	42 (48/52)
2	$ZrCl_4$ (0.5)	CH_2Cl_2	40	18	20 (47/53)
3	$ZnCl_2$ (0.5)	CH_2Cl_2	40	18	18 (47/53)
4	$SnCl_4$ (0.5)	CH_2Cl_2	40	18	24 (48/52)
5	I_2 (0.5)	CH_2Cl_2	40	20	30 (46/54)
6	I_2 (1.0)	CH_2Cl_2	40	20	52 (46/54)
7	TFA (1.0)	CH_2Cl_2	40	18	nr
8	$FeCl_3$ (1.0)	CH_2Cl_2	40	18	63 (48/52)
9	$BF_3{\cdot}OEt_2$ (1.0)	CH_2Cl_2	40	18	67 (47/53)
10	$BF_3{\cdot}OEt_2$ (1.0)	methanol	40	18	traces
11	$BF_3{\cdot}OEt_2$ (1.0)	hexane	40	18	traces
12	$BF_3{\cdot}OEt_2$ (1.0)	toluene	40	18	38 (47/53)
13	$BF_3{\cdot}OEt_2$ (1.0)	CH_3CN	40	18	62 (47/53)
14	$BF_3{\cdot}OEt_2$ (1.0)	$CHCl_3$	40	18	62 (47/53)
15	$BF_3{\cdot}OEt_2$ (1.5)	CH_2Cl_2	40	15	74 (47/53)
16	$BF_3{\cdot}OEt_2$ (1.5)	CH_2Cl_2	0–40	18	80 (47/53)
17	$BF_3{\cdot}OEt_2$ (1.75)	CH_2Cl_2	0–40	12	87 (47/53)
18	$BF_3{\cdot}OEt_2$ (1.0)	CH_2Cl_2	0–25	18	65 (47/53)
19	$BF_3{\cdot}OEt_2$ (1.75)	CH_2Cl_2	−30–40	18	87 (48/52)
20	$BF_3{\cdot}OEt_2$ (1.75)	CH_2Cl_2	−70–40	18	86 (48/52)

[a]All reactions were carried out with 3-ylidene oxindole **1** (0.5 mmol) and **7** (0.6 mmol) in 3 mL of solvent. [b]Combined yield of diastereomers after column chromatography. [c]The dr was determined by ^{1}H NMR of analysis crude product.

With the optimized reaction conditions in hand, the substrate scope of a wide range of ylidine oxindoles **1**–**6** were explored so as to determine the effect of electronic factors on the efficiency of the current protocol. It was noteworthy that the

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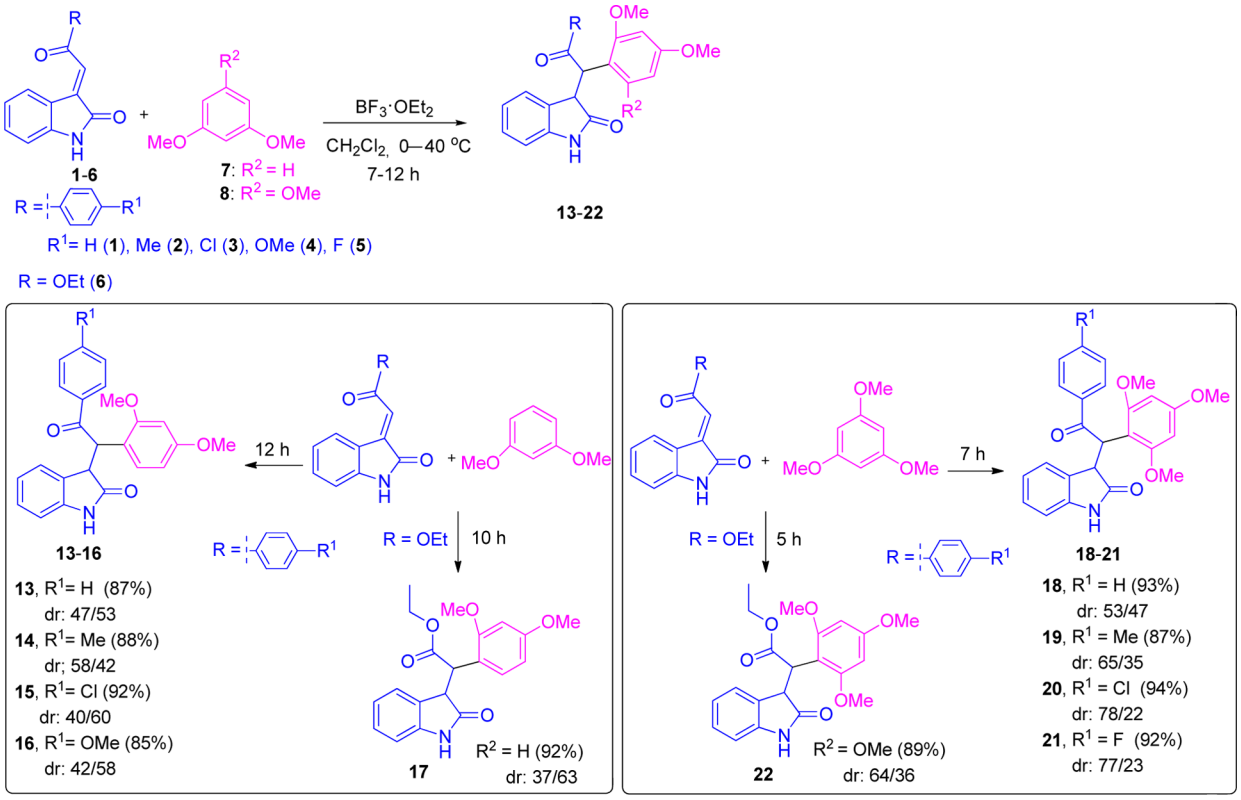
Scheme 1. F−C Reaction of 3-Ylidene Oxindoles with 1,3-Dimethoxybenzene and 1,3,5-Trimethoxybenzene

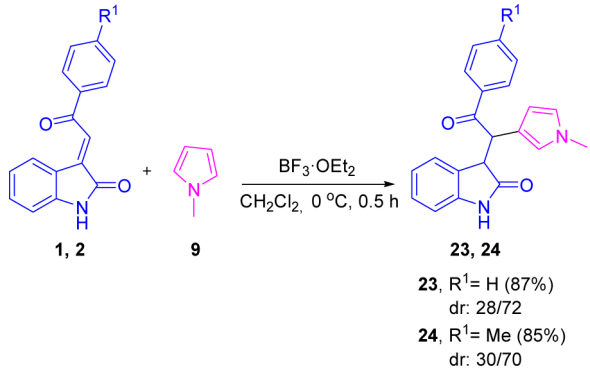


reaction demonstrated a wide tolerance for diverse substituents on 3-ylidene oxindoles. Much to our satisfaction, the electronic properties of the aryl substituents were shown to have little influence on the efficiency of the reaction, bearing either electron-withdrawing or -releasing groups.

Next, we turned our attention toward the scope and tolerance of the reaction with a series of electron-rich arenes **7**−**12**. The reaction of **1** with 1,3-dimethoxybenzene (**7**) under optimal conditions furnished **13** in 87% yield in 12 h (Scheme 1). Similarly, the reaction of **1** with 1,3,5-trimethoxybenzene (**8**) proceeded smoothly to endow the corresponding product **18** in 93% yield in 7 h (Scheme 1). The reaction of **1** with more nucleophilic 1,3,5-trimethoxybenzene required less time for completion and gave a higher yield than the reaction with 1,3-dimethoxybenzene. Halogen bearing ylidene oxindoles showed good diastereoselectivity with 1,3,5-trimethoxybenzene (~80:20) (Scheme 1). The observed improvement in the diastereoselectivity of compounds **20** and **21** appears to be the result of the presence of two *ortho*-methoxy groups in the nucleophilic component in addition to the electronic factors due to halogen atoms. The structure of the major diastereomer of **20** was confirmed by X-ray crystallography (see Supporting Information).[26] To explore further applicability of the ongoing methodolgy, we investigated the reaction of **1** with heteroarene *N*-methylpyrrole; the reaction progressed rapidly to furnish **23** in 87% yield in 0.5 h, and the diastereoselectivity was in line with the outcome of **20** and **21** derived from **8**. *N*-Methylpyrrole (**9**) also afforded the product **24** as a mixture of diastereomers with good diastereoselectivity (Scheme 2).

Inspired by the applicability of the current methodology, we next explored the reaction of **1** with resorcinol (**10**). The reaction was compatible under standard reaction conditions and proceeded smoothly to deliver the cyclized product **25** in

Scheme 2. F−C Reaction of 3-Ylidene Oxindoles with *N*-Methylpyrrole



90% yield in 10 h (Scheme 3). The structure of **25** was confirmed by ^{1}H NMR and HRMS (see Supporting Information).

Notably the reaction was completely regio- and diastereoselective. To support the generality of our methodology for resorcinol, the electronic effects of various groups on 3-ylidene oxindoles were also evaluated. A broad range of substrates bearing diverse functional groups including halogen, methyl, methoxy, and ester were well tolerated under optimized conditions. Marginally good yields were achieved for substrates having electron-withdrawing groups (halogens, COOMe) than electron-donating functionalities (Me, OMe). The reaction of oxindoles **1**−**5** with resorcinol affords a series of 2,3-difunctionalized benzofurans **25**−**29** in excellent yields (Scheme 3). Gratifyingly, the reaction of 3-ylidene oxindoles with resorcinol (**10**) showed excellent diastereoselectivity and the products **25**−**29** were all obtained as single isomers

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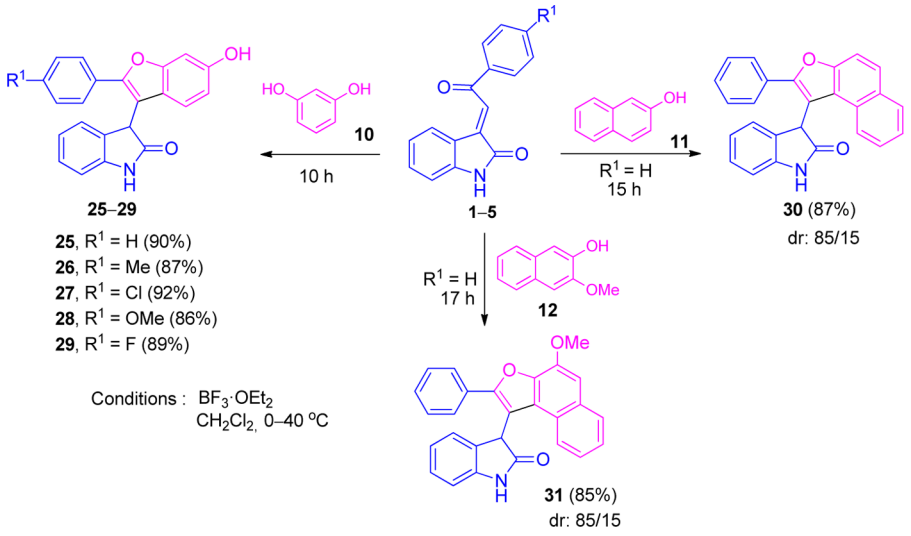
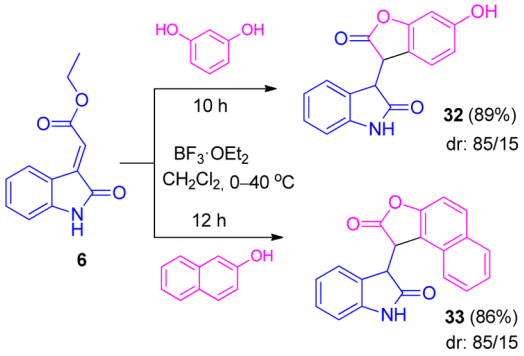
Scheme 3. F−C Reaction of 3-Ylidene Oxindoles with Resorcinol and Substituted β-Naphthols



(Scheme 3). To highlight the synthetic potential of this protocol for electron-rich phenols, we performed the reaction of **1** with β-naphthol (**11**) and 3-methoxy-β-naphthol (**12**). The reaction pleasingly delivered the 2,3-difunctionalized benzofuran incorporated products **30** and **31** in 87% and 85% yields, respectively (Scheme 3). The structure of **30** was unequivocally determined by X-ray crystallography.[27] Also, the reaction of **1** with β-naphthol (**11**) and 3-methoxy-β-naphthol (**12**) exhibited good diastereoselectivity (85:15) (Scheme 3). With the optimized conditions secured, we then performed the reaction of ethyl-(*E*)-2-(2-oxoindolin-3-ylidene)acetate (**6**) with resorcinol (**10**) and β-naphthol (**11**) to afford the lactone ring embraced products **32** and **33** in 89% and 86% yields respectively (Scheme 4). The reaction furnished completely regioselective products and also exhibits good diastereoselectivity (85:15).

Scheme 4. F−C Reaction of Ethyl (*E*)-2-(2-Oxoindolin-3-ylidene)acetate (6) with Resorcinol and β-Naphthol



Structure Elucidation. The assigned structures of the products were based on spectroscopic evidence, such as ^{1}H NMR (500 and 400 MHz), ^{13}C (100 and 125 MHz), and HRMS data. The reaction displayed excellent regioselectivity which was confirmed by ^{1}H NMR. From the ^{1}H NMR spectra of **13**−**24**, the displayed coupling constants of aliphatic protons show vicinal coupling and are in the range of 5.0−7.5 Hz which indicates that F−C reaction occurs exclusively on the α-position of the oxindoles (for details, see Supporting Information). Also, the reaction of ylidene oxindoles with resorcinol and β-naphthol was completely regioselective **25**−**33**. The regioselectivity was further confirmed by single crystal X-ray analyses of structures **20** and **30** (see Supporting Information).

According to the literature, the reaction of 3-ylidene oxindoles with electron-rich partners at the α-position exhibits less diastereoselectivity. The reactions of 3-ylidene oxindoles with nitromethane[24] and thiophenol[25] at the α-position resulted in the formation of corresponding addition products with less or moderate diastereoselectivity. Similarly, we observed less diastereoselective products in the case of 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene. More electron-deficient ylidene oxindoles bearing halogen groups exhibit good diastereoselective products (**20** and **21**) with 1,3,5-trimethoxybenzene. *N*-Methylpyrrole furnished products with good diastereoselectivity (30:70). Gratifyingly highly diastereoselective products (**25**−**29**) were obtained with resorcinol irrespective of the substituent attached to the aromatic ring of ylidene oxindole. The reaction of ylidene oxindole **1** with β-naphthol and 3-methoxy-β-naphthol displayed products **30** and **31** with good diastereoselectivity (85:15) (Scheme 3). The reaction of ethyl (*E*)-2-(2-oxoindolin-3-ylidene)acetate (**6**) with resorcinol and β-naphthol resulted in cyclized products **32** and **33** with satisfactory diastereoselectivity (85:15) (Scheme 4).

Based on the above results and literature studies,[28] a possible mechanism for the formation of **25** was proposed (Figure 3). Association of BF_3·OEt_2 with 3-ylidene oxindole **1** results in the F−C reaction of resorcinol on the α-carbon of the double bond at position 3, which was then followed by the nucleophilic attack of phenolic OH on the carbonyl group attached to arene; hence, cyclization occurred. Finally elimination of a water molecule and dissociation of BF_3·OEt_2 lead to the formation of desired product **25**.

■ CONCLUSIONS

In conclusion, we have successfully demonstrated novel and regioselective synthesis of a series of α-aryl substituted oxindoles via BF_3·OEt_2 under mild conditions. The protocol was compatible with different types of arenes. Also, we have developed a protocol for the facile synthesis of various

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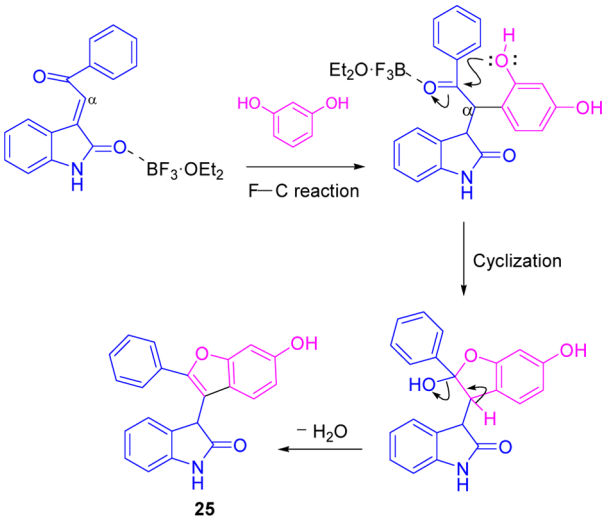

Figure 3. Proposed mechanism for the formation of **25**.

potentially biologically active 2,3-difunctionalized benzofuran and lactone embraced products by employing phenols and ylidene oxindoles as starting materials under the same conditions.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, chemicals were purchased from commercial suppliers at the highest purity grade available and were used without further purification. Thin layer chromatography was performed on 0.25 mm silica gel plates (60F-254) using UV light as the visualizing agent. Silica gel (100−200 mesh) was used for column chromatography. Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. Nuclear magnetic resonance spectra were recorded on a 400 and 500 MHz spectrometer, and chemical shifts are reported in δ units, parts per million (ppm), relative to residual chloroform (7.26 ppm) or DMSO (2.5 ppm) in the deuterated solvent or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.0 ppm, the middle peak) and DMSO-d_6 (δ 39.5 ppm, the middle peak). Coupling constants were expressed in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet. High-resolution mass spectra were recorded with a micro TOF-Q analyzer spectrometer by using the electrospray mode.

General Procedure. To a stirred solution of a 3-ylidene oxindole derivative (0.5 mmol) in 3 mL of CH_2Cl_2 was added an electron-rich arene (0.6 mmol), and the mixture was cooled to 0 °C. Then BF_3·OEt_2 (1.75 mmol) was added slowly dropwise, and the mixture was allowed to stir at 40 °C for an appropriate time. After completion of the reaction as shown by TLC, the reaction was quenched with 5 mL of saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3 × 5 mL), and the organic layer was separated, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh) using ethyl acetate/hexanes (40:60) as the eluting system. ^{1}H NMR data of the isolated part of one isomer obtained after column chromatography and washing with a mixture of solvents (EtOAc/hexanes, EtOAc/hexanes/DCM) are reported for compounds **13**−**24**. The ^{13}C NMR data of the 'mixture of two diastereomers' were obtained from the mixture before the separation of part of one isomer. The diagnostic peaks in ^{1}H NMR spectra of products **13**−**24** are shown in the Supporting Information.

3-(1-(2,4-Dimethoxyphenyl)-2-oxo-2-phenylethyl)indolin-2-one (***13***). Mixture of two diastereomers; yellow liquid; yield 168 mg (87%); t = 12 h. Single diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.21 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.16 (d, J = 8.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.78 (t, J = 7.5 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.34 (d, J = 8.5 Hz, 1H), 6.30 (s, 1H), 5.48 (d, J = 6.5 Hz, 1H), 4.46 (d, J = 6.5 Hz, 1H), 3.71 (s, 3H), 3.55 (s, 3H) ppm. Mixture of two diastereomers ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 198.4, 179.8, 179.4, 160.5, 160.3, 157.6, 157.5, 142.0, 141.8, 136.3, 136.8, 135.9, 132.8, 132.7, 130.9, 130.5, 128.85, 128.76, 128.6, 128.3, 127.7, 127.6, 127.4, 125.6, 124.8, 121.4, 117.0, 116.7, 109.6, 109.4, 104.5, 104.2, 98.8, 98.7, 55.5, 55.2, 55.1, 48.0, 47.7, 47.4, 46.6 ppm. HRMS (ESI): m/z calcd for HRMS (ESI): m/z calcd for $C_{24}H_{22}NO_4$ $[M + H]^+$: 388.1543; found: 388.1541.

3-(1-(2,4-Dimethoxyphenyl)-2-oxo-2-p-tolylethyl)indolin-2-one (***14***). Mixture of two diastereomers; yellow viscous liquid; yield: 176 mg (88%); t = 12 h. Single diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.85 (d, J = 7.5 Hz, 2H), 7.13 (d, J = 6.5 Hz, 3H), 7.05 (t, J = 8.0 Hz, 1H), 6.78 (t, J = 7.5 Hz, 1H), 6.70 (t, J = 7.0 Hz, 2H), 6.33 (d, J = 8.5 Hz, 1H), 6.30 (s, 1H), 5.46 (d, J = 6.5 Hz, 1H), 4.42 (d, J = 6.0 Hz, 1H), 3.71 (s, 3H), 3.57 (s, 3H), 2.32 (s, 3H) ppm. Mixture of two diastereomers; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.10, 198.07, 179.8, 179.3, 160.5, 160.2, 157.6, 157.5, 143.6, 143.4, 141.9, 141.8, 133.8, 133.4, 130.9, 130.5, 129.04, 129.00, 128.9, 128.8, 127.8, 127.5, 127.3, 125.7, 124.8, 121.4, 117.2, 117.0, 109.5, 109.3, 104.4, 104.1, 98.8, 98.7, 55.5, 55.2, 55.1, 47.9, 47.7, 47.3, 46.6, 21.54, 21.52 ppm. HRMS (ESI): m/z calcd for HRMS (ESI): m/z calcd for $C_{25}H_{24}NO_4$ $[M + H]^+$: 402.1699; found: 402.1697.

3-(2-(4-Chlorophenyl)-1-(2,4-dimethoxyphenyl)-2-oxoethyl)-indolin-2-one (***15***). Mixture of two diastereomers; yellow viscous liquid; yield: 194 mg (92%); t = 12 h. Single diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.80 (t, J = 7.5 Hz, 1H), 6.71 (t, J = 7.0 Hz, 2H), 6.36 (d, J = 8.5 Hz, 1H), 6.29 (s, 1H), 5.38 (d, J = 6.5 Hz, 1H), 4.43 (d, J = 6.5 Hz, 1H), 3.73 (s, 3H), 3.56 (s, 3H) ppm. Mixture of two diastereomers; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.31, 197.27, 179.5, 179.0, 160.7, 160.5, 157.51, 157.46, 141.9, 141.7, 139.2, 139.0, 134.7, 134.2, 130.2, 130.0, 128.7, 128.6, 128.6, 127.7, 127.5, 125.8, 124.8, 121.5, 116.7, 116.4, 109.5, 109.3, 104.7, 104.2, 98.9, 55.6, 55.3, 55.2, 48.1, 47.7, 47.5, 46.5 ppm. HRMS (ESI): m/z calcd for $C_{24}H_{20}NO_4ClNa$ $[M + Na]^+$: 444.0973; found: 444.0957.

3-(1-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-2-oxoethyl)-indolin-2-one (***16***). Mixture of two diastereomers; yellow viscous liquid; yield: 177 mg (85%); t = 12 h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.02 (s, 1H), 7.93 (d, J = 9.2 Hz, 2H), 7.79 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 7.06 (t, J = 7.6 Hz, 1H), 6.87−6.70 (m, 9H), 6.55 (s, 1H), 6.43−6.30 (m, 4H), 5.68 (d, J = 6.4 Hz, 1H), 5.44 (d, J = 6.4 Hz, 1H), 4.40 (d, J = 6.4 Hz, 1H), 4.05(d, J = 6.4 Hz, 1H), 3.91 (s, 2H), 3.80 (s, 5H), 3.78 (s, 2H), 3.73 (s, 3H), 3.59 (s, 3H) ppm. Mixture of two diastereomers; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.05, 197.96, 179.4, 179.0, 163.2, 163.2, 160.5, 160.3, 157.54, 157.46, 141.8, 141.6, 131.2, 131.0, 130.6, 130.5, 129.3, 129.1, 129.0, 127.9, 127.5, 127.3, 125.7, 124.9, 121.6, 117.5, 117.2, 113.5, 109.4, 109.1, 104.5, 104.2, 98.8, 98.7, 55.6, 55.3, 55.2, 44.8, 47.6, 47.2, 46.5 ppm. HRMS (ESI): m/z calcd for $C_{25}H_{24}NO_4$ $[M + H]^+$: 418.1649; found: 418.1647.

Ethyl 2-(2,4-Dimethoxyphenyl)-2-(2-oxoindolin-3-yl)acetate (***17***). Mixture of two diastereomers; white oil; yield: 162 mg (92%); t = 10 h. Single diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$):δ 8.12 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.85−6.84 (d, J = 5.5 Hz, 2H), 6.73 (d, J = 7.5 Hz, 1H), 6.41 (d, J = 8.5 Hz, 1H), 6.31 (s, 1H), 4.53 (d, J = 6.5 Hz, 1H), 4.26−4.18 (m, 3H), 3.77 (s, 3H), 3.56 (s, 3H), 1.23 (t, J = 7.5 Hz, 3H) ppm. Mixture of two diastereomers; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 178.5, 172.9, 172.0, 160.6, 160.4, 158.1, 142.0, 141.6, 130.4, 130.1, 128.0, 127.8, 127.4, 125.8, 125.0, 121.7, 117.1, 116.6, 109.5, 109.4, 104.4, 104.1, 98.62, 98.55, 61.2, 61.0, 55.5, 55.4, 55.3, 55.2, 48.2, 46.9, 45.4, 45.23, 45.16, 14.2, 14.0 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{21}O_5NNa$ $[M + Na]^+$: 378.1312; found: 378.1302.

3-(2-Oxo-2-phenyl-1-(2,4,6-trimethoxyphenyl)ethyl)indolin-2-one (***18***). Mixture of two diastereomers; off white solid; yield: 194 mg (93%); mp: 227−229 °C; t = 7 h. Single diastereomer; ^{1}H NMR (500

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MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.29−7.24 (m, 2H), 7.16 (t, J = 8.0 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.82 (t, J = 8.0 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.12 (s, 2H), 5.50 (d, J = 5.5 Hz, 1H), 3.95 (d, J = 5 Hz, 1H), 3.85 (s, 3H), 3.62 (s, 6H) ppm. Mixture of two diastereomers; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 197.2, 197.0, 179.1, 178.0, 160.3, 159.9, 157.5, 157.4, 142.2, 142.0, 136.1, 131.1, 131.0, 128.4, 127.4, 127.1, 126.6, 126.5, 126.3, 126.2, 124.6, 123.6, 119.85, 119.76, 108.5, 108.0, 106.7, 106.3, 90.0, 89.8, 54.51, 54.47, 54.3, 45.5, 45.4, 45.2, 44.5 ppm. HRMS (ESI): m/z calcd for $C_{25}H_{24}NO_5$ $[M + H]^+$: 418.1649; found: 418.1647.

3-(2-Oxo-2-p-tolyl-1-(2,4,6-trimethoxyphenyl)ethyl)indolin-2-one (**19**). Mixture of two diastereomers; light yellow solid; yield: 187 mg (87%); mp: 233−235 °C; t = 7 h. Single diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.4 Hz, 2H), 7.52 (s, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6.79 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.09 (s, 2H), 5.44 (d, J = 5.6 Hz, 1H), 3.91 (d, J = 5.6 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 6H), 2.28 (s, 3H) ppm. Mixture of two diastereomers; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 197.5, 197.4, 180.0, 178.8, 160.7, 160.2, 157.9, 142.2, 142.04, 141.99, 141.9, 133.92, 133.87, 128.9, 128.2, 127.9, 127.6, 127.18, 127.15, 126.7, 126.6, 125.1, 124.2, 120.5, 120.4, 109.0, 108.5, 107.2, 106.9, 90.3, 90.2, 54.92, 54.87, 54.7, 45.93, 45.86, 45.7, 45.2, 21.1 ppm. HRMS (ESI): m/z calcd for $C_{26}H_{25}NNaO_5$ $[M + Na]^+$: 454.1625; found: 454.1614.

3-(2-(4-Chlorophenyl)-2-oxo-1-(2,4,6-trimethoxyphenyl)ethyl)-indolin-2-one (**20**). Mixture of two diastereomers; white solid; yield: 212 mg (94%); mp: 241−243 °C; t = 7 h. Single diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.79 (t, J = 7.2 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 6.10 (s, 2H), 5.41 (d, J = 5.6 Hz, 1H), 3.89 (d, J = 5.2 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 6H) ppm. Mixture of two diastereomers; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 196.0, 195.8, 178.8, 177.8, 160.4, 159.9, 157.4, 157.2, 142.2, 142.0, 136.9, 136.8, 134.5, 128.44, 128.37, 128.1, 128.0, 127.9, 127.3, 127.2, 127.1, 126.2, 126.1, 124.4, 123.5, 119.7, 108.4, 107.9, 106.2, 105.8, 90.0, 89.93, 89.89, 89.7, 55.0, 54.4, 54.2, 53.8, 45.4, 45.3, 45.2 ppm. HRMS (ESI): m/z calcd for $C_{25}H_{23}ClNO_5$ $[M + H]^+$: 452.1259; found: 452.1264.

3-(2-(4-Fluorophenyl)-2-oxo-1-(2,4,6-trimethoxyphenyl)ethyl)-indolin-2-one (**21**). Mixture of two diastereomers; pinkish white solid; yield: 200 mg (92%); mp: 267−269 °C; t = 7 h. Single diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.71−7.69 (m, 2H), 7.13 (t, J = 7.5 Hz, 1H), 6.92−6.86 (m, 3H), 6.79 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 7.5 Hz, 1H), 6.10 (s, 2H), 5.43 (d, J = 5.5 Hz, 1H), 3.90 (d, J = 5.5 Hz, 1H), 3.83 (s, 3H), 3.60 (s, 6H) ppm. Mixture of two diastereomers; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 195.9, 195.8, 179.3, 178.2, 164.1 (d, $^1J_{C-F}$ = 250.8 Hz), 164.0 (d, $^1J_{C-F}$ = 250.8 Hz), 160.5, 160.1, 157.6, 157.5, 142.3, 142.1, 138.7, 132.7 (d, $^4J_{C-F}$ = 2.9 Hz), 132.6, 132.6 (d, $^4J_{C-F}$ = 2.9 Hz), 129.7 (d, $^3J_{C-F}$ = 8.5 Hz), 129.2 (d, $^3J_{C-F}$ = 8.6 Hz), 128.4, 127.5, 126.5, 126.4, 124.8, 123.8, 120.1, 120.0, 114.3 (d, $^2J_{C-F}$ = 21.9 Hz), 114.2 (d, $^2J_{C-F}$ = 21.9 Hz), 108.7, 108.2, 106.6, 106.2, 90.1, 89.9, 54.6, 54.5, 45.6, 45.4, 44.7 ppm. HRMS (ESI): m/z calcd for HRMS (ESI): m/z calcd for $C_{25}H_{23}FNO_5$ $[M + H]^+$: 436.1555; found: 436.1553.

Ethyl 2-(2-Oxoindolin-3-yl)-2-(2,4,6-trimethoxyphenyl)acetate (**22**). Mixture of two diastereomers; white solid; yield 171 mg (89%): mp: 192−193 °C; t = 5 h. Single diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.84−6.72 (m, 2H), 6.64 (d, J = 6.5 Hz, 1H), 6.21 (s, 2H), 4.87 (d, J = 5.5 Hz, 1H), 4.07−4.01 (m, 2H), 3.86 (s, 3H), 3.73 (d, J = 5.0 Hz, 1H), 3.71 (s, 6H), 1.12 (t, J = 7.5 Hz, 3H) ppm. Mixture of two diastereomers; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 178.9, 173.1, 172.2, 160.9, 160.5, 158.7, 142.0, 141.8, 128.5, 128.0, 127.42, 127.36, 127.3, 124.9, 121.1, 109.3, 109.2, 108.8, 106.0, 105.8, 90.5, 90.3, 60.8, 60.4, 55.31, 55.27, 55.1, 46.7, 46.3, 41.8, 41.6, 14.2, 14.0 ppm. HRMS (ESI): m/z calcd for $C_{21}H_{23}NNaO_6$ $[M + Na]^+$: 408.1418; found: 408.1401.

3-(1-(1-Methyl-1H-pyrrol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one (**23**). Mixture of two diastereomers; light brown solid; yield: 144 mg (87%); mp: 195−197 °C; t = 1/2 h. Single diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 7.85 (d, J = 7.5 Hz, 2H), 7.48 (t, J = 7.0 Hz, 1H), 7.39 (t, J = 7.0 Hz, 2H), 7.12 (t, J = 7.0 Hz, 1H), 6.84 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 6.51 (s, 1H), 6.40 (d, J = 6.5 Hz, 1H), 5.98 (s, 1H), 5.94 (s, 1H), 5.02 (d, J = 7.5 Hz, 1H), 4.64 (d, J = 7.5 Hz, 1H), 3.31 (s, 3H) ppm. Single diastereomer; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 179.1, 141.7, 136.6, 132.8, 128.6, 128.5, 128.1, 128.0, 127.1, 125.8, 125.4, 123.1, 122.2, 110.2, 109.7, 107.6, 48.4, 46.0, 33.9 ppm. HRMS (ESI): m/z calcd for $C_{21}H_{18}N_2NaO_2$ $[M + Na]^+$: 353.1260; found: 353.1247.

3-(1-(1-Methyl-1H-pyrrol-3-yl)-2-oxo-2-p-tolylethyl)indolin-2-one (**24**). Mixture of two diastereomers; light brown solid; yield 146 mg (85%); mp: 193−195 °C; t = 1/2 h. Single diastereomer; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.74 (d, J = 7.5 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 6.87 (t, J = 8.0 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.55 (d, J = 7.5 Hz, 1H), 6.50 (s, 1H), 5.95 (s, 1H), 5.87 (s, 1H), 5.05 (d, J = 7.5 Hz, 1H), 4.60 (d, J = 7.5 Hz, 1H), 3.36 (s, 3H), 2.35 (s, 3H) ppm. Single diastereomer; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 178.9, 143.7, 141.6, 133.9, 129.3, 129.2, 128.6, 128.1, 127.2, 126.0, 125.6, 122.9, 122.2, 110.1, 109.6, 107.6, 48.3, 46.0, 33.9, 21.6 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{20}N_2O_2Na$ $[M + Na]^+$: 345.1598; found: 345.1595.

3-(6-Hydroxy-2-phenylbenzofuran-3-yl)indolin-2-one (**25**). White solid; yield: 154 mg (90%); mp: 246−248 °C; t = 10 h. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 10.00 (s, 1H), 7.78 (s, 2H), 7.36−7.24 (m, 3H), 7.10 (t, J = 7.6 Hz, 2H), 6.87−6.74 (m, 4H), 6.40 (d, J = 8.4 Hz, 1H), 6.26 (s, 1H), 4.90 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 176.6, 155.0, 154.4, 152.1, 141.7, 129.6, 127.9, 127.7, 127.5, 126.4, 123.8, 121.2, 119.1, 111.3, 109.7, 109.1, 97.0, 42.8 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{16}NO_3$ $[M + H]^+$: 342.1125; found: 342.1132.

3-(6-Hydroxy-2-p-tolylbenzofuran-3-yl)indolin-2-one (**26**). White solid; yield: 154 mg (87%); mp: 297−299 °C; t = 10 h. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ 9.74 (s, 1H), 8.62 (s, 1H), 7.74 (d, J = 6.8 Hz, 2H), 7.20 (d, J = 7.2 Hz, 2H), 7.14 (d, J = 7.2 Hz, 1H), 6.92 (d, J = 7.2 Hz, 2H), 6.88−6.80 (m, 2H), 6.45 (d, J = 8.4 Hz, 1H), 6.31 (s, 1H), 4.95 (s, 1H), 2.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ 177.1, 155.0, 154.6, 152.8, 141.9, 138.0, 128.9, 128.0, 127.8, 127.2, 126.6, 124.2, 121.6, 119.6, 119.2, 111.5, 109.4, 109.3, 97.4, 43.2, 20.8 ppm. HRMS (ESI): m/z calcd for $C_{23}H_{17}NO_3Na$ $[M + Na]^+$: 378.1101; found: 378.1090.

3-(2-(4-Chlorophenyl)-6-hydroxybenzofuran-3-yl)indolin-2-one (**27**). White solid; yield: 172 mg (92%); mp: 304−306 °C; t = 10 h. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 10.16 (s, 1H), 7.90 (s, 2H), 7.42−7.39 (m, 3H), 6.96−6.91 (m, 4H), 6.54 (d, J = 7.6 Hz, 1H), 6.37 (s, 1H), 4.98 (s, 1H) ppm. ^{13}C NMR(100 MHz, $CDCl_3$ + DMSO-d_6): δ 176.4, 155.1, 154.4, 150.9, 141.7, 133.3, 128.2, 128.0, 127.6, 127.3, 123.9, 121.2, 119.2, 119.0, 111.4, 110.3, 109.2, 97.0, 42.8 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{14}ClNaNO_3$ $[M + Na]^+$: 398.0554; found: 398.0546.

3-(6-Hydroxy-2-(4-methoxyphenyl)benzofuran-3-yl)indolin-2-one (**28**). Light green solid; yield: 160 mg (86%); mp: 293−295 °C; t = 10 h. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 10.00 (s, 1H), 7.69 (d, J = 6.8 Hz, 2H), 7.07 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.4 Hz, 4H), 6.79−6.72 (m, 2H), 6.34 (d, J = 8.4 Hz, 1H), 6.19 (s, 1H), 4.80 (s, 1H), 3.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 176.8, 159.2, 154.7, 154.3, 152.4, 141.8, 128.0, 127.7, 127.6, 124.0, 122.4, 121.3, 119.4, 118.9, 113.4, 111.2, 109.2, 108.5, 97.1, 54.6, 43.0 ppm. HRMS (ESI): m/z calcd for $C_{23}H_{17}NO_4Na$ $[M + Na]^+$: 394.1050; found: 394.1043.

3-(2-(4-Fluorophenyl)-6-hydroxybenzofuran-3-yl)indolin-2-one (**29**). White solid; yield: 160 mg (89%); mp: 296−298 °C; t = 10 h. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 10.11 (s, 1H), 7.72 (s, 2H), 7.03−6.96 (m, 3H), 6.81−6.68 (m, 4H), 6.31 (d, J = 6.0 Hz, 1H), 6.15 (s, 1H), 4.73 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 176.5, 161.8 (d, $^1J_{C-F}$ = 246.9 Hz), 154.9, 154.2, 151.2, 141.6, 128.3 (d, $^3J_{C-F}$ = 7.6 Hz) 127.6, 127.3, 125.9, 123.8, 121.2, 119.0, 114.8 (d, $^2J_{C-F}$ = 20.1 Hz), 111.3, 109.5, 109.1, 97.0, 42.7 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{14}FNNaO_3$ $[M + Na]^+$: 382.0849; found: 382.0845.

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*3-(2-Phenylnaphtho[2,1-b]furan-1-yl)indolin-2-one (**30**).* Mixture of two diastereomers; white solid; yield: 163 mg (87%); mp: 278−280 °C; t = 15 h. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO−d_6): δ 10.13 (s, 1H), 7.45 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 6.8 Hz, 2H), 7.01 (d, J = 6.8 Hz, 2H), 6.85−6.60 (m, 6H), 6.54 (d, J = 7.6 Hz, 1H), 6.41 (t, J = 7.6 Hz, 1H), 4.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 176.2, 155.0, 151.4, 141.1, 129.4, 128.8, 128.1, 127.8, 127.4, 127.2, 126.8, 126.6, 126.3, 125.0, 124.7, 122.9, 122.7, 122.5, 121.1, 120.7, 111.3, 109.9, 109.2, 43.8 ppm. HRMS (ESI): m/z calcd for $C_{26}H_{16}NO_2$ $[M - H]^+$: 374.1176; found: 374.1182.

*3-(4-Methoxy-2-phenylnaphtho[2,1-b]furan-1-yl)indolin-2-one (**31**).* Mixture of two diastereomers; white solid; yield: 172 mg (85%); mp: 263−266 °C; t = 17 h. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 10.37 (s, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.15−7.07 (m, 3H), 6.88−6.72 (m, 2H), 6.73 (d, J = 7.2 Hz, 1H), 6.68 (s, 1H), 6.62−6.57 (m, 3H), 6.47 (t, J = 7.2 Hz, 1H), 4.88 (s, 1H), 3.68 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 176.4, 155.5, 144.5, 143.2, 141.2, 130.7, 128.7, 128.4, 127.9, 127.6, 127.5, 127.5, 126.9, 126.6, 122.5, 123.5, 122.8, 122.5, 122.4, 122.0, 121.3, 121.0, 110.2, 109.4, 102.8, 54.8, 43.9 ppm. HRMS (ESI): m/z calcd for $C_{27}H_{20}NO_3$ $[M + H]^+$: 406.1438; found: 406.1437.

*3-(6-Hydroxy-2-oxo-2,3-dihydrobenzofuran-3-yl)indolin-2-one (**32**).* Major diastereomer; white solid; yield: 107 mg (76%); mp: 274−276 °C; t = 10 h. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 9.71 (s, 1H), 9.17 (s, 1H), 7.10 (dd, J = 7.2 Hz, J = 12.0 Hz, 1H), 6.82−6.74 (m, 3H), 6.49 (d, J = 3.6 Hz, 1H), 6.41−6.35 (m, 2H), 4.22 (d, J = 4.0 Hz, 1H), 3.97 (d, J = 4.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 175.1, l74.4, 158.0, 154.0, 153.9, 142.5, 128.0, 124.9, 123.4, 122.8, 121.1, 113.2, 110.4, 109.2, 98.0, 46.3, 42.9 ppm. HRMS (ESI): m/z calcd for $C_{16}H_{11}NO_4Na$ $[M + Na]^+$: 304.0580; found: 304.0570.

*3-(2-Oxo-1,2-dihydronaphtho[2,1-b]furan-1-yl)indolin-2-one (**33**).* Major diastereomer; white solid; yield: 116 mg (73%); mp: 267−269 °C; t = 12 h. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 10.34 (s, 1H), 7.97 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.57−7.48 (m, 1H), 7.38−7.35 (m, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.70 (t, J = 7.2 Hz, 1H), 6.07 (d, J = 5.6 Hz, 1H), 5.94 (s, 1H), 4.95 (s, 1H), 4.38 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 175.2, 173.7, 151.4, 142.7, 130.4, 130.2, 129.0, 128.3, 127.4, 124.4, 122.9, 121.7, 121.2, 117.0, 110.8, 109.7, 45.8, 44.5 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{13}NO_3Na$ $[M + Na]^+$ 338.0788; found: 338.0781.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02395.

Copies of ^{1}H and ^{13}C NMR spectra for all new products, ORTEP diagram; HRMS spectra of products **13**−**33** (PDF)

X-ray data for compound **20** (CIF)

X-ray data for compound **30** (CIF)

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Notes

The authors declare no competing financial interest.

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