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Palladium-Catalyzed Direct Arylation of Polysubstituted Benzofurans

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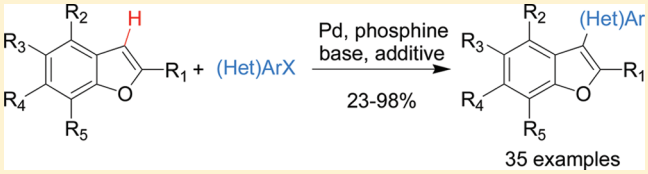
Supporting Information

ABSTRACT: An efficient access to 2-substituted 3-arylbenzofurans through a palladium-catalyzed C3 direct arylation of 2-substituted benzofurans with aryl bromides is described. The scope and limitation of this reaction was studied. The method tolerates a variety of functional groups on the aryl halide and has been successfully extended to polysubstituted benzofurans to obtain the corresponding 3-arylbenzofurans with good to excellent yields.



INTRODUCTION

Benzo[*b*]furan derivatives are an important class of heterocyclic compounds that exhibit biological activity on a wide range of targets.[1] Recently, benzofurans have been identified as selective adenosine A_{2A} receptor antagonists[2] for a novel nondopaminergic approach to PD therapy, nonacidic benzofuran EP1 receptor antagonists for the treatment of inflammatory pain,[3] kinase CK2 inhibitors as antitumor agents,[4] antagonists of the CXCR2 receptor as potential use for the treatment of inflammatory and related diseases,[5] uric acid transporter 1 (hURAT1) inhibitors with uricosuric activity,[6] and agonists of the retinoic acid receptor (RAR) subtypes for cancer therapy and prevention.[7] They are found as a key structural unit in many natural products, and pharmaceuticals, such as, for example, amiodarone, befunolol, or bergapten. As part of an ongoing medicinal chemistry project,[8] our interest was focused on the synthesis of 3-aryl-2-aroylbenzofurans. Two possible approaches to the construction of this class of compounds have already been described, by acylation of 3-arylbenzofurans[9a,b] or by condensation of 2-hydroxybenzophenone derivatives with α-bromoarylketones.[9c−e] However, these approaches required either drastic conditions or multistep synthesis of precursors and gave access to a limited variety of compounds. For these reasons, the developement of a more efficient method to obtain a wider range of polysubstituted benzofurans was needed. 2-Aroylbenzofurans are easily synthesized by Rap−Stoermer condensation from salicylaldehydes and α-bromoketones.[10] Recently, this reaction has been extensively studied, and novel applications under microwaves[11] or solvent-free[12] conditions gave excellent yields with a good tolerance toward functional groups. As an alternative, our investigations were focused on the direct arylation of 2-benzoylbenzofurans at the 3-position as a method for generating 3-aryl-2-benzoylbenzofurans (Scheme 1).

Over the past decade, direct arylation has become a powerful alternative to traditional cross-coupling reactions[13,14] in order to prepare biaryl molecules. It has also been successfully applied to many heteroaromatic compounds.[15] With this new synthetic pathway, there is no more need to preactivate the coupling partner as its halide or organometallic derivative (boron for Suzuki coupling or tin for Stille coupling). Therefore, direct arylation is more atom-economical and environmentally friendly. Up to now, very few examples of C3-arylation of benzofurans have been reported in the literature and only two of them deal with intermolecular arylation.[16,17] Indeed, in 2010, Fagnou et al. described the $Pd(OAc)_2$-catalyzed direct arylation of chlorine-containing heteroaromatics, among which only two examples were reported from 2-chlorobenzofuran. The same year, the palladium-catalyzed direct C3-arylation of 2-substituted benzofuran derivatives was published by Doucet et al., a study using $Pd(C_3H_5)Cl(dppb)$ or $Pd(OAc)_2$ in which few examples with benzofurans bearing electron-withdrawing groups (i.e., acetyl, formyl) at the 2-position are given. On the other hand, it should be noted that arylation of the C−H bonds of benzofuran is regioselective on position 2,[18] and in some cases, a C2/C3-diarylation was observed.[19] In the quest to expand the knowledge on the reactivity of 2-substituted benzofurans with aryl bromides using $Pd(OAc)_2$, we have studied herein the scope and limitation of the direct arylation with various electron-withdrawing groups (benzoyl, nitro,

Scheme 1. Strategy for the Synthesis of 3-Aryl-2-aroylbenzofurans

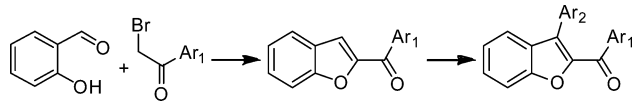


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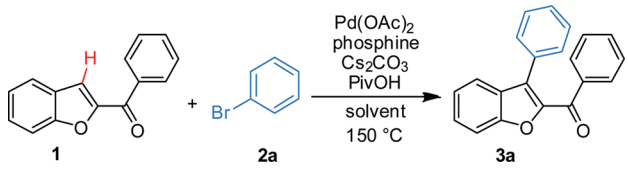
Table 1. Optimization of Direct Arylation of 2-Benzoylbenzofuran



entry	phosphine[c]	additive	solvent	conversion (%)[d]
1[a]	P(*t*-Bu)$_2$Me (10)	PivOH (30)	DMA	55
2[a]	PCy$_3$ (10)	PivOH (30)	DMA	11
3[a]	P(*t*-Bu)$_2$Me (10)	PivOH (60)	DMA	75
4[a]	P(*t*-Bu)$_2$Me (10)	PivOH (120)	DMA	80
5[a]	P(*t*-Bu)$_2$Me (10)	PivOH (60)	Mes	95
6[b]	P(*t*-Bu)$_2$Me (10)	PivOH (30)	Mes	>95
7[a]	PCy$_3$ (10)	PivOH (60)	Mes	95
8[b]	PPh$_3$ (10)	PivOH (30)	Mes	30
9[b]	P(*t*-Bu)$_2$Me (4)	PivOH (30)	Mes	85
10[b]	P(*t*-Bu)$_2$Me (8)	PivOH (30)	Mes	>95 (90[e])
11[b]	P(*t*-Bu)$_2$Me (8)		Mes	22

[a]Conditions: 2-benzoylbenzofuran (1 equiv), bromobenzene (2 equiv), Pd(OAc)$_2$ (2 mol %), phosphine (4−10 mol %), Cs$_2$CO$_3$ (2 equiv), and PivOH (30−120 mol %); 150 °C overnight; solvent. [b]K$_2$CO$_3$ was used as base instead of Cs$_2$CO$_3$. [c]Alkyl phosphines were used as HBF$_4$ salts. [d]Determined by ^{1}H NMR. [e]Isolated yield (%).

cyano, acetyl, *tert*-butyl-carbonyl, methyl ester) and electron-donating groups (ethyl, phenyl) in the position 2.

RESULTS AND DISCUSSION

Accordingly, our study began with the optimization of the reaction between 2-benzoylbenzofuran **1** and bromobenzene under various reaction conditions (Table 1).

The first attempt was performed under Fagnou direct arylation conditions.[16b] The catalytic system was composed of Pd(OAc)$_2$, an alkyl-phosphine as its phosphonium tetrafluoroborate salt (P(*t*-Bu)$_2$Me·HBF$_4$) and pivalic acid as a cocatalyst,[20] and cesium carbonate was used as a base (Table 1, entry 1). The reaction was heated at 150 °C in DMA overnight, and 55% of conversion to **3a** was then obtained without any degradation or presence of side products. Several bases were screened (K$_2$CO$_3$, KOAc, CsOAc), resulting in little improvement of the conversion rate, but rather in the formation of inseparable byproduct.[21] The conversion dropped when the phosphine was changed from P(*t*-Bu)$_2$Me·HBF$_4$ to PPh$_3$, PEt$_3$·HBF$_4$, or PCy$_3$·HBF$_4$ (entry 2).[21] Increasing the proportion of pivalic acid to 60 and 120 mol % allowed an improvement of the conversion from 55% to 75% and 80%, respectively (entries 3 and 4). Conducting the reaction in mesitylene (Mes) gave the best results with a conversion reaching 90% in 8 h, and even 95% after 16 h (entry 5). Prolonged heating had no further effect. Moreover, the optimal conversion was also obtained using 30 mol % pivalic acid in the presence of K$_2$CO$_3$ as a base (entry 6). Without pivalic acid, a significant drop in conversion was observed, which confirms its essential role as a cocatalyst (entry 11). The use of another alkyl phosphine, such as PCy$_3$·HBF$_4$, gave a similar result in mesitylene, in contrast to that in DMA (entry 7 vs entry 2). However, with an aryl phosphine, the conversion decreased to only 30% (entry 8). Decreasing the amount of phosphine to 4 mol % lowered the conversion slightly (85%), and Pd black was observed (entry 9). Finally, reduction of the phosphine amount to 8 mol % led to the optimized reaction conditions (entry 10).

To explore the scope and limitation of this method, the coupling reactions between a variety of aryl halides and 2-benzoylbenzofuran were investigated under optimal conditions (Table 2).

As general indications, a reaction time from 16 to 63 h was required depending on the aryl bromide used. In several cases (entries 1, 5, 6, 13, 15, and 16), complete conversion of **1** was not observed despite prolonged reaction times. Both electron-donating (entries 1, 4, 5, and 15) and electron-withdrawing (entries 6−14) aryl bromides were found to be reactive, providing the corresponding arylated benzofurans with moderate to excellent yields (37−96%). The method turned out to be tolerant toward a broad range of functional groups, such as nitrile, amide, ester, ether, or amine. The effect of sterical hindrance of the aryl group was then briefly evaluated. Arylation occurred with 1-bromo-2-methylbenzene in 61% yield (entry 15), but no conversion was observed with 2-bromo-1,3-dimethylbenzene. Surprisingly, an aryl iodide, such as 1-iodo-4-methoxybenzene, did not react with **1** (entry 2), whereas the literature reported many examples of direct arylations using aryl iodides, providing good yields.[22] Importantly, Fagnou and co-workers have already observed this phenomenon with aryl iodides and have demonstrated that this behavior is due to catalyst poisoning by the iodide anion.[23] Indeed, when Ag$_2$CO$_3$ was added to the reaction involving 1-iodo-4-methoxybenzene in order to sequester iodide anion, the highest yield in **3b** (98%) was reached (entry 3 vs entry 1). Direct arylation of benzofuran **1** has also been successfully performed with heteroaryl bromides, such as 2-bromopyridine and 3-bromopyridine, to provide the desired coupling products in 23 and 83% yields, respectively (entries 16 and 17).

The application of the method to other 2-substituted benzofurans was also examined under the optimized conditions (Table 3, Method A). Benzofurans substituted by electron-withdrawing groups were arylated in good yields (entries 1−3, 5−7). By contrast, no arylation was observed using the same method with benzofurans featuring electron-donating groups (entries 8 and 10), and the starting material was entirely recovered. Thus, to overcome the lack of reactivity in the latter case, another method was developed using the catalytic system Pd(OAc)$_2$/P(*t*-Bu)$_2$Me·HBF$_4$ with KOAc as a base in DMA

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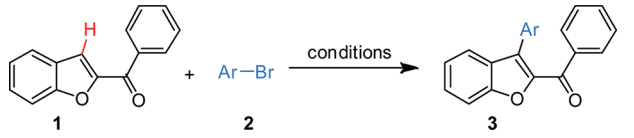
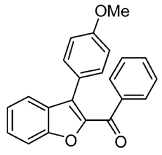
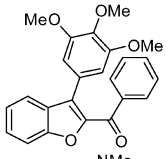
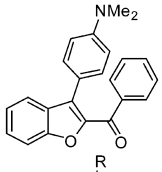
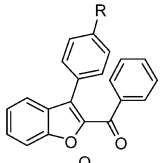
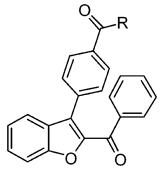
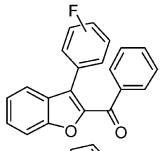
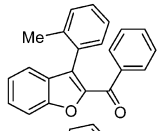
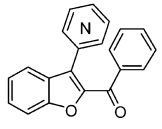
Table 2. Scope of Direct Arylation of 2-Benzoylbenzofuran with Various Aryl and Heteroaryl Bromides[a,b,c]



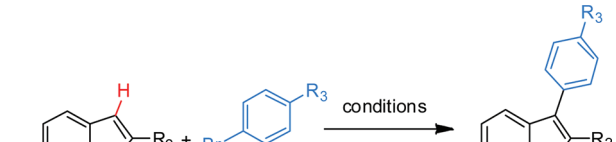
1 2 3

entry	product 3		time (h)	yield (%)[a]
1		**3b**	26	81
2[b]			26	-
3[b,c]			26	98
4		**3c**	40	88
5		**3d**	40	37
6		**3e** R = CN	18	70
7		**3f** R = NO_2	16	63
8		**3g** R = Cl	18	95
9		**3h** R = CF_3	40	94
10		**3i** R = Me	24	54
11		**3j** R = OMe	24	94
12		**3k** R = morpholine	24	96
13		**3l** *m*-F	48	59
14		**3m** *p*-F	21	84
15		**3n**	24	61
16		**3o** 2-pyridyl	63	23
17		**3p** 3-pyridyl	63	83

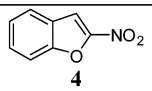
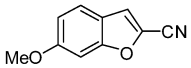
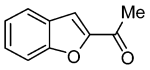
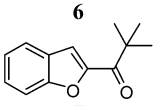
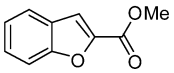
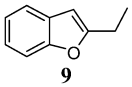
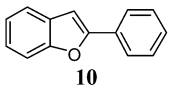
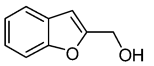
[a]Conditions: 2-benzoylbenzofuran (1 equiv), aryl bromide (2 equiv), $Pd(OAc)_2$ (2 mol %), P(*t*-Bu)$_2$Me·HBF_4 (8 mol %), K_2CO_3 (2 equiv), and PivOH (30 mol %); 150 °C; mesitylene. [b]1-Iodo-4-methoxybenzene was used instead of 4-bromo-4-methoxybenzene. [c]Ag_2CO_3 (1 equiv) was added.

(Method B).[24] The arylation reaction could be thus accomplished with 2-ethyl- or 2-phenyl benzofurans in good yields (Table 3, entries 9 and 11). This is a striking result with probable mechanistic consequences (vide infra) since Method B differs from Method A only in that it does not employ pivalate, replaces K_2CO_3 by KOAc, and uses a polar solvent (DMA). However, these reaction conditions were not well adapted for a benzofuran substituted with an electron-withdrawing group at C2, such as acetyl, as only traces of product were formed, and the reaction led mainly to degradation (entry 4). In addition, it

Table 3. Scope of Direct Arylation of 2-Substituted Benzofurans with Aryl Bromides[a,b]



4 - 8, 8 - 11 R_3 = CO_2Me (**2j**) R_3 = H (**2a**) **12j - 16j**, **16a - 19a**

entry	benzofuran	product	method	yield (%)[a]
1	 **4**	**12j**	A	77
2	 **5**	**13j**	A	81
3	 **6**	**14j**	A	56
4			B	degradation
5	 **7**	**15j**	A	68 (15[b])
6	 **8**	**16j**	A	78
7		**16a**	A	92
8	 **9**	**17a**	A	-
9			B	69
10	 **10**	**18a**	A	-
11			B	69
12	 **11**	**19a**	B	18

[a]Method A: benzofuran (1 equiv), arylbromide (2 equiv), $Pd(OAc)_2$ (2 mol %), P(*t*-Bu)$_2$Me·HBF_4 (8 mol %), K_2CO_3 (2 equiv), and PivOH (30 mol %); 150 °C; mesitylene. Method B: benzofuran (1 equiv), arylbromide (2 equiv), $Pd(OAc)_2$ (2 mol %), P(*t*-Bu)$_2$Me·HBF_4 (8 mol %), and KOAc (2 equiv); 150 °C; DMA. [b]Starting material yield.

should be noted that a benzofuran substituted with a non-protected alcohol could be arylated even though in low yield (entry 12).

It is noteworthy to point out the specific reactivity of the latter benzofuran when arylation was performed using Method A. Indeed, a one-pot oxidation/arylation sequence occurred to provide 3-phenylbenzofuran-2-carbaldehyde **22j** in 79% yield (Table 4, entry 1). It was possible to extend this reaction to the preparation of 3-aryl-2-ketobenzofurans from the corresponding secondary alcohols in very good yields (entries 2 and 3).

Importantly, it has been reported that aryl halides could be used as cooxidants in Pd-catalyzed oxidation of primary and secondary alcohols.[25] Accordingly, to understand the mechanism of this one-pot transformation, the influence of the aryl bromide on the reactivity was evaluated from benzofuran-2-yl(phenyl)methanol **21** (Table 5).

First, in the absence of methyl 4-bromobenzoate, 95% of the starting material **21** was recovered, and the ketone **1** was isolated in 5% yield (entry 1). The low yield formation of the latter could result from oxidation of the benzylic alcohol by a

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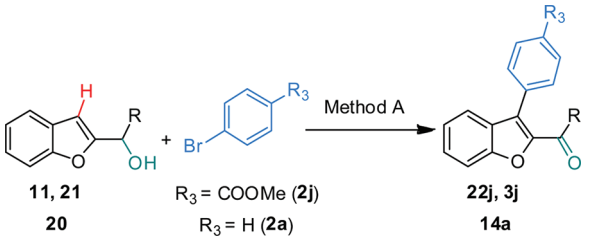
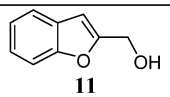
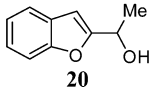
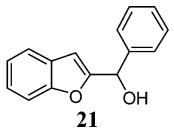
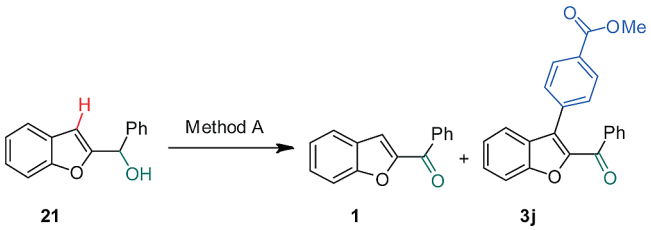
Table 4. Direct Arylation of Benzofurans Substituted by an Alcohol[a]



entry	benzofuran	product	time (h)	yield (%)[a]
1	 11	**22j**	23	79
2	 20	**14a**	17	96
3	 21	**3j**	23	84

[a]Method A: 2-substituted benzofuran (1 equiv), aryl bromide **2a** or **2j** (2 equiv), $Pd(OAc)_2$ (2 mol %), $P(t\text{-}Bu)_2Me{\cdot}HBF_4$ (8 mol %), K_2CO_3 (2 equiv), and PivOH (30 mol %); 150 °C; mesitylene.

Table 5. Influence of the Aryl Bromide on the One-Pot Oxidation/Direct Arylation



		yield (%)		
entry	equiv of **2j**	**21**	**1**	**3j**
1	0	95	5	
2	1		89	6
3	2			84

catalytic Pd(II) species, typically $Pd(OAc)_2$, according to literature data, with no cooxidant, such as molecular oxygen. With 1 equiv of aryl bromide **2j**, the reaction proceeded first by oxidation of the alcohol functionality in **21** to generate benzofuran-2-yl(phenyl)methanone **1** in 89% yield, and subsequent arylation produced phenyl(3-phenylbenzofuran-2-yl)-methanone **3j** in 6% yield (entry 2). With 2 equiv of the aryl bromide, the arylated ketone **3j** was obtained in 84% yield and no C3-arylated alcohol was observed (entry 3). We could thus conclude that alcohol **21** was first oxidized into the corresponding ketone **1**, which was then arylated to afford **3j**. This result is in full agreement with the fact that the arylation conditions of Method A are only applicable to benzofurans substituted by electron-withdrawing groups at C2.

This one-pot reaction oxidation/arylation of benzofurans can be assimilated to an autotandem catalysis according to Fogg et al. classification.[26] It involves two distinct catalytic mechanisms promoted by a single catalyst. The first catalytic cycle concerns the oxidation of the alcohol with an aryl halide as a cooxidant, whereas the second catalytic cycle corresponds to the C-3 arylation (Scheme 2). Several mechanisms have been proposed for direct arylation. In the case of Method A, the difference of reactivity between 2-substituted benzofurans featuring electron-donating groups versus electron-withdrawing groups provided evidence against an S_EAr mechanism[27] and led us to propose a concerted metalation−deprotonation (CMD) pathway.[28] Indeed, it has been shown that the arylation process following this latter route was faster with electron-deficient arenes. Moreover, the influence of pivalic acid has been demonstrated for this method (Table 1, entry 11), and with the CMD mechanism, it has been proposed that the pivalate anion could replace the bromine in the complex Ar−Pd−X, inducing a lower energy of C−H bond cleavage, explaining the key role of pivalic acid as a cocatalyst. As regards to Method B, wherein the palladium source, ligand, reactants, and temperatures are the same as in Method A, it is not obvious why the changes (i.e., no pivalic acid, KOAc, and DMA) would make such a large difference in reactivity, or how Method B fits into the overall mechanistic model. The results suggest another mechanism for electron-rich substrates, possibly the S_EAr pathway. This needs to be proven.

Finally, given the favorable reactivity of benzofurans substituted by electron-withdrawing groups on position 2 when method A was applied, it was interesting to evaluate its feasibility for the direct arylation of polysubstituted benzofurans. The question arose how the presence of electron-donating groups on the benzenic ring can affect the arylation process of benzofurans. For this purpose, a series of 2-benzoylbenzofurans **23**−**28** bearing electron-donating groups on positions 4, 5, 6, and/or 7 were synthesized by Rap−Stoermer condensation (Table 6).

The required polysubstituted benzofurans were obtained in good to high yields (86−94%) no matter the position and number of substituents (entries 1−5 and 7−9). Subsequent arylation of **23**−**28** by Method A led to **31**−**36**, respectively (Table 6). The position of the substitution on the benzenic ring turned out to be critical for the yields of the reaction. Indeed, methoxy substituents at positions 5 and 6 (entry 10) or at positions 5, 6, and 7 (entry 11) gave good yields. However, incomplete conversions were achieved with a methoxy substituent at position 4 whatever the presence or not of other methoxy substituents (entries 12−15) and even after a prolonged heating time (16−64 h, entries 12−15). Similar yields were found when this reaction was carried out with hydroxyl or methyl substituents at position 4 (entries 16 and 17). The effects of electron-donating groups at position 4 appear steric in nature, rather than electronic. Indeed, direct arylation on a 2-benzoylbenzofuran substituted by an electron-withdrawing substituent, such as the carbomethoxy group, on position 4 failed, and the starting material was almost entirely recovered (entry 18). By contrast, 2-benzoylbenzofuran substituted by this group on position 7 was arylated in 89% yield (entry 19). These results show that sterical hindrance was an important factor to take into account in C-3 direct arylation of benzofurans.

In summary, we have developed a straightforward and efficient access to 2-substituted 3-arylbenzofurans through a palladium-catalyzed C3 direct arylation of 2-substituted benzofurans with aryl bromides. Electron-donating and electron-withdrawing aryl bromides underwent arylation successfully along with pyridinyl bromides, and the method was compatible with many functional groups. This direct arylation was successfully extended to poly-substituted benzofurans, highlighting its sensitivity to the steric and electronic environment of the benzofuran core.

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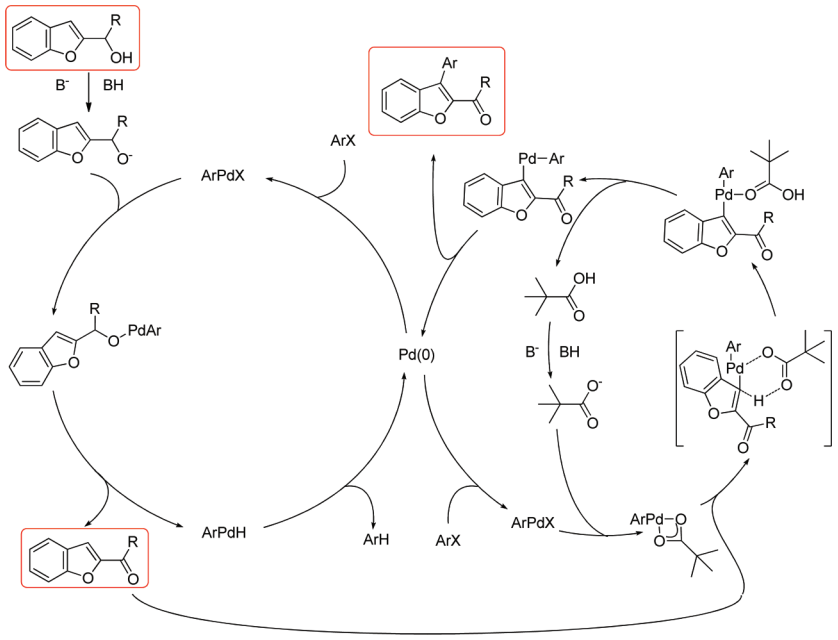
Scheme 2. Proposed Mechanism for the One-Pot Oxidation/Arylation of Benzofurans



EXPERIMENTAL SECTION

General Procedure for Direct Arylation of Benzofurans (Method A). Benzofuran (1 equiv), K_2CO_3 (2 equiv), P(*t*-Bu)$_2$Me·HBF$_4$ (8 mol %), and Pd(OAc)$_2$ (2 mol %) were weighed in air and placed in a screw cap vial equipped with a magnetic stir bar under argon. PivOH (30 mol %) was weighed in air, dissolved in mesitylene, and added to the vial. Aryl halide (2 equiv) was finally added (if liquid, otherwise it was introduced at the beginning with the other solids). The reaction mixture was then vigorously stirred at 150 °C (oil bath temperature) during the indicated time. After cooling to room temperature, the reaction was diluted with EtOAc and washed with water. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel to afford the desired product.

General Procedure for Direct Arylation of Benzofurans (Method B). Benzofuran (1 equiv), KOAc (2 equiv.), P(*t*-Bu)$_2$Me·HBF$_4$ (8 mol %), and Pd(OAc)$_2$ (2 mol %) were weighed in air and placed in a screw cap vial equipped with a magnetic stir bar under argon. DMA and the aryl halide (2 equiv) were then added. The reaction was then vigorously stirred at 150 °C (oil bath temperature) during the indicated time. The solution was cooled, diluted with EtOAc, and washed with water. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford the desired product.

General Procedure for the Rap−Soermer Condensation. To a solution of 2-bromo-1-phenylethanone (1.2 equiv) in acetone was added potassium carbonate (4.0 equiv) and the appropriate 2-hydroxybenzaldehyde (1.0 equiv) under argon. The resulting mixture was stirred at reflux overnight. After removal of the solvent, water and ethyl acetate were added. The aqueous layer was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford the desired product.

Benzofuran-2-yl(phenyl)methanone 1. Following the general procedure for Rap−Stoermer condensation, a mixture of 2-bromo-1-phenylethanone (5.14 g, 25.8 mmol) and 2-hydroxybenzaldehyde (3.00 g, 24.6 mmol) was stirred at reflux for 20 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5) to afford the desired product **1** (5.45 g, 24.5 mmol, 100%) as a white powder: mp 87 °C (recrystallized from hexane to give white crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1H), 7.67−7.62 (m, 2H), 7.56−7.48 (m, 4H), 7.37−7.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.4, 156.0, 152.2, 137.2, 132.9, 129.4 (2C), 128.5 (2C), 128.4, 127.0, 124.0, 123.3, 116.5, 112.6; IR ($CDCl_3$) ν_{max} 3068, 1647, 1547, 1330, 1300, 1280, 1187, 1117 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{15}H_{11}O_2$ [M + H]$^+$, 223.0759; found, 223.0765.

Phenyl(3-phenylbenzofuran-2-yl)methanone 3a. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (222 mg, 1.00 mmol) and bromobenzene (0.12 mL, 2.00 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 199:1) twice to afford the desired product **3a** (272 mg, 0.91 mmol, 91%) as a pale yellow solid: mp 93 °C (recrystallized from hexane to give pale yellow crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.57−7.47 (m, 4H), 7.41−7.32 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8, 154.6, 147.1, 137.2, 132.6, 130.9, 130.0 (2C), 129.8 (2C), 129.4, 128.33 (2C), 128.28, 128.2, 128.0 (2C), 123.9, 122.4, 112.4; IR ($CDCl_3$) ν_{max} 3066, 1648, 1601, 1559, 1492, 1447, 1371, 1292, 1261, 1013 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{21}H_{15}O_2$ [M + H]$^+$, 299.1072; found, 299.1079.

(3-(4-Methoxyphenyl)benzofuran-2-yl)(phenyl)methanone 3b. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (555 mg, 2.50 mmol) and 1-bromo-4-methoxybenzene (0.63 mL, 5.00 mmol) was stirred during 26 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 98:2) to afford the desired product **3b** (666 mg, 2.03 mmol, 81%) as a yellow solid: mp 84 °C (recrystallized from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 6.9 Hz, 2H), 7.72 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.55−7.44 (m, 4H), 7.39−7.32 (m, 3H), 6.91 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8, 159.7, 154.6, 146.9, 137.3, 132.6, 131.3 (2C), 129.8 (2C), 129.3, 128.2, 128.15, 128.05 (2C), 123.8, 123.0, 122.4, 113.9 (2C), 112.4, 55.3; IR ($CDCl_3$) ν_{max} 3066, 2960, 2839, 1647, 1612, 1560, 1508, 1447, 1375, 1290, 1251, 1175, 1035, 1014 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{22}H_{16}O_3Na$ [M + Na]$^+$, 351.0997; found, 351.1008.

Phenyl(3-(3,4,5-trimethoxyphenyl)benzofuran-2-yl)-methanone 3c. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1**

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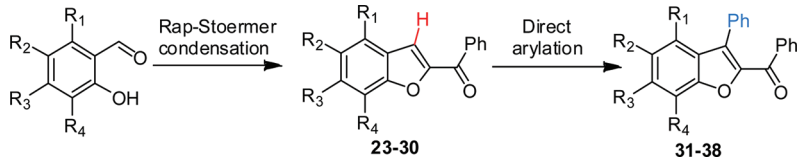
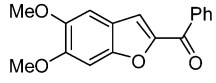
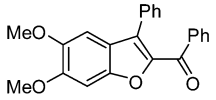
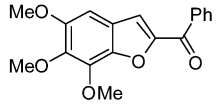
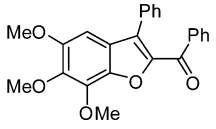
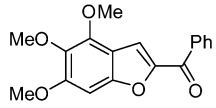
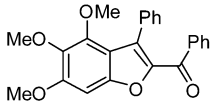
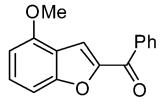
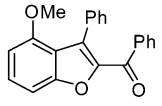
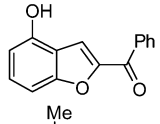
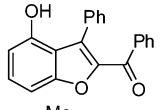
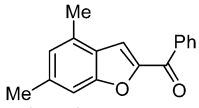
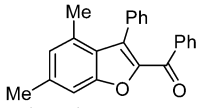
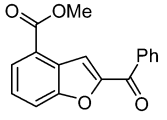
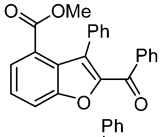
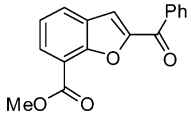
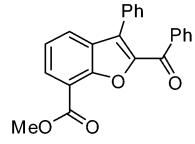
Table 6. Direct Arylation of Polysubstituted 2-Benzoylbenzofurans with Bromobenzene[a,b,c,d]



entry	2-benzoylbenzofuran[a]		Yield[a]	entry	2-benzoyl-3-phenylbenzofuran[c]		Time (h)	Yield (%)[c]
1		**23**	90	10		**31**	16	78
2		**24**	86	11		**32**	16	86
3		**25**	91	12 13		**33**	16 64	21 (43)[d] 41 (53)[d]
5		**26**	94	14 15		**34**	16 64	47 (42)[d] 41 (47)[d]
6		**27**	48[b]	16		**35**	16	42 (34)
7		**28**	93	17		**36**	16	33 (65)[d]
8		**29**	83	18		**37**	16	-
9		**30**	61	19		**38**	16	89

[a]Rap−Stoermer condensation: salicylaldehyde (1 equiv), bromoacetophenone (1.2 equiv), K_2CO_3 (4 equiv), acetone at reflux overnight. [b]Obtained by deprotection of **25** with BBr_3 (2 equiv), dichloromethane at r.t., 4 h. [c]Method A: benzofuran (1 equiv), bromobenzene (2 equiv), $Pd(OAc)_2$ (2 mol %), $P(t\text{-}Bu)_2Me{\cdot}HBF_4$ (8 mol %), K_2CO_3 (2 equiv), and PivOH (30 mol %); 150 °C; mesitylene. [d]NMR yields of the arylated product and starting material (in brackets), calculated from the isolated mixture.

(222 mg, 1.00 mmol) and 5-bromo-1,2,3-trimethoxybenzene (494 mg, 2.00 mmol) was stirred for 40 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 90:10) to afford the desired product **3c** (342 mg, 0.88 mmol, 88%) as a yellow solid: mp 104−105 °C (recrystallized from hexane/dichloromethane to give yellow needles); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 6.9 Hz, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.57−7.45 (m, 2H), 7.40−7.31 (m, 3H), 6.68 (s, 2H), 3.86 (s, 3H), 3.79 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.9, 154.6, 153.2 (2C), 147.1, 138.4, 137.5, 132.7, 129.6 (2C), 129.3, 128.3, 128.04 (2C), 127.99, 126.2, 124.0, 122.4, 112.5, 107.7 (2C), 60.8, 56.2 (2C); IR ($CDCl_3$) ν_{max} 3007, 2940, 2834, 1645, 1582, 1560, 1503, 1463, 1416, 1384, 1306, 1282, 1239, 1158, 1130 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{24}H_{20}O_5Na$ $[M + Na]^+$, 411.1208; found, 411.1227.

(3-(4-(Dimethylamino)phenyl)benzofuran-2-yl)(phenyl)-methanone 3d. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (555 mg, 2.50 mmol) and 4-bromo-*N*,*N*-dimethylaniline (1.0 g, 5.00 mmol) was stirred for 40 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 98:2 to 95:5) to afford the desired product **3d** (318 mg, 0.93 mmol, 37%) as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.2 Hz, 2H), 7.79 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.53−7.31 (m, 7H), 6.71 (d, J = 9.0 Hz, 2H), 2.99 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8, 154.7, 150.4, 146.5, 137.6, 132.3, 131.0 (2C), 130.1, 129.8 (2C), 128.4, 128.0 (3C), 123.5, 122.7, 118.1, 112.3, 111.9 (2C), 40.3 (2C); IR ($CDCl_3$) ν_{max} 2926, 2853, 2807, 1645, 1611, 1562, 1514, 1360, 1292, 1164 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{23}H_{20}NO_2$ $[M + H]^+$, 342.1494; found, 342.1507.

4-(2-Benzoylbenzofuran-3-yl)benzonitrile 3e. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (222 mg, 1.00 mmol) and 4-bromobenzonitrile (364 mg, 2.00 mmol) was stirred for 18 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 98:2 to 96:4) to afford the desired product **3e** (226 mg, 0.70 mmol, 70%) as a white solid: mp 145 °C (recrystallized from hexane/dichloromethane to give white crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 2H), 7.73−7.55 (m, 8H), 7.46−7.37 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 154.5, 147.6, 136.8, 136.0, 133.2, 132.1 (2C), 130.7 (2C), 129.9 (2C), 128.6, 128.3 (2C), 127.4, 127.3, 124.5, 121.7, 118.6, 112.6, 112.0; IR ($CDCl_3$) ν_{max} 3067, 2231, 1651, 1612, 1567, 1501, 1371, 1291, 1262, 1014 cm^{-1};

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HRMS (ES$^+$) m/z calculated for $C_{22}H_{14}NO_2$ $[M + H]^+$, 324.1025; found, 324.1034.

(3-(4-Nitrophenyl)benzofuran-2-yl)(phenyl)methanone 3f. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (555 mg, 2.50 mmol) and 1-bromo-4-nitrobenzene (1.01 g, 5.00 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 99:1 to 98:2) to afford the desired product **3f** (536 mg, 1.56 mmol, 63%) as an orange solid: mp 162 °C (recrystallized from hexane/dichloromethane to give a pale yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 8.7 Hz, 2H), 7.98 (d, J = 7.2 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 7.70−7.64 (m, 2H), 7.61−7.56 (m, 2H), 7.48−7.38 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 154.5, 147.7, 147.5, 138.0, 136.8, 133.3, 130.9 (2C), 129.9 (2C), 128.7, 128.4 (2C), 127.3, 127.0, 124.6, 123.6 (2C), 121.6, 112.7; IR ($CDCl_3$) ν_{max} 3070, 1651, 1602, 1560, 1521, 1350, 1292, 1262, 1014 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{21}H_{13}NO_4Na$ $[M + Na]^+$, 366.0742; found, 366.0755.

(3-(4-Chlorophenyl)benzofuran-2-yl)(phenyl)methanone 3g. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (222 mg, 1.00 mmol) and 1-bromo-4-chlorobenzene (383 mg, 2.00 mmol) was stirred for 18 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 199:1) to afford the desired product **3g** (315 mg, 0.95 mmol, 95%) as a pale yellow solid: mp 108 °C (recrystallized from hexane to give yellow crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 6.9 Hz, 2H), 7.68−7.63 (m, 2H), 7.57−7.34 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.4, 154.5, 147.2, 137.1, 134.4, 132.9, 131.2 (2C), 129.8 (2C), 129.4, 128.6 (2C), 128.4, 128.19 (2C), 128.16, 127.8, 124.1, 122.0, 112.5; IR ($CDCl_3$) ν_{max} 3067, 2955, 1701, 1649, 1601, 1555, 1492, 1370, 1291, 1250, 1092, 1014 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{21}H_{14}O_2Cl$ $[M + H]^+$, 333.0682; found, 333.0697.

Phenyl(3-(4-(trifluoromethyl)phenyl)benzofuran-2-yl)-methanone 3h. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (222 mg, 1.00 mmol) and 1-bromo-4-(trifluoromethyl)benzene (0.28 mL, 2.00 mmol) was stirred for 40 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 199:1 to 196:4) to afford the desired product **3h** (343 mg, 0.94 mmol, 94%) as a pale yellow solid: mp 135 °C (recrystallized from hexane to give pale yellow crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 2H), 7.68−7.65 (m, 6H), 7.59−7.52 (m, 2H), 7.44−7.36 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 154.5, 147.5, 137.0, 134.8, 133.0, 130.31 (q, J = 32 Hz), 130.31 (2C), 129.9 (2C), 128.5, 128.3 (2C), 127.9, 127.7, 125.3 (q, J = 3.8 Hz, 2C), 124.3, 124.0 (q, J = 270 Hz), 121.9, 112.5; IR ($CDCl_3$) ν_{max} 3067, 1650, 1564, 1322, 1292, 1262, 1171, 1132, 1068, 1014 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{22}H_{13}O_2F_3Na$ $[M + Na]^+$, 389.0765; found, 389.0782.

1-(4-(2-Benzoylbenzofuran-3-yl)phenyl)ethanone 3i. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (555 mg, 2.50 mmol) and 1-(4-bromophenyl)ethanone (995 mg, 5.00 mmol) was stirred for 23 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 99:1 to 97:3) to afford the desired product **3i** (450.5 mg, 1.33 mmol, 53%) as a pale yellow solid: mp 90 °C (recrystallized from hexane/dichloromethane to give yellow crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.7 Hz, 2H), 7.94 (d, J = 7.2 Hz, 2H), 7.69−7.63 (m, 4H), 7.59−7.71 (m, 2H), 7.43−7.36 (m, 3H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 185.3, 154.5, 147.5, 137.0, 136.6, 136.0, 133.0, 130.2 (2C), 129.9 (2C), 128.4, 128.3 (2C), 128.24 (2C), 128.18, 127.6, 124.2, 122.0, 112.5, 26.7; IR ($CDCl_3$) ν_{max} 3067, 1683, 1650, 1610, 1567, 1363, 1290, 1266, 1012 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{23}H_{17}O_3$ $[M + H]^+$, 341.1178; found, 341.1189.

Methyl 4-(2-benzoylbenzofuran-3-yl)benzoate 3j. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (555 mg, 2.50 mmol) and methyl 4-bromobenzoate (1.08 g, 5.00 mmol) was stirred for 23 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 96:4) to afford the desired product **3j** (837 mg, 2.35 mmol, 94%) as a yellow solid: mp 122 °C (recrystallized from hexane/dichloromethane to give yellow needles); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 7.2 Hz, 2H), 7.69−7.65 (m, 2H), 7.61−7.49 (m, 4H), 7.41−7.35 (m, 3H), 9.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.4, 166.7, 154.6, 147.4, 137.0, 135.8, 133.0, 130.0 (2C), 129.9 (2C), 129.8, 129.6 (2C), 128.4, 128.2 (3C), 127.7, 124.2, 122.0, 112.5, 52.2; IR ($CDCl_3$) ν_{max} 3067, 2954, 1719, 1650, 1612, 1571, 1438, 1289, 1114, 1014 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{23}H_{16}O_4Na$ $[M + Na]^+$, 379.0946; found, 379.0959.

(4-(2-Benzoylbenzofuran-3-yl)phenyl)(morpholino)-methanone 3k. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (222 mg, 1.00 mmol) and (4-bromophenyl)(morpholino)methanone (540 mg, 2.00 mmol) was stirred for 24 h. The residue was purified by flash chromatography over silica gel (dichloromethane/methanol 99:1) to afford the desired product **3k** (397 mg, 0.96 mmol, 96%) as a white solid: mp 254 °C (recrystallized from hexane/dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 7.2 Hz, 2H), 7.69−7.64 (m, 2H), 7.60−7.35 (m, 9H), 3.73−7.48 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.6, 169.9, 154.6, 147.3, 137.2, 135.1, 132.7 (2C), 130.2 (2C), 129.9 (2C), 128.4, 128.2 (3C), 127.8, 127.1 (2C), 124.2, 122.1, 112.5, 66.9 (4C); IR ($CDCl_3$) ν_{max} 3067, 2924, 2861, 1630, 1568, 1433, 1280, 1261, 1114, 1013 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{26}H_{22}NO_4$ $[M + H]^+$, 412.1549; found, 412.1566.

(3-(3-Fluorophenyl)benzofuran-2-yl)(phenyl)methanone 3l. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (555 mg, 2.50 mmol) and 1-bromo-4-chlorobenzene (0.64 mL, 5.00 mmol) was stirred for 48 h. The residue was purified twice by flash chromatography over silica gel (cyclohexane/ethyl acetate 199:1) to afford the desired product **3l** (468 mg, 1.48 mmol, 59%) as a pale yellow solid: mp 58 °C (recrystallized from hexane to give a pale yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.5 Hz, 2H), 7.71−7.64 (m, 2H), 7.57−7.50 (m, 2H), 7.42−7.22 (m, 6H), 7.09−7.02 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.5, 162.6 (d, J = 245 Hz), 154.5, 147.3, 137.1, 133.0 (d, J = 8.4 Hz), 132.9, 129.9 (d, J = 8.3 Hz), 129.8 (2C), 128.4, 128.2 (2C), 128.0 (d, J = 2.4 Hz), 127.7, 125.8 (d, J = 2.9 Hz), 124.1, 122.1, 116.9 (d, J = 22.3 Hz), 115.3 (d, J = 20.9 Hz), 112.5; IR ($CDCl_3$) ν_{max} 3068, 1650, 1614, 1563, 1448, 1292, 1262, 1233, 1168, 1021 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{21}H_{14}O_2F$ $[M + H]^+$, 317.0978; found, 317.0991.

(3-(4-Fluorophenyl)benzofuran-2-yl)(phenyl)methanone 3m. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (222 mg, 1.00 mmol) and 1-bromo-4-fluorobenzene (0.22 mL, 2.00 mmol) was stirred during 21 h. The residue was purified twice by flash chromatography over silica gel (cyclohexane/ethyl acetate 199:1) to afford the desired product **3m** (267 mg, 0.84 mmol, 84%) as a pale yellow solid: mp 80 °C (recrystallized from hexane to give a pale yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.2 Hz, 2H), 7.69−7.64 (m, 2H), 7.57−7.48 (m, 4H), 7.41−7.34 (m, 3H), 7.08 (t, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.6, 162.7 (d, J = 247 Hz), 154.5, 147.2, 137.2, 132.8, 131.75 (d, J = 8.2 Hz, 2C), 129.8 (2C), 128.4, 128.3, 128.1 (2C), 128.0, 126.8 (d, J = 3.4 Hz), 124.0, 122.1, 115.4 (d, J = 21.5 Hz, 2C), 112.4; IR ($CDCl_3$) ν_{max} 3066, 2959, 1649, 1601, 1563, 1506, 1374, 1292, 1261, 1227, 1161, 1014 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{21}H_{14}O_2F$ $[M + H]^+$, 317.0978; found, 317.0982.

Phenyl(3-*o*-tolylbenzofuran-2-yl)methanone 3n. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (222 mg, 1.00 mmol) and 1-bromo-2-methylbenzene (0.24 mL, 2.00 mmol) was stirred for 24 h. The residue was purified twice by flash chromatography over silica gel (cyclohexane/ethyl acetate 199:1) to afford the desired product **3n** (190 mg, 0.61 mmol, 61%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 6.9 Hz, 2H), 7.67 (d, J = 8.4 Hz, 1H), 7.56−7.19 (m, 10H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 154.5, 147.8, 137.1, 136.8, 132.6, 130.7, 130.2 (2C), 129.6 (2C), 129.1, 128.6, 128.3, 128.2, 128.0 (2C), 125.6, 123.8, 122.6, 112.4, 20.0; IR ($CDCl_3$)

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ν_{max} 2926, 1647, 1601, 1560, 1368, 1334, 1294, 1011 cm^{-1}; HRMS (ES^+) m/z calculated for $C_{22}H_{17}O_2$ $[M + H]^+$, 313.1229; found, 313.1231.

Phenyl(3-(pyridin-2-yl)benzofuran-2-yl)methanone 3o. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (555 mg, 2.50 mmol) and 2-bromopyridine (0.48 mL, 5.00 mmol) was stirred for 63 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 90:10) to afford the desired product **3o** (170 mg, 0.57 mmol, 23%) as a pale yellow solid: mp 87 °C (recrystallized from hexane/dichloromethane to give pale yellow crystals); ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (dt, J = 4.8, 1.5 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 7.2 Hz, 2H), 7.67−7.60 (m, 3H), 7.56−7.48 (m, 2H), 7.41−7.34 (m, 3H), 7.26−7.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.9, 154.7, 150.9, 149.6, 148.1, 137.2, 136.0, 132.9, 129.9 (2C), 128.16 (2C), 128.14, 127.9, 127.4, 125.9, 124.2, 123.2, 122.7, 112.2; IR ($CDCl_3$) ν_{max} 3064, 1651, 1595, 1563, 1464, 1369, 1293, 1260, 1168, 1018 cm^{-1}; HRMS (ES^+) m/z calculated for $C_{20}H_{14}NO_2$ $[M + H]^+$, 300.1025; found, 300.1028.

Phenyl(3-(pyridin-3-yl)benzofuran-2-yl)methanone 3p. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-yl(phenyl)methanone **1** (555 mg, 2.50 mmol) and 3-bromopyridine (0.48 mL, 5.00 mmol) was stirred for 63 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 70:30) to afford the desired product **3p** (622 mg, 2.08 mmol, 83%) as a white solid: mp 125 °C (recrystallized from hexane/dichloromethane to give white crystals); ^1H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, J = 1.8 Hz, 1H), 8.62 (dd, J = 4.8, 1.5 Hz, 1H), 7.95 (d, J = 7.2 Hz, 2H), 7.90 (dt, J = 7.8, 2.1 Hz, 1H), 7.70−7.66 (m, 2H), 7.60−7.53 (m, 2H), 7.45−7.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 154.5, 150.3, 149.3, 147.7, 137.4, 136.9, 133.0, 129.9 (2C), 128.6, 128.3 (2C), 127.6, 127.3, 125.9, 124.3, 123.1, 121.8, 112.6; IR ($CDCl_3$) ν_{max} 3064, 1650, 1600, 1555, 1371, 1292, 1262, 1229, 1013 cm^{-1}; HRMS (ES^+) m/z calculated for $C_{20}H_{13}NO_2Na$ $[M + Na]^+$, 322.0844; found, 322.0856.

Methyl 4-(2-nitrobenzofuran-3-yl)benzoate 12j. Following the general procedure for direct arylation (Method A), a mixture of 2-nitrobenzofuran **4**[29] (147 mg, 0.90 mmol) and methyl 4-bromobenzoate (387 mg, 2.00 mmol) was stirred during 20 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5) to afford the desired product **12j** (207 mg, 0.70 mmol, 77%) as an orange solid: mp 154 °C (recrystallized from hexane/dichloromethane to give an orange powder); ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 8.4 Hz, 2H), 7.71−7.61 (m, 5H), 7.44 (ddd, J = 8.1, 6.0, 2.1 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 151.7 (2C), 132.8, 131.1, 130.5, 130.0 (2C), 129.8 (2C), 127.2, 125.5, 123.1, 121.3, 112.7, 52.4; IR ($CDCl_3$) ν_{max} 3002, 2954, 2848, 1722, 1525, 1373, 1325, 1282, 1113 cm^{-1}; HRMS (ES^+) m/z calculated for $C_{16}H_{11}NO_5Na$ $[M + Na]^+$, 320.0535; found, 320.0538.

Methyl 4-(2-cyano-6-methoxybenzofuran-3-yl)benzoate 13j. Following the general procedure for direct arylation (Method A), a mixture of 6-methoxybenzofuran-2-carbonitrile **5**[30] (173 mg, 1.00 mmol) and methyl 4-bromobenzoate (430 mg, 2.00 mmol) was stirred for 23 h. The residue was purified by flash chromatography over silica gel (cyclohexane/dichloromethane 50:50) to afford the desired product **13j** (250 mg, 0.81 mmol, 81%) as a white solid: mp 197 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 9.3 Hz, 1H), 7.06−7.04 (m, 2H), 3.97 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 161.5, 157.3, 133.2, 132.4, 130.9, 130.5 (2C), 128.3 (2C), 123.0, 121.9, 117.9, 115.2, 112.5, 95.7, 55.9, 52.4; IR ($CDCl_3$) ν_{max} 2954, 2842, 2225, 1722, 1619, 1496, 1436, 1286, 1196, 1154, 1115 cm^{-1}; HRMS (ES^+) m/z calculated for $C_{18}H_{13}NO_4Na$ $[M + Na]^+$, 330.0742; found, 330.0755.

Methyl 4-(2-acetylbenzofuran-3-yl)benzoate 14j. Following the general procedure for direct arylation (Method A), a mixture of 1-(benzofuran-2-yl)ethanone **6**[31] (160 mg, 1.00 mmol) and methyl 4-bromobenzoate (430 mg, 2.00 mmol) was stirred for 23 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5) to afford the desired product **14j** (164 mg, 0.56 mmol, 56%) as a pale yellow solid: mp 195 °C (recrystallized from hexane/dichloromethane to give a pale yellow powder); ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 2H), 7.68−7.51 (m, 5H), 7.36−7.31 (m, 1H), 3.97 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 166.7, 154.1, 147.2, 135.6, 130.2, 130.0 (2C), 129.6 (2C), 128.6, 128.2, 126.5, 124.1, 122.2, 112.4, 52.2, 28.2; IR ($CDCl_3$) ν_{max} 3004, 2954, 1719, 1683, 1572, 1438, 1287, 1116, 1106 cm^{-1}; HRMS (ES^+) m/z calculated for $C_{18}H_{14}O_4Na$ $[M + Na]^+$, 317.0790; found, 317.0795.

Methyl 4-(2-pivaloylbenzofuran-3-yl)benzoate 15j. Following the general procedure for direct arylation (Method A), a mixture of 1-(benzofuran-2-yl)-2,2-dimethylpropan-1-one **7**[32] (202 mg, 1.00 mmol) and methyl 4-bromobenzoate (430 mg, 2.00 mmol) was stirred for 24 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 99:1 to 97:3) to afford the desired product **15j** (229 mg, 0.68 mmol, 68%) as a white solid: mp 82 °C (recrystallized from hexane to give white crystals); ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 2H), 7.63−7.59 (m, 3H), 7.55−7.50 (m, 2H), 7.35−7.30 (m, 1H), 3.95 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 166.8, 153.6, 147.1, 136.3, 129.9 (2C), 129.7, 129.5 (2C), 128.1, 127.8, 123.9, 121.9, 112.1, 52.2, 44.2, 26.4 (3C); IR ($CDCl_3$) ν_{max} 2956, 2909, 2875, 1719, 1673, 1613, 1559, 1438, 1281, 1183, 1114, 1053 cm^{-1}; HRMS (ES^+): m/z calculated for $C_{21}H_{21}O_4$ $[M + H]^+$, 337.1440; found, 337.1449.

Methyl 3-phenylbenzofuran-2-carboxylate 16a. Following the general procedure for direct arylation (Method A), a mixture of methyl benzofuran-2-carboxylate **8**[33] (440 mg, 2.50 mmol) and bromobenzene (0.53 mL, 5.00 mmol) was stirred for 15 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5) to afford the desired product **16a** (582.5 mg, 2.31 mmol, 92%) as a white solid: mp 92 °C (recrystallized from hexane to give a white powder); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65−7.58 (m, 4H), 7.54−7.45 (m, 4H), 7.35−7.29 (m, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 154.5, 139.8, 130.5, 129.9 (2C), 129.5, 128.5, 128.3, 128.2 (2C), 128.1, 123.8, 122.1, 112.3, 52.1; IR ($CDCl_3$) ν_{max} 3036, 2954, 1723, 1579, 1496, 1439, 1376, 1295, 1267, 1226, 1157, 1141 cm^{-1}; HRMS (ES^+) m/z calculated for $C_{16}H_{12}O_3Na$ $[M + Na]^+$, 275.0684; found, 275.0686.

Methyl 3-(4-(methoxycarbonyl)phenyl)benzofuran-2-carboxylate 16j. Following the general procedure for direct arylation (Method A), a mixture of methyl benzofuran-2-carboxylate **8** (176 mg, 1.00 mmol) and methyl 4-bromobenzoate (430 mg, 2.00 mmol) was stirred during 23 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5) to afford the desired product **16j** (241.6 mg, 0.78 mmol, 78%) as a white solid: mp 127 °C (recrystallized from hexane/dichloromethane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 2H), 7.68−7.63 (m, 3H), 7.58−7.49 (m, 2H), 7.33 (t, J = 8.1 Hz, 1H), 3.97 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 160.0, 154.5, 140.1, 135.3, 130.1, 130.0 (2C), 129.5 (2C), 128.4, 128.3, 127.8, 124.1, 121.8, 112.4, 52.5 (2C); IR ($CDCl_3$) ν_{max} 3003, 2954, 2360, 1722, 1614, 1590, 1438, 1376, 1291, 1142, 1110 cm^{-1}; HRMS (ES^+) m/z calculated for $C_{18}H_{15}O_5$ $[M + H]^+$, 311.0919; found, 311.0928.

2-Ethyl-3-phenylbenzofuran 17a.[34] Following the general procedure for direct arylation (Method B), a mixture of 2-ethylbenzofuran **9** (146 mg, 1.0 mmol) and bromobenzene (0.210 mL, 2.0 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (pentane) to afford the desired product **17a** (153 mg, 0.69 mmol, 69%) as a transparent liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.62−7.59 (m, 1H), 7.54−7.47 (m, 5H), 7.41−7.36 (m, 1H), 7.32−7.21 (m, 2H), 2.91 (t, J = 7.5 Hz, 2H), 2.39 (q, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 154.0, 132.8, 129.0 (2C), 128.8, 128.7 (2C), 126.9, 123.5, 122.5, 119.4, 116.1, 110.8, 20.2, 12.9; IR ($CDCl_3$) ν_{max} 3062, 2979, 2939, 1612, 1456, 1241, 1196, 1176 cm^{-1}; MS (ES^+) m/z 245 $[M + Na]^+$.

2,3-Diphenylbenzofuran 18a.[35] Following the general procedure for direct arylation (Method B), a mixture of 2-phenylbenzofuran **10**[36] (97 mg, 0.50 mmol) and bromobenzene (0.105 mL, 1.00 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (pentane) to afford the desired product **18a** (93 mg, 0.345 mmol, 69%) as a white solid: mp 123 °C (recrystallized from

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hexane to give white crystals) (lit. mp 123 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.65 (m, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.53−7.30 (m, 10H), 7.27−7.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 150.5, 132.8, 130.6, 130.2, 129.7 (2C), 128.9 (2C), 128.4 (2C), 128.3, 127.6, 127.0 (2C), 124.6, 122.9, 120.0, 117.4, 111.1; IR ($CDCl_3$) ν_{max} 3064, 3037, 1604, 1503, 1455, 1443, 1258, 1207, 1064, 1028 cm^{-1}; MS (ES$^+$) m/z 293 [M + Na]$^+$.

(3-Phenylbenzofuran-2-yl)methanol 19a.[37] Following the general procedure for direct arylation (Method B), a mixture of benzofuran-2-ylmethanol **11**[38] (148 mg, 1.00 mmol) and bromobenzene (0.21 mL, 2.00 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (dichloromethane) to afford the desired product **19a** (40 mg, 0.18 mmol, 18%) as a yellow solid: mp 79 °C (recrystallized from hexane to give white crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.64 (m, 1H), 7.58−7.48 (m, 5H), 7.44−7.33 (m, 2H), 7.30−7.25 (m, 1H), 4.84 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 151.6, 131.6, 129.1 (2C), 128.9 (2C), 127.9, 127.6, 124.9, 123.0, 120.4, 119.8, 111.4, 56.4; IR ($CDCl_3$) ν_{max} 3608, 3063, 2930, 2874, 1613, 1454, 1262, 1222, 1177, 1016 cm^{-1}; MS (ES$^+$) m/z 247 [M + Na]$^+$.

Methyl 4-(2-formylbenzofuran-3-yl)benzoate 22j. Following the general procedure for direct arylation (Method A), a mixture of benzofuran-2-ylmethanol **11** (148 mg, 1.00 mmol) and methyl 4-bromobenzoate (430 mg, 2.00 mmol) was stirred for 23 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5) to afford the desired product **22j** (220 mg, 0.79 mmol, 79%) as a white solid: mp 136 °C (recrystallized from hexane/dichloromethane to give a white powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.24 (d, J = 8.7 Hz, 2H), 7.77−7.67 (m, 4H), 7.63−7.57 (m, 1H), 7.43−7.38 (m, 1H), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 166.4, 155.4, 147.8, 133.8, 132.5, 131.0, 130.3 (2C), 130.0 (2C), 129.8, 126.8, 124.5, 122.4, 112.9, 52.4; IR ($CDCl_3$) ν_{max} 2954, 2853, 1722, 1673, 1287, 1115 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{17}H_{13}O_4$ [M + H]$^+$, 281.0814; found, 281.0822.

1-(3-Phenylbenzofuran-2-yl)ethanone 14a.[39] Following the general procedure for direct arylation (method A), a mixture of 1-(benzofuran-2-yl)ethanol **20**[40] (405 mg, 2.50 mmol) and bromobenzene (0.53 mL, 5.00 mmol) was stirred for 17 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 99:1 to 95:5) to afford a mixture of the desired product **14a** (566 mg, 2.40 mmol, 96%) as a yellow solid: mp 95 °C (recrystallized from hexane to give white crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.46 (m, 8H), 7.34−7.28 (m, 1H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 154.1, 147.1, 130.8, 129.9 (2C), 128.7, 128.44 (2C), 128.42, 127.9, 123.8, 122.5, 112.2, 28.3; IR ($CDCl_3$) ν_{max} 3066, 3035, 1680, 1562, 1494, 1375, 1290, 1214, 1103 cm^{-1}; MS (ES$^+$) m/z 259 [M + Na]$^+$.

(5,6-Dimethoxybenzofuran-2-yl)(phenyl)methanone 23. Following the general procedure for Rap−Stoermer condensation, a mixture of 2-bromo-1-phenylethanone (1.15 g, 5.80 mmol) and 2-hydroxy-4,5-dimethoxybenzaldehyde (1.00 g, 5.49 mmol) was stirred at reflux for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 80:20 to 70:30) to afford the desired product **23** (1.39 g, 4.93 mmol, 90%) as a yellow solid: mp 130 °C (recrystallized from heptane/ethyl acetate to give a yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.2 Hz, 2H), 7.65−7.59 (m, 1H), 7.53 (t, J = 7.2 Hz, 2H), 7.46 (d, J = 0.9 Hz, 1H), 7.13 (s, 1H), 7.07 (s,1H), 3.98 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.5, 151.9, 151.8, 151.77, 147.7, 137.5, 132.5, 129.3 (2C) 128.4 (2C), 119.1, 117.4, 102.6, 95.1, 56.3 (2C); IR ($CDCl_3$) ν_{max} 2964, 2941, 2837, 1638, 1541, 1490, 1296, 1252, 1234, 1214, 1197, 1120 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{17}H_{15}O_4$ [M + H]$^+$, 283.0977; found, 283.0970.

Phenyl(5,6,7-trimethoxybenzofuran-2-yl)methanone 24. Following the general procedure for Rap−Stoermer condensation, a mixture of 2-bromo-1-phenylethanone (0.98 g, 4.94 mmol) and 2-hydroxy-4,5,6-trimethoxybenzaldehyde (1.00 g, 4.72 mmol) was stirred at reflux for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 85:15 to 80:20) to afford the desired product **24** (1.27 g, 4.07 mmol, 86%) as a brown solid: mp 92 °C (recrystallized from hexane to give a white product); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 6.9 Hz, 2H), 7.66−7.60 (m, 1H), 7.53 (t, J = 6.9 Hz, 2H),7.48 (s, 1H), 6.82 (s, 1H), 4.27 (s, 3H), 3.96 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.5, 152.8, 151.8, 143.2, 142.0, 139.3, 137.3, 132.7, 129.4 (2C), 128.4 (2C), 123.1, 116.7, 97.2, 61.6, 61.0, 56.3; IR ($CDCl_3$) ν_{max} 3006, 2940, 2835, 1645, 1553, 1486, 1357, 1302, 1256, 1226, 1124 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{18}H_{17}O_5$ [M + H]$^+$, 313.1076; found, 313.1077.

Phenyl(4,5,6-trimethoxybenzofuran-2-yl)methanone 25. Following the general procedure for Rap−Stoermer condensation, a mixture of 2-bromo-1-phenylethanone (0.98 g, 4.94 mmol) and 2-hydroxy-4,5,6-trimethoxybenzaldehyde (1.00 g, 4.72 mmol) was stirred at reflux for 17.5 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 90:10 to 80:20) to afford the desired product **25** (1.34 g, 4.30 mmol, 91%) as a yellow powder: mp 90 °C (recrystallized from hexane to give a white product); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 2H), 7.65−7.59 (m, 2H), 7.53 (t, J = 7.2 Hz, 2H), 6.87 (s, 1H), 4.13 (s, 3H), 3.95 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.5, 156.0, 153.5, 151.0, 147.2, 137.5, 137.4, 132.6, 129.2 (2C), 128.5 (2C), 115.7, 113.4, 90.2, 61.4, 61.3, 56.4; IR ($CDCl_3$) ν_{max} 2967, 2940, 1641, 1649, 1541, 1485, 1469, 1301, 1274, 1200, 1152, 1129 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{18}H_{17}O_5$ [M + H]$^+$, 313.1076; found, 313.1082.

(4-Methoxybenzofuran-2-yl)(phenyl)methanone 26. Following the general procedure for Rap−Stoermer condensation, a mixture of 2-bromo-1-phenylethanone (1.36 g, 6.83 mmol) and 2-hydroxy-4-methoxy-benzaldehyde (1.00 g, 6.50 mmol) was stirred at reflux for 16.5 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5 to 90:10) to afford the desired product **26** (1.54 g, 6.10 mmol, 94%) as a white powder: mp 100 °C (recrystallized from heptane to give white crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.66−7.61 (m, 2H), 7.53 (t, J = 7.2 Hz, 2H), 7.43 (t, J = 8.1 Hz, 1H), 7.26−7.23 (m, 1H), 6.71 (d, J = 7.8 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 157.1, 155.1, 150.9, 137.3, 132.7, 129.5, 129.3 (2C), 128.5 (2C), 118.0, 114.7, 105.2, 103.5, 55.6; IR ($CDCl_3$) ν_{max} 2965, 2946, 2842, 1646, 1542, 1498, 1339, 1266, 1134, 1089 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{16}H_{13}O_3$ [M + H]$^+$, 253.0865; found, 253.0874.

(4-Hydroxybenzofurane-2-yl)(phenyl)methanone 27. To a solution of (4-methoxybenzofuran-2-yl)(phenyl)methanone **26** (100 mg, 0.40 mmol, 1.0 equiv) in dichloromethane was added a solution of boron tribromide in dichloromethane (0.80 mL, 0.80 mmol, 2.0 equiv) under argon at 0 °C. The resulting mixture was stirred at room temperature for 4 h. After quenching with water, saturated Na_2CO_3 solution was added until pH = 7. The aqueous layer was extracted two times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 90:10) to afford the desired product **27** (46 mg, 0.19 mmol, 48%) as a brown powder: mp 180 °C (recrystallized from hexane/ethyl acetate to give brown crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 6.9 Hz, 2H), 7.68 (s, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 8.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 158.0, 151.7, 151.5, 137.6, 133.4, 130.0, 129.9 (2C), 129.0 (2C), 117.6, 115.0, 108.8, 105.5; IR ($CDCl_3$) ν_{max} 3359, 3066, 1648, 1622, 1603, 1544, 1342, 1274, 1180 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{15}H_{11}O_3$ [M + H]$^+$, 239.0708; found, 239.0700.

(4,6-Dimethylbenzofuran-2-yl)(phenyl)methanone 28. Following the general procedure for Rap−Stoermer condensation, a mixture of 2-bromo-1-phenylethanone (0.70 g, 3.50 mmol) and 2-hydroxy-4,6-dimethylbenzaldehyde (0.50 g, 3.33 mmol) was stirred at reflux for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5 to 90:10) to afford the desired product **28** (0.83 g, 3.32 mmol, 100%) as a yellow solid: mp 77 °C (recrystallized from hexane to give yellow crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 6.9 Hz, 2H), 7.67−7.61 (m, 1H),

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7.57−7.50 (m, 3H), 7.26 (s, 1H), 6.96 (s, 1H), 2.52 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 156.6, 151.4, 139.5, 137.5, 133.0, 132.6, 129.3 (2C), 128.5 (2C), 125.9, 124.7, 115.7, 109.8, 22.0, 18.5; IR ($CDCl_3$) ν_{max} 3028, 2921, 1642, 1539, 1343, 1270 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{17}H_{15}O_2$ [M + H]$^+$, 251.1072; found, 251.1063.

Methyl 2-benzoylbenzofuran-4-carboxylate 29. Following the general procedure for Rap−Stoermer condensation, a mixture of 2-bromo-1-phenylethanone (829 mg, 4.16 mmol) and methyl 2-formyl-3-hydroxybenzoate (500 mg, 2.78 mmol) was stirred at reflux for 20 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5) to afford the desired product **29** (643 mg, 2.30 mmol, 83%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09−8.05 (m, 4H), 7.86 (d, J = 8.4 Hz, 1H), 7.69−7.64 (m, 1H), 7.60−7.54 (m, 3H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 166.0, 155.9, 152.9, 136.8, 133.0, 129.4 (2C), 128.5 (2C), 127.4, 127.0, 126.5, 124.6, 117.0, 116.8, 52.1; IR ($CDCl_3$) ν_{max} 3067, 3002, 2954, 1718, 1650, 1600, 1544, 1438, 1331, 1289, 1274, 1208, 1169, 1120 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{17}H_{13}O_4$ [M + H]$^+$, 281.0814; found, 281.0805.

Methyl 2-benzoylbenzofuran-7-carboxylate 30. Following the general procedure for Rap−Stoermer condensation, a mixture of 2-bromo-1-phenylethanone (1.20 g, 5.84 mmol) and methyl 3-formyl-2-hydroxybenzoate (1.00 g, 5.56 mmol) was stirred at reflux for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 98:2) to afford the desired product **30** (0.944 g, 3.40 mmol, 61%) as a yellow solid: mp 75 °C (recrystallized from hexane to give a white product); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 7.2 Hz, 2H), 8.19 (dd, J = 7.5, 1.2 Hz, 1H), 7.95 (dd, J = 8.1, 1.2 Hz, 1H), 7.69−7.64 (m, 2H), 7.59−7.54 (m, 2H), 7.43 (t, J = 7.8 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.3, 164.9, 153.8, 153.6, 136.5, 133.2, 130.6, 129.9 (2C), 128.51, 128.48 (2C), 128.2, 123.7, 116.1, 114.9, 52.5; IR ($CDCl_3$) ν_{max} 3072, 2954, 1721, 1650, 1600, 1556, 1296, 1217, 1143 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{17}H_{13}O_4$ [M + H]$^+$, 281.0814; found, 281.0800.

(5,6-Dimethoxy-3-phenylbenzofuran-2-yl)(phenyl)-methanone 31. Following the general procedure for direct arylation, a mixture of (5,6-dimethoxybenzofuran-2-yl)(phenyl)methanone **23** (282 mg, 1.00 mmol) and bromobenzene (0.21 mL, 2.00 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 80:20 to 75:25) to afford the desired product **31** (279 mg, 0.78 mmol, 78%) as a brown solid: mp 109 °C (recrystallized from hexane to give a yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 6.9 Hz, 2H), 7.49−7.41 (m, 3H), 7.40−7.30 (m, 5H), 7.13 (s, 1H), 6.99 (s, 1H), 3.99 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 151.8, 150.2, 147.9, 146.9, 137.6, 132.2, 131.3, 130.5, 129.8 (2C), 129.7 (2C), 128.3 (2C), 128.2, 127.9 (2C), 120.1, 101.7, 95.0, 56.4 (2C); IR ($CDCl_3$) ν_{max} 2963, 2940, 2836, 1637, 1552, 1492, 1302, 1256, 1223, 1135 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{23}H_{19}O_4$ [M + H]$^+$, 359.1283; found, 359.1288.

Phenyl(5,6,7-trimethoxy-3-phenylbenzofuran-2-yl)-methanone 32. Following the general procedure for direct arylation, a mixture of phenyl(5,6,7-trimethoxybenzofuran-2-yl)methanone **24** (312 mg, 1.00 mmol) and bromobenzene (0.21 mL, 2.00 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5 to 85:15) to afford the desired product **32** (332 mg, 0.86 mmol, 86%) as a brown solid: mp 113 °C (recrystallized from hexane to give yellow crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 6.9 Hz, 2H), 7.51−7.47 (m, 3H), 7.44−7.35 (m, 5H), 6.73 (s, 1H), 4.25 (s, 3H), 3.97 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 151.9, 147.5, 141.8, 141.6, 139.1, 137.3, 132.5, 130.9, 129.9, 129.8 (2C), 129.7 (2C), 128.4 (2C), 128.3, 128.0 (2C), 124.2, 96.2, 61.6, 60.9, 56.4; IR ($CDCl_3$) ν_{max} 3053, 3011, 2986, 2940, 1645, 1462, 1423, 1376, 1264, 1238,1137, 1048 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{24}H_{21}O_5$ [M + H]$^+$, 389.1389; found, 389.1370.

Phenyl(4,5,6-trimethoxy-3-phenylbenzofuran-2-yl)-methanone 33. Following the general procedure for direct arylation, a mixture of phenyl(4,5,6-trimethoxybenzofuran-2-yl)methanone **25** (312 mg, 1.00 mmol) and bromobenzene (0.21 mL, 2.00 mmol) was stirred for 64 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 97:3 to 95:5) to afford a mixture of the starting material **25** and the desired product **33** (326 mg, **25**/**33** = 1.30 determined by ^{1}H NMR, calculated yield: 41% of **33** and 53% of **25**) as a brown solid: mp 94 °C (recrystallized from hexane to give yellow crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.2 Hz, 2H), 7.44−7.39 (m, 3H), 7.31−7.26 (m, 5H), 6.92 (s, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 155.8, 151.9, 148.4, 146.8, 139.5, 137.4, 132.1, 131.4, 130.3 (2C), 130.1, 129.6 (2C), 127.9 (3C), 127.4 (2C), 114.9, 91.1, 61.5, 61.3, 56.4; IR ($CDCl_3$) ν_{max} 2967, 2940, 2835, 1615, 1552, 1494, 1305, 1273, 1229, 1200, 1137, 1052 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{24}H_{20}O_5Na$ [M + Na]$^+$, 411.1208; found, 411.1199.

(4-Methoxy-3-phenylbenzofuran-2-yl)(phenyl)methanone 34.[41] Following the general procedure for direct arylation, a mixture of (4-methoxybenzofuran-2-yl)(phenyl)methanone **26** (252 mg, 1.00 mmol) and bromobenzene (0.21 mL, 2.00 mmol) was stirred for 64 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 99:1 to 90:10) to afford a mixture of the starting material **26** and the desired product **34** (254 mg, **26**/**34** = 1.15 determined by ^{1}H NMR, calculated yield: 41% of **34** and 47% of **26**) as a brown solid: mp 86 °C (recrystallized from hexane to give yellow crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.2 Hz, 2H), 7.47−7.39 (m, 4H), 7.31−7.24 (m, 6H), 6.70 (d, J = 7.8 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7, 156.2, 155.8, 146.6, 137.2, 132.3, 131.5, 130.7 (2C), 129.64 (2C), 129.57, 129.1, 127.9 (2C), 127.7, 127.1 (2C), 117.4, 105.1, 103.9, 55.5; IR ($CDCl_3$) ν_{max} 3063, 2965, 2944, 1643, 1602, 1501, 1370, 1267, 1254, 1098 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{22}H_{17}O_3$ [M + H]$^+$, 329.1178; found, 329.1168.

(4-Hydroxy-3-phenylbenzofuran-2-yl)(phenyl)methanone 35.[41] Following the general procedure for direct arylation, a mixture of (4-hydroxybenzofurane-2-yl)(phenyl)methanone **27** (186 mg, 0.78 mmol) and bromobenzene (0.165 mL, 1.56 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 98:2 to 95:5) to afford the desired product **35** (102 mg, 0.33 mmol, 42%) as a brown solid: mp 181 °C (recrystallized from hexane to give a yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.2 Hz, 2H), 7.53−7.34 (m, 9H), 7.22 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 5.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 155.5, 152.1, 146.4, 137.0, 132.7, 131.3, 129.7 (2C), 129.6, 129.5 (2C), 129.0 (2C), 128.98, 128.1 (2C), 127.9, 116.1, 109.3, 104.7; IR ($CDCl_3$) ν_{max} 3066, 3032, 1648, 1598, 1558, 1499, 1273, 1171, 1043 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{21}H_{15}O_3$ [M + H]$^+$, 315.1017; found, 315.1017.

(4,6-Dimethyl-3-phenylbenzofuran-2-yl)(phenyl)methanone 36. Following the general procedure for direct arylation, a mixture of (4,6-dimethylbenzofuran-2-yl)(phenyl)methanone **28** (250 mg, 1.00 mmol) and bromobenzene (0.21 mL, 2.00 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 97:3) to afford a mixture of the starting material **28** and the desired product **36** (254 mg, **28**/**36** = 1.99 determined by ^{1}H NMR, calculated yield: 33% of **36** and 65% of **28**) as a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 6.9 Hz, 2H), 7.50−7.44 (m, 1H), 7.38−7.33 (m, 7H), 7.29 (s, 1H), 6.89 (s, 1H), 2.48 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 155.1, 147.4, 138.9, 137.4, 134.0, 132.8, 132.3, 130.6, 130.0 (2C), 129.6 (2C), 127.9 (2C), 127.85, 127,80 (2C), 127.1, 124.4, 109.9, 21.8, 19.4; IR ($CDCl_3$) ν_{max} 3064, 3029, 2924, 1643, 1556, 1364, 1269, 1234 cm^{-1}; HRMS (ES$^+$) m/z calculated for $C_{23}H_{19}O_2$ [M + H]$^+$, 327.1385; found, 327.1392.

Methyl 2-benzoyl-3-phenylbenzofuran-7-carboxylate 38. Following the general procedure for direct arylation, a mixture of methyl 2-benzoylbenzofuran-7-carboxylate **30** (280 mg, 1.00 mmol) and bromobenzene (0.21 mL, 2.00 mmol) was stirred for 16 h. The residue was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 95:5) to afford the desired product **38** (315 mg, 0.89 mmol, 89%) as a brown solid: mp 124 °C (recrystallized from hexane to give a yellow powder); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (dd, J = 7.5, 1.2 Hz, 1H), 8.17 (d, J = 7.2 Hz, 2H), 7.90 (dd, J = 7.8, 1.2 Hz, 1H), 7.58−7.54 (m, 3H), 7.48−7.41 (m, 6H), 4.04 (s, 3H); ^{13}C NMR (75 MHz,

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$CDCl_3$) δ 184.3, 165.0, 152.5, 147.8, 136.9, 133.0, 130.7, 130.7, 130.4, 130.3 (2C), 129.9 (2C), 129.8, 128.9, 128.6, 128.4 (2C), 128.1 (2C), 123.7, 116.0, 52.4; IR ($CDCl_3$) ν_{max} 3069, 3032, 2954, 1720, 1651, 1298, 1215, 1141 cm^{-1}; HRMS (ES^+) m/z calculated for $C_{23}H_{16}O_4Na$ $[M + Na]^+$, 379.0946; found, 379.0941.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^1H and ^{13}C spectra for new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) For leading references: (a) Ziegert, R. E.; Toräng, J.; Knepper, K.; Bräse, S. *J. Comb. Chem.* **2005**, *7*, 147−169. (b) Kirilmis, C.; Ahmedzade, M.; Servi, S.; Koca, M.; Kizirgil, A.; Kazaz, C. *Eur. J. Med. Chem.* **2008**, *43*, 300−308. (c) Abdel-Wahab, B. F.; Abdel-Aziz, H. A.; Ahmed, E. M. *Eur. J. Med. Chem.* **2009**, *44*, 2632−2635.

(2) Saku, O.; Saki, M.; Kurokawa, M.; Ikeda, K.; Takizawa, T.; Uesaka, N. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1090−1093.

(3) Allan, A. C.; Billinton, A.; Brown, S. H.; Chowdhury, A.; Eatherton, A. J.; Fieldhouse, C.; Giblin, G. M. P.; Goldsmith, P.; Hall, A.; Hurst, D. N.; Naylor, A.; Rawlings, D. A.; Sime, M.; Scoccitti, T.; Theobald, P. J.; Saku, O.; Saki, M.; Kurokawa, M.; Ikeda, K.; Takizawa, T.; Uesaka, N. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4343−4348.

(4) Kucklaender, U. K. U.; Bollig, R.; Frank, W.; Gratz, A.; Jose, J. *Bioorg. Med. Chem.* **2011**, *19*, 2666−2674.

(5) Teague, S. J.; Barber, S. *Tetrahedron Lett.* **2010**, *51*, 4720−4722.

(6) Wempe, M. F.; Jutabha, P.; Quade, B.; Iwen, T. J.; Frick, M. M.; Ross, I. R.; Rice, P. J.; Anzai, N.; Endou, H. *J. Med. Chem.* **2011**, *54*, 2701−2713.

(7) Santin, E. P.; Khanwalkar, H.; Voegel, J.; Collette, P.; Mauvais, P.; Gronemeyer, H.; de Lera, A. R. *ChemMedChem* **2009**, *4*, 780−791.

(8) Carrër, A.; Florent, J.-C.; Auvrouin, E.; Rousselle, P.; Bertounesque, E. *J. Org. Chem.* **2011**, *76*, 2502−2520.

(9) (a) Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, *43*, 1293−1310. (b) Black, D. S.; Craig, D. C.; Kumar, N.; Rezaie, R. *Tetrahedron* **2002**, *58*, 5125−5134. (c) Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498−6499. (d) Smith, R. A.; Chen, J.; Mader, M. M.; Muegge, I.; Moehler, U.; Katti, S.; Marrero, D.; Stirtan, W. G.; Weaver, D. R.; Xiao, H.; Carley, W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2875−2878. (e) Park, K. K.; Jeong, J. *Tetrahedron* **2005**, *61*, 545−553.

(10) (a) Buuhoi, N. P.; Saintruf, G.; Loc, T. B.; Xuong, N. D. *J. Chem. Soc.* **1957**, 2593−2596. (b) Bachelet, J. P.; Demerseman, P.; Royer, R.; Cavier, R.; Lemoine, J. *Eur. J. Med. Chem.* **1982**, *17*, 323−325.

(11) Rao, M. L. N.; Awasthi, D. K.; Banerjee, D. *Tetrahedron Lett.* **2007**, *48*, 431−434.

(12) Yoshizawa, K.; Toyota, S.; Toda, F.; Csoregh, I. *Green Chem.* **2003**, *5*, 353−356.

(13) For a general review: Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469.

(14) For examples of cross-coupling on C3 of benzofuran: (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432−1434. (b) Deprets, S.; Kirsch, G. *Eur. J. Org. Chem.* **2000**, 1353−1357. (c) Vedejs, E.; Zajac, M. A. *Org. Lett.* **2001**, *3*, 2451−2454. (d) Dai, W. M.; Lai, K. W. *Tetrahedron Lett.* **2002**, *43*, 9377−9380. (e) Colobert, F.; Castanet, A. S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334−3341. (f) James, C. A.; Coelho, A. L.; Gevaert, M.; Forgione, P.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4094−4103.

(15) For recent reviews: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173−1193. (c) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269−10310. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826.

(16) For intermolecular arylation: (a) Ionita, M.; Roger, J.; Doucet, H. *ChemSusChem* **2010**, *3*, 367−376. (b) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047−1060.

(17) For intramolecular arylation: (a) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460−7461. (b) Ohno, H.; Iuchi, M.; Fujii, N.; Tanaka, T. *Org. Lett.* **2007**, *9*, 4813−4815. (c) Shimizu, M.; Mochida, K.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9760−9764. (d) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572−577. (e) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cara, C. L.; Cruz-Lopez, O.; Tolomeo, M.; Grimaudo, S.; Cristina, A. D.; Pipitone, M. R.; Balzarini, J.; Zonta, N.; Brancale, A.; Hamel, E. *Bioorg. Med. Chem.* **2009**, *17*, 6862−6871.

(18) (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951−1958. (b) Liu, Z. J.; Zhang, X. X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716−15717. (c) Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, *49*, 1045−1048. (d) Yang, S. D.; Sun, C. L.; Fang, Z.; Li, B. H.; Li, Y. Z.; Shi, Z. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473−1476. (e) Do, H. O.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185−15192. (f) Matsuda, S.; Takahashi, M.; Monguchi, D.; Mori, A. *Synlett* **2009**, 1941−1944. (g) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826−1834. (h) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850−12852. (i) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguchi, D.; Mori, A. *J. Org. Chem.* **2010**, *75*, 6998−7001.

(19) (a) Dyker, G. *J. Org. Chem.* **1993**, *58*, 234−238. (b) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449−1451. (c) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137−3139.

(20) (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299−2302. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496−16497.

(21) See the Supporting Information for details.

(22) (a) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677−1680. (b) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979−1982. (c) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926−2927.

(23) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *128*, 581−590.

(24) See the Supporting Information for optimization details.

(25) (a) Muzart, J. *Tetrahedron* **2003**, *59*, 5789−5816. (b) Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 1286−1292.

(26) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379.

(27) (a) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159−1162. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057.

(28) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754−8756. (b) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754−13755. (c) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880−6886. (d) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066−1067. (e) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848−10849.

(29) Tromelin, A.; Demerseman, P.; Royer, R. *Synthesis* **1985**, 1074−1076.

(30) Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Davis, J. A.; Doxey, J. C.; Higgins, S. D.; Myers, M.; Roach, A. G.; Smith, C. F. C.; Stillings, M. R.; Welbourn, A. P. *J. Med. Chem.* **1984**, *27*, 570−576.
(31) Lamotte, G.; Demerseman, P.; Royer, R. *Synthesis* **1984**, 1068−1070.
(32) Gill, M. *Tetrahedron* **1984**, *40*, 621−626.
(33) Della Rosa, C.; Kneeteman, M. N.; Mancini, P. M. E. *Tetrahedron Lett.* **2005**, *46*, 8711−8714.
(34) Fan, J. M.; Wan, C. F.; Wang, Q.; Gao, L. F.; Zheng, X. Q.; Wang, Z. Y. *Org. Biomol. Chem.* **2009**, *7*, 3168−3172.
(35) Kraus, G. A.; Gupta, V. *Tetrahedron Lett.* **2009**, *50*, 7180−7183.
(36) (a) Davies, W.; Middleton, S. *J. Chem. Soc.* **1958**, 822−825. (b) Geary, L. M.; Hultin, P. G. *Org. Lett.* **2009**, *11*, 5478−5481.
(37) Gabriele, B.; Mancuso, R.; Salerno, G. *J. Org. Chem.* **2008**, *73*, 7336−7341.
(38) Tseng, P.-W.; Yeh, S.-W.; Chou, C.-H. *J. Org. Chem.* **2008**, *73*, 3481−3485.
(39) Demerseman, P.; Guillaumel, J.; Cheutin, A.; Royer, R. *Bull. Soc. Chim. Fr.* **1970**, 2253−2261.
(40) Adam, W.; Sauter, M. *Tetrahedron* **1994**, *50*, 11441−11446.
(41) Yeh, J.-Y.; Coumar, M. S.; Horng, J.-T.; Shiao, H.-Y.; Kuo, F.-M.; Lee, H.-L.; Chen, I.-C.; Chang, C.-W.; Tang, W.-F.; Tseng, S.-N.; Chen, C.-J.; Shih, S.-R.; Hsu, J. T.-A.; Liao, C.-C.; Chao, Y.-S.; Hsieh, H.-P. *J. Med. Chem.* **2010**, *53*, 1519−1533.