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Synthesis of 3-Aryl-2-arylamidobenzofurans Based on the Curtius Rearrangement

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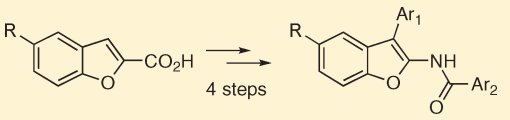
Supporting Information

ABSTRACT: The synthesis of novel 3-aryl-2-arylamidobenzofurans has been accomplished via a Curtius rearrangement strategy in four steps from benzofuran-2-carboxylic acids. The requisite Suzuki−Miyaura cross-coupling, with benzyl 3-bromobenzofuran-2-ylcarbamate or 2-arylamido-3-bromobenzofurans, revealed an unusual reductive debromination process due to the presence of the free NH group. This dehalogenation can be suppressed by *N*-alkylation. DMAP is an efficient reagent for the one-pot conversion of benzyl benzofuran-2-ylcarbamates into the corresponding benzofuran-2-arylamides through aroylation, thus acting both as an acyl transfer reagent and a deprotecting agent of the Cbz group. A mechanism is postulated.



INTRODUCTION

Benzo[*b*]furan derivatives are of considerable interest because of their widespread occurrence among natural products such as amurensin H (**1**), malibatol A (**2**), and (±)-frondosin B (**3**) (Figure 1).[1,2] In addition, they occupy a prominent place in medicinal chemistry due to their diverse pharmacological activities[3] such as anti-HIV,[4] anticancer,[5] and antiinflammatory (i.e., COX-2 inhibitors).[6] Prescribed agents featuring the benzofuran scaffold include the antidepressant (−)-BPAP[7] and the antiarrythmic amiodarone.[8]

Some benzofurans were also identified as 5-lipoxygenase inhibitors,[9] angiotensin II inhibitors,[10] calcium entry blockers,[11] PTP-1B inhibitors,[12] estrogen receptor modulators,[13] highly selective MMP-13 inhibitors,[14] PKCθ inhibitors,[15] H_3 antagonists,[16] BLT1 and/or BLT2 antagonists,[17] and as direct inhibitors of thrombin and factor Xa.[18] Many other activities have been reported for benzofurans.[19] Recently, a series of structures containing the benzofuran nucleus, such as SKF-63058 (**4**) and SKF-64346 (**5**), have been identified as efficient inhibitors of β-amyloid aggregation,[20] and **6** as inhibitors of glycogen synthase kinase-3β (GSK-3β),[21] affording a new class of potential multifunctional drugs for Alzheimer's disease (Figure 2).

Thus synthetic access to benzofurans is of considerable interest, and numerous approaches to this scaffold have been disclosed in the literature.[22] Major synthetic strategies[23] utilized include the dehydrative cyclization of α-(phenoxy)alkyl ketones, dehydration of *o*-hydroxybenzyl ketones under acidic conditions, decarboxylation of *o*-acylphenoxyacetic acids or esters on treatment with a base, cyclofragmentation of oxiranes, palladium(II)-catalyzed cyclization of arylacetylenes (C−O cyclization),[24]

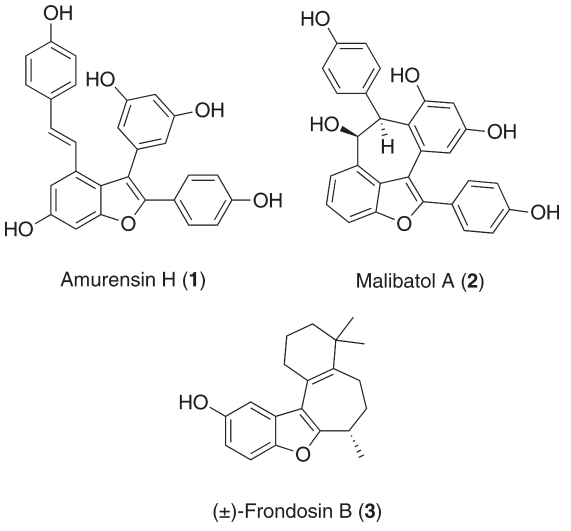


Figure 1. Benzofuran-containing natural products.

copper(I)-catalyzed coupling of acetylenes,[25] palladium-catalyzed enolate arylation with *o*-bromophenols,[26] electrophilic cyclization chemistry developed by Larock and co-workers,[27] thermolytic Claisen rearrangement and cyclization of aryl prop-2-ynyl ethers,[28] and intramolecular cyclization via carbon−carbon bond (C−C) cyclization.[29]

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To the best of our knowledge, 3-aryl-2-arylamidobenzofurans are not described so far in the literature. Additionally, reports are very scarce on 2-arylamidobenzofurans. As examples, 3-hydroxy-*N*-(3-methoxybenzofuran-2-yl)naphthalene-2-carboxamide **7** was mentioned in a patent entitled "Dyed cellulose and protein textiles" published in 1965.[30] At the same time, more functionalized compounds such as 2,6-bis-benzoylamino-benzo[1,2-*b*;4,5-*b*′]difuran-3,7-dicarboxylic acid diethyl ether **8** and its derivative **9** appeared in the context of the chemistry of color reactions.[31] A decade later, derivatives of 2-amino-3-carbethoxy-5-hydroxybenzofuran were described such as **10**.[32] Recently *N*-7-azabicyclo-[2.2.1]heptan-2-yl)-2-phenylamidobenzofuran carboxamides **11** and **12** were described for therapeutic use as nicotinic acetylcholine receptor agonists.[33] In the case of 2-alkylamido- and chiral 2-carbamate benzofurans exemplified by **13** and **14**, respectively, it is worthwhile mentioning an elegant synthesis from a range of *O*-anisyl ynamides was described via a Rh(I)-catalyzed demethylation−cyclization (Figure 3).[34]

As part of our medicinal chemistry program aimed at the search for novel benzofuran-based bioactive molecules, we were seeking an efficient method to prepare 3-aryl-2-arylamidobenzofurans **15** (Figure 4).

Several potential strategies could be envisionned to access 2-arylamidobenzofurans directly from the benzofuran skeleton. We were inspired by the work of Royer and co-workers that reported, 40 years ago, the transposition of 1-(3-phenylbenzofuran-2-yl)ethanone oxime (**A**) to give *N*-(3-phenylbenzofuran-2-yl)ethanamide, but in very low yields (AcOH saturated with HCl, 5 h, reflux, 20% or PCl_5, Et_2O, reflux, 10%).[35] This approach would involve the Beckmann transposition of aryl benzofuranyl oximes (Scheme 1, routes 1 and 2) but under milder conditions, the benzofuran scaffold being accessible through a classical synthetic methodology involving cyclodehydration of α-(phenoxy)alkyl aryl ketones (route 1) or Rap-Stoermer reaction (route 2).[36] Importantly, note that 30 years later, Deprets and Kirsch[37] confirmed the shortcomings, in this context, of applying the Beckmann rearrangement, since it was unsuccessful from 1-(5-(methylthio)-3-phenylbenzofuran-2-yl)-ethanone oxime (**B**) (PPA, toluene, reflux, degradation)—an analogue of oxime (**A**) and aryl(3-arylbenzofuran-2-yl)methanone oximes (**C**) (Scheme 1)—and successful from 1-(3-phenylbenzo-[*b*]thiophen-2-yl)ethanone oxime (83%) or 1-(3-phenylbenzo[*b*]-selenophen-2-yl)ethanone oxime (73%).

The second approach would take advantage of the regioselective nitration at the 2-position of 3-aryl-2-trimethylstannyl benzofurans, prepared by lithiation of 3-arylbenzofurans followed by reaction with trimethyltin chloride (Scheme 2, route 3).[38] The synthesis of 2-arylamidobenzofurans would then be carried out by a two-step sequence, reduction of the nitro group into amine followed by *N*-acylation. The third approach could benefit from the recent work described by Lebel and Leogane[39]

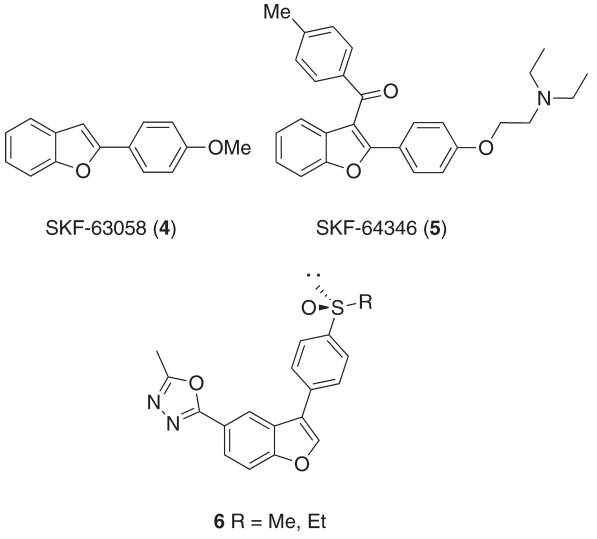

Figure 2. Potential multifunctional drugs for Alzheimer's disease.

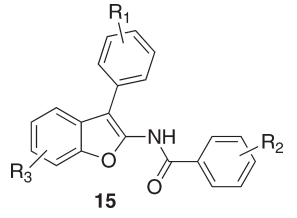

Figure 4. *N*-(3-Arylbenzofuran-2-yl)arylamides **15**.

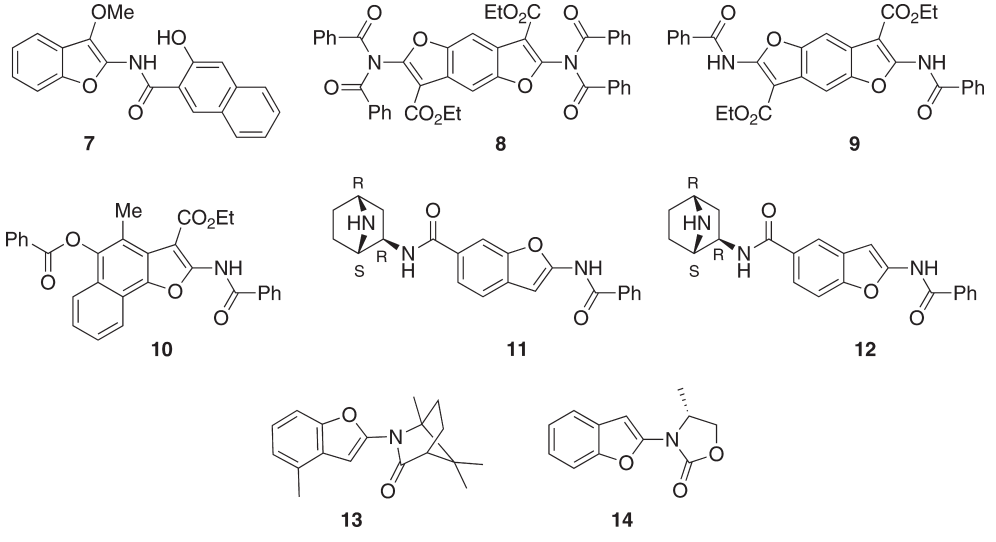

Figure 3. 2-Amidobenzofurans **7**−**13** and benzofuran-2-ylcarbamate **14**.

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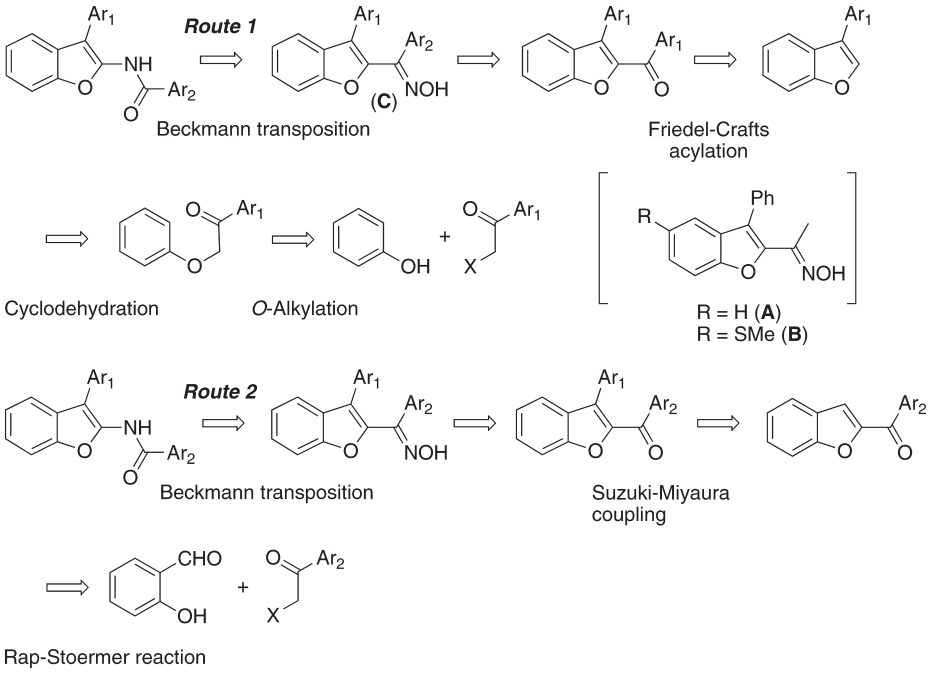
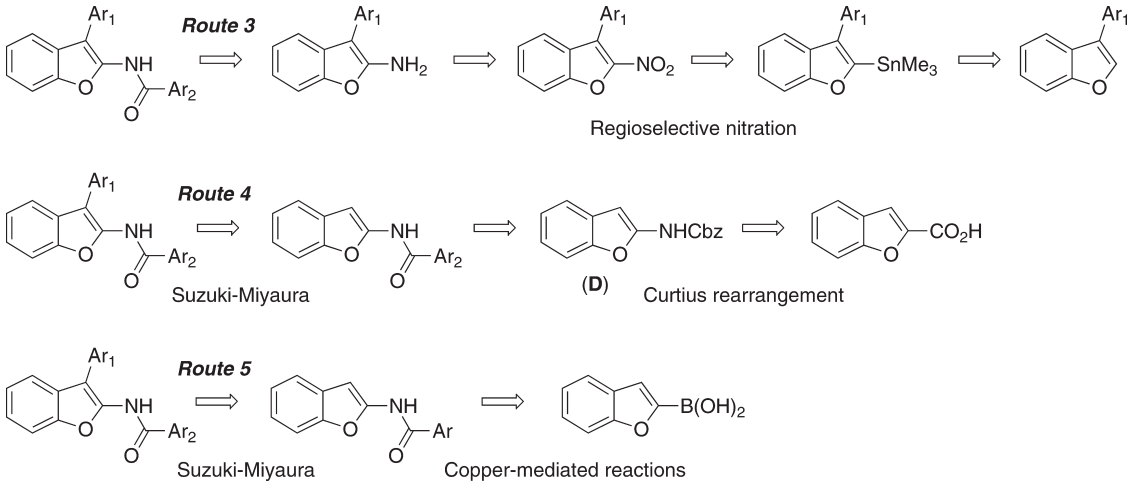
Scheme 1. Potential Synthetic Strategies Based on the Beckmann Transposition



Scheme 2. Potential Synthetic Strategies: Regioselective Nitration, Curtius Rearrangement, or Copper-Mediated Reactions



on the Curtius rearrangement of aromatic carboxylic acids, wherein benzyl benzofuran-2-ylcarbamate (**D**) was prepared by a one-pot procedure from benzofuran-2-carboxylic acid (route 4). The Cbz carbamate group could serve as a precursor of the amido functionality after or prior to the installation of the aryl group at the 3-position through the Suzuki−Miyaura reaction. Finally, the fourth approach would be to attempt the copper-mediated reactions,[40] discovered independently by Chan, Evans, and Lam,[41] between aryl amides and benzofuran 2-boronic acid (route 5).

After having briefly examined the application of these attractive copper-mediated reactions, our choice turned to the development of route 4 so as to take advantage of an efficient one-pot reaction for the formation of the C−N bond at the C2 position of the benzofuran ring system, and to avoid contamination of toxic stannyl compounds (route 3). We report herein the synthesis of 3-aryl-2-arylamidobenzofurans **15** via a Curtius rearrangement from benzofuran-2-carboxylic acid.

RESULTS AND DISCUSSION

To the best of our knowledge, the reaction of amines or amides with benzofuran-2-boronic acid **16a**[42] as donor has not been previously mentioned. As an indication of potential feasibility, it should be noted that furan-2-boronic acid and benzothiophene-2-boronic acid have been used to *N*-arylate *tert*-butyl carbazate under catalysis by CuCl at room temperature

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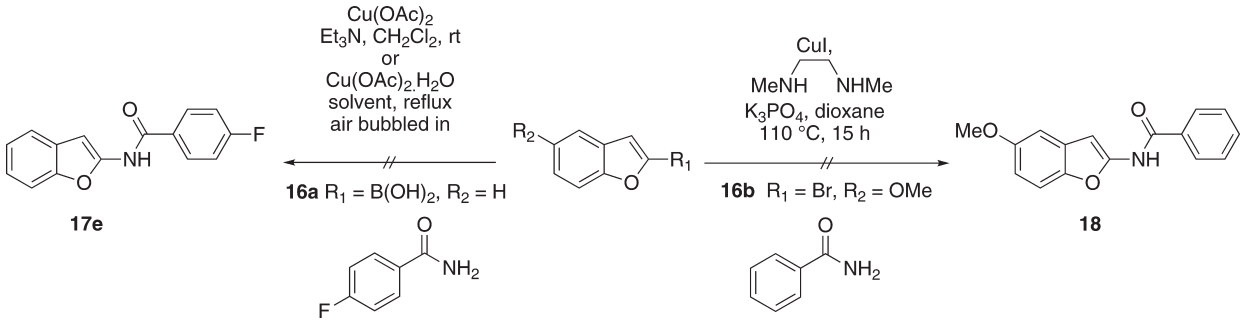
Scheme 3



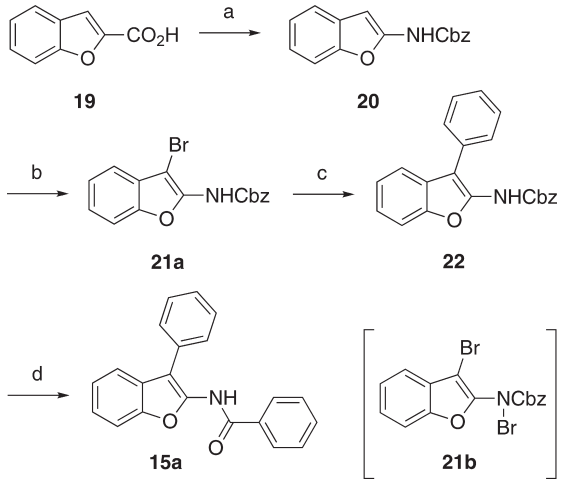
(pyridine, 1,2-dichloroethane, 3 Å molecular sieves, rt, dry air).[43] In addition, copper-catalyzed *N*-arylation of triazoles with such boronic acids has been recently reported.[44] Therefore, prior to investigating the Curtius approach, the application of the Cu(II)-catalyzed *N*-arylation reaction was evaluated for the coupling of 4-fluorobenzamide with benzofuran-2-boronic acid **16a** by using $Cu(OAc)_2$[41a] or $Cu(OAc)_2 \cdot H_2O$[45] (Scheme 3, route 5). Such coupling was not successful whatever the reaction conditions. In addition, the Cu-catalyzed Goldberg reaction, using *N*-based chelating ligands (CuI, K_3PO_4, N^1,N^2-dimethylethane-1,2-diamine, dioxane, 110 °C, 15 h),[46] was tried with no more success with benzamide and 2-bromo-5-methoxybenzofuran **16b**[47] as coupling partners.

We then initiated the study of route 4 with the synthesis of *N*-(3-phenylbenzofuran-2-yl)benzamide **15a** (R_1, R_2, R_3 = H) from 2-benzofuran carboxylic acid in 4 steps (Scheme 4).

The Curtius rearrangement of 2-benzofuran carboxylic acid described by Lebel and Leogane[39] led to benzyl benzofuran-2-ylcarbamate **20** in 69% yield, presumably through the formation of the corresponding benzyl carbonazidate. Subsequent bromination[48] at the C-2 position (**21a**) required the search for reaction conditions. Indeed, its treatment with bromine[49] (1.08 equiv) in CCl_4 (0 °C then room temperature, overnight) led only to the degradation of the reaction mixture. This reaction carried out in AcOH as solvent in the presence of AcONa (4 equiv) at room temperature (40 min) gave benzyl bromo(3-bromobenzofuran-2-yl)carbamate **21b** in 65% yield after flash chromatography (see the Supporting Information). Upon reduction with 12% aqueous sodium sulfite[50] at 5−10 °C (0.5 h), the initially *N*-bromoadduct formed was transformed in situ into the desired benzyl 3-bromobenzofuran-2-ylcarbamate **21a** in 68% yield. On the other hand, bromination with NBS[51] (1.2 equiv) in THF (room temperature, overnight) only gave an unidentified compound in place of the expected bromide. However, low-temperature, acid-catalyzed C-2 bromination (NBS 1.2 equiv, PTSA 0.1 equiv, THF, −78 °C, 25 min) provided **21a** in 74% yield.

The Suzuki−Miyaura (SM) cross-coupling[52,53] between **21a** and phenyl boronic acid[54] was next investigated by using various catalysts, bases, and solvants (Table 1). Reaction of **21a** with phenyl boronic acid (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (5 mol %) and sodium carbonate (4.5 equiv) in a mixture of dimethoxyethane/H_2O (4:1) for 2 h at reflux gave the desired coupling product **22** in 22% yield along with the dehalogenated compound **20** in 34% yield (entry 1). The reaction was then screened with a variety of base to increase the yield of **22**. Thus, the use of K_2CO_3, $NaHCO_3$, Cs_2CO_3, or CsF (entries 2−5) allowed us to increase the yield, by up to 40% with CsF, but did not prevent the concomitant formation of **20** as the major

Scheme 4[a]



[a] Reagents: (a) NaN_3 (1.7 equiv), CbzCl (1.3 equiv), *t*BuONa (0.15 equiv), DME, 75 °C, 20 h, 69%; (b) NBS (1.2 equiv), PTSA (0.1 equiv), THF, −78 °C, 25 min, 74%; (c) $Pd(PPh_3)_4$ (5 mol %), CsF (11 equiv), $PhB(OH)_2$ (5 equiv), dioxane/H_2O 4:1 reflux, 1 h, 55%; (d) PhCOCl (3 equiv), Et_3N (6 equiv), DMAP (1.5 equiv), $CHCl_3$, reflux, 16 h, 61%.

product (31−44%). With use of $Ba(OH)_2$, NaOH, or *t*BuOK (entries 6−8), the method was ineffecient (4−10% yields). By choosing CsF as the best base, the search for other palladium catalysts was disappointing (entries 9−11). $PdCl_2(dppf)$ gave 36% yield of **22**, and much lower yields were obtained with $Pd(OAc)_2$−XantPhos and $Pd(OAc)_2$−Cyclohexyl JohnPhos. On the basis of $Pd(PPh_3)_4$ as the catalyst and CsF as the base, the solvent effect was also examined (entries 12−14). The reaction is faster in dioxane/H_2O (1.5 h, entry 12) as compared with DME/H_2O (entry 5) or toluene/H_2O (entry 13), furnishing **22** in a slightly increased yield (46%) along with **20** (39%). In an attempt to eliminate the formation of the reduced product, the reaction was conducted in the absence of water as the cosolvent but failed to give the cross-coupling product (entry 14).

The optimized yield was found to be 55% by stirring 5 mol % of $Pd(PPh_3)_4$, 11 equiv of CsF, and 5 equiv of phenyl boronic acid for 1 h; however, 34% of the dehalogenated product **20** were also isolated (entry 15). Finally, the effect of the proportion of water on the yield of **22** was examined by forcing the reaction conditions with 5 equiv of $PhB(OH)_2$ in dioxane/H_2O 6:1 (entry 15 vs entry 16). It was found that the reactions resulted

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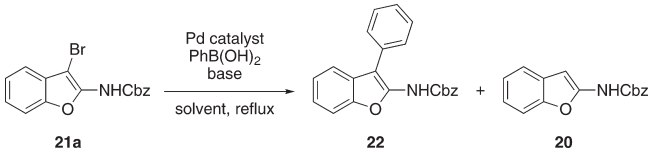
Table 1. Optimization of the Suzuki−Miyaura Reaction with Phenyl Boronic Acid

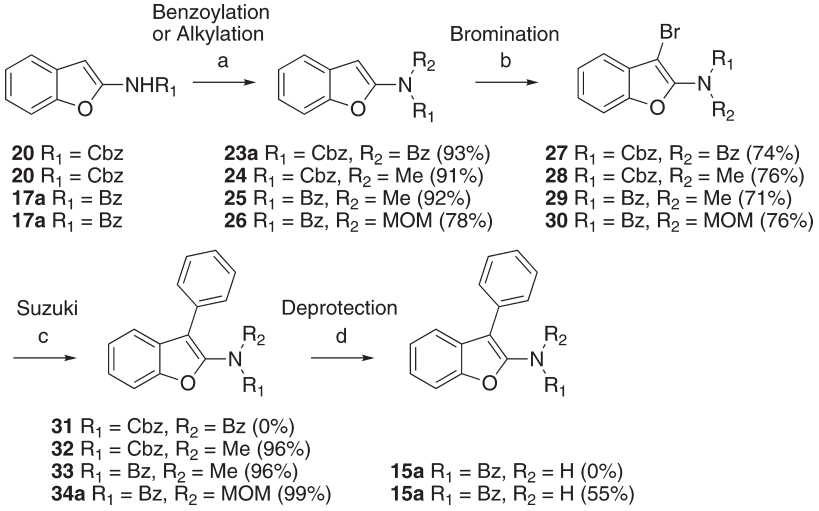


21a 22 20

						yield (%)	
entry	$PhB(OH)_2$	base	Pd	solvent	time (h)[e]	**22**	**20**
1[a]	1.5 equiv	Na_2CO_3	$Pd(PPh_3)_4$	DME/H_2O 4:1	2	22	34
2[a]		K_2CO_3			1.5	31	31
3[a]		$NaHCO_3$			1.5	32	41
4[a]		Cs_2CO_3			1.5	26	34
5[a]		CsF			3	40	44
6[a]		$Ba(OH)_2$			3	4	14
7[a]		NaOH			3	10	30
8[a]		*t*BuOK			3	9	28
9[b]		CsF	$PdCl_2$(dppf)		10	36	44
10[b]			$Pd(OAc)_2$−ligand[c]		10	8	56
11[b]			$Pd(OAc)_2$−ligand[d]		10	13	40
12[a]			$Pd(PPh_3)_4$	DME/H_2O 4:1	1.5	46	39
13[a]				toluene/H_2O 4:1	4	42	55
14[a]				dioxane	3	0	11
15[a]	5 equiv	11 equiv		dioxane/H_2O 4:1	1	55	34
16[a]	5 equiv	11 equiv		dioxane/H_2O 6:1	1	52	42

[a] To a solution of arylbromide (1 equiv), phenyl boronic acid (1.5 or 5 equiv), and base (4.5 or 11 equiv) in degassed solvent/water was added $Pd(PPh_3)_4$ (5 mol %). The mixture was refluxed during 1 to 4 h. [b] To a solution of arylbromide (1 equiv), phenyl boronic acid (1.5 equiv), and CsF (4.5 equiv) in degassed DME/water 4:1 was added Pd catalyst (5 mol %) and ligand (5% XantPhos or 10% Cyclohexyl JohnPhos). After 5 h at reflux, TLC control indicated the presence of arylbromide, therefore 0.05 equiv of Pd catalyst was added and the reflux was pursued for 5 h. [c] XantPhos. [d] Cyclohexyl JohnPhos. [e] The reaction mixture was stirred until the TLC analysis showed the complete disappearance of the starting material.

Scheme 5[a]



[a] Reagents: (a) Benzoylation: see Table 3, or alkylation: MeI (1.3 equiv), NaH 60% in mineral oil (1.3 equiv), DMF, 0 °C then room temperature, 3−4 h, or MOMCl (3 equiv), NaH 60% in mineral oil (3 equiv), Et_3N (3 equiv), DMF, 0 °C then 55 °C, overnight; (b) NBS (1.2 equiv), PTSA (0.1 equiv), THF, 0 °C (**27**) or −78 °C (**28**−**30**); (c) $Pd(PPh_3)_4$ (5 mol %), $PhB(OH)_2$ (1.5 equiv), CsF (4.5 equiv), dioxane/H_2O 4:1, reflux; (d) TMSCl (4.5 equiv), NaI (4.5 equiv), MeCN, 5 °C, overnight then Et_3N (3 equiv), MeOH, 55 °C, 1 h (**15a** from **34a** 55%).

in similar improved yields for **22** but no effect of the water concentration was found from these two experiments. Finally, acylation of **22** gave directly access to *N*-(3-phenylbenzofuran-2-yl)benzamide **15a** via a one-pot process involving initial *N*-

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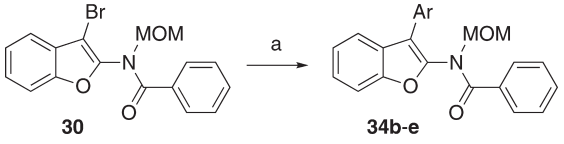
acylation followed by in situ Cbz deprotection (PhCOCl 3 equiv, Et_3N 6 equiv, DMAP 1.5 equiv, $CHCl_3$, rt to reflux, 16 h, 61%). The overall yield of the synthesis of **15a** was 17%.

To explain the observed reductive debromination of **21a**, the role of the free NH moiety[55,56] was examined by performing the Suzuki coupling reactions from various *N*-protected derivatives **27**−**30** with phenyl boronic acid (Scheme 5).

The Suzuki reaction with **27** bearing a Cbz group, prepared by bromination of **23a**, led only to degradation. The use of Me or MOM as protecting groups was then investigated. First, methylation of **20** and **17a** followed by bromination with *N*-bromosuccinimide furnished the required compounds **28** and **29**, respectively. Importantly, no reduction of the 3-bromobenzofuran derivatives could be detected for the Suzuki−Miyaura reactions with **28** or **29** and phenyl boronic acid under the optimized conditions developed in Scheme 4, and the yield of the cross-coupling products **32** and **33** was high with a 96% yield for both compounds. *N*-Demethylation of **33** failed by treatment with benzoyl peroxide (CH_2Cl_2, 80 °C, overnight),[57] only starting material being recovered. Second, similarly as above, MOM alkylation of **17a** followed by bromination gave **30**. Subsequent Suzuki−Miyaura coupling reaction with phenyl boronic acid resulted exclusively in the formation of **34a** in 96% yield.

Table 2. Suzuki Reaction of 30 with Various Aryl Boronic Acids



30 **34b-e**

entry	Ar	product	yield (%)[a]
1	4-$CF_3C_6H_4$	**34b**	93
2	4-$CO_2MeC_6H_4$	**34c**	89
3	2-$MeOC_6H_4$	**34d**	94
4	3,4,5-$(MeO)_3C_6H_4$	**34e**	91

[a] $Pd(PPh_3)_4$ (5 mol %), $ArB(OH)_2$ (1.5 equiv), CsF (4.5 equiv), dioxane/H_2O 4:1, reflux, 5−6 h.

Attempts to deprotect the latter failed with concentrated HCl[58] or TFA[59] leading to degradation. However, the deprotection could be achieved, with TMSI generated in situ from TMSCl and NaI,[60] to afford *N*-(3-phenylbenzofuran-2-yl)benzamide **15a** in 55% yield.

N-Alkylation turned out to be crucial to suppress the problematic reduction side reaction. Two hypotheses may explain this unexpected reductive debromination. An intramolecular proton-transfer process could occur on the palladium benzofuranyl complex formed by oxidative addition.[61] The second explanation would involve electronic effects due to the free NH group that could diminish the stability of this organopalladium species, thus limiting the process of transmetalation from boron to palladium.

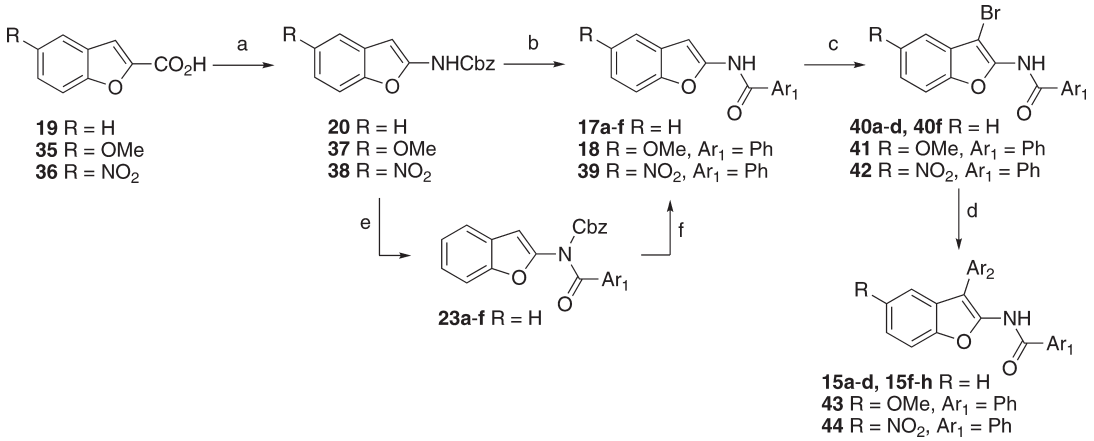
To further extend the application of our methodology through MOM-protection of **17a**, we have examined the Suzuki reaction of **30** with various aryl boronic acids (Table 2). Both electron-deficient and electron-rich aryl boronic acids smoothly underwent the coupling process to provide **34b**−**e** in excellent yields (89−94%).

In a parallel way and simultaneously before the optimization of the Suzuki reaction conditions were reached, a modified reaction sequence was carried out to generalize the access to 3-aryl-2-arylamidobenzofurans, with the free NH group for biological assays, involving the early one-pot *N*-acylation-*N*-Cbz deprotection sequence (Scheme 6).

The one-pot reactions of **20** with an excess of benzoyl chlorides generated 2-arylamidobenzofurans **17a**−**d** in 66−84% yields (Table 3, method A, entries 1−4). In the case where this method led to the impossibility of isolating **17e** and **17f** from the unreacted starting material **20** by flash chromatography, a two-step synthesis was then performed (Table 3, method B). It consisted of *N*-acylation of **20** (method C, entries 13 and 14) in the first step (**23e**,**f**) followed by hydrogenation over palladium-on-charcoal to provide **17e** and **17f** in 59% and 60% yields (entries 5 and 6), respectively. To complete the study of *N*-acylation of **20** with aroyl chlorides (method C, entries 9-11), compounds **23a**−**c** were also prepared (71−92%).

Next, the Curtius rearrangement of 5-methoxybenzofuran-2-carboxylic acid **35** and 5-nitrobenzofuran-2-carboxylic acid **36**

Scheme 6[a]



19 R = H
35 R = OMe
36 R = NO_2

20 R = H
37 R = OMe
38 R = NO_2

17a-f R = H
18 R = OMe, Ar_1 = Ph
39 R = NO_2, Ar_1 = Ph

40a-d, 40f R = H
41 R = OMe, Ar_1 = Ph
42 R = NO_2, Ar_1 = Ph

23a-f R = H

15a-d, 15f-h R = H
43 R = OMe, Ar_1 = Ph
44 R = NO_2, Ar_1 = Ph

[a] Reagents: (a) NaN_3 (1.7 equiv), CbzCl (1.3 equiv), *t*BuONa (0.15 equiv), DME, 75 °C, 20 h, 49−69%; (b) DMAP (1.5 equiv), Et_3N (6 equiv), NaH (1.2 equiv), 15 min, 0 °C, THF then Ar_1COCl (1.01 to 3 equiv), reflux, 16 h, 66−84% (**17a**−**d**, **18**, **39**); (c) NBS (1.2 equiv) PTSA (0.1 equiv), THF, −78 °C, 35−60 min, 55−80%; (d) $PdCl_2$dppf (6 mol %), Na_2CO_3 (2.4 or 4 equiv), $Ar_2B(OH)_2$ (1.2 or 2 equiv), DME/H_2O (4:1), reflux, 40 min to 6 h, 6−33%; (e) NaH (60% in mineral oil, 3 equiv), THF, 0 °C, 15 min then Ar_1COCl (3 equiv), reflux, 16 h; (f) Pd/C 10%, H_2, MeOH, room temperature, 4 h (**17e**,**f**).

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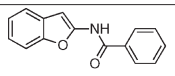
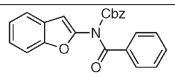
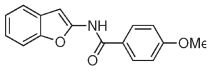
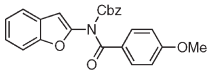
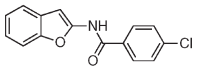
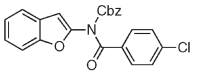
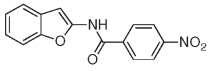
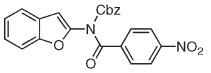
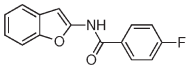
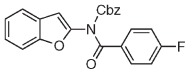
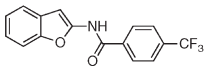
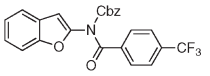
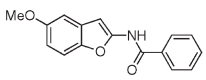
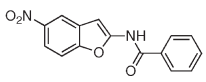
Table 3. One-Pot *N*-Acylation/*N*-Cbz Deprotection Sequence: *N*-Acylation of 20, 37, and 38

entry	product		method	yield%	entry	product		yield%
1		**17a**	A	84[a]	9		**23a**	93[e]
		**17b**	A	77[a,b]	10		**23b**	71[e]
3		**17c**	A	66[a]	11		**23c**	90[e]
4		**17d**	A	73[a,c]	12		**23d**	ND[f]
5		**17e**	B	59[d]	13		**23e**	83[e]
6		**17f**	B	60[d]	14		**23f**	73[e,g]
7		**18**	A	80[a]				
8		**39**	A	71[a]				

[a] Method A (one-pot procedure): DMAP (1.5 equiv), Et_3N (6 equiv), NaH (1.2 equiv), aroyl chloride (1 to 3 equiv), THF, reflux, overnight. [b] An inseparable mixture of monoacylated and diacylated products (ratio 79:21 by ^1H NMR) was obtained with 3 equiv of 4-methoxybenzoyl chloride. Monoacylation took place with 1 equiv of 4-methoxybenzoyl chloride. [c] Room temperature, 50 min. [d] Method B (two-step procedure): (a) NaH 60% in mineral oil (3 equiv), aroyl chloride (3 equiv), THF, reflux, overnight. (b) 10% Pd/C, H_2, MeOH, room temperature, 4 h. Overall yield (two steps). [e] Method C: NaH 60% in mineral oil (3 equiv), aroyl chloride (3 equiv), THF, reflux, overnight. [f] Not done. [g] Yield based on ^1H NMR analysis, the compound **23f** being isolated as an inseparable mixture with the starting material **20**.

gave benzyl 5-methoxybenzofuran-2-ylcarbamate **37** and benzyl 5-nitrobenzofuran-2-ylcarbamate **38** (low solubility) in 67% and 49% yields, respectively. The *N*-acylation−deprotection protocol applied to **37** and **38** furnished the expected compounds **18** and **39** in 81% and 71% yields, respectively.

Bromination of **17a**−**d** and **17f** at the C3 position was accomplished with *N*-bromosuccinimide to give the corresponding bromides **40a**−**d** and **40f** in 55−79% yields (Table 4, entries 1−5). Likewise, bromination of the 5-substituted benzofuran derivatives **18** and **39** afforded bromides **41** and **42** in 40% and 81% yields (entries 9 and 10), respectively. The low yield of **41** was due to its low solubility, leading to an uneasy purification by flash chromatography. Subsequent Suzuki cross-coupling reactions between **40a**−**d** and **40f** and phenyl boronic acid with $PdCl_2$(dppf) led to **15a**−**d** and **15f**, respectively, in low yields ranging from 6% to 30% due to the reductive dehalogenation of the bromides (Table 4, entries 11 and 13−16). In addition, bromides **40a** and **40b** were examined for the Suzuki reaction with an electron-rich aryl boronic acid as 4-methoxyphenyl boronic acid which, however, offered no benefit in term of yields (entries 17 and 18). Bromide **40f** reacted with (*E*)-styrylboronic acid to give the corresponding vinylogous derivative **15i** in very low yield (not shown in Scheme 6). Besides, the reactivity of **40a** was tested in the Suzuki−Miyaura reaction for comparison with **21a**, under the best reaction conditions ($Pd(PPh_3)_4$, CsF, dioxane/H_2O) obtained in the first reaction sequence (Table 1, entry 15 vs Table 4, entry 12). As a result, the formation of the coupling product decreased slightly (**22** 55% vs **15a** 42%) while the formation of the reductive dehalogenated product increased almost in the same proportion (**20** 34% vs **17a** 46%). However, the yield of **15a** was slightly improved to 42% by using these conditions (Table 4, entry 11 vs entry 12). Finally, in this context, the Suzuki−Miyaura reaction applied to *N*-(3-bromo-5-methoxybenzofuran-2-yl)benzamide **41** provided **43**, though also in low yield (entry 20), and was unsuccessful for an electron-deficient benzofuran such as *N*-(3-bromo-5-nitrobenzofuran-2-yl)benzamide **42** leading to the corresponding dehalogenated product **39** in 88% yield (entry 21).

The mechanistic understanding of this one-pot *N*-acylation-*N*-Cbz deprotection sequence was achieved from **20** (Table 5). It is worthwhile to mention that the direct conversion of the *N*-Cbz carbamate **20** into 2-arylamidobenzofurans **17** is very attractive because the intermediate 2-aminobenzofuran **45** is unstable and cannot be isolated (Scheme 7). Indeed, an attempt to reduce 2-nitrobenzofuran **46** to 2-aminobenzofuran **45** exclusively gave the hydrolysis product benzofuran-2(3*H*)-one **47** accompanied by 2-benzofuroxime **48**.[62] Alternatively, hydrogenation of **20** over Pd/C also failed to provide **45**.

As an analogy in methodology, it is interesting to note the one-pot transformation of *N*-Boc carbamates into amides by

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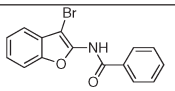
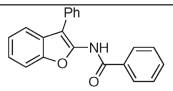
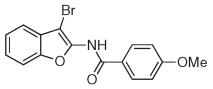
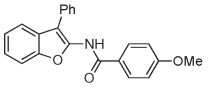
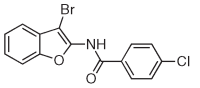
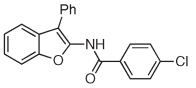
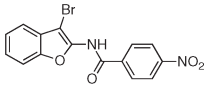
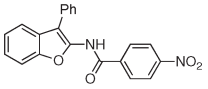
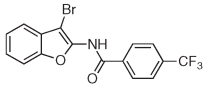
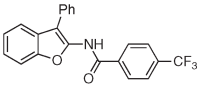
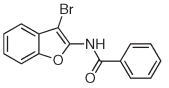
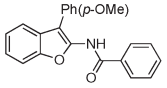
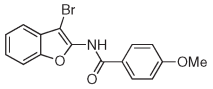
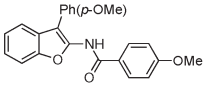
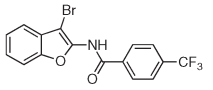
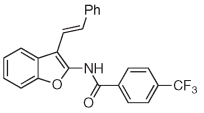
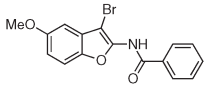
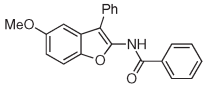
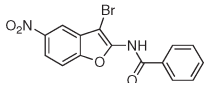
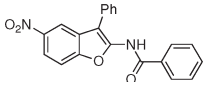
Table 4. Bromination and Suzuki−Miyaura Reactions

entry	bromide		yield%	entry	product[a]		yield%[b]
1		**40a**	79	11 12		**15a**	30 (18)[c] 42[d] (46)[c]
2		**40b**	55	13		**15b**	26 (28)[c]
3		**40c**	79	14		**15c**	14 (18)[c]
4		**40d**	69	15		**15d**	(18)[c,e]
5		**40f**	55	16		**15f**	6 (11)[c]
6		**40a**		17		**15g**	33 (19)[c]
7		**40b**		18		**15h**	22 (29)[c]
8		**40f**		19		**15i**	8 (34)[c]
9		**41**	40	20		**43**	33[d] (36)[c]
10		**42**	81	21		**44**	(88)[c,d,e]

[a] Brominated product (1 equiv), boronic acid (1.2 to 2 equiv), sodium carbonate (2.4 to 4 equiv), $PdCl_2$dppf (6 mol %) in DME/H_2O 4:1, 85 °C, 40 min to 6 h. [b] The reaction mixture was degassed by bubbling with argon and stirred under argon. [c] Yield of the debrominated product. [d] $Pd(PPh_3)_4$ (5 mol %), CsF (11 equiv), $PhB(OH)_2$ (5 equiv), dioxane/H_2O 4:1, reflux, 1−3.5 h. [e] No Suzuki cross-coupling was observed.

treatment with acyl halide−methanol mixtures.[63] This method also avoids the isolation of the intermediate amines, which sometimes can be unstable in some cases.

Treatment of **20** under the reaction conditions used at first (i.e., PhCOCl 3 equiv, Et_3N 6 equiv, DMAP 1.5 equiv, THF, reflux, 16 h) provided *N*-(benzofuran-2-yl)benzamide **17a** in 66% yield (Table 5, entry 1) along with 22% of recovered starting material. Reaction of **20** in THF with benzoylchloride acid (3 equiv) in the presence of NaH (5 equiv) as base, for 16 h, furnished exclusively benzyl benzofuran-2-yl(phenylcarbonyl)carbamate **23a** in excellent yield (entry 2). The optimized yield for **17a** (84%) was obtained by adding NaH (1.2 equiv) as a strong base, through improving the formation of the intermediate **23a** by anionic acylation of **20** (entry 3).

The identification of the reagent responsible for the *N*-Cbz deprotection reaction was then undertaken. Compound **20** was found unreactive toward benzoyl chloride with no addition of base (entry 4). The presence of Et_3N as a base led to the *N*-benzoylation of **20** to give **23a** in 93% yield (entry 5). Importantly, replacement of Et_3N by DMAP (3 equiv) as a hypernucleophilic acylation catalyst allowed the exclusive formation of *N*-(benzofuran-2-yl)benzamide **17a** in 84% yield (entry 6). Consequently, DMAP[64] also acts in this context as a deprotecting agent.[65] Further confirmation could be obtained when the isolated *N*,*N*-bisacylated compound **23a** was treated with 3 equiv of DMAP to lead to both **17a** and **20** in 50% and 22% yields, respectively (Scheme 8).

Taken together, the data provided in Table 5 (entries 1 and 6) and the results depicted in Scheme 8, a mechanism could be proposed for the formation of **17a** (Scheme 9).

The formation of *N*-acylpyridinium salt **I** by the addition of DMAP to benzoyl chloride is followed by nucleophilic addition of **20** to salt **I**, for which the reversibility is possible. Indeed, DMAP behaves as a nucleophile toward both the carbonyl

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Scheme 7

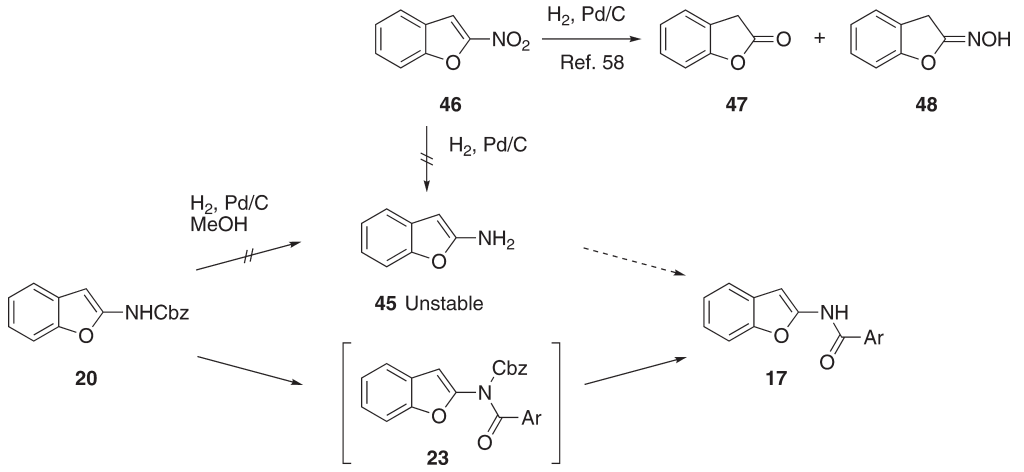
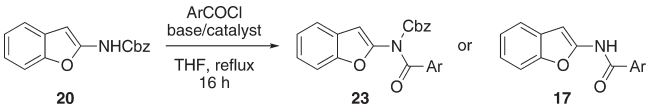


Table 5. One-Pot *N*-Acylation/*N*-Cbz Deprotection Sequence



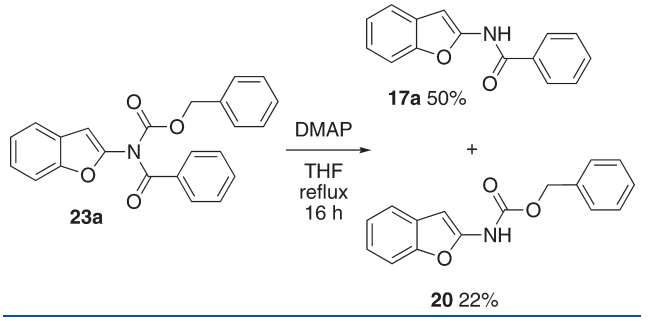
entry	base/catalyst	Ar	product	yield (%)
1[a]	Et_3N (6 equiv)	Ph	**17a**	66
	DMAP (1.5 equiv)			
2[a]	NaH (5 equiv)	Ph	**23a**	92
3[a]	Et_3N (6 equiv)			
	DMAP (1.5 equiv)	Ph	**17a**	84
	NaH (1.2 equiv)			
4[b]		Ph		0
5[b]	Et_3N (3 equiv)	Ph	**23a**	93
6[b]	DMAP (3 equiv)	Ph	**17a**	84

[a] PhCOCl (3 equiv). [b] PhCOCl (1.5 equiv).

groups of **23a**. Then, the resulting *N*,*N*-biacetylated compound **23a** can also lead to *N*-acylpyridinium salt **II** via the nucleophilic addition of DMAP to the benzyloxy carbonyl group.[66,67] The benzoxylate anion thus generated is trapped by benzoyl chloride to form the isolated benzyl benzoate. The hydrolysis product of **II**, namely the unstable carbamic acid derivative **49**, loses carbon dioxide to give *N*-(benzofuran-2-yl)benzamide **17a**. The reaction conditions, that is to say the number of equivalents of DMAP and benzoyl chloride, allow the exclusive formation of **17a** with no trace of starting material remaining.

From the above results, it appears that the second reaction sequence (Scheme 6) is equivalent to the first one (Scheme 4) in terms of overall yield for compound **15a** (17% vs 15%, 4 steps from **19**), applying the optimized Suzuki protocol (Table 4, entry 12). In other respects, a MOM protecting group strategy did not allow an improvement of the yield of **15a** (19%, 6 steps from **19**). The Suzuki reaction from 2-arylamido-3-bromobenzofurans containing free NH groups remains a signicant challenge for efficient large-scale syntheses.

Scheme 8



CONCLUSIONS

In summary, the synthesis of novel 3-aryl-2-arylamidobenzofurans has been achieved through a Curtius rearrangement strategy, in four steps from 2-benzofuran carboxylic acids. The two reaction sequences outlined above have proved to be of use in their synthesis. The study of the Suzuki reaction showed that both benzyl 3-bromobenzofuran-2-ylcarbamate and 2-arylamido-3-bromobenzofurans containing a free NH moiety, in the presence of boronic acids, favor significantly the reductive debromination process. This dehalogenation can be suppressed by *N*-alkylation. A one-pot procedure was discovered to transform benzyl benzofuran-2-ylcarbamates into the corresponding benzofuran-2-arylamides through *N*-aroylation, in which DMAP acts both as an acyl transfer reagent and a deprotecting agent of the Cbz group. A mechanism is postulated for this transformation that avoids the isolation of the intermediate 2-aminobenzofurans, which are unstable in some cases.

EXPERIMENTAL SECTION

All reactions were performed under argon atmosphere unless otherwise noted. THF and DME were dried over Na/benzophenone. Catalysts $Pd(PPh_3)_4$ (99%) and $Pd(dppf)Cl_2$ were purchased from Aldrich and Alfa Aesar, respectively. All other commercial reagents and solvents were used as received without additional purification. Reactions were followed with TLC (0.25 mm silica gel 60-F plates). Visualization was accomplished with UV light. Flash chromatographies were carried out on silica gel 320−400 mesh. Yields refer to chromatographically and

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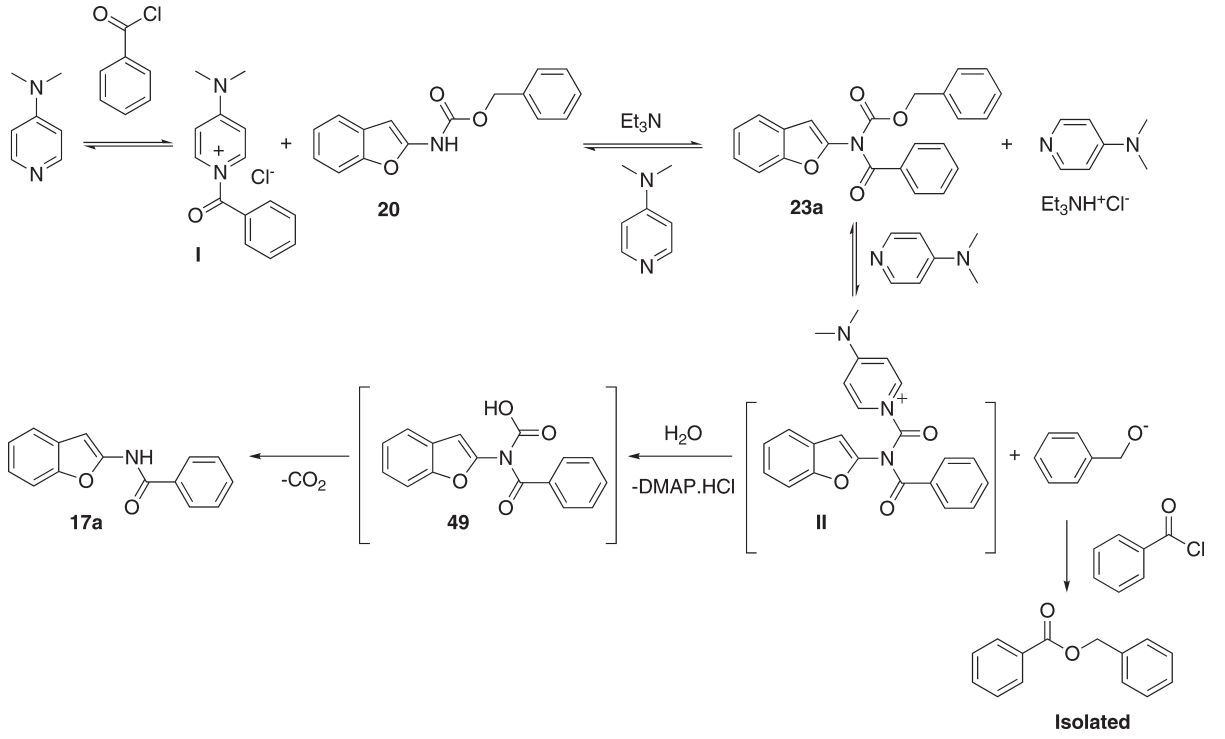
Scheme 9. Postulated Mechanism



spectroscopically pure materials. Melting points were determined by capillary method and are uncorrected. Infrared spectra were recorded on a FTIR spectrometer. Low-resolution mass spectra were recorded on a ESI-QMS instrument and high-resolution mass spectra were recorded on a TOF-ESI-MS instrument. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer. ^{13}C NMR spectra were recorded at 75 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the residual solvent peak as the internal reference, and coupling constants are given in hertz. Peak assignment was unambiguously performed by using HMQC, HMBC, and COSY experiments.

General Procedure for Curtius Rearrangement: Synthesis of 20, 37, and 38. To a solution of carboxylic acid (1 equiv), sodium azide (1.7 equiv), and sodium *tert*-butoxide (0.15 equiv) in anhydrous DME (0.12 M) at room temperature under argon was added benzylchloroformate (1.3 equiv). After 20 h at 75 °C the mixture was then quenched with water and extracted three 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.

General Procedure for Bromination: Synthesis of 21a, 27−30, and 40−42. To a solution of the requisite benzofuran (1 equiv) in THF (0.4 M) at room temperature under argon was added a solution of PTSA (0.1 equiv) in THF (0.1 M), and at −78 °C, the resulting mixture was treated by dropwise addition of a solution of NBS (1.2 equiv) in THF (0.35 M). After being stirred at −78 °C in the absence of light for the indicated time period, the reaction was quenched at room temperature with a saturated aqueous solution of $NaHCO_3$ extracted three times with ethyl acetate. The combined organic layers were washed with a solution of sodium thiosulfate 12% w/v and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel to afford the desired product. Brominated products are not stable and are stocked at −30 °C. Beside compounds **21a** and **40a**, the brominated products were only described with ^{1}H NMR and LRMS and directly engaged in the Suzuki−Miyaura reaction due to their fast degradation.

General Procedure for the Suzuki−Miyaura Reaction

Method A: To a solution of brominated benzofuran **40** (1 equiv), boronic acid (1.2 to 2 equiv), and sodium carbonate (4 equiv) in DME/H_2O (4:1, 0.1M) at room temperature under argon was added $PdCl_2$(dppf) (0.06 equiv). After the indicated time period at 85 °C (see Table 4), the mixture was quenched with water and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel to afford the desired product **15**.

Method B: To a solution of brominated benzofuran **21a**, **40a** or **41** (1 equiv), phenyl boronic acid (5 equiv), and cesium fluoride (11 equiv) in dioxane/H_2O (4:1, 0.1 M) at room temperature under argon was added $Pd(PPh_3)_4$ (0.05 equiv). After 1 h at 101 °C (see Table 4), the mixture was quenched with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel to afford the desired product **22**, **15a**, or **43**, respectively.

Method B′: To a solution of brominated benzofuran **28−30** (1 equiv), phenyl boronic acid (1.5 equiv), and cesium fluoride (4.5 equiv) in dioxane/H_2O (4:1, 0.1 M) at room temperature under argon was added $Pd(PPh_3)_4$ (0.05 equiv). After 5 h at 101 °C, the mixture was quenched with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel to afford the desired product **32−34**, respectively.

General Procedure for *N*-Methylation: Synthesis of 24 and 25. To a solution of benzofuran derivative **20** or **17a** (1 equiv) in DMF

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(0.2 M) was added NaH 60% in mineral oil (1.3 equiv) by portions at 0 °C under argon. After 15 min at 0 °C, methyl iodide (1.3 equiv) was added at room temperature and the resulting mixture was stirred during the indicated time. The reaction was quenched into ice water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel to afford the desired product **24** or **25**, respectively.

General Procedure for One-Pot *N*-Acylation/Deprotection: Synthesis of 17a−d (Method A). To a solution of benzyl benzofuran-2-ylcarbamate **20** (1 equiv) in anhydrous THF (0.075 M) at room temperature under argon was added DMAP (1.5 equiv) and then sodium hydride 60% in mineral oil (1.2 equiv) by portions (1/3 equiv for each portion) at 0 °C. After 15 min at 0 °C, the requisite aroyl chloride (1.01 or 3 equiv) and triethylamine (6 equiv) were added dropwise and the resulting mixture was stirred at reflux during the indicated time period. The reaction was quenched into ice water and extracted three times with ethyl acetate. The combined organic layers were washed with a solution of saturated sodium bicarbonate and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel to afford the desired product **17**.

General Procedure for *N*-Acylation: Synthesis of 23a−c, 23e, and 23f (Method B). To a solution of benzyl benzofuran-2-ylcarbamate **20** (1 equiv) in anhydrous THF (0.075 M) at 0 °C under argon was added sodium hydride 60% in mineral oil (3 equiv) by portions. After 15 min at 0 °C, the requisite aroyl chloride (3 equiv) was added dropwise. After the indicated time period at reflux, the reaction was quenched into ice water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel to afford the desired product **23**.

General Procedure for Deprotection: Synthesis of 17e and 17f (Method B). A solution of protected 2-arylamidobenzofuran **23e** or **23f** (1 mmol) in methanol (0.02 M) at room temperature was stirred with 10% Pd/C under hydrogen atmosphere. After the indicated time period, the resulting reaction was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel to afford the desired product **17e** or **17f**, respectively.

Benzyl Benzofuran-2-ylcarbamate 20. Following the general procedure for Curtius rearrangement,[39] a mixture of benzofuran-2-carboxylic acid **19** (1.00 g, 6.17 mmol), sodium azide (682 mg, 10.49 mmol), sodium *tert*-butoxide (89 mg, 0.93 mmol), and benzylchloroformate (970 μL, 6.79 mmol) was stirred in DME (50 mL) at 75 °C for 20 h. After workup, the crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc 95:5) to afford the desired product **20** (1.14 g, 4.26 mmol, 69% yield) as a pale yellow powder: mp 97 °C (recrystallized from heptane to give pale yellow crystals); IR (CH_2Cl_2) ν_{max} 3410, 3052, 2960, 1745, 1624, 1524, 1457, 1284, 1244, 1206, 1186, 1059 cm^{-1}; ^1H NMR (300 MHz, MeOD) δ 7.43−7.28 (m, 7H), 7.16−7.07 (m, 2H), 6.42 (brs, 1H), 5.21 (s, 2H); ^{13}C NMR (75 MHz, MeOD) δ 153.0, 150.2, 149.4, 136.2, 129.5, 128.2 (2C), 127.7 (2C), 127.9, 122.7, 121.9, 119.3, 109.5, 87.6, 66.9; MS (ES^+) m/z 290 $[M + Na]^+$, (ES^-) m/z 266 $[M - H]^-$.

Benzyl 3-Bromobenzofuran-2-ylcarbamate 21a from 20. Following the general procedure for bromination, a mixture of benzyl benzofuran-2-ylcarbamate **20** (600 mg, 2.25 mmol), PTSA (43 mg, 0.23 mmol), and NBS (480 mg, 2.7 mmol) was stirred in THF at −78 °C for 25 min. After workup, the crude product was purified by flash chromatography over silica gel (toluene) to afford the desired product **21a** (575 mg, 1.66 mmol, 74% yield) as a pale yellow solid.

Benzyl 3-Bromobenzofuran-2-ylcarbamate 21a from 21b. To a solution of benzyl bromo(3-bromobenzofuran-2-yl)carbamate **21b** (17.3 mg, 0.04 mmol) in ethyl acetate (1 mL) at 0 °C was added a solution of sodium thiosulfate 12% w/v (1.5 mL). After 1 h at 0 °C, the layers were separated. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired product **21a** (14.3 mg, 0.04 mmol, 100% yield) as a pale yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.26 (m, 9H), 6.69 (brs, 1H), 5.25 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 151.0, 143.3, 135.3, 128.7 (2C), 128.6 (2C), 128.4, 127.7, 125.4, 123.7, 119.5, 111.5, 89.3, 68.2; MS (ES^+) m/z 346 $[M + H]^+$ (^{79}Br), 348 $[M + H]^+$ (^{81}Br).

Benzyl Bromo(3-bromobenzofuran-2-yl)carbamate 21b. To a solution of benzyl benzofuran-2-ylcarbamate **20** (75 mg, 0.28 mmol) in acetic acid (2 mL, 0.14 M) at room temperature under argon was added successively sodium acetate (92 mg, 1.12 mmol) and a solution of bromine in acetic acid (750 μL, C = 0.1 g/mL, 0.48 mmol) dropwise. After 40 min at room temperature, the mixture was quenched at 0 °C with a solution of sodium hydroxide 30% w/v until pH 8 and extracted three times with ethyl acetate. The combined organic layers were washed with a solution of sodium hydroxide 10% w/v, a solution of sodium thiosulfate 12% w/v, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc/triethylamine 98:2:0.2) to afford the desired product **21b** (77 mg, 0.18 mmol, 65% yield) as an orange powder: ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.6, 1.1 Hz, 1H), 7.47−7.35 (m, 6H), 7.27 (dt, J = 7.6, 1.0 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 157.9, 150.5, 135.0, 132.7, 130.2, 128.61 (3C), 128.60 (2C), 125.9, 125.8, 111.5, 69.0; MS (ES^+) m/z 424 $[M + H]^+$ ($C_{16}H_{11}{}^{79}Br_2NO_3$), 426 $[M + H]^+$ ($C_{16}H_{11}{}^{79}Br^{81}BrNO_3$), 428 $[M + H]^+$ ($C_{16}H_{11}{}^{81}Br_2NO_3$).

Benzyl 3-Phenylbenzofuran-2-ylcarbamate 22. Following the general procedure for the Suzuki−Miyaura reaction (method B), a mixture of the brominated product **21a** (100 mg, 0.29 mmol), phenyl boronic acid (176 mg, 1.44 mmol), $Pd(PPh_3)_4$ (16.7 mg, 0.014 mmol), and CsF (483 mg, 3.18 mmol) was stirred in dioxane/H_2O (3.6 mL, 4:1) at 101 °C for 1 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50 to 100:0) to afford the desired product **22** (54.5 mg, 0.16 mmol, 55% yield) as a yellow solid: mp 102 °C (recrystallized from heptane to give off-white needles); IR (CH_2Cl_2) ν_{max} 3399, 3066, 3037, 1746, 1641, 1503, 1480, 1470, 1455, 1309, 1216, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 7.01 Hz, 1H), 7.55−7.43 (m, 5H), 7.39−7.24 (m, 8H), 6.64 (brs, 1H), 5.19 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 151.7, 141.6, 135.5, 131.0, 129.0 (3C), 128.6 (2C), 128.5 (2C), 128.3, 127.8, 127.6 (2C), 124.8, 123.2, 120.1, 112.5, 111.4, 68.0; HRMS (ES^+) m/z calcd for $C_{22}H_{17}NO_3Na$ $[M + Na]^+$ 366.1106, found 366.1100.

***N*-(3-Phenylbenzofuran-2-yl)benzamide 15a from 22.** To a solution of benzyl 3-phenylbenzofuran-2-ylcarbamate **22** (50 mg, 0.15 mmol) in $CHCl_3$ (1 mL) at room temperature under argon was added successively DMAP (26.7 mg, 0.22 mmol), triethylamine (0.12 mL, 0.87 mmol), and benzoyl chloride (0.05 mL, 0.44 mmol). The resulting mixture was stirred at reflux for 16 h. The reaction was quenched into ice water and extracted three times with ethyl acetate. The combined organic layers were washed with a solution of saturated sodium bicarbonate and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50 to 100:0) to afford the desired product **15a** (27.8 mg, 0.09 mmol, 61% yield).

***N*-(3-Phenylbenzofuran-2-yl)benzamide 15a from 40a.** Following the general procedure for the Suzuki−Miyaura reaction (method B), a mixture of the brominated product **40a** (183 mg, 0.58 mmol), phenyl boronic acid (354 mg, 2.90 mmol), $Pd(PPh_3)_4$ (33.4 mg, 0.029 mmol), and CsF (970 mg, 6.38 mmol) was stirred in dioxane/H_2O (7.1 mL, 4:1) at 101 °C for 1 h. After workup, the crude product

was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50 to 100:0) to afford the desired product **15a** (76 mg, 0.24 mmol, 42% yield) as a pale yellow solid: mp 175 °C (recrystallized from heptane to give a pale yellow powder); IR (CH_2Cl_2) ν_{max} 3409, 3065, 2927, 1697, 1635, 1502, 1464, 1271, 1251, 1181 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (brs, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.70−7.67 (m, 1H), 7.61−7.44 (m, 8H), 7.39−7.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 152.1, 142.2, 132.9, 132.5, 131.2, 129.0 (2C), 128.8 (2C), 128.4 (2C), 127.75, 127.62, 127.56 (2C), 124.7, 123.2, 120.0, 112.9, 111.5; HRMS (ES^+) m/z calcd for $C_{21}H_{15}NO_2Na$ $[M + Na]^+$ 336.1000, found 336.1009.

***N*-(Benzofuran-2-yl)benzamide 17a.** Following the general procedure for one-pot *N*-acylation/deprotection, to a solution of benzyl benzofuran-2-ylcarbamate **20** (100 mg, 0.37 mmol) in anhydrous THF (5 mL) at room temperature under argon was added DMAP (68.5 mg, 0.56 mmol) and then sodium hydride 60% in mineral oil (18 mg, 0.45 mmol) by portions at 0 °C. After 15 min at 0 °C, benzoyl chloride (0.13 mL, 1.12 mmol) and triethylamine (0.31 mL, 2.25 mmol) were added and the resulting mixture was stirred at reflux overnight. After workup, the crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50) to afford the desired product **17a** (75 mg, 0.31 mmol, 84% yield) as a pale yellow solid: mp 128 °C (recrystallized from heptane to give white crystals); IR (CH_2Cl_2) ν_{max} 3421, 3055, 1689, 1610, 1600, 1520, 1491, 1456, 1249, 1189 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.6 (brs, 1H), 7.92 (d, J = 7.3 Hz, 2H), 7.61−7.47 (m, 4H), 7.33 (d, J = 7.9 Hz, 1H), 7.26−7.17 (m, 2H), 6.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 149.7, 147.8, 133.1, 132.5, 129.5, 129.0 (2C), 127.2 (2C), 123.3, 122.9, 120.5, 110.2, 90.7; HRMS (ES^+) m/z calcd for $C_{15}H_{12}NO_2$ $[M + H]^+$ 238.0868, found 238.0858.

Benzyl Benzofuran-2-yl(benzoyl)carbamate 23a. Following the general procedure for *N*-acylation, to a solution of benzyl benzofuran-2-ylcarbamate **20** (100 mg, 0.375 mmol) in anhydrous THF (5 mL) at 0 °C under argon was added sodium hydride 60% in mineral oil (75 mg, 1.87 mmol) by portions. After 15 min at 0 °C, benzoyl chloride (0.13 mL, 1.12 mmol) was added dropwise. Stirring at reflux overnight was followed by workup. The crude product was purified by flash chromatography over silica gel (toluene) to afford the desired product **23a** (129 mg, 0.35 mmol, 93% yield) as a pale yellow solid: mp 91 °C (recrystallized from heptane to give a white powder); IR (CH_2Cl_2) ν_{max} 3685, 3068, 3037, 1752, 1715, 1613, 1453, 1330, 1238, 1162, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.2 Hz, 2H), 7.54−7.45 (m, 3H), 7.37 (t, J = 7.5 Hz, 2H), 7.32−7.26 (m, 4H), 7.26−7.15 (m, 3H), 6.6 (s, 1H), 5.21 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 153.0, 152.8, 146.0, 134.5, 133.9, 132.8, 128.9 (2C), 128.51 (3C), 128.47 (2C), 128.1 (2C), 127.8, 125.0, 123.2, 121.4, 111.4, 103.2, 69.2; HRMS (ES^+) m/z calcd for $C_{23}H_{18}NO_4$ $[M + H]^+$ 372.1236, found 372.1227.

Benzyl Benzofuran-2-yl(methyl)carbamate 24. Following the general procedure for *N*-methylation, to a solution of benzyl benzofuran-2-ylcarbamate **20** (500 mg, 1.87 mmol) in DMF (10 mL) at 0 °C under argon was added sodium hydride 60% in mineral oil (97 mg, 2.43 mmol) by portions. After 15 min at 0 °C, MeI (0.55 mL, 2.43 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 90:10) to afford the desired product **24** (481 mg, 1.71 mmol, 91% yield) as a pale yellow solid: IR (CH_2Cl_2) ν_{max} 3685, 3035, 1721, 1597, 1456, 1394, 1359, 1275, 1249, 1154, 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.47 (m, 1H), 7.41−7.33 (3, 6H), 7.23−7.20 (m, 2H), 6.50 (s, 1H), 5.26 (s, 2H), 3.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 150.9 (2C), 135.9, 128.6 (4C), 128.3, 128.0, 123.1 (2C), 120.5, 110.6, 94.7, 68.1, 35.0; HRMS (ES^+) m/z calcd for $C_{17}H_{15}NO_3Na$ $[M + Na]^+$ 304.0950, found 304.0940.

***N*-(Benzofuran-2-yl)-*N*-methylbenzamide 25.** Following the general procedure for *N*-methylation, to a solution of *N*-(benzofuran-2-yl)benzamide **17a** (430 mg, 1.81 mmol) and MeI (0.15 mL, 2.36 mmol) in DMF (9 mL) was treated with NaH 60% in mineral oil (94 mg, 2.36 mmol) by portions at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After workup, the crude product was purified by flash chromatography over silica gel (cyclohexane/ethyl acetate 97:3) to afford the desired product **25** (416 mg, 1.66 mmol, 92%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.15 (m, 9H), 6.04 (s, 1H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 152.4, 151.7, 134.9, 130.6, 128.1 (2C), 128.0, 127.9 (2C), 124.4, 123.1, 121.0, 111.1, 99.5, 36.3; HRMS (ES^+) m/z calcd for $C_{16}H_{13}NO_2Na$ $[M + Na]^+$ 274.0844, found 274.0856.

***N*-(Benzofuran-2-yl)-*N*-(methoxymethyl)benzamide 26.** To a solution of *N*-(benzofuran-2-yl)benzamide **17a** (381.0 mg, 1.61 mmol, 1 equiv) in DMF (8 mL, 0.2 M) was added sodium hydride 60% in mineral oil (193 mg, 4.82 mmol, 3 equiv) by portions at 0 °C under argon. After 15 min at 0 °C, triethylamine (0.67 mL, 4.82 mmol, 3 equiv) and chloro(methoxy)methane (0.37 mL, 4.82 mmol, 3 equiv) were added at room temperature and the resulting mixture was stirred overnight at 55 °C. The reaction was quenched into ice water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (toluene/EtOAc 99:1 to 97:3) to afford the desired product **26** (353.0 mg, 1.26 mmol, 78%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 6.9 Hz, 2H), 7.42−7.15 (m, 7H), 6.27 (s, 1H), 5.29 (s, 2H), 3.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 151.9, 150.4, 134.4, 130.9, 128.0 (2C), 127.9, 127.8 (2C), 124.4, 123.0, 120.9, 111.1, 100.9, 79.0, 56.9; HRMS (ES^+) m/z calcd for $C_{17}H_{16}NO_3$ $[M + H]^+$ 282.1130, found 282.1143.

Benzyl Benzoyl(3-bromobenzofuran-2-yl)carbamate 27. Following the general procedure for bromination, a mixture of benzyl benzofuran-2-yl(benzoyl)carbamate **23a** (330 mg, 0.89 mmol), PTSA (17.0 mg, 0.09 mmol), and NBS (190 mg, 1.07 mmol) was stirred in THF at 0 °C for 90 min. After workup, the residue was purified by flash chromatography over silica gel (toluene/cyclohexane 70:30) to afford the desired product **27** (297 mg, 0.66 mmol, 74% yield) as a yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 6.9 Hz, 2H), 7.53−7.26 (m, 10H), 7.19−7.16 (m, 2H), 5.22 (s, 2H); MS (ES^+) m/z 472 $[M + Na]^+$ (^{79}Br), 474 $[M + Na]^+$ (^{81}Br)

Benzyl-3-bromobenzofuran-2-yl(methyl)carbamate 28. Following the general procedure for bromination, a mixture of benzyl benzofuran-2-yl(methyl)carbamate **24** (480 mg, 1.70 mmol), PTSA (32 mg, 0.17 mmol), and NBS (364 mg, 2.04 mmol) was stirred in THF at −78 °C for 25 min. After workup, the residue was purified by flash chromatography over silica gel (toluene) to afford the desired product **28** (469 mg, 1.30 mmol, 76% yield) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.52−7.49 (m, 1H), 7.44−7.26 (m, 8H), 5.20 (s, 2H), 3.33 (s, 3H); MS (ES^+) m/z 360 $[M + H]^+$ (^{79}Br), 362 $[M + H]^+$ (^{81}Br), 382 $[M + Na]^+$ (^{79}Br), 384 $[M + Na]^+$ (^{81}Br).

***N*-(3-Bromobenzofuran-2-yl)-*N*-methylbenzamide 29.** Following the general procedure for bromination, a mixture of 2-arylamidobenzofuran **25** (317 mg, 1.26 mmol), PTSA (24 mg, 0.13 mmol), and NBS (270 mg, 1.51 mmol) was stirred in THF at −78 °C for 20 min. After workup, the crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc 98:2) to afford the desired product **29** (296 mg, 0.90 mmol, 71% yield) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.46 (m, 2H), 7.40−7.23 (m, 5H), 7.21−7.16 (m, 2H), 3.45 (s, 3H); MS (ES^+) m/z 352 $[M + Na]^+$ (^{79}Br), 354 $[M + Na]^+$ (^{81}Br).

***N*-(3-Bromobenzofuran-2-yl)-*N*-(methoxymethyl)benzamide 30.** Following the general procedure for bromination, a mixture of 2-arylamidobenzofuran **26** (250 mg, 0.89 mmol), PTSA (17.0 mg, 0.09 mmol), and NBS (190 mg, 1.07 mmol) was stirred in THF at −78 °C for 20 min. After workup, the residue was purified by flash chromatography

over silica gel (toluene/EtOAc 98:2) to afford the desired product **30** (243 mg, 0.68 mmol, 76% yield) as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 6.9 Hz, 2H), 7.45−7.42 (m, 1H), 7.38−7.18 (m, 6H), 5.32 (s, 2H), 3.59 (s, 3H); MS (ES^+) m/z 382 $[M + Na]^+$ (^{79}Br), 384 $[M + Na]^+$ (^{81}Br).

Benzyl Methyl(3-phenylbenzofuran-2-yl)carbamate 32. Following the general procedure for the Suzuki coupling (method B′), a mixture of the brominated product **28** (105.0 mg, 0.29 mmol), phenyl boronic acid (53.0 mg, 0.43 mmol), $Pd(PPh_3)_4$ (16.7 mg, 0.015 mmol), and cesium fluoride (198 mg, 1.30 mmol) was stirred in dioxane/H_2O (3.5 mL, 4:1) at 101 °C for 5 h. After workup, the crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc 98:2) to afford the desired product **32** (100.0 mg, 0.28 mmol, 96% yield) as a pale yellow oil: IR (CH_2Cl_2) ν_{max} 3066, 3036, 2954, 1721, 1636, 1454, 1390, 1333, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 6.9 Hz, 1H), 7.50−7.10 (m, 13H), 5.06 (s, 2H), 3.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 151.7, 146.7, 135.9, 131.1, 128.9 (4C), 128.4, 128.1, 127.80, 127.6 (4C), 125.0, 123.1, 120.4, 113.1, 111.4, 68.0, 36.7; HRMS (ES^+) m/z calcd for $C_{23}H_{19}NO_3Na$ $[M + Na]^+$ 380.1263, found 380.1267.

***N*-Methyl-*N*-(3-phenylbenzofuran-2-yl)benzamide 33.** Following the general procedure for the Suzuki coupling (method B′), a mixture of the brominated product **29** (191.5 mg, 0.58 mmol), phenyl boronic acid (106.0 mg, 0.87 mmol), $Pd(PPh_3)_4$ (33.4 mg, 0.029 mmol), and cesium fluoride (396 mg, 2.61 mmol) was stirred in dioxane/H_2O (7.1 mL, 4:1) at 101 °C for 4 h. After workup, the residue was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 90:10) to afford the desired product **33** (181.6 mg, 0.56 mmol, 96% yield) as a pale yellow solid: mp 136 °C (recrystallized from heptane to give white crystals); IR (CH_2Cl_2) ν_{max} 3063, 1665, 1634, 1454, 1388, 1349, 1125, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.45 (m, 2H), 7.38−7.29 (m, 4H), 7.25−7.12 (m, 2H), 7.02−6.92 (m, 6H), 3.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 151.6, 148.2, 134.8, 130.5, 130.1, 128.9 (2C), 127.9 (2C), 127.53, 127.47 (2C), 127.4, 127.2 (2C), 125.1, 123.2, 120.3, 113.9, 111.4, 36.2; HRMS (ES^+) m/z calcd for $C_{22}H_{17}NO_2Na$ $[M + Na]^+$ 350.1157, found 350.1160.

***N*-(Methoxymethyl)-*N*-(3-phenylbenzofuran-2-yl)benzamide 34a.** Following the general procedure for the Suzuki coupling (method B′), a mixture of the brominated product **30** (180 mg, 0.50 mmol), phenyl boronic acid (91.5 mg, 0.75 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), and cesium fluoride (342 mg, 2.25 mmol) was stirred in dioxane/H_2O (6.1 mL, 4:1) at 101 °C for 6 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene) to afford the desired product **34a** (177.0 mg, 0.495 mmol, 99% yield) as a yellow oil: IR ($CDCl_3$) ν_{max} 3064, 2938, 1673, 1454, 1394, 1350, 1297, 1187, 1094, 1081 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.38−7.30 (m, 4H), 7.26−7.16 (m, 2H), 7.10−7.09 (m, 2H), 7.01−6.99 (m, 4H), 5.35 (s, 2H), 3.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 151.6, 146.2, 134.3, 130.5, 130.2, 128.7 (2C), 128.2 (2C), 127.5−127.3 (6C), 125.1, 123.2, 120.3, 115.0, 111.4, 79.0, 57.8; HRMS (ES^+) m/z calcd for $C_{23}H_{20}NO_3$ $[M + H]^+$ 358.1443, found 358.1440.

***N*-(Methoxymethyl)-*N*-(3-(4-(trifluoromethyl)phenyl)benzofuran-2-yl)benzamide 34b.** Following the general procedure for the Suzuki coupling (method B′), a mixture of the brominated product **30** (200 mg, 0.56 mmol), 4-(trifluoromethyl)phenyl boronic acid (158.0 mg, 0.83 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), and cesium fluoride (376 mg, 2.48 mmol) was stirred in dioxane/H_2O (6.7 mL, 4:1) at 101 °C for 5 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 98:2) to afford the desired product **34b** (219.0 mg, 0.52 mmol, 93% yield) as a pale yellow solid: IR ($CDCl_3$) ν_{max} 3064, 2940, 1675, 1454, 1325, 1297, 1171, 1130, 1069 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.54 (m, 3H), 7.42−7.36 (m, 2H), 7.28−7.18 (m, 4H), 7.02−6.94 (m, 4H), 5.36 (s, 2H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 151.6, 146.9, 134.1, 133.8, 130.8, 129.5 (q, J = 32.4 Hz), 128.4 (2C), 127.7 (2C), 127.3 (2C), 127.0, 125.7 (2C, q, J = 3.75 Hz), 125.5, 124.0 (q, J = 270 Hz), 123.6, 119.9, 113.9, 111.6, 78.9, 57.9; HRMS (ES^+) m/z calcd for $C_{24}H_{18}NO_3F_3Na$ $[M + Na]^+$ 448.1136, found 448.1147.

Methyl 4-(2-(*N*-(Methoxymethyl)benzamido)benzofuran-3-yl)benzoate 34c. Following the general procedure for the Suzuki coupling (method B′), a mixture of the brominated product **30** (200 mg, 0.56 mmol), 4-(methoxycarbonyl)phenylboronic acid (150.0 mg, 0.83 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), and cesium fluoride (376 mg, 2.48 mmol) was stirred in dioxane/H_2O (6.7 mL, 4:1) at 101 °C for 5 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 95:5) to afford the desired product **34c** (205.0 mg, 0.49 mmol, 89% yield) as an orange solid: IR ($CDCl_3$) ν_{max} 3064, 2953, 1717, 1675, 1454, 1290, 1185, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.44−7.35 (m, 2H), 7.26−7.18 (m, 4H), 7.02−6.97 (m, 4H), 5.36 (s, 2H), 3.95 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 166.7, 151.6, 146.8, 135.0, 133.9, 130.6, 129.9 (2C), 128.9, 128.0 (2C), 127.6 (2C), 127.2 (2C), 126.9, 125.3, 123.4, 120.0, 114.3, 111.5, 78.9, 57.9, 52.1; HRMS (ES^+) m/z calcd for $C_{25}H_{21}NO_5Na$ $[M + Na]^+$ 438.1317, found 438.1321.

***N*-(Methoxymethyl)-*N*-(3-(2-methoxyphenyl)benzofuran-2-yl)benzamide 34d.** Following the general procedure for the Suzuki coupling (method B′), a mixture of the brominated product **30** (200 mg, 0.56 mmol), 2-methoxyphenyl boronic acid (127 mg, 0.83 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), and cesium fluoride (376 mg, 2.48 mmol) was stirred in dioxane/H_2O (6.7 mL, 4:1) at 101 °C for 6 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 95:5) to afford the desired product **34d** (202.0 mg, 0.52 mmol, 94% yield) as an orange solid: IR ($CDCl_3$) ν_{max} 3064, 3001, 2939, 1671, 1455, 1298, 1248, 1095, 1079, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 8.1 Hz, 1H), 7.33−7.14 (m, 5H), 7.09−6.99 (m, 4H), 6.87−6.79 (m, 3H), 5.34 (s, 2H), 3.62 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 156.5, 151.5, 147.4, 134.5, 130.8, 130.3, 129.2, 128.4, 127.5−127.4 (5C), 124.5, 122.8, 120.7, 120.5, 118.5, 111.2, 110.5, 79.0, 57.4, 54.9; HRMS (ES^+) m/z calcd for $C_{24}H_{21}NO_4Na$ $[M + Na]^+$ 410.1368, found 410.1383.

***N*-(Methoxymethyl)-*N*-(3-(3,4,5-trimethoxyphenyl)benzofuran-2-yl)benzamide 34e.** Following the general procedure for the Suzuki coupling (method B′), a mixture of the brominated product **30** (200 mg, 0.56 mmol), 3,4,5-trimethoxyphenyl boronic acid (176.5 mg, 0.83 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), and cesium fluoride (376 mg, 2.48 mmol) was stirred in dioxane/H_2O (6.7 mL, 4:1) at 101 °C for 6 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 95:5 to 85:15) to afford the desired product **34e** (225.0 mg, 0.50 mmol, 91% yield) as a pale yellow solid: IR ($CDCl_3$) ν_{max} 3005, 2940, 1675, 1581, 1510, 1455, 1357, 1301, 1129, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.39−7.33 (m, 1H), 7.26−7.16 (m, 2H), 7.04−7.00 (m, 4H), 6.34 (s, 2H), 5.34 (s, 2H), 3.89 (s, 3H), 3.76 (s, 6H), 3.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 153.5 (2C), 151.5, 146.3, 137.3, 134.2, 130.4, 127.5 (2C), 127.42 (2C), 127.37, 125.6, 125.1, 123.3, 120.1, 114.7, 111.4, 105.1 (2C), 78.8, 60.9, 57.8, 56.0 (2C); HRMS (ES^+) m/z calcd for $C_{26}H_{25}NO_6Na$ $[M + Na]^+$ 470.1580, found 470.1602.

Benzyl 5-Methoxybenzofuran-2-ylcarbamate 37. Following the general procedure for Curtius rearrangement, a mixture of 5-methoxybenzofuran-2-carboxylic acid **35** (2.37 g, 12.34 mmol), sodium azide (1.36 g, 20.92 mmol), sodium *tert*-butoxide (178 mg, 1.85 mmol), and benzylchloroformate (2.3 mL, 13.58 mmol) was stirred in DME (45 mL) at 75 °C for 20 h. After workup, the crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc

90:10 to 70:30) to afford the desired product **37** (2.45 g, 8.25 mmol, 67% yield) as an orange powder: mp 103 °C (recrystallized from heptane to give pale orange crystals); IR ($CDCl_3$) ν_{max} 3425, 2958, 1743, 1614, 1525, 1478, 1315, 1207, 1177, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.36 (m, 5H), 7.20 (d, J = 8.7 Hz, 1H), 7.09 (brs, 1H), 6.94 (d, J = 2.7 Hz, 1H), 6.74 (dd, J = 2.7, 8.7 Hz, 1H), 6.47 (brs, 1H), 5.26 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 151.8, 148.4, 144.8, 135.3, 130.1, 128.6 (2C), 128.5, 128.3 (2C), 110.5, 110.4, 103.2, 89.1, 67.8, 55.8; HRMS (ES^-) m/z calcd for $C_{17}H_{14}NO_4$ $[M - H]^-$ 296.0923, found 296.0918.

Benzyl 5-Nitrobenzofuran-2-ylcarbamate 38. Following the general procedure for Curtius rearrangement, a mixture of 5-nitrobenzofuran-2-carboxylic acid **36** (2.55 g, 12.32 mmol), sodium azide (1.36 g, 20.92 mmol), sodium *tert*-butoxide (178 mg, 1.85 mmol), and benzylchloroformate (2.3 mL, 6.79 mmol) was stirred in DME (45 mL) at 75 °C for 20 h. After workup, the crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc 90:10 to 50:50) to afford the desired product **38** (1.87 g, 5.99 mmol, 49% yield) as a yellow powder: mp 150 °C (recrystallized from EtOAc/heptane to give yellow crystals); IR ($CDCl_3$) ν_{max} 3420, 3068, 1747, 1617, 1524, 1347, 1257, 1209, 1158, 1068 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.44 (s, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.05 (dd, J = 2.4, 8.7 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.46−7.33 (m, 5H), 6.65 (s, 1H), 5.24 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.6, 152.4, 152.0, 143.9, 135.8, 130.2, 128.5−128.2 (5C), 117.9, 115.6, 110.8, 87.7, 66.8; HRMS (ES^-) m/z calcd for $C_{16}H_{11}N_2O_5$ $[M - H]^-$ 311.0668, found 311.0681.

***N*-(Benzofuran-2-yl)-4-methoxybenzamide 17b.** Following the general procedure for one-pot *N*-acylation/deprotection, to a solution of benzyl benzofuran-2-ylcarbamate **20** (2.50 g, 9.36 mmol) in anhydrous THF (85 mL) at room temperature under argon was added DMAP (1.71 g, 14 mmol) and then sodium hydride 60% in mineral oil (375 mg, 9.37 mmol) by portions at 0 °C. After 15 min at 0 °C, 4-methoxybenzoyl chloride (1.27 mL, 9.36 mmol) and triethylamine (7.8 mL, 56 mmol) were added and the resulting mixture was stirred at reflux overnight. After workup, the crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 60:40 to 100:0) to afford the desired product **17b** (1.92 g, 7.18 mmol, 77% yield) as a pale yellow solid: mp 147 °C (recrystallized from heptane to give off-white crystals); IR ($CDCl_3$) ν_{max} 3682, 3436, 2966, 2937, 2842, 2250, 1683, 1605, 1527, 1503, 1456, 1249, 1177, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (brs, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.51−7.48 (m, 1H), 7.35−7.32 (m, 1H), 7.25−7.15 (m, 2H), 6.97 (d, J = 8,7 Hz, 2H), 6.91 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 163.0, 149.7, 148.1, 129.7, 129.2 (2C), 125.3, 123.3, 122.8, 120.5, 114.2 (2C), 110.1, 90.4, 55.5; HRMS (ES^+) m/z calcd for $C_{16}H_{14}NO_3$ $[M + H]^+$ 268.0974, found 268.0961.

***N*-(Benzofuran-2-yl)-4-chlorobenzamide 17c.** Following the general procedure for one-pot *N*-acylation/deprotection, to a solution of benzyl benzofuran-2-ylcarbamate **20** (1.0 g, 3.75 mmol) in anhydrous THF (50 mL) at room temperature under argon was added DMAP (685 mg, 5.62 mmol) and then sodium hydride 60% in mineral oil (230 mg, 5.62 mmol) by portions at 0 °C. After 15 min at 0 °C, 4-chlorobenzoyl chloride (1.44 mL, 11.24 mmol) and triethylamine (3.1 mL, 22.5 mmol) were added and the resulting mixture was stirred at reflux overnight. After workup, the crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50 to 100:0) to afford the desired product **17c** (678 mg, 2.50 mmol, 66% yield) as a yellow solid: mp 176 °C (recrystallized from heptane to give pale yellow crystals); IR (CH_2Cl_2) ν_{max} 3686, 3420, 3055, 1693, 1608, 1595, 1522, 1487, 1456, 1260, 1188, 1101, 1014 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (brs, 1H), 7.86 (dt, J = 8.9, 2.2 Hz, 2H), 7.53 (m, 1H), 7.50 (dt, J = 8.9, 2.2 Hz, 2H), 7.37 (m, 1H), 7.22 (m, 2H), 6.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 149.8, 147.5, 139.0, 131.4, 129.4, 129.3 (2C), 128.6 (2C), 123.4, 123.1, 120.6, 110.2, 91.0; HRMS (ES^+) m/z calcd for $C_{15}H_{10}NO_2NaCl$ $[M + Na]^+$ 294.0298, found 294.0298.

***N*-(Benzofuran-2-yl)-4-nitrobenzamide 17d.** Following the general procedure for one-pot *N*-acylation/deprotection, to a solution of benzyl benzofuran-2-ylcarbamate **20** (100 mg, 0.37 mmol) in anhydrous THF (5 mL) at room temperature under argon was added DMAP (68.5 mg, 0.56 mmol) and then sodium hydride 60% in mineral oil (18 mg, 0.45 mmol) by portions at 0 °C. After 15 min at 0 °C, 4-nitrobenzoyl chloride (208 mg, 1.12 mmol) and triethylamine (0.31 mL, 2.25 mmol) were added and the resulting mixture was stirred at room temperature for 50 min. After workup, the crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 80:20 to 100:0) to afford the desired product **17d** (77 mg, 0.27 mmol, 73% yield) as an orange solid: mp 210 °C (recrystallized from heptane to give an orange powder); IR (CH_2Cl_2) ν_{max} 3397, 1747, 1641, 1503, 1470, 1452, 1394, 1307, 1216, 1177, 1059 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 10.93 (brs, 1H), 8.40 (d, J = 9.1 Hz, 2H), 8.35 (d, J = 9.1 Hz, 2H), 7.59−7.55 (m, 1H), 7.43−7.38 (m, 1H), 7.26−7.19 (m, 2H), 6.98 (d, J = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 162.1, 150.1, 149.8, 149.1, 139.0, 129.4, 129.2 (2C), 123.7 (2C), 123.3, 123.0, 120.4, 110.1, 90.7; HRMS (ES^+) m/z calcd for $C_{15}H_{11}N_2O_4$ $[M + H]^+$ 283.0719, found 283.0727.

***N*-(Benzofuran-2-yl)-4-fluorobenzamide 17e.** Following the general procedure for deprotection, a solution of protected 2-arylamidobenzofuran **23e** (430 mg, 1.10 mmol) in methanol (60 mL) at room temperature was stirred with 10% Pd/C under hydrogen atmosphere. After 3 h, the resulting reaction was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (toluene) to afford the desired product **17e** (201.5 mg, 0.79 mmol, 72% yield) as a pale yellow solid: mp 160 °C (recrystallized from heptane to give off-white crystals); IR ($CDCl_3$) ν_{max} 3433, 3065, 2250, 1687, 1603, 1526, 1502, 1456, 1248, 1187, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (brs, 1H), 7.96−7.92 (m, 2H), 7.54−7.50 (m, 1H), 7.38−7.35 (m, 1H), 7.26−7.18 (m, 4H), 6.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 (d, J = 252 Hz), 162.5, 149.8, 147.7, 129.7 (2C, d, J = 9.2 Hz), 129.5, 129.3 (d, J = 3.1 Hz), 123.4, 123.1, 120.6, 116.2 (2C, d, J = 22 Hz), 110.2, 90.9; HRMS (ES^+) m/z calcd for $C_{15}H_{10}NO_2FNa$ $[M + Na]^+$ 278.0593, found 278.0590.

***N*-(Benzofuran-2-yl)-4-(trifluoromethyl)benzamide 17f.** Following the general procedure for *N*-acylation, to a solution of benzyl benzofuran-2-ylcarbamate **20** (2.0 g, 7.5 mmol) in anhydrous THF (80 mL) at 0 °C under argon was added sodium hydride 60% in mineral oil (540 mg, 22.5 mmol) by portions. After 15 min at 0 °C, 4-(trifluoromethyl)benzoyl chloride (4.7 g, 22.5 mmol) was added dropwise. Stirring at reflux overnight was followed by workup. The crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50 to 100:0) to afford the product **23f** as an inseparable mixture with the starting material **20** (2.39 g, 5.44 mmol, 73% yield based on ^1H NMR analysis). Following the general procedure for deprotection, a solution of the mixture of **23f** and **20** in methanol (300 mL) at room temperature was stirred with 10% Pd/C under hydrogen atmosphere. After 4 h, the resulting reaction was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (toluene) to afford the desired product **17f** (1.36 g, 4.46 mmol, 60% overall yield, two steps) as a pale yellow solid: mp 181 °C (recrystallized from heptane to give white cotton); IR ($CDCl_3$) ν_{max} 3693, 3430, 3065, 2250, 1691, 1609, 1525, 1508, 1456, 1326, 1250, 1177, 1139, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (brs, 1H), 8.04 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.56−7.53 (m, 1H), 7.39−7.36 (m, 1H), 7.27−7.22 (m, 2H), 6.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 149.8, 147.3, 136.3, 134.2 (q, J = 32.7 Hz), 129.3, 127.7 (2C), 126.1 (2C, q, J = 3.7 Hz), 123.5, 123.4 (q, J = 271 Hz), 123.3, 120.7, 110.3, 91.4; HRMS (ES^+) m/z calcd for $C_{16}H_{11}NO_2F_3$ $[M + H]^+$ 306.0742, found 306.0746.

***N*-(5-Methoxybenzofuran-2-yl)benzamide 18.** Following the general procedure for one-pot *N*-acylation/deprotection, to a

solution of benzyl 5-methoxybenzofuran-2-ylcarbamate **37** (297 mg, 1.00 mmol) in anhydrous THF (15 mL) at room temperature under argon was added DMAP (183 mg, 1.50 mmol) and then sodium hydride 60% in mineral oil (48 mg, 1.20 mmol) by portions at 0 °C. After 15 min at 0 °C, benzoyl chloride (0.12 mL, 1.01 mmol) and triethylamine (0.83 mL, 6.00 mmol) were added and the resulting mixture was stirred at reflux overnight. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 98:2) to afford the desired product **18** (213.0 mg, 0.80 mmol, 80% yield) as a pale yellow solid: mp 138 °C (recrystallized from heptane/EtOAc to give off-white crystals); IR ($CDCl_3$) ν_{max} 3432, 2956, 1688, 1601, 1521, 1477, 1209, 1187, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (brs, 1H), 7.91 (d, J = 6.9 Hz, 2H), 7.63−7.58 (m, 1H), 7.55−7.50 (m, 2H), 7.25 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 2.7 Hz, 1H), 6.90 (s, 1H), 6.79 (dd, J = 2.7, 9.0 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 156.2, 148.5, 144.5, 133.0, 132.4, 130.1, 128.8 (2C), 127.2 (2C), 111.0, 110.5, 103.4, 91.1, 55.8; HRMS (ES^+) m/z calcd for $C_{16}H_{14}NO_3$ $[M + H]^+$ 268.0974, found 268.0986.

***N*-(5-Nitrobenzofuran-2-yl)benzamide 39.** Following the general procedure for one-pot *N*-acylation/deprotection, to a solution of benzyl 5-nitrobenzofuran-2-ylcarbamate **38** (624 mg, 2.00 mmol) in anhydrous THF (24 mL) at room temperature under argon was added DMAP (366 mg, 3.00 mmol) and then sodium hydride 60% in mineral oil (96 mg, 2.40 mmol) by portions at 0 °C. After 15 min at 0 °C, benzoyl chloride (0.23 mL, 2.02 mmol) and triethylamine (1.7 mL, 12.00 mmol) were added and the resulting mixture was stirred at reflux overnight. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 90:10) to afford the desired product **39** (402.0 mg, 1.43 mmol, 71% yield) as a yellow solid: mp 224 °C (recrystallized from EtOAc/heptane to give a pale yellow powder); IR ($CDCl_3$) ν_{max} 3431, 1696, 1609, 1526, 1491, 1347, 1260, 1070 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.54 (s, 1H), 8.12 (d, J = 8.7 Hz, 1H), 8.05 (d, J = 7.8 Hz, 2H), 7.76 (d, J = 8.7 Hz, 1H), 7.68−7.63 (m, 1H), 7.59−7.54 (m, 2H), 7.09 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.3, 152.4, 152.2, 144.0, 132.7, 132.4, 130.0, 128.5 (2C), 128.0 (2C), 118.4, 116.1, 110.8, 90.4; HRMS (ES^-) m/z calcd for $C_{15}H_9N_2O_4$ $[M - H]^-$ 281.0562, found 281.0563.

Benzyl Benzofuran-2-yl(4-methoxybenzoyl)carbamate 23b. Following the general procedure for *N*-acylation, to a solution of benzyl benzofuran-2-ylcarbamate of **20** (500 mg, 1.87 mmol) in anhydrous THF (20 mL) at 0 °C under argon was added sodium hydride 60% in mineral oil (135 mg, 5.62 mmol) by portions. After 15 min at 0 °C, 4-methoxybenzoyl chloride (0.76 mL, 5.62 mmol) was added dropwise. Stirring at reflux overnight was followed by workup. The crude product was purified by flash chromatography over silica gel (toluene) to afford the desired product **23b** (533 mg, 1.33 mmol, 71% yield) as a pale yellow solid: mp 128 °C (recrystallized from heptane to give off-white crystals); IR (CH_2Cl_2) ν_{max} 3067, 3037, 2968, 2939, 2843, 1748, 1706, 1605, 1512, 1454, 1421, 1381, 1328, 1312, 1275, 1252, 1170, 1045, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (dt, J = 8.7, 1.6 Hz, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 9.6 Hz, 1H), 7.33−7.26 (m, 4H), 7.26−7.20 (m, 3H), 6.84 (dt, J = 8.7, 1.8 Hz, 2H), 6.58 (s, 1H), 5.24 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 163.6, 153.2, 152.7, 146.5, 134.7, 131.7 (2C), 128.51 (2C), 128.46, 128.1 (2C), 127.9, 125.8, 124.9, 123.1, 121.4, 113.9 (2C), 111.4, 102.5, 69.1, 55.5; HRMS (ES^+) m/z calcd for $C_{24}H_{19}NO_5Na$ $[M + Na]^+$ 424.1161, found 424.1158.

Benzyl Benzofuran-2-yl(4-chlorobenzoyl)carbamate 23c. Following the general procedure for *N*-acylation, to a solution of benzyl benzofuran-2-ylcarbamate of **20** (250 mg, 0.94 mmol) in anhydrous THF (11 mL) at 0 °C under argon was added sodium hydride 60% in mineral oil (68 mg, 2.81 mmol) by portions. After 15 min at 0 °C, 4-chlorobenzoyl chloride (0.36 mL, 2.81 mmol) was added dropwise. Stirring at reflux overnight was followed by workup. The crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50 to 100:0) to afford the desired product **23c** (345 mg, 0.85 mmol, 90% yield) as a yellow solid: mp 118 °C (recrystallized from heptane to give pale yellow crystals); IR (CH_2Cl_2) ν_{max} 3416, 3068, 3037, 2964, 1753, 1713, 1613, 1593, 1522, 1488, 1454, 1402, 1380, 1329, 1252, 1162, 1092, 1046, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (dt, J = 8.6, 2.1 Hz, 2H), 7.53 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.35−7.29 (m, 6H), 7.26−7.16 (m, 3H), 6.60 (s, 1H), 5.21 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 152.8 (2C), 145.7, 139.3, 134.4, 132.3, 130.2 (2C), 128.8 (2C), 128.7, 128.6 (2C), 128.3 (2C), 127.7, 125.2, 123.3, 121.5, 111.4, 103.4, 69.4; HRMS (ES^+) m/z calcd for $C_{23}H_{17}NO_4Cl$ $[M + H]^+$ 406.0846, found 406.0857.

Benzyl Benzofuran-2-yl(4-fluorobenzoyl)carbamate 23e. Following the general procedure for *N*-acylation, to a solution of benzyl benzofuran-2-ylcarbamate **20** (500 mg, 1.87 mmol) in anhydrous THF (25 mL) at 0 °C under argon was added sodium hydride 60% in mineral oil (135 mg, 5.62 mmol) by portions. After 15 min at 0 °C, 4-fluorobenzoyl chloride (0.66 mL, 5.62 mmol) was added dropwise. Stirring at reflux overnight was followed by workup. The crude product was purified by flash chromatography over silica gel (toluene) to afford the desired product **23e** (602 mg, 1.54 mmol, 83% yield) as a yellow solid: mp 111 °C (recrystallized from heptane to give pale yellow crystals); IR (CH_2Cl_2) ν_{max} 3068, 3037, 2964, 1753, 1712, 1603, 1508, 1453, 1380, 1329, 1238, 1158, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (ddt, J = 8.9, 5.25, 2.1 Hz, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.38−7.29 (m, 4H), 7.26−7.18 (m, 3H), 7.02 (tt, J = 8.8, 2.1 Hz, 2H), 6.59 (s, 1H), 5.22 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 165.5 (d, J = 253.4 Hz), 152.9, 152.8, 145.9, 134.5, 131.6 (2C, d, J = 9.3 Hz), 130.0 (d, J = 3.2 Hz), 128.7, 128.6 (2C), 128.2 (2C), 127.8, 125.1, 123.3, 121.5, 115.8 (2C, d, J = 22.1 Hz), 111.4, 103.2, 69.3; HRMS (ES^+) m/z calcd for $C_{23}H_{16}NO_4FNa$ $[M + Na]^+$ 412.0961, found 412.0956.

Benzyl Benzofuran-2-yl(4-(trifluoromethyl)benzoyl)carbamate 23f. To a solution of 2-arylamidobenzofuran **17f** (250 mg, 0.82 mmol) in anhydrous THF (5 mL) at 0 °C under argon was added sodium hydride 60% in mineral oil (50 mg, 1.2 mmol). After 15 min at 0 °C benzylchloroformate (130 μL, 0.9 mmol) was added dropwise and the resulting mixture was stirred at room temperature during 6 h. The reaction was dropped on icy water. The aqueous layer was extracted three 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 (toluene/cyclohexane, 75:25) to afford the desired product **23f** (330 mg, 0.75 mmol, 92% yield) as a pale yellow solid: mp 127 °C (recrystallized from hexane to give white needles); IR (CH_2Cl_2) ν_{max} 3685, 3053, 1722, 1622, 1596, 1458, 1440, 1394, 1360, 1276, 1154, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.57−7.54 (m, 1H), 7.49−7.46 (m, 1H), 7.37−7.23 (m, 5H), 7.15 (dd, J = 5.6, 1.9 Hz, 2H), 6.64 (d, J = 0.8 Hz, 1H), 5.20 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 152.9, 152.7, 145.3, 137.5, 134.1, 134.0 (q, J = 33 Hz), 128.84 (2C), 128.80, 128.6 (2C), 128.3 (2C), 127.7, 125.5 (2C, q, J = 3.5 Hz), 125.3, 123.4, 123.4 (q, J = 271 Hz), 121.6, 111.5, 103.7, 69.6; HRMS (ES^+) m/z calcd for $C_{24}H_{16}NO_4F_3Na$ $[M + Na]^+$ 462.0929, found 462.0919.

***N*-(3-Bromobenzofuran-2-yl)benzamide 40a.** Following the general procedure for bromination, a mixture of 2-arylamidobenzofuran **17a** (440 mg, 1.86 mmol), PTSA (35 mg, 0.18 mmol), and NBS (397 mg, 2.23 mmol) was stirred in THF at −78 °C for 35 min. After workup, the residue was purified by flash chromatography over silica gel (toluene) to afford the desired product **40a** (467 mg, 1.48 mmol, 79% yield) as a pale yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.95−7.92 (m, 2H), 7.87 (brs, 1H), 7.64−7.59 (m, 1H), 7.54−7.45 (m, 4H), 7.35−7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 151.2, 143.9, 132.7, 132.6, 128.8 (2C), 127.75, 127.69 (2C), 125.3, 123.6, 119.5, 111.5, 90.0; MS (ES^+) m/z 316 $[M + H]^+$ (^{79}Br), 318 $[M + H]^+$ (^{81}Br).

***N*-(3-Bromobenzofuran-2-yl)-4-methoxybenzamide 40b.** Following the general procedure for bromination, a mixture of 2-arylamidobenzofuran **17b** (1.92 g, 7.19 mmol), PTSA (0.14 g, 0.72 mmol), and NBS (1.54 g, 8.63 mmol) was stirred in THF at −78 °C for 60 min. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 99:1) to afford the desired product **40b** (1.37 g, 3.96 mmol, 55% yield) as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.7 Hz, 2H), 7.78 (brs, 1H), 7.51−7.44 (m, 2H), 7.37−7.29 (m, 2H), 6.99 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H).

***N*-(3-Bromobenzofuran-2-yl)-4-chlorobenzamide 40c.** Following the general procedure for bromination, a mixture of 2-arylamidobenzofuran **17c** (1.23 g, 4.50 mmol), PTSA (86 mg, 0.45 mmol), and NBS (0.97 g, 5.45 mmol) was stirred in THF at −78 °C for 45 min. The residue was purified by flash chromatography over silica gel (toluene) to afford the desired product **40c** (1.25 g, 3.57 mmol, 79% yield) as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (brs, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.49−7.46 (m, 1H), 7.44−7.39 (m, 3H), 7.37−7.28 (m, 2H); MS (ES^-) m/z 348 $[M - H]^-$ (^{79}Br), 350 $[M - H]^-$ (^{81}Br).

***N*-(3-Bromobenzofuran-2-yl)-4-nitrobenzamide 40d.** Following the general procedure for bromination, a mixture of 2-arylamidobenzofuran **17d** (1.55 g, 5.50 mmol), PTSA (0.10 g, 0.55 mmol), and NBS (1.17 g, 6.60 mmol) was stirred in THF at −78 °C for 1 h. After workup, the residue was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 90:10) to afford the desired product **40d** (1.37 g, 3.79 mmol, 69% yield) as a bright yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 8.4 Hz, 2H), 7.92 (brs, 1H), 7.54−7.51 (m, 1H), 7.49−7.46 (m, 1H), 7.41 to 7.32 (m, 2H); MS (ES^+) m/z 359 $[M + H]^+$ (^{79}Br); 361 $[M + H]^+$ (^{81}Br).

***N*-(3-Bromobenzofuran-2-yl)-4-(trifluoromethyl)benzamide 40f.** Following the general procedure for bromination, a mixture of 2-arylamidobenzofuran **17f** (1.00 g, 3.28 mmol), PTSA (62 mg, 0.33 mmol), and NBS (700 mg, 3.93 mmol) was stirred in THF at −78 °C for 40 min. After workup, the crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 90/10) to afford the desired product **40f** (700 mg, 1.82 mmol, 55% yield) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.1 Hz, 2H), 7.90 (brs, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.53−7.50 (m, 1H), 7.49−7.46 (m, 1H), 7.40−7.31 (m, 2H); MS (ES^+) m/z 384 $[M + H]^+$ (^{79}Br), 386 $[M + H]^+$ (^{81}Br), (ES^-) m/z 382 $[M - H]^-$ (^{79}Br), 384 $[M - H]^-$ (^{81}Br).

***N*-(3-Bromo-5-methoxybenzofuran-2-yl)benzamide 41.** Following the general procedure for bromination, a mixture of 2-arylamidobenzofuran **18** (400 mg, 1.50 mmol), PTSA (28.5 mg, 0.15 mmol), and NBS (320 mg, 1.80 mmol) was stirred in THF at −78 °C for 20 min. After workup, the residue was purified by flash chromatography over silica gel (toluene/EtOAc 95:5 to 50:50) to afford the desired product **41** (207.5 mg, 0.60 mmol, 40% yield) as a pale brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 6.9 Hz, 2H), 7.86 (brs, 1H), 7.64−7.59 (m, 1H), 7.55−7.49 (m, 2H), 7.35 (d, J = 9.6 Hz, 1H), 6.95−6.91 (m, 2H), 3.88 (s, 3H); MS (ES^-) m/z 344 $[M - H]^-$ (^{79}Br), 346 $[M - H]^-$ (^{81}Br).

***N*-(3-Bromo-5-nitrobenzofuran-2-yl)benzamide 42.** Following the general procedure for bromination, a mixture of 2-arylamidobenzofuran **39** (282 mg, 1.00 mmol), PTSA (19 mg, 0.10 mmol), and NBS (214 mg, 1.20 mmol) was stirred in THF at −78 °C for 20 min. After workup, the residue was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 95:5) to afford the desired product **42** (293 mg, 0.81 mmol, 81% yield) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 2.4 Hz, 1H), 8.27 (dd, J = 2.4, 9.0 Hz, 1H), 8.02 (brs, 1H), 7.95 (d, J = 7.2 Hz, 2H), 7.68−7.52 (m, 4H); MS (ES^-) m/z 359 $[M - H]^-$ (^{79}Br), 361 $[M - H]^-$ (^{81}Br).

4-Methoxy-*N*-(3-phenylbenzofuran-2-yl)benzamide 15b. Following the general procedure for the Suzuki coupling (method A), a mixture of the brominated product **40b** (350 mg, 1.01 mmol), phenyl boronic acid (247 mg, 2.02 mmol), $PdCl_2$(dppf) (50 mg, 0.06 mmol), and sodium carbonate (430 mg, 4.05 mmol) was stirred in DME/H_2O (10 mL, 4:1) at 85 °C for 40 min. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 95:5) to afford the desired product **15b** (90 mg, 0.26 mmol, 26% yield) as a pale yellow solid: mp 165 °C (recrystallized from heptane to give white cotton); IR (CH_2Cl_2) ν_{max} 3687, 3412, 3063, 2940, 2842, 1693, 1607, 1456, 1253, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (brs, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.49 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 7.2 Hz, 2H), 7.36−7.25 (m, 3H), 6.90 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 163.0, 152.1, 142.5, 131.3, 129.6 (2C), 129.0 (2C), 128.4 (2C), 127.8, 127.5, 125.1, 124.6, 123.1, 120.0, 114.0 (2C), 112.7, 111.5, 55.5; HRMS (ES^+) m/z calcd for $C_{22}H_{18}NO_3$ $[M + H]^+$ 344.1287, found 344.1277.

4-Chloro-*N*-(3-phenylbenzofuran-2-yl)benzamide 15c. Following the general procedure for the Suzuki coupling (method A), a mixture of the brominated product **40c** (310 mg, 0.88 mmol), phenyl boronic acid (129 mg, 1.06 mmol), $PdCl_2$(dppf) (43.3 mg, 0.05 mmol), and sodium carbonate (235 mg, 2.21 mmol) was stirred in DME/H_2O (8.1 mL, 4:1) at 85 °C for 4 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene) to afford the desired product **15c** (41 mg, 0.12 mmol, 14% yield) as a pale yellow solid: mp 176 °C (recrystallized from heptane to give a white powder); IR (CH_2Cl_2) ν_{max} 3687, 3406, 2360, 1699, 1636, 1596, 1502, 1456, 1257, 1182, 1096, 1014 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (brs, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.68−7.65 (m, 1H), 7.57−7.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 152.1, 141.8, 138.9, 131.2, 131.1, 129.08 (2C), 129.05 (2C), 128.97 (2C), 128.3 (2C), 127.7, 127.6, 124.9, 123.3, 120.1, 113.1, 111.5; HRMS (ES^+) m/z calcd for $C_{21}H_{15}NO_2Cl$ $[M + H]^+$ 348.0791, found 348.0787.

***N*-(3-Phenylbenzofuran-2-yl)-4-(trifluoromethyl)benzamide 15f.** Following the general procedure for the Suzuki coupling (method A), a mixture of the brominated product **40f** (350 mg, 0.91 mmol), phenyl boronic acid (134 mg, 1.09 mmol), $PdCl_2$(dppf) (44.6 mg, 0.05 mmol), and sodium carbonate (242 mg, 2.28 mmol) was stirred in DME/H_2O (9.1 mL, 4:1) at 85 °C for 6 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50 to 100:0) to afford the desired product **15f** (22 mg, 0.058 mmol, 6% yield) as a pale yellow solid: mp 192 °C (recrystallized from heptane to give a white powder); IR ($CDCl_3$) ν_{max} 3693, 3415, 3065, 2257, 1701, 1467, 1454, 1326, 1177, 1138, 1067 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.90 (m, 3H), 7.71−7.66 (m, 3H), 7.56−7.43 (m, 5H), 7.39−7.27 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 152.1, 141.5, 136.1, 134.1 (q, J = 33.0 Hz), 131.0, 129.1 (2C), 128.3 (2C), 128.0 (2C), 127.8, 127.6, 125.8 (2C, q, J = 3.6 Hz), 125.0, 123.5 (q, J = 252.1 Hz), 123.4, 120.2, 113.4, 111.5; HRMS (ES^+) m/z calcd for $C_{22}H_{15}NO_2F_3$ $[M + H]^+$ 382.1055, found 382.1062.

***N*-(3-(4-Methoxyphenyl)benzofuran-2-yl)benzamide 15g.** Following the general procedure for the Suzuki coupling (method A), a mixture of the brominated product **40a** (210 mg, 0.67 mmol), 4-methoxyphenyl boronic acid (193 mg, 1.33 mmol), $PdCl_2$(dppf) (32.5 mg, 0.04 mmol), and sodium carbonate (282 mg, 2.66 mmol) was stirred in DME/H_2O (6.3 mL, 4:1) at 85 °C for 3 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50 to 100/0) to afford the desired product **15g** (75 mg, 0.22 mmol, 33% yield) as a pale yellow solid: mp 160 °C (recrystallized from heptane to give an off-white powder); IR (CH_2Cl_2) ν_{max} 3684, 3408, 3065, 3040, 2961, 2940, 1696, 1609, 1517, 1464, 1250, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (brs, 1H), 7.85 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 7.3 Hz, 1H), 7.56−7.46 (m, 6H), 7.34−7.25 (m, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.1, 152.0, 141.6, 133.0, 132.5, 129.6 (2C), 128.8 (2C), 128.0, 127.5 (2C), 124.7, 123.4,

123.1, 120.0, 114.5 (2C), 112.7, 111.5, 55.3; HRMS (ES^+) m/z calcd for $C_{22}H_{18}NO_3$ $[M + H]^+$ 344.1287, found 344.1285.

4-Methoxy-*N*-(3-(4-methoxyphenyl)benzofuran-2-yl)benzamide 15h. Following the general procedure for the Suzuki coupling (method A), a mixture of the brominated product **40b** (350 mg, 1.01 mmol), 4-methoxyphenyl boronic acid (205 mg, 1.34 mmol), $PdCl_2$-(dppf) (50 mg, 0.06 mmol), and sodium carbonate (430 mg, 4.05 mmol) in DME/H_2O (10 mL, 4:1) was stirred at 85 °C for 40 min. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 90:10) to afford the desired product **15h** (81 mg, 0.22 mmol, 22% yield) as a pale yellow solid: mp 175 °C (recrystallized from heptane to give a white-off powder); IR (CH_2Cl_2) ν_{max} 3686, 3411, 3010, 2939, 2841, 1691, 1607, 1516, 1456, 1251, 1175, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.8 Hz, 2H), 7.81 (s, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 7.3 Hz, 1H), 7.35−7.24 (m, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 163.0, 159.0, 152.0, 142.0, 129.6 (4C), 128.0, 125.2, 124.5, 123.5, 123.0, 120.0, 114.5 (2C), 114.0 (2C), 112.5, 111.4, 55.5, 55.3; HRMS (ES^+) m/z calcd for $C_{23}H_{19}NO_4Na$ $[M + Na]^+$ 396.1212, found 396.1231.

(*E*)-*N*-(3-Styrylbenzofuran-2-yl)-4-(trifluoromethyl)benzamide 15i. Following the general procedure for the Suzuki coupling (method A), a mixture of the brominated product **40f** (200.0 mg, 0.52 mmol), phenyl boronic acid (92.5 mg, 0.62 mmol), $PdCl_2$(dppf) (25.5 mg, 0.03 mmol), and sodium carbonate (138 mg, 1.3 mmol) was stirred in DME/H_2O (5.7 mL, 4:1) at 85 °C for 4.5 h. After workup, the residue was purified by flash chromatography over silica gel (toluene/cyclohexane 50:50 to 100:0) to afford the desired product **15i** (16.8 mg, 0.04 mmol, 8% yield) as an orange solid: mp 212 °C (recrystallized from heptane/EtOAc to give a yellow powder); IR ($CDCl_3$) ν_{max} 3410, 2959, 1702, 1455, 1326, 1178, 1139, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (brs, 1H), 8.03 (d, J = 7.9 Hz, 2H), 7.91−7.88 (m, 1H), 7.73 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.44−7.39 (m, 1H), 7.36−7.31 (m, 4H), 7.28−7.24 (m, 1H), 7.21 (d, J = 16.5 Hz, 1H), 7.08 (d, J = 16.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 152.1, 143.1, 137.4, 136.1, 134.0, 130.5, 128.7 (2C), 128.1 (2C), 127.8, 126.5, 126.3 (2C), 126.0 (2C, q, J = 3.5 Hz), 125.0, 123.5, 123.5 (q, J = 271 Hz), 121.0, 117.8, 111.4, 110.3; HRMS (ES^+) m/z calcd for $C_{24}H_{17}NO_2F_3$ $[M + H]^+$ 408.1211, found 408.1230.

***N*-(5-Methoxy-3-phenylbenzofuran-2-yl)benzamide 43.** Following the general procedure for the Suzuki coupling (method B), a mixture of the brominated product **41** (144 mg, 0.42 mmol), phenyl boronic acid (254 mg, 2.08 mmol), $Pd(PPh_3)_4$ (24 mg, 0.021 mmol), and CsF (696 mg, 4.58 mmol) was stirred in dioxane/H_2O (5.2 mL, 4:1) at 101 °C for 3.5 h. After workup, the crude product was purified by flash chromatography over silica gel (toluene/EtOAc 100:0 to 97:3) to afford the desired product **43** (47.5 mg, 0.14 mmol, 33% yield) as a pale yellow solid: mp 175 °C (recrystallized from heptane to give white crystals); IR ($CDCl_3$) ν_{max} 3418, 3065, 2957, 2836, 1694, 1601, 1502, 1476, 1259, 1229, 1189, 1156 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (brs, 1H), 7.85 (d, J = 7.8 Hz, 2H), 7.59−7.55 (m, 3H), 7.49−7.34 (m, 6H), 7.11 (d, J = 2.7 Hz, 1H), 6.94 (dd, J = 2.4, 9.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 156.2, 146.9, 142.8, 132.9, 132.5, 131.3, 129.0 (2C), 128.8 (2C), 128.3 (2C), 128.2, 127.54, 127.50 (2C), 113.2, 112.9, 112.0, 102.6, 55.9; HRMS (ES^+) m/z calcd for $C_{22}H_{17}NO_3Na$ $[M + Na]^+$ 366.1106, found 366.1117.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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