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Base-mediated intramolecular cyclization of (2-propargyl ether) arylimines: an approach to 3-amino-benzofurans

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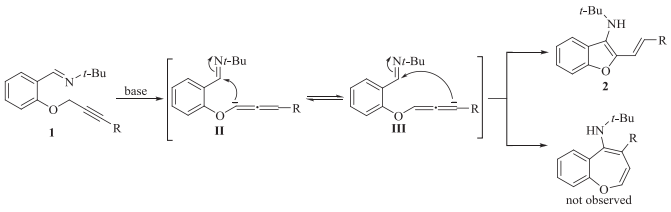
ABSTRACT

We present here a practical synthesis of functional 3-amino-benzofurans through base-promoted intramolecular cyclization of (2-propargyl ether) arylimines. A systematic study of the cyclization system revealed that the presence and the amount of base played an essential role in this reaction. The results showed that the cyclization proceeded cleanly and smoothly under mild reaction conditions, employing potassium *tert*-butoxide as base, THF as solvent, at room temperature in a short reaction time (1 h). The generality of this reaction has been established with (2-propargyl ether) arylimines having both electron-withdrawing and electron-donating groups.

1. Introduction

Propargyl ethers are versatile building blocks for a variety of important compounds, many of which are pharmaceutically significant.[1] They have also proven to be efficient starting materials to a wide range of interesting transformations, such as Claisen rearrangement,[2] transition-metal-catalyzed isomerization,[3] Csp^3–H bond activation[4] and propargylation reactions.[5] In addition, a number of synthetic protocols have been reported to date for the synthesis of carbocycles and heterocycles, which are based on the intramolecular cyclization of propargyl ethers.[6] In this regard, the transition-metal-catalyzed cyclization reactions represent a very attractive alternative since simple substrates can be transformed in more elaborated structures in a stepwise manner. Usually, transition-metals, such as Au,[7] Fe,[8] Pd,[9] In,[10] Ni,[11] and Pt[12] are used to promote these cyclization reactions. Nevertheless, new alternative strategies to intramolecular cyclization of propargyl ethers through simplified routes are always desired. In this context, the carbanionic cyclization method for both carbocycles and heterocycles formation has emerged as a powerful tool in organic synthesis.[13] It is known that propargyl ethers react with bases to give the corresponding carbanions. The generation of such carbanions could result in the intermediates allenyl anions **II** and **III** and with two carbons having nucleophilic character, which may undergo intramolecular cyclization (Scheme 1). Although, much attention has been paid to the synthesis of carbocycles and heterocycles applying carbanion intramolecular attack to an activated carbon–carbon bond from alkynes and alkenes,[14] the use of imines as electrophilic center in an intramolecular cyclization was unprecedented. Therefore, in this study we explored the behavior of imines, as electrophilic center, on the base-promoted cyclization reaction of (2-propargyl ether) arylimines **1** to the preparation of 3-amino-benzofuran derivatives **2** (Scheme 1).



Scheme 1.

2. Results and discussion

The (2-propargyl ether) arylimines **1** were prepared by reacting the corresponding salicylaldehyde with propargyl bromides in the presence of K_2CO_3 in acetonitrile at 80 °C for 4 h.[15] After that, to the introduction of *N*-*tert*-butylimine group, we reacted (2-propargyl ether) benzaldehyde with *tert*-butylamine (10 equiv), without

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solvent, at room temperature for 24 h.[16] (2-Propargyl ether) arylimines **1** were very sensitive to hydrolysis and were used without further purification. We prepared a number of (2-propargyl ether) arylimines **1** and the generality and scope of the reaction are summarized in the Supplementary data. To explore the optimal reaction condition to the base-promoted cyclization, we began our study with the reaction between substrate **1a** and *t*-BuOK (2.5 equiv) in DMF at room temperature (Table 1, entry 1). In this first condition, the starting material was completely consumed after 1 h and two products were observed in the TLC, as two spots, which have very close R_f. 3-Amino-benzofuran **2a** was isolated by flash chromatography, followed by crystallization in 50% yield. Its structure was determined by NMR spectroscopy and confirmed by X-ray diffraction analysis (Fig. 1).[17] The ^{1}H NMR showed two doublets, which resonate at 7.24 and 7.12 ppm, respectively, with a coupling constant of 16 Hz. The second compound was isolated in 5% yield by column chromatography as oil. This compound showed two doublets in 6.60 and 6.52 ppm with a coupling constant of 12 Hz, which indicates a cis-stereochemistry for vinylic hydrogens. Other NMR experiments and, in particular, the data extracted from the two dimensional experiments (HMQC) confirmed the assignment of the *Z* isomer. We next proceeded to examine the optimization of this cyclization in order to improve the reaction yield obtained in the first experiment (Table 1, entry 1). The influence of solvent in the cyclization of (2-propargyl ether) arylimine **1a** was then evaluated, and the results are shown in Table 1, entries 2–10. The best result was obtained by using THF, which gave the desired 3-amino-benzofuran **2a** in 81% yield in a mixture of *E* and *Z* isomers with a higher proportion of *E* isomers (Table 1, entry 10). The amount of base was also optimized; the cyclization was not be significantly improved by either increasing the *t*-BuOK amount to 3 equiv or decreasing until to the catalytic amount (Table 1, entries 11–15). However, when the reaction was carried out using 2 equiv of *t*-BuOK the desired 3-amino-benzofuran **2a** was obtained in 75% yield after purification by column chromatography, in the complete absence of *Z* isomer (Table 1, entry 12). We noticed that the use of other bases, such as K_2CO_3, NaH, KOH, Cs_2CO, and Et_3N demonstrated to be stagnant to this reaction (Table 1, entries 17–21). In the case of temperature study, the change from 0 °C to reflux did not improve the reaction results. At various interval times, during the optimization reactions, samples of the reaction mixture were analyzed by TLC, which showed that 1 h was the reaction time necessary to the complete consume of starting material. On the basis of the above investigation, the optimal conditions for this intramolecular cyclization reaction are the use of (2-propargyl ether) arylimine **1a** (0.25 mmol), *t*-BuOK (2 equiv), THF (3 mL) as solvent, at room temperature for 1 h.

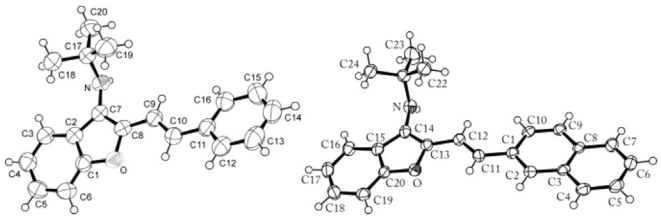
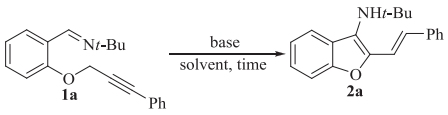


Fig. 1. ORTEP view of the 3-amino-benzofurans **2a** (right) and **2h** (left).

Table 1
Effect of reaction conditions on the cyclization of (2-propargyl ether) arylimine **1a**[a]



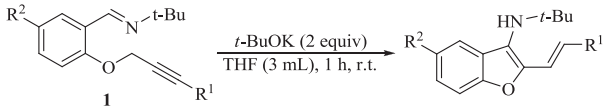
#	Base (equiv)	Solvent	Yield[b] (%)
1	*t*-BuOK (2.5)	DMF	50
2	*t*-BuOK (2.5)	DMSO	60 (10:1)[c]
3	*t*-BuOK (2.5)	Dioxane	0
4	*t*-BuOK(2.5)	*t*-BuOH	0
5	*t*-BuOK(2.5)	MeOH	0
6	*t*-BuOK (2.5)	H_2O	0
7	*t*-BuOK (2.5)	CH_2Cl_2	0
8	*t*-BuOK (2.5)	Hexane	0
9	*t*-BuOK (2.5)	Toluene	0
10	*t*-BuOK(2.5)	THF	81 (6.6:1)[c]
11	*t*-BuOK (3.0)	THF	85 (4:1)[c]
12	*t*-BuOK (2.0)	THF	75
13	*t*-BuOK (1.0)	THF	63
14	*t*-BuOK (0.5)	THF	69 (6.5:1)[c]
15	*t*-BuOK (0.2)	THF	59 (5.7:1)[c]
16	*t*-BuOK (2.0)	THF	73 (12:1)[c,d]
17	K_2CO_3 (2.0)	THF	0
18	NaH (2.0)	THF	0
19	KOH (2.0)	THF	0
20	Cs_2CO_3 (2.0)	THF	0
21	Et_3N (2.0)	THF	0

[a] The reaction was performed in the presence of **1a** (0.25 mmol), base, solvent (3 mL), under argon atmosphere for 1 h at room temperature.
[b] Yield of isolated compounds by column chromatography.
[c] *E*/*Z* ratio was determined by ^{1}H NMR spectra.
[d] The reaction was continued for 24 h.

In order to test the utility of the optimized reaction conditions, the reaction described in Table 1, entry 12, was applied in a somewhat more complex (2-propargyl ether) arylimines **1** (Table 2). At the beginning, we studied the effect of the substituent on the aryl bonded to alkyne. On the one hand, the reaction yields do not seem to be strongly influenced by the electronic effects of the substituents since different aryl groups bearing neutral, electron-withdrawing, and electron-donating groups in the aromatic rings were compatible with the reaction conditions and yielded the corresponding 3-amino-benzofurans in very similar yields (Table 2, entries 1–5). On the other hand, the results shown in Table 2 revealed that the stereoselectivity was influenced by the electronic effect of the substituent in the aromatic rings, where the strong electron-withdrawing, fluorine group, exerted significant negative effects (Table 2, entry 6). Furthermore, the heteroaryl thiophene, directly bonded to the alkyne, was also a suitable reactant in this cyclization conditions, giving 3-amino-benzofuran **2i** in 57% yield (Table 2, entry 7). The results in Table 2 showed that only moderated amount of product was obtained for the cyclization of (2-propargyl ether) arylimines having naphthyl group, where the steric hindrance may exert significant negative effects (Table 2, entry 8). We also examined the cyclization of starting materials having a substituent on the central aromatic ring. With substrates having both electron-withdrawing and electron-donating groups at this position, the cyclization proceeded in almost comparable yields, with the exception of the nitro group, that afforded 40% yield of an inseparable mixture of *E* and *Z* isomer (3.5:1) (Table 2, entries 9–16). Particularly interesting was the cyclization reaction of **1q**, which has a terminal alkyne instead of an aromatic group, that proceeded smoothly, giving the corresponding 3-amino-benzofuran **2q** with a terminal olefin moiety intact. One limitation of our methodology was that extending the optimized conditions to (2-propargyl ether) arylimine **1r**, having an alkyl group directly bonded to alkyne, the reaction did not afford the expected product **2r** (Table 2, entry 18).

Based on these results, we propose the reaction mechanism for potassium *tert*-butoxide cyclization of (2-propargyl ether) arylimines as illustrated in Scheme 2. The formation of *Z*-benzofuran derivatives **2** could involve the abstraction of proton from **1** by *t*-BuOK generating the progargyl carbanion **I** in equilibrium with the allenes intermediated **II** and **III**.[18] Deprotonation of the carbon atom α to the nitrogen, followed by the aromatization of cyclic

Table 2
Synthesis of 3-amino-benzofuran derivatives **2**[a]



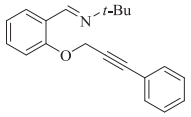
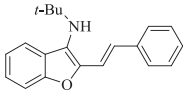
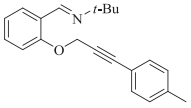
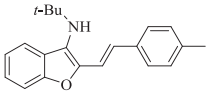
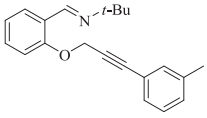
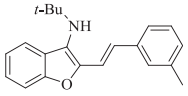
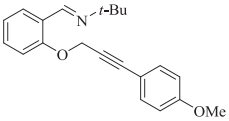
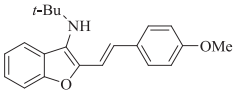
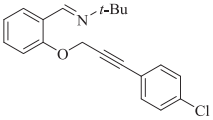
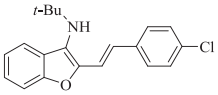
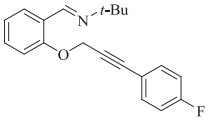
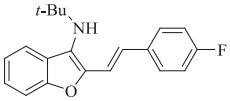
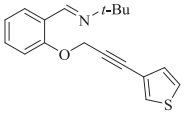
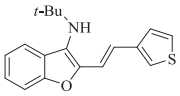
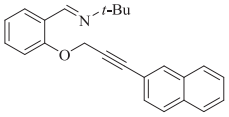
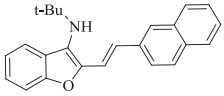
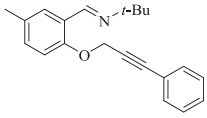
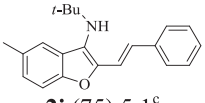
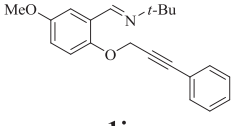
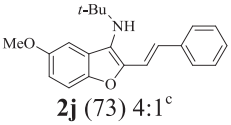
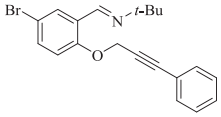
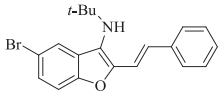
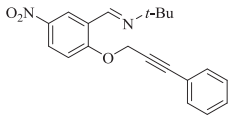
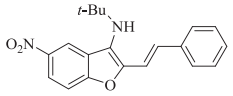
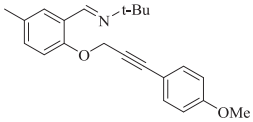
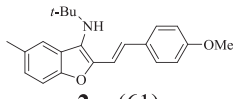
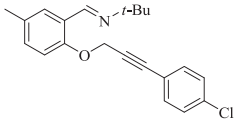
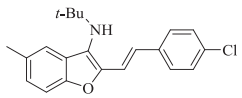
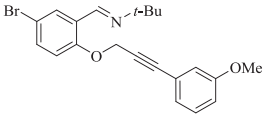
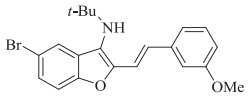
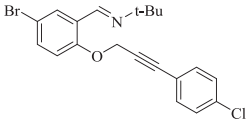
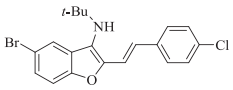
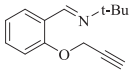
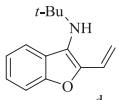
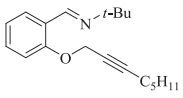
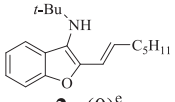
#	Substrate **1**	Product **2** yield[b] (%)
1	 **1a**	 **2a** (75)
2	 **1b**	 **2b** (62)
3	 **1c**	 **2c** (63)
4	 **1d**	 **2d** (67)
5	 **1e**	 **2e** (60)
6	 **1f**	 **2f** (72) 2:1[c]
7	 **1g**	 **2g** (57)
8	 **1h**	 **2h** (60)
9	 **1i**	 **2i** (75) 5:1[c]
10	 **1j**	 **2j** (73) 4:1[c]

Table 2 (*continued*)

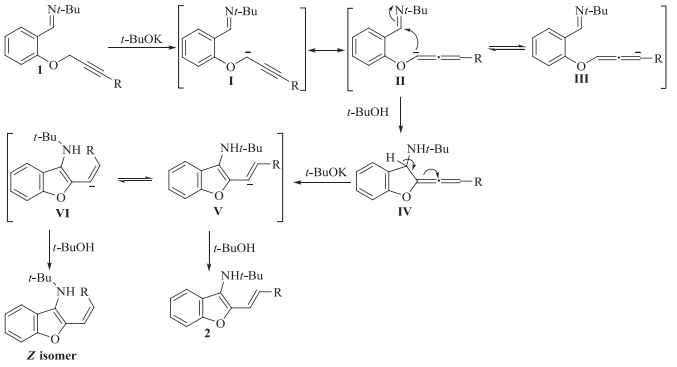
#	Substrate **1**	Product **2** yield[b] (%)
11	 **1k**	 **2k** (74) 5:1[c]
12	 **1l**	 **2l** (40) 3.4:1[c]
13	 **1m**	 **2m** (61)
14	 **1n**	 **2n** (77) 3:1[c]
15	 **1o**	 **2o** (62) 15:1[c]
16	 **1p**	 **2p** (85) 3.6:1[c]
17	 **1q**	 **2q** (84)[d]
18	 **1r**	 **2r** (0)[e]

[a] The reaction was performed in the presence of (2-propargyl ether) arylimines **1** (0.25 mmol), *t*-BuOK (2.0 equiv) in THF (3 mL), under argon atmosphere for 1 h at room temperature.
[b] Isolated yields after column chromatography.
[c] *E*/*Z* ratio was determined by ^{1}H NMR spectra.
[d] The reaction was carried out at the reflux temperature.
[e] No product was obtained.

adduct leads to vinyl carbanion **V**, which affords benzofuran derivatives **2**. Since isomerization of *E* to *Z* isomers can potentially occur through vinyl anions,[19] we assume that the trace amount obtained for the *Z* isomers may be formed via isomerization of vinylic carbanion **V** (Scheme 2).

3. Conclusion

In conclusion, we found that *t*-BuOK is a valuable cyclization promoter of (2-propargyl ether) arylimines to prepare 3-amino-



Scheme 2.

benzofurans. The main advantages of this methodology are based on the easy assembly of the starting materials from readily available precursors, the incorporation of two different useful functionalities in the structure and the mild reaction conditions. Another improvement of this protocol is the high regioselectivity regarding to a possible nucleophilic competition between the five and seven heterocycle formation. We believe that this approach to 3-amino-benzofurans should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting alkene and amine functionalities into other substituents.

4. Experimental section

4.1. General

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 200 MHz or at 400 MHz spectrometer. Spectra were recorded in $CDCl_3$ solutions. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained either at 50 MHz or at 100 MHz spectrometer. Spectra were recorded in $CDCl_3$ solutions. Mass spectra were recorded on a spectrometer using EI at 70 eV. High resolution mass spectra were recorded on an LC–MS-IT-TOF. Column chromatography was performed using Silica Gel (230–400 mesh). Thin layer chromatography (TLC) was performed using Silica Gel GF_{254}, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. Most reactions were monitored by TLC for disappearance of starting material.

4.2. General procedure for the synthesis of 3-amino-benzofurans 2

To a solution of (2-propargyl ether) arylimines **1** (0.5 mmol) in dry THF (3 mL) was added *t*-BuOK (2.0 equiv). The resulting solution was stirred at room temperature under an argon atmosphere until complete consumption of the starting material (1 h). The progress of the reaction was monitored by TLC. The residue was dissolved in ethyl acetate, and the solution was washed with saturated NH_4Cl, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography over silica gel to provide benzofurans **2**. Column chromatography was carried out using hexane/ethyl acetate (8:2) as eluent.

*4.2.1. (E)-N-tert-Butyl-2-styrylbenzofuran-3-amine (**2a**).* Isolated as a yellow solid. Yield: 0.109 g (75%), mp: 80–83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56–7.47 (m, 3H), 7.43–7.31 (m, 3H), 7.30–7.15 (m, 4H), 7.12 (d, J=16.1 Hz, 1H), 2.49 (sl, 1H), 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 149.3, 137.3, 129.2, 128.7, 128.2, 127.7, 126.5, 124.7, 124.6, 122.4, 119.7, 114.7, 111.0, 54.5, 30.6. MS (relative intensity) m/z: 291 (58), 235 (100), 206 (31), 178 (17), 120 (48), 102 (35), 77 (25), 57 (24). HRMS calcd for $C_{20}H_{21}NNaO$: 314.1521. Found: 314.1525.

*4.2.2. (E)-N-tert-Butyl-2-(4-methylstyryl)benzofuran-3-amine (**2b**).* Isolated as a yellow oil. Yield: 0.093 g (62%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, J=7.6 Hz, 1H), 7.43–7.34 (m, 3H), 7.25–7.10 (m, 5H), 7.06 (d, J=16.1 Hz, 1H), 2.58 (sl, 1H), 2.32 (s, 3H), 1.24 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6, 149.5, 137.6, 134.5, 129.4, 129.3, 128.2, 126.5, 124.5, 124.2, 122.3, 119.6, 113.7, 110.9, 54.4, 30.6, 21.2. MS (relative intensity) m/z: 305 (73), 249 (100), 233 (17), 220 (26), 178 (12), 130 (24), 120 (27), 57 (18). HRMS calcd for $C_{21}H_{24}NO$: 306.1858. Found: 306.1861.

*4.2.3. (E)-N-tert-Butyl-2-(3-methylstyryl)benzofuran-3-amine (**2c**).* Isolated as a yellow oil. Yield: 0.096 g (63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, J=7.6 Hz, 1H), 7.39 (d, J=8.0 Hz, 1H), 7.36–7.30 (m, 2H), 7.28–7.15 (m, 4H), 7.10 (d, J=16.1 Hz, 1H), 7.06 (d, J=7.3 Hz, 1H), 2.60 (sl, 1H), 2.36 (s, 3H), 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 149.4, 138.2, 137.2, 129.3, 128.6, 128.5, 128.3, 127.3, 124.6, 124.5, 123.7, 122.3, 119.6, 114.4, 111.0, 54.4, 30.6, 21.3. MS (relative intensity) m/z: 305 (76), 249 (100), 233 (18), 220 (20), 130 (29), 120 (32), 57 (18). HRMS calcd for $C_{21}H_{24}NO$: 306.1858. Found: 306.1865.

*4.2.4. (E)-N-tert-Butyl-2-(4-methoxystyryl)benzofuran-3-amine (**2d**).* Isolated as a yellow oil. Yield: 0.107 g (67%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52–7.43 (m, 3H), 7.39 (d, J=7.9 Hz, 1H), 7.27–7.14 (m, 3H), 6.98 (d, J=16.1 Hz, 1H), 6.89 (d, J=8.8 Hz, 2H), 3.80 (s, 3H), 2.40 (sl, 1H), 1.25 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 153.5, 149.6, 130.0, 129.3, 127.8, 127.7, 124.3, 123.6, 122.3, 119.5, 114.2, 112.6, 110.8, 55.3, 54.5, 30.5. MS (relative intensity) m/z: 321 (88), 265 (100), 250 (43), 221 (17), 165 (12), 146 (11), 57 (10). HRMS calcd for $C_{21}H_{24}NO_2$: 322.1807. Found: 322.1811.

*4.2.5. (E)-N-tert-Butyl-2-(4-chlorostyryl)benzofuran-3-amine (**2e**).* Isolated as a yellow oil. Yield: 0.097 g (60%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.49 (d, J=7.6 Hz, 1H), 7.45–7.37 (m, 3H), 7.30 (d, J=8.3 Hz, 2H), 7.28–7.21 (m, 1H), 7.20–7.12 (m, 2H), 7.07 (d, J=15.9 Hz, 1H), 2.62 (sl, 1H), 1.25 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6, 148.9, 135.7, 133.2, 129.1, 128.9, 127.6, 126.6, 124.8, 122.4, 119.7, 115.1, 111.0, 54.5, 30.6. MS (relative intensity) m/z: 325 (51), 269 (100), 233 (31), 204 (14), 178 (10), 120 (55), 57 (17). HRMS calcd for $C_{20}H_{21}ClNO$: 326.1312. Found: 326.1317.

*4.2.6. (E)-N-tert-Butyl-2-(4-fluorostyryl)benzofuran-3-amine (**2f**).* Isolated as a yellow oil. Yield: 0.111 g (72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53–7.34 (m, 5.5H), 7.28–7.11 (m, 4.7H), 7.07–6.92 (m, 4.2H), 6.53 (d, J=12.7 Hz, 0.5H, *Z* isomer), 6.49 (d, J=12.5 Hz, 0.5H, *Z* isomer), 2.54 (sl, 1H), 1.26 (s, 9H), 1.21 (s, 4.5H, *Z* isomer). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4 (d, J=248.0 Hz), 162.1 (d, J=247.0 Hz, *Z* isomer), 153.6, 153.3, 149.1, 147.4, 133.4 (d, J=3.0 Hz), 133.3 (d, J=3.0 Hz), 130.8 (d, J=8.0 Hz, *Z* isomer), 129.2, 128.3, 128.1, 128.0 (d, J=8.0 Hz), 126.9, 126.1, 124.8, 124.7, 124.5, 124.4, 122.3, 119.9, 119.6, 115.7 (d, J=21.1 Hz), 115.6 (d, J=1.5 Hz, *Z* isomer), 114.8 (d, J=22.0 Hz, *Z* isomer), 114.4 (d, J=2.2 Hz), 111.2 (*Z* isomer), 111.0, 54.7, 54.5, 30.6, 30.5 (*Z* isomer). MS (relative intensity) m/z: 309 (51), 253 (100), 224 (24), 120 (38), 57 (13). HRMS calcd for $C_{20}H_{20}FNNaO$: 332.1427. Found: 332.1430.

*4.2.7. (E)-N-tert-Butyl-2-(2-(thiophen-3-yl)vinyl)benzofuran-3-amine (**2g**).* Isolated as a yellow solid. Yield: 0.084 g (57%), mp: 103–105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, J=7.6 Hz, 1H), 7.38 (d, J=7.9 Hz, 1H), 7.36–7.14 (m, 6H), 6.95 (d, J=16.0 Hz, 1H), 2.45 (sl, 1H), 1.25 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6, 149.1, 140.0, 129.3, 126.2, 124.8, 124.5, 124.2, 122.7, 122.4, 122.3, 119.5, 114.7,

110.9, 54.5, 30.6. MS (relative intensity) *m*/*z*: 297 (97), 241 (65), 226 (100), 208 (50), 152 (13), 120 (21), 77 (15), 57 (17). HRMS calcd for $C_{18}H_{20}NOS$: 298.1266. Found: 298.1274.

*4.2.8. (E)-N-tert-Butyl-2-(2-(naphthalen-2-yl)vinyl)benzofuran-3-amine (**2h**).* Isolated as a yellow solid. Yield: 0.102 g (60%), mp: 113–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (s, 1H), 7.81–7.68 (m, 4H), 7.53–7.35 (m, 5H), 7.27–7.14 (m, 3H), 2.60 (sl, 1H), 1.27 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 149.3, 134.7, 133.7, 133.1, 129.2, 128.3, 128.2, 128.0, 127.7, 126.8, 126.3, 126.0, 124.7, 123.3, 122.4, 119.7, 114.8, 111.0, 54.5, 30.6. MS (relative intensity) *m*/*z*: 341 (75), 285 (73), 256 (20), 166 (100), 120 (36), 57 (16). HRMS calcd for $C_{24}H_{24}NO$: 342.1858. Found: 342.1862.

*4.2.9. (E)-N-tert-Butyl-5-methyl-2-styrylbenzofuran-3-amine (**2i**).* Isolated as a yellow solid. Yield: 0.114 g (75%), mp: 89–111 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, *J*=7.0 Hz, 2H), 7.45 (d, *J*=7.3 Hz, 0.4H, *Z* isomer), 7.41–7.17 (m, 6.2H), 7.16–6.98 (m, 2H), 6.57 (d, *J*=12.6 Hz, 0.1H, *Z* isomer), 6.50 (d, *J*=12.6 Hz, 0.1H, *Z* isomer), 2.61–2.24 (m, 4.6H), 1.26 (s, 9H), 1.19 (s, 1.7H, *Z* isomer). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1, 151.8 (*Z* isomer), 149.4, 137.3, 131.8, 129.3, 128.9, 128.7, 128.5 (*Z* isomer), 128.3 (*Z* isomer), 128.0, 127.8, 127.6, 127.4, 126.5, 126.0, 125.9, 125.7 (*Z* isomer), 124.4 (*Z* isomer), 119.7 (*Z* isomer), 119.4, 116.1 (*Z* isomer), 114.7, 110.7 (*Z* isomer), 110.5, 54.6 (*Z* isomer), 54.5, 30.6, 30.4 (*Z* isomer), 21.4 (2C). MS (relative intensity) *m*/*z*: 305 (68), 249 (100), 220 (17), 178 (10), 134 (35), 116 (18), 57 (16). HRMS calcd for $C_{21}H_{23}NNaO$: 328.1677. Found: 328.1681.

*4.2.10. (E)-N-tert-Butyl-5-methoxy-2-styrylbenzofuran-3-amine (**2j**).* Isolated as a yellow solid. Yield: 0.117 g (73%), mp: 115.3–118.7 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, *J*=7.6 Hz, 2H), 7.45 (d, *J*=7.3 Hz, 0.5H, *Z* isomer), 7.39–7.18 (m, 5.3H), 7.15 (d, *J*=8.8 Hz, 0.2H, *Z* isomer), 7.09 (d, *J*=16.1 Hz, 1H), 6.99–6.93 (m, 1.1H), 6.89–6.80 (m, 1H), 6.59 (d, *J*=12.6 Hz, 0.1H, *Z* isomer), 6.49 (d, *J*=12.6 Hz, 0.1H, *Z* isomer), 3.83 (s, 3H), 3.81 (s, 0.7H, *Z* isomer), 2.50 (sl, 1H), 1.26 (s, 9H), 1.18 (s, 2.5H, *Z* isomer). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 155.7 (*Z* isomer), 150.2, 148.6, 148.5 (*Z* isomer), 148.4 (*Z* isomer), 137.3 (*Z* isomer), 137.2, 129.7, 129.5, 129.0, 128.9, 128.7, 128.1, 127.7, 127.5, 126.5, 125.9, 124.7, 116.1 (*Z* isomer), 114.6, 113.4 (*Z* isomer), 113.1, 111.6 (*Z* isomer), 111.4, 102.6 (*Z* isomer), 102.5, 55.9 (2C), 54.8 (*Z* isomer), 54.6, 30.6, 30.4 (*Z* isomer). MS (relative intensity) *m*/*z*: 321 (77), 265 (100), 221 (16), 167 (15), 150 (34), 116 (16), 57 (20). HRMS calcd for $C_{21}H_{23}NNaO_2$: 344.1626. Found: 344.1630.

*4.2.11. (E)-5-Bromo-N-tert-butyl-2-styrylbenzofuran-3-amine (**2k**).* Isolated as a yellow solid. Yield: 0.137 g (74%), mp: 61.3–64.7 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.56 (m, 1.2H), 7.50 (d, *J*=7.3 Hz, 2H), 7.45–7.16 (m, 6.6H), 7.07 (d, *J*=16.1 Hz, 1H), 6.63 (d, *J*=12.6 Hz, 0.1H, *Z* isomer), 6.48 (d, *J*=12.6 Hz, 0.1H, *Z* isomer), 2.45 (sl, 1H), 1.24 (s, 9H), 1.16 (s, 2H, *Z* isomer). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3, 152.0 (*Z* isomer), 150.6, 148.9 (*Z* isomer), 137.0 (*Z* isomer), 136.9, 131.3, 130.6, 130.5 (*Z* isomer), 129.1, 128.9, 128.7, 128.1, 127.9, 127.7, 127.3, 126.6, 125.0 (*Z* isomer), 123.7, 122.6 (*Z* isomer), 122.3, 115.6, 115.5 (*Z* isomer), 114.1, 112.7 (*Z* isomer), 112.4, 54.7 (*Z* isomer), 54.5, 30.5, 30.4 (*Z* isomer). MS (relative intensity) *m*/*z*: 371 (51), 313 (100), 233 (29), 204 (30), 178 (13), 116 (44), 57 (45). HRMS calcd for $C_{20}H_{20}BrNNaO$: 392.0626. Found: 392.0630.

*4.2.12. (E)-N-tert-Butyl-5-nitro-2-styrylbenzofuran-3-amine (**2l**).* Isolated as an orange solid. Yield: 0.067 g (40%), mp: 105–126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44 (d, *J*=2.4 Hz, 0.3H, *Z* isomer), 8.42 (d, *J*=2.2 Hz, 1H), 8.18 (dd, *J*=8.8 Hz, *J*=2.2 Hz, 1H), 8.13 (dd, *J*=8.8 Hz, *J*=2.2 Hz, 0.3H, *Z* isomer), 7.54 (d, *J*=7.3 Hz, 2H), 7.47 (d, *J*=8.8 Hz, 1H), 7.43–7.27 (m, 6.1H), 7.10 (d, *J*=16.4 Hz, 1H),6.74 (d, *J*=12.5 Hz, 0.3H, *Z* isomer), 6.52 (d, *J*=12.5 Hz, 0.3H, *Z* isomer), 2.50 (sl, 1H), 1.29 (s, 9H), 1.19 (s, 2.7H, *Z* isomer). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.3, 156.1 (*Z* isomer), 152.3, 150.6 (*Z* isomer), 144.1, 143.9 (*Z* isomer), 136.9 (*Z* isomer), 136.5, 132.0, 130.4, 129.9, 129.1 (*Z* isomer), 128.8, 128.7, 128.4, 128.2, 128.0 (*Z* isomer), 126.8, 126.6 (*Z* isomer), 124.5, 120.3, 120.2 (*Z* isomer), 116.6 (*Z* isomer), 116.0, 115.2 (*Z* isomer), 113.5, 111.5 (*Z* isomer), 111.2, 54.8 (*Z* isomer), 54.7, 30.5, 30.4 (*Z* isomer). MS (relative intensity) *m*/*z*: 336 (40), 280 (100), 234 (23), 204 (22), 165 (15), 116 (26), 57 (40). HRMS calcd for $C_{20}H_{21}N_2O_3$: 337.1552. Found: 337.1560.

*4.2.13. (E)-N-tert-Butyl-2-(4-methoxystyryl)-5-methylbenzofuran-3-amine (**2m**).* Isolated as a yellow solid. Yield: 0.107 g (64%), mp: 137–139 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (d, *J*=8.7 Hz, 2H), 7.30–7.22 (m, 2H), 7.16 (d, *J*=16.1 Hz, 1H), 7.02 (d, *J*=8.5 Hz, 1H), 6.96 (d, *J*=16.1 Hz, 1H), 6.88 (d, *J*=8.7 Hz, 2H), 3.79 (s, 3H), 2.42 (s, 4H), 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 152.0, 149.8, 131.7, 130.2, 129.5, 127.7, 127.6, 125.6, 123.6, 119.3, 114.3, 112.9, 110.4, 55.3, 54.4, 30.6, 21.3. MS (relative intensity) *m*/*z*: 335 (93), 278 (100), 264 (40), 250 (24), 207 (11), 146 (9), 57 (17). HRMS calcd for $C_{22}H_{25}NNaO_2$: 358.1783. Found: 358.1790.

*4.2.14. (E)-N-tert-Butyl-2-(4-chlorostyryl)-5-methylbenzofuran-3-amine (**2n**).* Isolated as a yellow solid. Yield: 0.130 g (77%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.37 (m, 2.8H), 7.31–7.24 (m, 5.0H), 7.17–7.00 (m, 3.8H), 6.51 (d, *J*=12.7 Hz, 0.3H, *Z* isomer), 6.47 (d, *J*=12.5 Hz, 0.3H, *Z* isomer), 4.70 (sl, 0.2H, *Z* isomer), 2.45–2.40 (m, 3.8H), 2.20 (sl, 1H), 1.25 (s, 9H), 1.21 (s, 2.7H, *Z* isomer). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1, 151.8 (*Z* isomer), 149.1, 147.5 (*Z* isomer), 135.8, 135.7 (*Z* isomer), 133.1, 133.0 (*Z* isomer), 131.8 (2C), 130.4, 129.1, 128.8, 128.2, 128.0, 127.6, 127.4, 126.4, 126.2 (2C), 126.1, 124.8, 119.6 (*Z* isomer), 119.4, 116.2 (*Z* isomer), 115.2, 110.8 (*Z* isomer), 110.5, 54.7 (*Z* isomer), 54.5, 30.6, 30.5 (*Z* isomer), 21.3 (2C). MS (relative intensity) *m*/*z*: 339 (47), 283 (100), 247 (29), 207 (12), 134 (60), 115 (19), 57 (33). HRMS calcd for $C_{21}H_{23}ClNO$: 340.1468. Found: 340.1475.

*4.2.15. (E)-5-Bromo-N-tert-butyl-2-(3-methoxystyryl)benzofuran-3-amine (**2o**).* Isolated as a yellow solid. Yield: 0.124 g (62%), mp: 106–112 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, *J*=1.9 Hz, 0.1H, *Z* isomer), 7.59 (d, *J*=1.7 Hz, 1H), 7.31 (dd, *J*=1.9 Hz, *J*=8.6 Hz, 1H), 7.29–7.16 (m, 3H), 7.11 (d, *J*=7.6 Hz, 1H), 7.08–6.97 (m, 2.1H), 6.81 (dd, *J*=1.9 Hz, *J*=8.3 Hz, 1H), 6.59 (d, *J*=12.5 Hz, 0.1H, *Z* isomer), 6.47 (d, *J*=12.5 Hz, 0.1H, *Z* isomer), 3.81 (s, 3H), 3.73 (s, 0.2H, *Z* isomer), 2.48 (sl, 1H), 1.23 (s, 9H), 1.16 (s, 0.6H, *Z* isomer). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 159.3 (*Z* isomer), 152.3, 150.4, 148.8 (*Z* isomer), 138.3, 131.3, 130.4 (*Z* isomer), 129.7, 129.0 (*Z* isomer), 128.9, 127.4 (*Z* isomer), 127.3, 125.2 (*Z* isomer), 123.8, 122.6 (*Z* isomer), 122.2, 121.6 (*Z* isomer), 119.3, 115.7 (*Z* isomer), 115.6, 115.5 (*Z* isomer), 114.4, 113.9 (*Z* isomer), 113.8 (*Z* isomer), 113.4, 112.6 (*Z* isomer), 112.4, 112.1, 55.1 (2C), 54.6 (*Z* isomer), 54.5, 30.5, 30.3 (*Z* isomer). MS (relative intensity) *m*/*z*: 401 (48), 343 (64), 263 (14), 198 (13), 146 (100), 131 (32), 57 (27). HRMS calcd for $C_{21}H_{23}BrNO_2$: 400.0912. Found: 400.0913.

*4.2.16. (E)-5-Bromo-N-tert-butyl-2-(4-chlorostyryl)benzofuran-3-amine (**2p**).* Isolated as a yellow solid. Yield: 0.171 g (85%), mp: 149–162 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63–7.54 (m, 1.2H), 7.44–7.19 (m, 7.2H), 7.14 (d, *J*=16.1 Hz, 1H), 7.09 (d, *J*=8.7 Hz, 0.2H, *Z* isomer), 7.02 (d, *J*=16.1 Hz, 1H), 6.53 (d, *J*=12.6 Hz, 0.1H, *Z* isomer), 6.47 (d, *J*=12.6 Hz, 0.1H, *Z* isomer), 2.48 (sl, 1H), 1.23 (s, 9H), 1.19 (s, 2.5H, *Z* isomer). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3, 152.0 (*Z* isomer), 150.3, 148.7 (*Z* isomer), 135.5 (*Z* isomer), 135.4, 133.5, 133.3 (*Z* isomer), 131.2, 130.3, 130.2 (*Z* isomer), 128.9, 128.7 (*Z* isomer), 128.0, 127.7, 127.6, 127.5, 125.6 (*Z* isomer), 124.1 (*Z* isomer), 122.5 (*Z* isomer), 122.3, 115.7, 114.6, 112.7 (*Z* isomer), 112.4, 54.7 (*Z* isomer), 54.5, 30.5, 30.4 (*Z* isomer). MS (relative intensity) *m*/*z*: 405 (42), 349

(100), 311 (11), 198 (23), 150 (11), 115 (16), 57 (38). HRMS calcd for $C_{20}H_{20}BrClNO$: 404.0417. Found: 404.0420.

*4.2.17. N-tert-Butyl-2-vinylbenzofuran-3-amine (**2q**).* Isolated as brown oil. Yield: 0.09 g (84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, J=7.6 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.23 (t, J=7.3 Hz, 1H), 7.16 (t, J=7.6 Hz, 1H), 6.75 (dd, J=17.3 Hz, J=11.2 Hz, 1H), 5.87 (dd, J=17.4 Hz, J=1.5 Hz, 1H), 5.29 (dd, J=11.2 Hz, J=1.5 Hz, 1H), 1.46 (sl, 1H), 1.22 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.5, 148.7, 129.0, 124.6, 124.0, 123.2, 122.3, 119.9, 113.4, 111.1, 54.4, 30.5. MS (relative intensity) m/z: 215 (29), 200 (5), 159 (100), 130 (57), 115 (4), 103 (8), 57 (8). HRMS calcd for $C_{14}H_{17}NNaO$: 238.1208. Found: 238.1212.

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Supplementary data

Experimental procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra for the products. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.04.053.

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