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Concise Synthesis of α-Substituted 2-Benzofuranmethamines and Other 2-Subsituted Benzofurans via α-Substituted 2-Benzofuranmethyl Carbocation Intermediates

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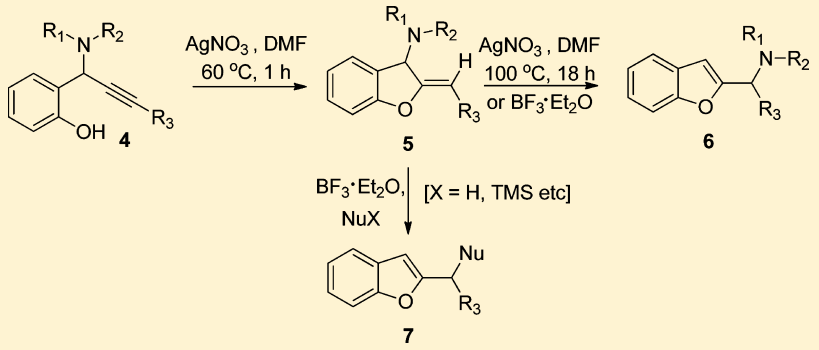
Supporting Information



ABSTRACT: Propargyl amines **4**, where R^3 is aryl, undergo 5-*exo-dig* cyclization reactions under relatively mild conditions ($AgNO_3$, DMF, 60 °C, 1 h) to give 3-amino-2,3-dihydro-2-arylmethylidenebenzofurans **5** (R^3 = aryl). In contrast, substrates where R^3 is alkyl undergo competing 6-*endo-dig* and 5-*exo-dig* cyclization processes. The hydroxymethyl substrate **4** (R^3 = CH_2OH), however, was smoothly converted to its corresponding 5-*exo-dig* cyclization product **5**, likely due to the assistance of the primary hydroxyl group in the 5-*exo-dig* cyclization process by silver cation coordination. Under more enforcing conditions ($AgNO_3$, DMF, 100 °C, 18 h), the initially formed products **5** undergo a 1,3-allylic rearrangement to their corresponding 2-substituted benzofuran derivatives **6**. This rearrangement can also be effected by treating **5** with $AgNO_3$ in DMF at 100 °C for 18 h or $BF_3{\cdot}Et_2O$ at rt. 2-(3-Butenyl)benzofurans **7** (Nu = allyl) can be prepared by treatment of **5** with $BF_3{\cdot}Et_2O$ and allyltributylstannane. Furan and MeOH could also be employed as external nucleophiles in these $BF_3{\cdot}Et_2O$-promoted reactions.

INTRODUCTION

α-Aryl-2-benzofuranmethamines have valuable medicinal chemistry properties. For example, compounds of the general structure **1** have been reported to be s-1 receptor ligands,[1] have analgesic[2] and Ca^{2+} antagonist[3] properties, and applications in the treatment of arrhythmic, histaminic, and tussive conditions (Figure 1).[4] These compounds have been prepared from the corresponding carbinols **2** via amine substitution reactions of the corresponding chlorides **3**.[4] The prerequisite carbinols **2** are generally prepared from 2-lithiobenzofuran and an arylaldehyde (Figure 1).[4] More recently, the Petasis, boronic acid Mannich reaction has been used to prepare a single α-aryl-2-benzofuranmethamine, 4-(2-benzofuranylphenylmethyl)-morpholine (**1**, where NR^1R^2 = morpholino and Ar = 2-hydroxyphenyl), in yields varying from 23[5] to 95%.[6] This reaction, however, will be limited to the preparation of 2-hydroxyaryl derivatives. We report here a new method for preparing α-aryl (or α-alkyl)-2-benzofuranmethamines **6** via a novel Lewis-acid-catalyzed 1,3-allylic rearrangement of 3-amino-2,3-dihydro-2-arylmethylidenebenzofurans **5** (Scheme

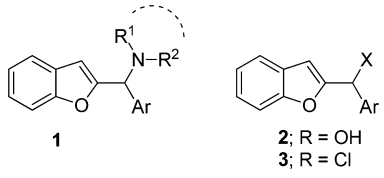


Figure 1. α-Aryl-2-benzofuranmethamines (**1**) and their synthetic precursors **2** and **3**.

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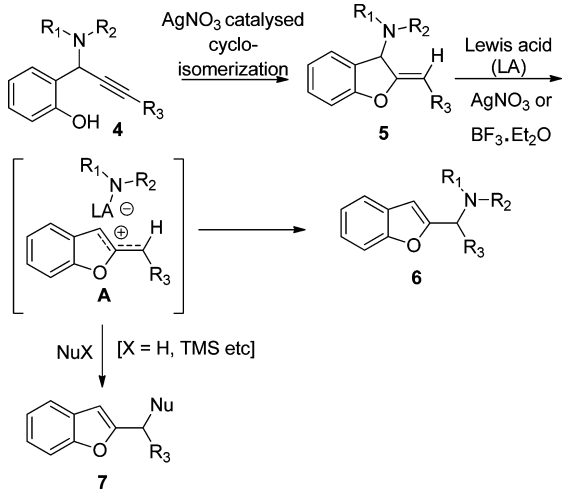
1). These compounds are readily obtained from propargyl amines **4** via $AgNO_3$-catalyzed 5-*exo-dig* cycloisomerization

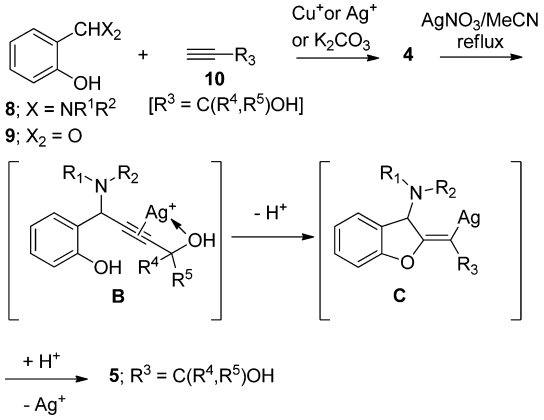
Scheme 1



reactions without the need to prepare reactive and sensitive organolithium or aryl halide reagents. We also report the isolation of novel products from unexpected 6-*endo-dig* cyclization processes and the preparation of other 2-substituted benzofurans **7** via trapping of the intermediate α-aryl (or α-alkyl) 2-benzofuranmethyl carbocation **A** with other, nonamine, nucleophiles (Scheme 1).

In 2002, Ukhin et al.[7] reported the synthesis of 2-methylidenebenzofurans **5**, from the cyclizaton reactions of propargyl amines **4**, prepared from aminals **8** of salicylaldehyde **9** and propargyl alcohols **10** according to Scheme 2. Cyclization

Scheme 2

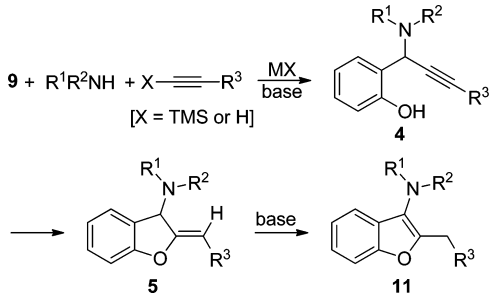


of **4** (X = piperidino, R^3 = R^4 = Me) with either $AgNO_3$ (10 mol %) in MeCN at reflux temperature for 15 min or by treatment with KOH in MeOH at reflux temperature for 40 min gave **5** (R^1/R^2 = piperidino R^4 = R^5 = Me) in yields of 63 and 74%, respectively. Treatment of aminal **8** (X = morpholino, R^4/R^5 = cyclohexyl) with the propargylic alcohol **10** (R^4/R^5 = cyclohexyl) and a stoichiometric amount of CuI in MeCN at reflux temperature for 30 min gave **5** (R^1/R^2 = morpholino, R^4/R^5 = cyclohexyl) directly in 39% yield (Scheme 2).

These results were supported by a study by Li et al.,[8] who reported that treatment of salicylaldehyde with a cyclic amine (2 equiv) and a propargyl alcohol (2 equiv) or an alkyne having a remote OH (or a propargylic NHTs group in one case) in the presence of 5 mol % of CuI with microwave heating at 130 °C for 30 min gave 3-amino-2,3-dihydro-2-arylmethylidenebenzofurans **5** (R^3 = CR^4,R^5(OH)), or their corresponding analogues, in yields ranging from 44 to 88%. Conditions employing 5 mol % of AgCl/MeCN/80 °C/16 h were also effective but provided **5** (R^3 = CR^4,R^5(OH)) in slightly lower yields. Importantly, they demonstrated that this reaction did not work with 3,3-dimethylbut-1-yne, which suggested that the hydroxyl (or NHTs) group on the alkyne component **10** was important to assist cyclization via a metal coordination process in intermediate **B** (Scheme 2).

In 2008, Sakai et al.[9] demonstrated that these multicomponent reactions can be performed on 1-TMS-alkynes, without the requirement of a propargylic hydroxyl group. They employed salicylaldehyde (1.5 equiv), a cyclic or acyclic secondary amine (1 equiv), 1-TMS-alkyne (1.5 equiv), 5 mol % of $Cu(OTf)_2$, and 5 mol % of CuCl with 1 molar equiv of DMAP in MeCN at reflux temperature for 6 h. Under these conditions, poor to excellent yields (22−99%) of 2-alkyl-3-aminobenzofuran products **11** resulted from a base-catalyzed isomerization of the initially formed, but never isolated, 3-amino-2,3-dihydro-2-aryl- (or alkyl-) methylidenebenzofurans **5** (Scheme 3).

Scheme 3



A subsequent study by Li et al.[10] found similar results using salicylaldehyde (2 equiv), a cyclic or acyclic secondary amine (1 equiv), and a terminal alkyne (1.5 equiv) using 20 mol % of CuI, K_2CO_3 (1 equiv), and Bu_4NBr (1 equiv) in toluene at 110 °C for 2−3 h. Of significance, to our study, was their singly reported finding that in the absence of K_2CO_3 and Bu_4NBr the propargyl amine **4** (R^1/R^2 = morpholine, R^3 = phenyl) was obtained in 84% yield. Further, in one other example, using 1-octyne, a separable mixture (ca. 1:1) of **5** and **11** (R^1/R^2 = morpholine, R^3 = hexyl) was obtained, suggesting to us that our targeted compounds of general structure **5** might be isolatable in better yields under less basic conditions. A related study by Zhang and Fan[11] demonstrated that these reactions to give compounds **11** could be performed efficiently using salicylaldehyde (1 equiv), a cyclic or acyclic secondary amine (1.2 equiv), and a terminal alkyne (1.5 equiv), CuI (10 mol %), and [bmim]OAc (20 mol %) in [bmim]PF_6 at 80 °C for 6−9 h.

The cyclization reactions of the propargyl alcohol analogues of the propargyl amines **4** (R^3 = H or aryl but not alkyl) have been previously studied. These reactions give the analogous 3-hydroxy-2,3-dihydro-2-arylmethylidenebenzofurans (the 3-hydroxy analogues of **5**) which undergo rearrangement to 2-hydroxmethyl benzofurans or 2-alkoxybenzofurans upon exposure to acid or an alcohol and acid, respectively.[12]

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RESULTS AND DISCUSSION

The prerequisite propargyl amines **4**, required for the synthesis of compounds **5** and then **6**, were prepared using the method of Li[10] (method A, Table 1), or a modification of this method

Table 1. Synthesis of Propargyl Amines 4a−i and 5g and 12 (Schemes 1 and 4)

entry	NR^1/R^2	R^3	method[a]	products (% yield)[b]
1	morpholino	Ph	A	**4a** (63)
2	morpholino	Ph	B	**4a** (84)
3	piperidino	Ph	B	**4b** (87)
4	pyrrolidino	Ph	B	**4c** (47)
5	morpholino	4-FC_6H_4	B	**4d** (86)
6	morpholino	4-$MeOC_6H_4$	B	**4e** (92)
7	morpholino	*n*-pentyl	A	**4f** (50)
8	morpholino	*n*-pentyl	B	**4f** (13), **12** (0.7)
9	morpholino	*n*- pentyl	C	**4f** (97)
10	piperidino	CH_2OH	B	**4g** (43), **5g** (44)
11	piperidino	CH_2OH	C	**4g** (0), **5g** (73)
12	piperidino	$(CH_2)_3CH_2OH$	C	**4h** (98)
13	dibutylamino	Ph	C	**4i** (90)
14	dibenzylamino	Ph	B or C	**4j** (0)
15	diallylamino	Ph	B or C	**4k** (0)
16	*N*-methylanilino	Ph	B or C	**4l** (0)

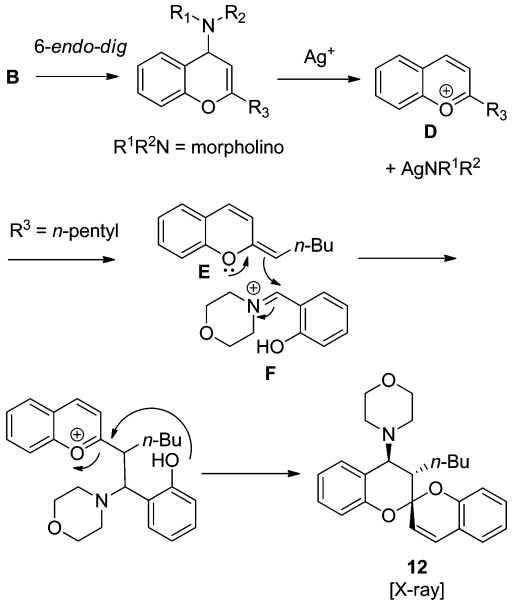
[a]Method A (from Li et al.):[10] **9** (2 equiv), HNR^1R^2 (1 equiv) and $HC{\equiv}CR^3$ (1.5 equiv), CuI (20 mol %), 110 °C, 24 h. Method B: **9** (2 equiv), HNR^1R^2 (1 equiv) and $HC{\equiv}CR^3$ (1.5 equiv), $AgNO_3$ (20 mol %), 110 °C, 24 h. Method C (from Adapa et al.):[13] **9** (1 equiv), HNR^1R^2 (1.3 equiv) and $HC{\equiv}CR^3$ (1.5 equiv), $Zn(OAc)_2{\cdot}2H_2O$ (10 mol %), 120 °C, 24 h. [b]After purification by column chromatography.

using $AgNO_3$ instead of CuI (method B) or the method of Adapa[13] (method C, Table 1) from the one-pot reactions of salicylaldehyde **9**, a cyclic or acyclic secondary amine (HNR^1R^2), and a terminal alkyne ($HC{\equiv}CR^3$) in toluene solution using either CuI (20 mol %), $AgNO_3$ (20 mol %), or $Zn(OAc)_2{\cdot}2H_2O$ (10 mol %) as catalysts, respectively, at 110−120 °C (Table 1).

Method A provided the propargyl amine **4a** in 63% yield (Table 1, entry 1). However, we found that a better yield of **4a** could be obtained using $AgNO_3$ as the catalyst rather than CuI. Method B provided the propargyl amines **4a−4e** (Table 1, entries 2−6), all in good yields (84−92%) except for the pyrrolidino adduct **4c** (47% yield). While method C was more efficient (97% yield) in giving the propargyl amine **4f** from heptyne when compared to method A or B (Table 1, entries 7−9). Interestingly, method B (Table 1, entry 8) also provided a small amount (0.7%) of the novel spirocyclic compound **12** whose structure was determined by a single-crystal X-ray analysis (Supporting Information). A possible mechanism for the formation of **12** is shown in Scheme 4. This mechanism involves formation of the flavylium ion intermediate **D**,[14] formed from cyclization of the intermediate **B** (Scheme 2) via a 6-*endo-dig* process[15] (Scheme 4). Coupling of intermediates **E** and **F** followed by an intramolecular spirocyclization process gives the spirocyclic compound **12**.

In the reactions involving salicylaldehyde **9**, piperidine, and propargyl alcohol (Table 1, entries 10 and 11), method B gave a separable mixture of **4g** and the 2-methylidenebenzofuran **5g**, while method C gave only **5g** in 73% yield. These results were consistent with those of Li[8] and the assistance of the primary

Scheme 4



hydroxyl group in the 5-*exo-dig* cyclization process by metal coordination in intermediate **B** (Scheme 2). In contrast, the reaction of **9**, piperidine, and 4-pentyn-1-ol gave only the propargyl amine product **4h** in 98% yield (Table, 1, entry 10, method B). Clearly, the hydroxyl group in **4h** is too remote to assist in cyclization to **5h**. Method B also provided **4i** in 90% yield from the reaction of **9** with the acylic amine, dibutylamine, and phenylacetylene (Table 1, entry 14). The amines, dibenzylamine, diallylamine, or *N*-methylaniline, were not effective (Table 1, entries 14−16).

For the cyclization reactions of **4a** to **5a** (Scheme 1), several metal salt catalysts were examined (CuI, $AgNO_3$, $Au(Ph_3P)Cl$, or $PdCl_2(Ph_3P)_2$/CuI) in various solvents (CH_2Cl_2, THF, MeCN, DMF) and at several temperatures (60−120 °C). Of these, 20 mol % of $AgNO_3$/DMF proved to be the most efficient. These results are summarized in Table 2. Treatment of **4a** with 20 mol % of $AgNO_3$ at 60 °C for 1 h gave the 2-phenylmethylidenebenzofuran **5a** in 90% yield (Table 1, entry 1). When this reaction was performed at 100 °C for 18 h, the 1,3-allylic rearrangement product **6a** was produced in 60% yield along with a small amount (5%) of **5a** (Table 1, entry 2). The former, milder conditions also worked well for the substrates **4b−d** and **4g** and **4i** (Table 2, entries 3, 5, 7, 13, and 15), providing the corresponding 2-methylidenebenzofurans **5b−d** and **5g** and **5i** in yields ranging from 65 to 85%. The more electron-rich 4-methoxyphenyl-substituted derivative **4e**, however, gave the 1,3-allylic rearrangement product **6e** in 68% yield (Table 2, entry 9). This product was also formed exclusively under the harsher (100 °C for 18 h) reaction conditions (Table 2, entry 10). The reactions of the *n*-pentyl derivative **4f** at 60 or 100 °C gave **5f** in low yields (32 and 23%, Table 2, entries 11 and 12). These low yields were most likely due to a competing 6-*endo-dig* cyclization process that resulted in the formation of many colored unidentifiable products apart from the (*E*)-enone **13**, which was isolated in 6% yield (Scheme 5). Similarly, the cyclization reaction of **4h** resulted in mixtures from competing 6-*endo-dig* and 5-*exo-dig* processes. The major product (51% yield) was the known spirocyclic compound **14**[16] formed by intramolecular trapping of the flavylium ion intermediate **D**[14] (Scheme 5). The 5-*exo-dig* products **5h** (32%) and **6h** (7%)

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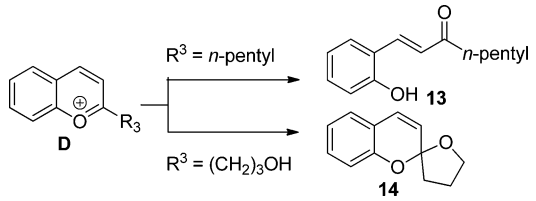
Table 2. Synthesis of 3-Amino-2,3-dihydro-2-arylmethylidenebenzofurans 5 and/or α-Aryl (or α-Alkyl) 2-Benzofuranmethamines 6 from the $AgNO_3$-Catalyzed Cyclization Reactions of Propargyl Amines 4 (Schemes 1 and 5)[a]

entry	propargyl amine **4** (NR^1R^2/R^3)	$AgNO_3$ (20 mol %), DMF temp (°C)/time (h)	products (% yield)[a]
1	**4a** (morpholino/Ph)	60/1	**5a** (90)
2	**4a** (morpholino/Ph)	100/18	**5a** (5), **6a** (60)
3	**4b** (piperidino/Ph)	60/1	**5b** (78)
4	**4b** (piperidino/Ph)	100/18	**5b** (17), **6b** (53)
5	**4c** (pyrrolidino/Ph)	60/1	**5c** (65)
6	**4c** (pyrrolidino/Ph)	100/18	**5c** (2), **6c** (36)
7	**4d** (morpholino/4F-C_6H_4)	60/1	**5d** (81)
8	**4d** (morpholino/4F-C_6H_4)	100/18	**5d** (13), **6d** (52)
9	**4e** (morpholino/4MeO-C_6H_4)	60/1	**6e** (68)
10	**4e** (morpholino/4MeO-C_6H_4)	100/18	**6e** (69)
11	**4f** (morpholino/*n*-pentyl)	60/1	**5f** (32), **13** (6)
12	**4f** (morpholino/*n*-pentyl)	100/18	**5f** (23)
13	**4g** (piperidino/CH_2OH)	60/1	**5g** (84)
14	**4h** (piperidino/$(CH_2)_3CH_2OH$	60/1	**5h** (32), **14** (51)
15	**4i** (dibutylamino/Ph)	60/1	**5i** (85)

[a]After purification by column chromatography.

Scheme 5



were also obtained (Table 2, entry 13). The hydroxymethyl substrate **4g** ($R^3 = CH_2OH$), however, was smoothly converted to the 5-*exo-dig* cyclization product **5g** in 84% yield (Table 2, entry 13), for the reasons discussed above.

Heating a solution of **5a** with $AgNO_3$ (20 mol %) in DMF at 100 °C for 24 h also provided the rearranged benzofuran **6a** in 68% yield. No detectable (TLC or NMR analysis) amount of **6a** was formed when a DMF solution of **5a** was heated at 100 °C for 24 h in the absence of $AgNO_3$.

Table 3 provides a summary of our study on the $BF_3{\cdot}Et_2O$-catalyzed 1,3-allylic rearrangements of **5** to **6** and the preparation of other 2-substituted benzofurans **15**–**17** via trapping of the assumed ion pair intermediate **A** (Scheme 1) with an external nucleophile (Scheme 6).

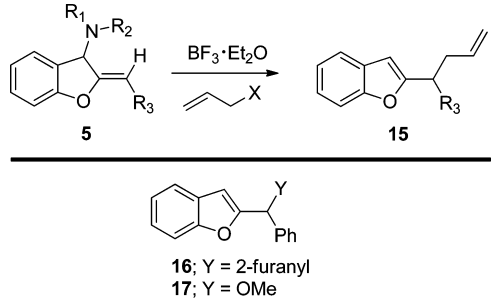
Treatment of a CH_2Cl_2 solution of **5a** with $BF_3{\cdot}Et_2O$ (1.5 equiv) at rt for 2 h gave the rearranged benzofuran **6a** in 87% yield (Table 3, entry 1). In contrast, the rearrangement reactions of the corresponding piperidino and pyrrolidino derivatives, **5b** and **5c**, were considerably slower and required reaction times of 18–24 h to obtain close to 50% conversions.

Table 3. Synthesis of 6 and 13–15 from the $BF_3{\cdot}Et_2O$-Catalyzed Reactions of 5 with or without an External Nucleophile (Schemes 1 and 6)[a]

entry	benzofuran **5** (NR^1R^2/R^3)	time (h)/temp (°C)/external nucleophile (equiv)	products (% yield)[a]
1	**5a** (morpholino/Ph)	2/rt/–	**6a** (87)
2	**5b** (piperidino/Ph)	18/rt/–	**6b** (58), **5b** (41)
3	**5c** (pyrrolidino/Ph)	24/rt/–	**6c** (43), **5c** (56)
	5d (morpholino/4F-C_6H_4)	2/rt/–	**6d** (96)
4	**5f** (morpholino/*n*-pentyl)	6/rt/–	**6f** (22), **5f** (66)
5	**5i** (morpholino/*n*-pentyl)	24/rt/–	**6i** (87)
6	**5a** (morpholino/Ph)	2/rt/allylBF_3K (3)	**15a** (0), **6a** (96)
7	**5a** (morpholino/Ph)	2/rt/allylTMS (3)	**15a** (46), **6a** (53)
8	**5a** (morpholino/Ph)	2/rt/allyl$SnBu_3$ (3)	**15a** (73), **6a** (26)
9	**5a** (morpholino/Ph)	2/rt/furan (10)	**16** (43), **6a** (54)
10	**5a** (morpholino/Ph)	2/rt/MeOH (10)	**17** (52), **6a** (48)
11	**5b** (piperidino/Ph)	18/rt/allyl$SnBu_3$ (3)	**15a** (87)
12	**5d** (morpholino/4F-C_6H_4)	2/rt/allyl$SnBu_3$ (3)	**15d** (69), **6d** (30)
13	**6e** (morpholino/4MeO-C_6H_4)	2/rt/allyl$SnBu_3$ (3)	**15e** (36)
14	**5f** (morpholino/*n*-pentyl)	2/rt/allyl$SnBu_3$ (3)	**15f** (87)

[a]After purification by column chromatography.

Scheme 6



This resulted in lower yields of **6b** and **6c**, respectively, due to reisolation of unreacted starting materials (Table 3, entries 2 and 3). Compound **6b** was more readily prepared from the cyclization of **4b** with $AgNO_3$ at 100 °C (Table 2, entry 4). The morpholino derivative **5d**, having a deactivating 4-fluorophenyl substituent, also underwent smooth conversion to its rearranged product **6d** in 96% yield. The *n*-pentyl derivative **5f** was found to react even more sluggishly than **5b** or **5c** and provided **6f** in only 22% yield along with 66% yield of recovered unreacted starting material (Table 3, entry 4). The dibutylamino compound **5i**, however, provided the rearranged product **6i** in 87% yield (Table 3, entry 5). Clearly, the morpholino derivatives **5a** and **5d** underwent $BF_3{\cdot}Et_2O$-promoted rearrangements to their corresponding benzofurans **6a**,**d** more readily than their piperidino and pyrrolidino analogues **5b** and **5c**. These results are in accord with the relative basicities (K_b values)[17] of these amino groups, where

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the less basic morpholino group would be expected to be a better leaving group (form a more stable BF_3-coordinated incipient amide ion in the ion pair **A**) and more readily form the carbocation ion pair **A** (Scheme 1). However, the observed similar reactivity of the morpholino and dibutylamino substrates, **5a** and **5i**, suggests that other factors are important in controling the rates of these reactions. Indeed, very few examples are known for unactivated allylic amines undergoing 1,3-allylic rearrangements.[18] In our cases, the driving force for rearrangement of **5** to **6** is clearly the formation of a more stable benzofuran product **6**.

In an attempt to form the allylated derivative **15a**, we treated a CH_2Cl_2 solution of **5a** with $BF_3{\cdot}Et_2O$ (1.5 equiv) and potassium allyltrifluoroborate (3 equiv). This gave only the rearranged product **6a** (Table 3, entry 6). Allyltrimethylsilane gave a 46% yield of **15a** while allyltributylstannane gave **15a** in a much improved yield of 73%. In each case, the rearranged benzofuran **6a** was also formed (Table 3, entries 7 and 8). Under similar reaction conditions, **15a** could be prepared in high yield from **5b** and allyltributylstannane; however, the reaction time was 18 h (Table 3, entry 8). Similarly, compounds **5d** and **5f** could be converted to their corresponding allylated derivatives, **15d** and **15f**, respectively (Table 3, entries 12 and 14). The methoxy-activated derivative **6e** could also be converted to its allylated derivative **15e** but in low yield (36%, Table 3, entry 13). The furan and methanol adducts, **16** and **17**, respectively, could be prepared from the $BF_3{\cdot}Et_2O$ (1.5 equiv)-promoted reactions of **5a** in the presence of furan (10 equiv) and MeOH (10 equiv), respectively. These products were separated from nearly equal amounts of **6a** (Table 3, entries 9 and 10).

In summary, the propargyl amines **4**, where R^3 is aryl, undergo cyclization under relatively mild conditions ($AgNO_3$, DMF, 60 °C, 1 h) to give ready access to 3-amino-2,3-dihydro-2-arylmethylidenebenzofurans **5** (R^3 = aryl). These reactions proceed through a 5-*exo*-*dig* cyclization process. Under these nonbasic conditions, the corresponding 2-alkyl-3-aminobenzofuran products **11**, as reported previously,[10] are not observed. In contrast, the substrates **4f** and **4h**, where R^3 is alkyl, undergo competing 6-*endo*-*dig* and 5-*exo*-*dig* cyclization processes as evident of the isolation of compounds **13** and **14**. The hydroxymethyl substrate **4g** (R^3 = CH_2OH), however, was smoothly converted to the 5-*exo*-*dig* cyclization product **5g** in 84% yield, likely due to the assistance of the primary hydroxyl group in the 5-*exo*-dig cyclization process by metal coordination in intermediate **B** (R^3 = CH_2OH) (Scheme 2). Under more enforcing conditions ($AgNO_3$, DMF, 100 °C, 18 h), the initially formed 2,3-dihydro-2-substituted methylidenebenzofurans **5** undergo a 1,3-allylic rearrangement to their corresponding 2-substituted benzofuran derivatives **6**. This rearrangement can also be effected by treating **5** with $AgNO_3$ in DMF at 100 °C for 18 h or $BF_3{\cdot}Et_2O$ (1.5 equiv) at rt. 2-(3-Butenyl)-benzofurans **15** can be prepared by treatment of **5** with $BF_3{\cdot}Et_2O$ and allyltributylstannane; however, compound **6** is often also formed as a minor product. Furan and MeOH could also be employed as external nucleophiles in the $BF_3{\cdot}Et_2O$-promoted reactions of **5a**.

EXPERIMENTAL SECTION

Melting points were determined on a capillary tube melting point apparatus and are uncorrected. All IR spectra were run as neat samples. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solution using TMS and residual $CHCl_3$ as an internal standard (δ_H 0.00, δ_C 77.16). ^1H NMR data were listed in order of the number of protons, multiplicity [singlet (s), broad singlet (brs), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m)], coupling constants (J) in hertz, and assignment of nuclei concerned. NMR assignments are based upon gCOSY, HSQC, HMBC, and, sometimes, gNOESY experiments. High-resolution ESI mass spectra were obtained on a QTOF (ESI) mass spectrometer. Thin layer chromatography (TLC) was performed with precoated Merck silica gel 60 PF_{254} aluminum sheets, and the spots were visualized under UV light (254 and 366 nm) and further by spraying with an acidified aqueous solution of ammonium molybdate and cerium(IV) sulfate then heating until charred. Column chromatography (CC) was performed with Merck silica gel 60 (40–60 μm) and under pressure from compressed air. All air-sensitive reactions were carried out in predried glassware apparatus under a dry nitrogen atmosphere.

2-(1-Morpholino-3-phenylprop-2-ynyl)phenol (4a). *Method A:* A mixture of CuI (762 mg, 4.0 mmol), salicylaldehyde (4.88 g, 40 mmol), phenylacetylene (3.07 g, 30 mmol), and morpholine (1.75 g, 20 mmol) in anhydrous toluene (20 mL) was heated under N_2 at 110 °C for 48 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) and then crystallization with EtOAc/petrol to give product **4a** (3.68 g, 63%) as colorless crystals: mp 96–98 °C; R_f = 0.34 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3053, 2961, 2848, 2230, 1588, 1488, 1245, 1115, 1095, and 690 cm^{-1}; ^1H NMR (300 MHz) δ 10.81 (1H, brs, ArO*H*), 7.57–7.53 (3H, m, Ar*H*), 7.37–7.35 (3H, m, Ar*H*), 7.25 (1H, t, J = 7.2 Hz, Ar*H*), 6.89–6.86 (2H, m, ArH), 5.09 (1H, s, C*H*N), 3.80 (4H, brs, 2 × CH_2O), 2.79 (4H, brs, 2 × CH_2N); ^{13}C NMR (75 MHz) δ 157.1 (ArCO), 132.0 (2 × ArCH), 129.9 (ArCH), 128.89 (ArCH), 128.88 (ArCH), 128.6 (ArCH), 122.4 (ArC), 120.7 (ArC), 119.6 (ArCH), 116.6 (ArCH), 90.5 (C≡CAr), 81.7 (C≡CAr), 67.0 (2 × CH_2O), 60.9 (CHN) (due to line broadening signals for (2 × CH_2N) were not observed); HRESIMS calcd for $C_{19}H_{20}NO_2$ $(M + H)^+$ 294.1494; found, 294.1504.

Method B: A mixture of $AgNO_3$ (679 mg, 4.0 mmol), salicylaldehyde (4.88 g, 40 mmol), phenylacetylene (3.07 g, 30 mmol), and morpholine (1.75 g, 20 mmol) in anhydrous toluene (20 mL) was heated under N_2 at 110 °C for 48 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) and then crystallization with EtOAc/petrol to give product **4a** (4.903 g, 84%).

2-(3-Phenyl-1-(piperidin-1-yl)prop-2-yn-1-yl)phenol (4b). A mixture of $AgNO_3$ (68 mg, 0.4 mmol), salicylaldehyde (489 mg, 4.0 mmol), phenylacetylene (306 mg, 3.0 mmol), and piperidine (170 mg, 2.0 mmol) in anhydrous toluene (10 mL) was heated under N_2 at 110 °C for 48 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:19)) to product **4b** (511 mg, 87%) as a yellow solid: mp 60–62 °C; IR (neat) ν_{max} 3062, 3037, 2942, 2837, 2211, 1603, 1583, 1459, 1319, 1242, 671, and 634 cm^{-1}; R_f = 0.24 (EtOAc/petrol (1:19)); ^1H NMR (300 Hz) δ 7.53 (3H, brs, Ar*H*), 7.34 (3H, brs, Ar*H*), 7.20 (1H, t, J = 7.2 Hz, Ar*H*), 6.82 (2H, d, J = 7.2 Hz, Ar*H*), 5.07 (1H, s,C*H*N), 2.70 (4H, brs, 2 × CH_2N), 1.65 (4H, brs, 2 × CH_2), 1.49 (2H, brs, CH_2); ^{13}C NMR (75 MHz) δ 157.7 (ArCOH), 132.0 (2 × ArCH), 129.5 (ArCH), 128.7 (2 × ArCH), 128.5 (2 × ArCH), 122.7 (ArC), 121.4 (ArC), 119.1 (ArCH), 116.4 (ArCH), 89.9 (C≡CAr), 82.4 (C≡CAr), 61.2 (2 × CH_2N), 52.9 (CH_2N), 26.1 (CH_2), 24.1 (2 × CH_2); HRESIMS calcd for $C_{20}H_{22}NO$ $(M + H)^+$ 292.1701; found, 292.1708.

2-(3-Phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-yl)phenol (4c). A mixture of $AgNO_3$ (68 mg, 0.4 mmol), salicylaldehyde (489 mg, 4.0 mmol), phenylacetylene (306 mg, 3.0 mmol), and pyrrolidine (143 mg, 2.0 mmol) in anhydrous toluene (10 mL) was heated under N_2 at 110 °C for 48 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (5% EtOAc/petrol (1:19)) to give the product **4c** (532 mg, 47%) as a yellow viscous oil: R_f = 0.33 (EtOAc/petrol (1:5)); IR (neat) ν_{max} 3053, 2967, 2840, 2219, 1590, 1465, 1348, 1257, 690, and 633 cm^{-1}; ^1H NMR (300 MHz) δ 10.99 (1H, brs, ArO*H*), 7.55–7.50 (3H, m, Ar*H*), 7.34–7.31 (3H, m, Ar*H*), 7.20 (1H, dt, J = 7.2, 0.9 Hz,

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ArH), 6.87−6.81 (2H, m, ArH), 5.25 (1H, s, CHN), 2.87−2.76 (4H, m, 2 × CH_2N), 1.86−1.82 (4H, m, 2 × CH_2); ^{13}C NMR (75 MHz) δ 157.6 (ArCOH), 131.9 (2 × ArCH), 129.4 (ArCH), 128.6 (2 × ArCH), 128.4 (ArCH), 127.9 (ArCH), 122.6 (ArCH), 122.2 (ArC), 119.0 (ArCH), 116.3 (ArCH), 89.1 (C≡CAr), 83.0 (C≡CAr), 57.0 (CHN), 48.9 (2 × CH_2N), 23.9 (2 × CH_2); HRESIMS calcd for $C_{19}H_{20}NO$ $(M + H)^+$ 278.1545; found 278.1546.

2-(3-(4-Fluorophenyl)-1-morpholinopro-2-yn-1-yl)phenol (4d). A mixture of $AgNO_3$ (68 mg, 0.4 mmol), salicylaldehyde (489 mg, 4.0 mmol), 1-ethynyl-4-fluorobenzene (391 mg, 3.0 mmol), and morpholine (174 mg, 2.0 mmol) in anhydrous toluene (5 mL) was heated under N_2 at 110 °C for 48 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) and then crystallization with EtOAc/petrol to give the product **4d** (572 mg, 91.9%) as a pale yellow solid: mp 104−106 °C; R_f = 0.33 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3050, 2961, 2851, 2232, 1600, 1586, 1506, 1454, 1397, 1232, 1115, 1094, 660, and 635 cm^{-1}; ^{1}H NMR (500 MHz) δ 10.71(1H, brs, ArOH), 7.54−7.50 (3H, m, ArH), 7.23 (1H, t, J = 7.5 Hz, ArH), 7.04 (2H, t, J = 7.5 Hz, ArH), 6.88−6.86 (2H, m, ArH), 5.05 (1H, s, CHN), 3.77 (4H, brs, 2 × CH_2O), 2.75 (4H, brs, 2 × CH_2N); ^{13}C NMR (125 MHz) δ 162.8 (d, J = 248 Hz, ArCF), 157.05 (ArCO), 133.8 (d, J = 8.6 Hz, ArCH), 129.8 (ArCH), 128.7 (ArCH), 120.5 (ArC), 119.5 (ArCH), 118.4 (d, J = 3.9 Hz, ArC), 116.6 (ArCH), 115.8 (d, J = 22 Hz, ArCH), 89.3 (C≡CAr), 81.0 (C≡CAr), 66.9 (2 × CH_2O), 60.7 (CHN), 52.1 (2 × CH_2N); HREIMS calcd for $C_{19}H_{19}FNO_2$ $(M + H^+)$ 312.1400; found 312.1397.

2-(3-(4-Methoxyphenyl)-1-morpholinopro-2-yn-1-yl)phenol (4e). A mixture of $AgNO_3$ (68 mg, 0.4 mmol), salicylaldehyde (489 mg, 4.0 mmol), *p*-ethynylanisole (396 mg, 3.0 mmol), and morpholine (174 mg, 2.0 mmol) in anhydrous toluene (5 mL) was heated under N_2 at 110 °C for 48 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (10% EtOAc/petrol (1:9)) and then crystallization with EtOAc/petrol to give product **4e** (559 mg, 86%) as a pale yellow solid: mp 144−146 °C; R_f = 0.24 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3058, 3034, 2937, 2845, 2208, 1603, 1508, 1467, 1248, 1112, 829, and 803 cm^{-1}; ^{1}H NMR (300 MHz) δ 10.87 (1H, brs, OH), 7.57 (1H, d, J = 7.5 Hz, ArH), 7.49−7.46 (2H, m, ArH), 7.24 (1H, t, J = 7.5 Hz, ArH), 6.90−6.85 (3H, m, ArH), 5.07 (1H, s,CHN), 3.83 (3H, s, OCH_3), 3.80 (4H, brs, 2 × CH_2O), 2.78 (4H, brs, 2 × CH_2N); ^{13}C NMR (75 MHz) δ 160.0 (ArCOCH$_3$), 157.1 (ArCOH), 133.5 (2 × ArCH), 129.8 (ArCH), 129.0 (ArCH), 120.9 (ArC), 119.5 (ArCH), 116.6 (ArCH), 114.4 (ArC), 114.2 (2 × ArCH), 90.4 (C≡CAr), 80.2 (C≡CAr), 67.0 (OCH_3), 60.9 (2 × CH_2O), 55.5 (2 × CH_2N); HRESIMS calcd for $C_{20}H_{22}NO_3$ $(M + H)^+$ 324.1600; found 324.1597.

2-(1-Morpholinooct-2-yn-1-yl)phenol (4f) and 4-(3-(pentan-2-yl)spiro[chroman-2,2′-chromen]-4-yl)morpholine (12). *Method A:* A mixture of $AgNO_3$ (68 mg, 0.4 mmol), salicylaldehyde (489 mg, 4.0 mmol), 1-heptyne (289 mg, 3.0 mmol), and morpholine (174 mg, 2.0 mmol) in anhydrous toluene (5 mL) was heated under N_2 at 110 °C for 48 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:19)) and then crystallization with EtOAc/petrol to give compound **4f** (75 mg, 13.0%) and compound **12** (6 mg, 0.7%). **Compound 4f:** colorless viscous oil; R_f = 0.24 (EtOAc/petrol (1;9)); IR (neat) ν_{max} 3041, 2956, 2852, 2234, 1587, 1455, 1275, 1242, 1116, 1093, and 753 cm^{-1}; ^{1}H NMR (300 MHz) δ 10.93 (1H, brs, OH), 7.48 (1H, dt, J = 7.5, 1.2, ArH), 7.21 (1H, ddd, J = 7.5, 1.8, 0.6 Hz, ArH), 6.88−6.81 (3H, m, ArH), 4.84 (1H, s, CHN), 3.76 (4H, brs, 2 × CH_2O), 2.67 (4H, brs, 2 × CH_2N), 2.34 (2H, t, J = 7.2 Hz, (C≡CCH_2), 1.61 (2H, quint, J = 7.2 Hz, (C≡CCH$_2$CH$_2$CH$_2$), 1.50−1.30 (4H, m, 2 × CH_2), 0.93 (3H, t, J = 6.9 Hz, CH_2CH_3); ^{13}C NMR (75 MHz) δ 157.1 (ArCOH), 129.6 (ArCH), 128.9 (ArCH), 121.2 (ArC), 119.3 (ArCH), 116.4 (ArCH), 91.2 (C≡CCH_2), 72.2 (C≡CCH_2), 66.9 (2 × CH_2O), 60.4 (CHN), 31.2 ($CH_2CH_2CH_2$), 28.6 (C≡CCH_2CH_2), 22.3 (CH_2CH_3), 18.8 (C≡CCH_2), 14.1 (CH_2CH_3) [signals for 2 × CH_2N were not observed due to line broadening]; HRESIMS calcd for $C_{18}H_{26}NO_2$ $(M + H^+)$ 288.1964; found 288.1959. **Compound 12:** colorless crystals; mp 125−127 °C; R_f = 0.48 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3069, 3031, 2930, 2855, 1641, 1582, 1482, 1451, 1230, 1194, 1108, and 757 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.51 (1H, d, J = 7.8 Hz, ArCH), 7.17−7.05 (3H, m, ArCH), 6.97−6.92 (2H, m, ArCH), 6.82 (1H, d, J = 9.6 Hz, CH=CHAr), 6.71 (1H, d, J = 8.1 Hz, ArCH), 6.66 (1H, d, J = 8.1 Hz, ArCH), 5.88 (1H, d, J = 9.6 Hz, CH=CHAr), 4.12 (1H, d, J = 10.5 Hz, CHN), 3.71−3.69 (4H, m, 2 × CH_2O), 2.95−2.70 (4H, m, 2 × CH_2N), 2.22−2.16 (1H, m, CH), 1.80−1.60 (2H, m, CH_2), 1.55−1.40 (2H, m, CH_2), 1.30 (2H, sext, J = 7.2 Hz, CH_2CH_3), 0.89 (3H, t, J = 7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz) δ 152.2 (ArCO), 151.1 (ArCO), 129.5 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 127.1 (CH=CHAr), 127.0 (ArCH), 124.5 (ArC), 123.2 (CH=CHAr), 121.8 (ArCH), 121.1 (ArCH), 120.1 (ArC), 117.5 (ArCH), 116.7 (ArCH), 100.8 (C(O)$_2$), 68.2 (2 × CH_2O), 61.6 (CHN), 50.2 (2 × CH_2N), 44.1 (CH), 30.6 (CH_2), 30.3 (CH_2), 23.4 (CH_2CH_3), 14.2 (CH_2CH_3); HRESIMS calcd for $C_{25}H_{30}NO_3$ $(M + H)^+$ 392.2226; found 392.2231.

Method B: A mixture of CuI (381 mg, 2.0 mmol), salicylaldehyde (2.44 g, 20 mmol), 1-heptyne (1.44 g, 15 mmol), and morpholine (872 mg, 10 mmol) in anhydrous toluene (10 mL) was heated under N_2 at 110 °C for 48 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (5% EtOAc/petrol (1:19)) and then crystallization with EtOAc/petrol to give compound **4f** (1.44 g, 50%) as a colorless oil.

Method C: A mixture of Zn(OAc)$_2$.2H$_2$O (88 mg, 0.2 mmol), salicylaldehyde (489 mg, 4.0 mmol), 1-heptyne (577 mg, 6.0 mmol), and morpholine (453 mg, 5.2 mmol) in anhydrous toluene (10 mL) was heated under N_2 at 120 °C for 24 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:19)) and then crystallization with EtOAc/petrol to give compound **4f** (1.13 g, 97%) as a colorless oil.

2-(4-Hydroxy-1-(piperidin-1-yl)but-2-yn-1-yl)phenol (4g) and 2-(3-(Piperidin-1-yl)benzofuran-2(3*H*)-ylidene)ethanol (5g). A mixture of $AgNO_3$ (68 mg, 0.4 mmol), salicylaldehyde (489 mg, 4.0 mmol), phenylacetylene (306 mg, 3.0 mmol), and piperidine (170 mg, 2.0 mmol) in anhydrous toluene (10 mL) was heated under N_2 at 110 °C for 24 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:1)) to give compound **4g** (211 mg, 43%) and compound **5g** (216 mg, 44%).

*Compound **4g**:* a brown viscous oil; R_f = 0.24 (EtOAc/petrol (1:1)); IR (neat) ν_{max} 3405, 3042, 2934, 2854, 2234, 1608, 1589, 1664, 1366, 1275, 1245, 1060, and 753 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.56 (1H, brs, ArOH), 7.45 (1H, d, J = 7.5 Hz, ArH), 7.15 (1H, t, J = 7.5 Hz, ArH), 6.82 (2H, d, J = 7.5 Hz, ArH), 6.79 (1H, t, J = 7.5 Hz, ArH), 4.83 (1H, s, CHN), 4.12 (2H, s, CH_2OH), 2.59 (4H, brs, 2 × CH_2N), 1.59 (4H, brs, 2 × CH_2), 1.45 (2H, brs, CH_2); ^{13}C NMR (75 MHz) δ 157.0 (ArCOH), 129.2 (ArCH), 128.2 (ArCH), 120.9 (ArC), 119.0 (ArCH), 116.1 (ArCH), 88.2 (C≡CCH_2), 77.8 (C≡CCH_2), 60.3 (CHN), 50.4 (CH_2OH), 45.5 (2 × CH_2N), 25.7 (2 × CH_2), 23.f (CH_2); HRESIMS calcd for $C_{15}H_{20}NO_2$ $(M + H)^+$ 246.1494; found 246.1506.

*Compound **5g**:* a brown viscous oil; R_f = 0.24 (EtOAc/petrol (1:1)); IR (neat) ν_{max} 3332, 3051, 2934, 2807, 1699, 1595, 1463, 1322, 1229, 1086, 969, 750, and 729 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.38 (1H, d, J = 7.8 Hz, ArH), 7.20 (1H, dt, J = 8.1, 0.9 Hz, ArH), 6.97 (1H, dt, J = 7.2, 0.9 Hz, ArH), 6.93 (1H, d, J = 8.1 Hz, ArH), 4.87 (1H, s, CHN), 4.46−4.41 (2H, m, CH_2OH), 3.15 (1H, brs, OH), 2.60−2.35 (4H, m, 2 × CH_2N), 1.55−1.51 (4H, brs, 2 × CH_2), 1.40−1.38 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7 (OC=C), 154.7 (ArCO), 129.4 (ArCH), 126.2 (ArCH), 125.5 (ArC), 121.9 (ArCH), 109.6 (ArCH), 105.2 (C=CH), 67.0 (CHN), 56.9 (CH_2OH), 49.4 (2 × CH_2N), 26.2 (CH_2), 24.4 (CH_2); HRESIMS calcd for $C_{15}H_{20}NO_2$ $(M + H)^+$ 246.1494; found 246.1486.

2-(6-Hydroxy-1-(piperidin-1-yl)hex-2-yn-1-yl)phenol (4h). A mixture of Zn(OAc)$_2$·2H$_2$O (88 mg, 0.4 mmol), salicylaldehyde (489 mg, 4.0 mmol), 4-pentyn-1-ol (505 mg, 6.0 mmol), and piperidine (443 mg, 5.2 mmol) in anhydrous toluene (10 mL) was heated under N_2 at 120 °C for 24 h. The solvent was removed under reduced

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pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:1)) to give product **4h** (1.076 g, 98%) as a colorless viscous oil: R_f = 0.44 (EtOAc/petrol (1:1)); IR (neat) ν_{max} 3397, 3042, 2934, 2852, 2234, 1607, 1589, 1464, 1368, 1274, 1246, 1154, 1058, 981, 858, and 805 cm^{-1}; ^1H NMR (500 MHz) δ 7.44 (1H, d, J = 8.00 Hz, Ar*H*), 7.18 (1H, t, J = 8.00 Hz, Ar*H*), 6.84−6.80 (2H, m, Ar*H*), 4.82 (1H, s, C*H*N), 3.81 (2H, t, J = 6.0 Hz, CH_2CH_2OH), 2.63−2.58 (4H, m, 2 × CH_2N), 2.50−2.47 (2H m, CH_2), 1.86 (2H, quint, J = 6.5 Hz, CH_2), 1.64 (4H, brs, 2 × CH_2), 1.50 (2H, brs, CH_2); ^{13}C NMR (125 MHz) δ 157.7 (ArCOH), 129.3 (ArCH), 128.4 (ArCH), 121.9 (Ar*C*), 119.0 (ArCH), 116.3 (ArCH), 89.5 (C≡CCH_2), 73.4 (C≡CCH_2), 61.8 (CH_2OH), 60.8 (CHN), 31.8 (CH_2), 26.0 (2 × CH_2), 24.1 (CH_2), 15.5 (CH_2), [signals for 2 × CH_2N were not observed due to line broadening]; HRESIMS calcd for $C_{17}H_{24}NO_2$ $(M + H)^+$ 274.1807; found 274.1796.

2-(1-(Dibutylamino)-3-phenylprop-2-yn-1-yl)phenol (4i). A mixture of $Zn(OAc)_2{\cdot}2H_2O$ (88 mg, 0.4 mmol), salicylaldehyde (489 mg, 4.0 mmol), phenylacetylene (613 mg, 6.0 mmol), and dibutylamine (672 mg, 5.2 mmol) in anhydrous toluene (10 mL) was heated under N_2 at 120 °C for 18 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:19)) to give product **4i** (1.20 g, 90%) as a yellow viscous oil: R_f = 0.20 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3054, 2961, 2848, 2232, 1588, 1473, 1257, 1245, 1115, 1072, 689, and 636 cm^{-1}; ^1H NMR (300 MHz) δ 11.35 (1H, brs, ArO*H*), 7.60 (1H, d, J = 7.5 Hz, Ar*H*), 7.55−7.52 (2H, m, Ar*H*), 7.34−7.32 (3H, m, Ar*H*), 7.23 (1H, t, J = 7.5 Hz, Ar*H*), 6.88−6.83 (4H, m, 2 × CH_2N) 5.30 (1H, s,C*H*N), 2.72−2.52 (4H, m, 2 × CH_2N), 1.68−1.49 (4H, m, 2 × CH_2); 1.48−1.21 (4H, m, 2 × CH_2), 0.90 (6H, t, J = 7.5 Hz, 2 × CH_2CH_3); ^{13}C NMR (75 MHz) δ 157.4 (ArCO), 131.9 (2 × ArCH), 129.4 (ArCH), 128.6 (2 × ArCH), 128.4 (2 × ArCH), 122.7 (Ar*C*), 122.0 (Ar*C*), 119.1 (ArCH), 116.4 (ArCH), 89.2 (C≡CAr), 82.8 (*C*≡CAr), 57.1 (CHN), 51.0 (2 × CH_2N), 30.0 (2 × $CH_2CH_2CH_2$), 20.7 (2 × CH_2CH_3), 14.0 (2 × CH_2CH_3); HRESIMS calcd for $C_{23}H_{30}NO$ $(M + H)^+$ 336.2327; found 336.2343.

4-(2-Benzylidene-2,3-dihydrobenzofuran-3-yl)morpholine (5a). A mixture of $AgNO_3$ (240 mg, 1.41 mmol) and **4a** (2.00 g, 6.82 mmol) in anhydrous DMF (30 mL) was heated under N_2 at 60 °C for 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:4)) and then crystallization with EtOAc/petrol to give product **5a** (1.80 g, 90%) as colorless crystals: mp 104−106 °C; R_f = 0.23 (EtOAc/petrol (1:19)); IR (neat) ν_{max} 3035, 2939, 2849, 1681, 1608, 1447, 1339, 1229, 1209, 1109, 727, and 690 cm^{-1}; ^1H NMR (300 MHz) δ 7.70 (2H, d, J = 8.0 Hz, Ar*H*), 7.35 (1H, d, J = 7.0 Hz, Ar*H*), 7.34 (2H, t, J = 7.5 Hz, Ar*H*), 7.25 (1H, t, J = 7.5 Hz, Ar*H*), 7.17 (1H, t, J = 7.0 Hz, Ar*H*), 7.00 (1H, d, J = 8.0 Hz, Ar*H*), 6.99 (1H, d, J = 7.5 Hz, Ar*H*), 5.85 (1H, s, C═C*H*Ar), 4.95 (1H, s, C*H*N), 3.75−3.65 (4H, m, 2 × CH_2O), 2.80−2.66 (2H, m, CH_2N), 2.60−2.50 (2H, m, CH_2N); ^{13}C NMR (75 MHz) δ 158.2 (Ar*C*), 153.8 (*C*═CHAr), 135.0 (Ar*C*), 129.7 (ArCH), 128.5 (2 × ArCH), 128.46 (2 × ArCH), 126.4 (ArCH), 126.2 (ArCH), 124.4 (Ar*C*), 122.3 (ArCH), 110.3 (ArCH), 105.7 (C═CHAr), 68.2 (CHN), 67.4 (2 × CH_2O), 48.8 (2 × CH_2N); HRESIMS calcd for $C_{19}H_{20}NO_2$ $(M + H)^+$ 294.1494; found 294.1490.

1-(2-Benzylidene-2,3-dihydrobenzofuran-3-yl)piperidine (5b). A mixture of $AgNO_3$ (161 mg, 0.95 mmol) and **4b** (1.385 g, 4.75 mmol) in anhydrous DMF (25 mL) was heated under N_2 at 60 °C for 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) to give product **5b** (1.086 g, 78%) as a pale yellow solid: mp 78−80 °C; R_f = 0.25 (EtOAc/petrol (1:9)); IR (neat) ν_{max} 3050, 2942, 2808, 1686, 1606, 1590, 1459, 1331, 1227, 1209, 753, and 691 cm^{-1}; ^1H NMR (300 MHz) δ 7.73 (2H, d, J = 8.0 Hz, Ar*H*), 7.42−7.33 (3H, m, Ar*H*), 7.26−7.19 (2H, m, Ar*H*), 7.04−7.01 (2H, m, Ar*H*), 5.85 (1H, s, C═C*H*Ar), 4.96 (1H, s, C*H*N), 2.72−2.63 (2H, m, CH_2N), 2.52−2.42 (2H, m, CH_2N), 1.59−1.50 (4H, m, 2 × CH_2), 1.43−1.34 (2H, m, CH_2); ^{13}C NMR (75 MHz) δ 158.2 (ArCO), 154.9 (OC═CH), 135.4 (Ar*C*), 129.4 (ArCH), 128.5 (2 × ArCH), 126.2 (2 × ArCH), 125.4 (Ar*C*), 122.1 (Ar*C*H), 110.1 (ArCH), 105.0 (C═CHAr), 68.8 (CHN), 49.8 (2 × CH_2N), 26.6 (2 × CH_2), 24.6 (CH_2); HRESIMS calcd for $C_{20}H_{22}NO$ $(M + H)^+$ 292.1701; found 292.1710.

1-(2-Benzylidene-2,3-dihydrobenzofuran-3-yl)pyrrolidine (5c). A mixture of $AgNO_3$ (229 mg, 1.35 mmol) and **4c** (1.883 g, 6.79 mmol) in anhydrous DMF (30 mL) was heated under N_2 at 60 °C for 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:19)) to give product **5c** (1.221 g, 65%) as a brown viscous oil: R_f = 0.23 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3053, 2965, 2811, 1686, 1611, 1594, 1461, 1347, 1228, 1210, 1069, 748, and 692 cm^{-1}; ^1H NMR (300 MHz) δ 7.72 (2H, d, J = 7.5 Hz, Ar*H*), 7.41 (1H, d, J = 7.0 Hz, Ar*H*), 7.35 (2H, J = 7.5 Hz, d, Ar*H*), 7.25 (1H, t, J = 7.5 Hz, Ar*H*), 7.04 (1H, d, J = 7.5 Hz, Ar*H*), 7.00 (1H, t, J = 7.0 Hz, Ar*H*), 5.83 (1H, s, C═C*H*Ar), 5.16 (1H, s, C*H*N), 2.77−2.62 (4H, m, 2 × CH_2N), 1.78−1.72 (4H, m, 2 xCH_2); ^{13}C NMR (75 MHz) δ 158.3 (*C*═CHAr), 154.8 (ArCO), 135.2 (Ar*C*), 129.5 (ArCH), 128.6 (2 × ArCH), 128.5 (2 × ArCH), 126.3 (ArCH), 126.2 (ArCH), 125.6 (Ar*C*), 122.2 (Ar*C*H), 110.3 (Ar*C*H), 105.7 (C═CHAr), 63.9 (*C*HN), 48.2 (2 × CH_2N), 23.5 (2 × CH_2); HRESIMS calcd for $C_{19}H_{20}NO$ $(M + H)^+$ 278.1545; found 278.1544.

1-(2-Benzylidene-2,3-dihydrobenzofuran-3-yl)pyrrolidine (5c) and 1-(Benzofuran-2-yl(phenyl)methyl)pyrrolidine (6c). A mixture of $AgNO_3$ (35 mg, 0.21 mmol) and **4c** (285 mg, 1.03 mmol) in anhydrous DMF (5 mL) was heated under N_2 at 100 °C for 18 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (5% EtOAc/petrol) to give **5c** (102 mg, 35.8%) and **6c** (6 mg, 2.1%). **Compound 6c:** a viscous yellow oil; R_f = 0.38 (20% EtOAc/petrol); IR (neat) ν_{max} 3052, 3029, 2965, 2874, 2786, 1584, 1492, 1452, 1251, 1134, 801, 744, and 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56 (2H, d, J = 7.50 Hz, Ar*H*), 7.46 (2H, t, J = 7.50 Hz, Ar*H*), 7.34−7.16 (5H, m, Ar*H*), 6.63 (1H, s, C═C*H*), 4.42 (1H, s, C*H*N), 2.52 (4H, brs, 2 × CH_2N), 1.80 (4H, brs, 2 × CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.8 (OC═CH), 154.9 (ArCO), 140.6 (Ar*C*), 128.5 (2 × ArCH), 128.3 (Ar*C*), 128.3 (2 × ArCH), 127.7 (ArCH), 123.8 (ArCH), 122.7 (ArCH), 120.8 (ArCH), 111.5 (Ar*C*H), 103.6 (OC═*C*H), 69.4 (*C*HN), 53.5 (2 × CH_2N), 23.5 (2 × CH_2); HRESIMS calcd for $C_{19}H_{20}NO$ $(M + H)^+$ 278.1545; found 278.1553.

4-(2-(4-Fluorobenzylidene)-2,3-dihydrobenzofuran-3-yl)-morpholine (5d). A mixture of $AgNO_3$ (22 mg, 0.13 mmol) and **4d** (203 mg, 0.65 mmol) in anhydrous DMF (5 mL) was heated under N_2 at 60 °C for 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (15:85)) and then crystallization with EtOAc/petrol to give product **5d** (165 mg, 81%) as a pale yellow solid: mp 128−130 °C; R_f = 0.15 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3063, 2973, 2932, 2823, 1690, 1593, 1508, 1457, 1340, 1228, 1210, 1106, 909, and 850 cm^{-1}; ^1H NMR (300 MHz) δ 7.71−7.66 (2H, m, Ar*H*), 7.43 (1H, d, J = 7.8 Hz, Ar*H*), 7.30 (1H, t, J = 7.8 Hz, Ar*H*), 7.09−7.02 (4H, m, Ar*H*), 5.84 (1H, s,C═C*H*Ar), 4.98 (1H, s, C*H*N), 3.71−3.68 (4H, m, 2 × CH_2O), 2.79−2.72 (2H, m, CH_2N), 2.58−2.51 (2H, m, CH_2N); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.4 (d, J = 245 Hz, ArCF), 158.2 (ArCO), 153.5 (*C*═CHAr), 131.2 (Ar*C*), 130.2 (ArCH), 130.1 (ArCH), 129.8 (ArCH), 126.3 (ArCH), 124.5 (Ar*C*), 122.4 (ArCH), 115.5 (d, J = 21 Hz, ArCH), 115.2 (ArCH), 110.3 (ArCH), 104.6 (C═CHAr), 68.2 (CHN), 67.5 (2 × CH_2O), 48.8 (2 × CH_2N); HRESIMS calcd for $C_{19}H_{19}NO_2F$ $(M + H)^+$ 312.1400; found 312.1413.

4-(Benzofuran-2-yl(4-methoxyphenyl)methyl)morpholine (6e). A mixture of $AgNO_3$ (21 mg, 0.12 mmol) and **4e** (203 mg, 0.63 mmol) in anhydrous DMF (5 mL) was heated under N_2 at 60 °C for 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) to give product **6e** (137 mg, 68%) as a viscous yellow oil: R_f = 0.28 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3065, 3035, 2956, 2851, 2806, 1607, 1509, 1452, 1247, 1172, 1114, 1032, 1005, 811, and 746 cm^{-1}; ^1H NMR (300 MHz) δ 7.50−7.42 (4H, m, Ar*H*), 7.23−7.14 (2H, m, Ar*H*), 6.86 (2H, d, J = 8.7 Hz, Ar*H*), 6.63 (1H, s, C═C*H*Ar), 4.45 (1H, s, C*H*N), 3.76 (3H, s, OCH_3), 3.72 (4H, t, J = 4.5 Hz, 2 × CH_2O), 2.52−2.38 (2H, m, 2 × CH_2N); ^{13}C NMR ($CDCl_3$,

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75 MHz) δ 159.3 (ArCO), 157.3 (*C*=CHAr), 155.0 (Ar*C*O), 130.7 (Ar*C*), 129.8 (2 × ArCH), 128.2 (Ar*C*), 123.9 (ArCH), 122.8 (ArCH), 120.8 (ArCH), 119.0 (2 × ArCH),111.5 (ArCH), 105.0 (C=*C*HAr), 69.2 (OCH_3), 67.1 (2 × CH_2O), 55.3 (CHN), 52.3 (2 × CH_2N); HRESIMS calcd for $C_{20}H_{22}NO_3$ $(M + H)^+$ 324.1600; found 324.1612.

4-(2-Hexylidene-2,3-dihydrobenzofuran-3-yl)morpholine (5f) and (*E*)-1-(2-Hydroxyphenyl)oct-1-en-3-one (13). A mixture of $AgNO_3$ (51 mg, 0.30 mmol) and **4f** (432 mg, 1.50 mmol) in anhydrous DMF (10 mL) was heated under N_2 at 60 °C for 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (NH_3/EtOAc/petrol (1:2.5:44)) to give **5f** (136 mg, 31.5%) and **13** (21 mg, 6.4%).

*Compound **5f**:* Light yellow viscous oil; R_f = 0.30 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3048, 2956, 2924, 2853, 1604, 1596, 1460, 1378, 1232, 1114, 898, and 751 cm^{-1}; ^1H NMR (300 MHz) δ 7.36 (1H, dd, J = 7.5, 0.6 Hz, Ar*H*), 7.22 (1H, dt, J = 7.5, 0.9 Hz, Ar*H*), 6.96 (1H, dt, J = 7.5, 0.9 Hz, Ar*H*), 6.90 (2H, d, J = 8.4 Hz, Ar*H*), 4.87 (1H, dt, J = 7.2, 1.5 Hz, C=C*H*CH_2), 4.76 (1H, s, C*H*N), 3.68−3.65 (4H, m, 2 × CH_2O), 2.68−2.59 (2H, m, CH_2N), 2.49−2.42 (2H, m, CH_2N), 2.28 (2H, appr q, J = 7.8 Hz, C=CHCH_2), 1.46−1.31 (6H, m, 3 × CH_2), 0.90 (3H, t, J = 6.6 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.3 (ArCO), 151.9 (OC=CH), 129.6 (ArCH), 126.3 (ArCH), 125.5 (Ar*C*), 121.6 (ArCH), 109.7 (ArCH), 107.0 (C=*C*HCH$_2$), 67.5 (2 × CH_2O), 66.5 (*C*HN), 48.5 (2 × CH_2N), 31.7 (CH_2), 29.6 (CH_2), 25.3 (C=HCH_2), 22.7 (CH_2), 14.3 (CH_2CH_3); HRESIMS calcd for $C_{18}H_{26}NO_2$ $(M + H)^+$ 288.1964; found 288.1959.

*Compound **13**:* pale yellow solid; mp 72−74 °C; R_f = 0.25 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3160, 2934, 2859, 1665, 1600, 1453, 1250, 1179, 975, and 745 cm^{-1}; ^1H NMR (300 MHz) δ 8.11 (1H, brs, ArO*H*), 7.69 (1H, d, J = 16.5 Hz, ArC*H*=CH), 7.47 (1H, dd, J = 8.0, 1.5 Hz, Ar*H*), 7.24 (1H, dt, J = 8.0, 1.5 Hz, ArC*H*), 7.02 (1H, d, J = 16.5 Hz, ArCH=C*H*), 6.96 (1H, d, J = 7.5 Hz, Ar*H*), 6.89 (1H, t, J = 7.5 Hz, Ar*H*), 2.71 (2H, t, J = 7.5 Hz, C*H*$_2$C=O), 1.69 (2H, quint, J = 7.5 Hz, CH_2), 1.36−1.31 (2H, m, CH_2CH$_3$), 0.90 (3H, t, J = 6.5 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz) δ 204.1 (C=O), 156.5 (ArCO), 140.2 (ArCH=CH), 130.0 (ArCH), 129.5 (ArCH), 126.6 (ArCH=*C*H), 121.8 (Ar*C*), 120.6 (ArCH), 116.8 (ArCH), 40.3 (CH$_2$C=O), 31.7 (*C*H$_2$), 24.6 (*C*H$_2$), 22.6 (*C*H$_2$CH$_3$), 14.1 (CH$_2$*C*H$_3$); HRESIMS calcd for $C_{14}H_{19}O_2$ $(M + H)^+$ 219.1385; found 219.1392.

2-(3-(Piperidin-1-yl)benzofuran-2(3*H*)-ylidene)ethanol (5g). A mixture of $AgNO_3$ (235 mg, 1.38 mmol) and **4g** (1.695 g, 6.61 mmol) in anhydrous DMF (40 mL) was heated under N_2 at 60 °C for 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:1)) to give product **5g** (1.426 g, 84%) as a viscous yellow oil. See above for physical and spectroscopic data.

4-(3-(Piperidin-1-yl)benzofuran-2(3*H*)-ylidene)butan-1-ol (5h) and 4′,5′-Dihydro-3′*H*-spiro[chromene-2,2′-furan] (14). A mixture of $AgNO_3$ (138 mg, 0.81 mmol) and **4h** (1,113 mg, 4.07 mmol) in anhydrous DMF (20 mL) was heated under N_2 at 60 °C for 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (50% EtOAc/petrol) to give **12a** (393 mg, 51.3%) and **5h** (356 mg, 32.0%).

*Compound **14**:* colorless oil; R_f = 0.20 (5% EtOAc/petrol (1:19)); IR (neat) ν_{max} 3046, 2981, 2886, 1642, 1605, 1487, 1189, 1121, 1063, 984 949, 842, and 754 cm^{-1}; ^1H NMR (300 MHz) δ 7.20−7.09 (2H, m, Ar*H*), 6.92−6.88 (2H, m, Ar*H*), 6.68 (1H, d, J = 9.6 Hz, ArC*H*=CH), 5.72 (1H, d, J = 9.6 Hz, ArCH=C*H*), 4.20−3.85 (2H, m, CH_2O), 2.37−2.32 (2H, m), 2.04−1.98 (2H, m); ^{13}C NMR (75 MHz) δ 151.8 (ArCO), 129.2 (ArCH), 126.88 (ArCH), 126.85 (ArCH=CH), 122.6 (ArCH=CH), 121.2 (ArCH), 120.4 (Ar*C*), 116.5 (ArCH), 105.3 (C(O)$_2$), 68.3 (CH$_2$O), 39.2 (CH$_2$), 24.5 (CH$_2$); ESIMS m/z 189 $(M + H)^+$. Spectroscopic data are identical to those in the literature.[16]

*Compound **5h**:* brown viscous oil; R_f = 0.27 (50% EtOAc/petrol); IR (neat) ν_{max} 3336, 2934, 2853, 1699, 1612, 1595, 1462, 1323, 1227, 1086, 750, and 729 cm^{-1}; ^1H NMR (500 MHz) δ 7.36 (1H, d, J = 7.5 Hz, Ar*H*), 7.20 (1H, t, J = 8.0 Hz, Ar*H*), 6.95 (1H, t, J = 7.5 Hz, Ar*H*), 6.87 (1H, d, J = 8.0 Hz, Ar*H*), 4.89 (1H, dt, J = 7.5, 1.5 Hz, C=C*H*), 4.75 (1H, s, C*H*N), 3.69 (2H, t, J = 6.5 Hz, CH_2OH), 2.75 (1H, brs, O*H*), 2.54−2.52 (2H, m, CH_2N), 2.41−2.34 (4H, m, CH_2N and C=CHCH_2), 1.73 (2H, quint, J = 7.0 Hz, CH$_2$CH_2CH$_2$), 1.56−1.48 (4H, m, 2 × CH_2), 1.40−1.36 (2H, m, CH_2); ^{13}C NMR (125 MHz) δ 158.0 (ArCO), 153.3 (OC=CHAr), 129.3 (ArCH), 126.3 (ArCH), 125.9 (Ar*C*), 121.6 (ArCH), 109.5 (ArCH), 105.1 (C=CHAr), 66.9 (*C*HN), 62.1 (CH$_2$OH), 49.4 (2 × *C*H$_2$N), 32.5 (CH$_2$), 26.3 (2 × CH$_2$), 24.5 (CH$_2$), 21.5 (C=CHCH$_2$); HRESIMS calcd for $C_{17}H_{24}NO_2$ $(M + H)^+$ 274.1807; found 274.1807.

2-Benzylidene-*N*,*N*-dibutyl-2,3-dihydrobenzofuran-3-amine (5i). A mixture of $AgNO_3$ (109 mg, 0.64 mmol) and **4i** (1.080 g, 3.22 mmol) in anhydrous DMF (20 mL) was heated under N_2 at 60 °C for 1 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:49)) to give product **5i** (1.086 g, 84.5%) as a viscous yellow oil: R_f = 0.70 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3055, 3024, 2955, 2929, 2865, 2820, 1685, 1610, 1595, 1460, 1341, 1228, 1209, 1083, 917, 747, and 693 cm^{-1}; ^1H NMR (300 MHz) δ 7.70 (2H, d, J = 7.5 Hz, Ar*H*), 7.38−7.33 (3H, m, Ar*H*), 7.25−7.15 (2H, m, Ar*H*), 7.03−7.95 (2H, m, Ar*H*), 5.80 (1H, s,C=C*H*Ar), 5.19 (1H, s, C*H*N), 2.63−2.44 (2H, m, 2 × CH_2N), 1.45 (4H, quint, J = 7.5 Hz, 2 × CH_2), 1.30 (4H, sext, J = 7.2 Hz, 2 × CH_2CH$_3$), 0.86 (6H, t, J = 7.2 Hz, 2 × CH$_2$CH_3); ^{13}C NMR (75 MHz) δ 158.0 (ArCO), 156.2 (OC=CHAr), 135.5 (Ar*C*), 129.2 (ArCH), 128.5 (2 × ArCH), 128.4 (2 × ArCH), 126.4 (Ar*C*), 126.1 (ArCH), 125.9 (ArCH),122.1 (ArCH), 110.3 (ArCH), 104.2 (C=CHAr), 64.3 (*C*HN), 50.9 (2 × *C*H$_2$N), 31.1 (2 × *C*H$_2$), 20.5 (2 × *C*H$_2$CH$_3$), 14.2 (2 × CH$_2$*C*H$_3$); HRESIMS calcd for $C_{23}H_{30}NO$ $(M + H)^+$ 336.2327; found 336.2332.

4-(Benzofuran-2-yl(phenyl)methyl)morpholine (6a). *Method A:* A mixture of $AgNO_3$ (12 mg, 0.07 mmol) and **5a** (97 mg, 0.33 mmol) in anhydrous DMF (5 mL) was heated under N_2 at 100 °C for 24 h. The solvent was removed under reduced pressure, and the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:5)) to give **6a** (66 mg, 68%) as a yellow viscous oil: R_f = 0.40 (20% EtOAc/petrol (1:4); IR (neat) ν_{max} 3061, 3030, 2956, 2852, 2807, 1584, 1492, 1451, 1393, 1251, 1114, 870, 746, and 701 cm^{-1}; ^1H NMR (300 MHz) δ 7.53 (2H, d, J = 7.5 Hz, Ar*H*), 7.49 (1H, d, J = 8.0 Hz, Ar*H*), 7.45 (1H, d, J = 8.5 Hz, Ar*H*), 7.33 (2H, t, J = 8.0 Hz, Ar*H*), 7.26 (1H, t, J = 7.5 Hz, Ar*H*), 7.22 (1H, t, J = 7.0 Hz, Ar*H*), 7.18 (1H, t, J = 7.0 Hz, Ar*H*), 6.65 (1H, s, C=C*H*), 4.50 (1H, s, C*H*N), 3.73 (4H, t, J = 5.0 Hz, 2 × CH_2O), 2.52−2.42 (4H, m, 2 × CH_2N); ^{13}C NMR (75 MHz) δ 157.0 (C=CO), 155.1 (ArCO), 138.7 (Ar*C*), 128.7 (2 × ArCH), 128.6 (2 × ArCH), 128.2 (Ar*C*), 127.9 (ArCH), 124.0 (ArCH), 122.8 (ArCH), 120.9 (ArCH), 111.5 (ArCH), 105.3 (C=*C*H), 69.9 (*C*HN), 67.1 (2 × *C*H$_2$O), 52.3 (2 × *C*H$_2$N); HRESIMS calcd for $C_{19}H_{20}NO_2$ $(M + H)^+$ 294.1494; found 294.1501.

Method B in MeCN: To a solution of **5a** (89 mg, 0.30 mmol) in anhydrous CH_3CN (5 mL) at rt was added $BF_3{\cdot}Et_2O$ (60 μL, 0.46 mmol) dropwise under N_2, and the mixture was stirred at rt for 4 h. The solution was treated with saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (2 × 15 mL). The combined EtOAc extract was washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) to give product **6a** (86 mg, 97%).

Method B in CH_2Cl_2: To a solution of **5a** (100 mg, 0.34 mmol) in anhydrous CH_2Cl_2 (5 mL) at rt was added $BF_3{\cdot}Et_2O$ (63 μL, 0.51 mmol) dropwise under N_2, and the mixture was stirred at rt for 2 h. After a workup procedure similar to that described above, the crude mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) to give **6a** (87 mg, 87%).

1-(Benzofuran-2-yl(phenyl)methyl)piperidine (6b). The title compound was prepared according to method B above from **5b** (102 mg, 0.35 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (65 μL, 0.53 mmol). After stirring the solution at rt for 18 h, the reaction mixture was worked up as described above. The crude mixture was purified using flash column chromatography (EtOAc/petrol (1:23)) to give **6b** (59 mg, 58%) and staring material (**5b**) (42 mg, 41%). Compound **6b** was obtained as a brown viscous oil: R_f = 0.28 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3062, 3029, 2932, 2852, 2796, 1583, 1491, 1450, 1252,

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1160, 807, 744, and 699 cm^{-1}; ^1H NMR (300 MHz) δ 7.51−7.42 (4H, m, ArH), 7.34−7.12 (5H, m, ArH), 6.61 (1H, s, OC=CH), 4.55 (1H, s, CHN), 2.41 (4H, brs, 2 × CH_2N), 1.58 (4H, brs, 2 × CH_2), 1.41 (2H, brs, CH_2); ^{13}C NMR (75 MHz) δ 157.9 (OC=CH),155.0 (ArCO), 139.4 (ArC), 128.6 (2 × ArCH), 128.4 (2 × ArCH), 127.5 (ArCH), 123.7 (ArCH), 122.7 (ArCH), 120.7 (ArCH), 111.5 (ArCH), 105.0 (OC=CH), 69.9 (CHN), 52.9 (2 × CH_2N), 26.2 (2 × CH_2), 24.6 (CH_2); HRESIMS calcd for $C_{20}H_{22}NO$ $(M + H)^+$ 292.1701; found 292.1708.

1-(Benzofuran-2-yl(phenyl)methyl)pyrrolidine (6c). The title compound was prepared according to method B above from **5c** (100 mg, 0.36 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (66 μL, 0.54 mmol). After stirring the solution at rt for 24 h, the reaction mixture was worked up as described above. The crude mixture was purified using flash column chromatography (EtOAc/petrol (1:23)) to give **6c** (43 mg, 43%) and recovered staring material (**5c**) (56 mg, 56%). The physical and spectroscopic data for **6c** are described above.

4-(Benzofuran-2-yl(4-fluorophenyl)methyl)morpholine (6d). The title compound was prepared according to method B above from **5d** (105 mg, 0.30 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (55 μL, 0.45 mmol). After stirring the solution at rt for 1 h, the reaction mixture was worked up as described above. The crude mixture was purified using flash column chromatography (20% EtOAc/petrol (1:4)) to give **6d** (101 mg, 96%) as a pale yellow solid: mp 56−58 °C; R_f = 0.35 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3061, 3039, 2931, 2874, 2853, 2823, 1689, 1592, 1508, 1458, 1227, 1209, 1107, 1007, 909, 849, and 758 cm^{-1}; ^1H NMR (300 MHz) δ 7.55−7.44 (4H, m, ArH), 7.27−7.16 (2H, m, ArH), 7.02 (2H, appr t, J = 15 Hz, ArH), 6.64 (1H, d, J = 0.9 Hz, C=CH), 4.49 (1H, s, CHN), 3.73 (4H, t, J = 4.8 Hz, 2 × CH_2O); 2.52−2.38 (4H, m, 2 × CH_2N); ^{13}C NMR (75 MHz) δ 162.4 (J = 245 Hz, ArCF), 156.6 (OC=C), 155.1 (ArCO), 134.5 (d, J = 3.8 Hz, ArC), 130.3 (d, J = 8.0 Hz, ArCH), 128.1 (ArC), 124.2 (ArCH), 122.9 (ArCH), 120.9 (ArCH), 115.5 (d, J = 21.5 Hz, ArCH), 111.5 (ArCH), 105.4 (CH=C), 69.0 (CHN), 67.1 (2 × CH_2O), 52.3 (2 × CH_2N); HRESIMS calcd for $C_{19}H_{19}FNO_2$ $(M + H)^+$ 312.1400; found 312.1397.

4-(1-(Benzofuran-2-yl)hexyl)morpholine (6f). The title compound was prepared according to method B above from **5f** (101 mg, 0.35 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (65 μL, 0.53 mmol). After stirring the solution at rt for 6 h, the reaction mixture was worked up as described above. The crude mixture was purified using flash column chromatography (EtOAc/petrol (1:23)) to give **6f** (22 mg, 22%) and recovered staring material (**5f**) (67 mg, 66%). Compound **6f** was obtained as a light yellow oil; R_f = 0.28 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3064, 3036, 2954, 2929, 2853, 1613, 1577, 1452, 1251, 1116, 1004, and 743 cm^{-1}; ^1H NMR (300 MHz) δ 7.52 (1H, d, J = 7.5 Hz, ArH), 7.46 (1H, d, J = 7.5 Hz, ArH), 7.24−7.20 (2H, m, ArH), 6.51 (1H, s, OC=CH), 3.71−3.68 (4H, m, 2 × CH_2O), 3.58 (1H, t, J = 6.5 Hz, CHN), 2.62−2.50 (4H, m, 2 × CH_2N), 1.95−1.85 (2H, m, CH_2), 1.49−1.22 (6H, m, 3 × CH_2), 0.85 (3H, t, J = 6.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz) δ 156.9 (OC=CH), 154.8 (ArCO), 128.2 (ArC), 123.8 (ArCH), 122.7 (ArCH), 120.8 (ArCH), 111.4 (ArCH), 105.2 (OC=CH), 67.4 (2 × CH_2O), 63.6 (CHN), 50.5 (2 × CH_2N), 31.9 (CH_2), 30.4 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 14.1 (CH_2CH_3); HRESIMS calcd for $C_{18}H_{26}NO_2$ $(M + H)^+$ 288.1964; found 288.1967.

***N*-(Benzofuran-2-yl(phenyl)methyl)-*N*-butylbutan-1-amine (6i).** The title compound was prepared according to method B above from **5i** (107 mg, 0.32 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (59 μL, 0.48 mmol). After stirring the solution at rt for 24 h, the reaction mixture was worked up as described above. The crude mixture was purified using flash column chromatography (EtOAc/petrol (1:49)) to give **6i** (99 mg, 87%) as a light yellow viscous oil: R_f = 0.70 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3062, 3030, 2956, 2928, 2865, 1600, 1579, 1452, 1377, 1251, 1165, 1071, 744, and 698 cm^{-1}; ^1H NMR (300 MHz) δ 7.54−7.45 (4H, m, ArH), 7.343−7.18 (5H, m, ArH), 6.60 (1H, s, C=CHAr), 5.12 (1H, s, CHN), 2.62−2.53 (2H, m, CH_2N), 2.49−2.40 (2H, m, CH_2N), 1.52−1.41 (4H, m, 2 × CH_2), 1.34−1.18 (4H, m, 2 × CH_2CH_3), 0.85 (6H, t, J = 7.5 Hz, 2 × CH_2CH_3); ^{13}C NMR (75 MHz) δ 157.7 (OC=CHAr) 155.0 (ArCO), 140.2 (ArC), 128.7 (2 × ArCH), 128.4 (ArCH), 128.2 (2 × ArCH), 127.3 (2 × ArCH), 123.7 (ArCH), 122.7 (ArCH), 120.8 (ArCH), 111.5 (ArCH), 105.8 (C=CHAr), 63.6 (CHN), 50.5 (2 × CH_2N), 30.0 (2 × CH_2), 20.6 (2 × CH_2CH_3), 14.3 (2 × CH_2CH_3); HRESIMS calcd for $C_{23}H_{30}NO$ $(M + H)^+$ 336.2327; found 336.2318.

2-(1-Phenylbut-3-en-1-yl)benzofuran (15a). *Method A: Using Allyl Trimethylsilane.* To a solution of **5a** (103 mg, 0.35 mmol) and allyl trimethylsilane (168 μL, 1.05 mmol) in anhydrous CH_2Cl_2 (5 mL) at rt was added $BF_3{\cdot}Et_2O$ (65 μL, 0.53 mmol) dropwise under N_2. After stirring at rt for 2 h, the reaction mixture was treated with saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined CH_2Cl_2 extract was washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude reaction mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) to give **6a** (55 mg, 53%) and **15a** (40 mg, 46%). Compound **15a** was obtained as a colorless viscous oil: R_f = 0.50 (EtOAc/petrol (1:23)); IR (neat) ν_{max} 3064, 3030, 1638, 1581, 1451, 1252, 916, 744, and 698 cm^{-1}; ^1H NMR (500 MHz) δ 7.48−7.46 (1H, m, ArH), 7.42−7.38 (1H, m, ArH), 7.32−7.26 (4H, m, ArH), 7.24−7.16 (3H, m, ArH), 6.46 (1H, s, OC=CH), 5.82−5.69 (1H, m, CH=CH_2), 5.11−4.96 (2H, m, CH=CH_2), 4.15 (1H, t, J = 7.5 Hz, $CHCH_2$), H4), 3.08−2.41 (2H, m, CH_2); ^{13}C NMR (125 MHz) δ 160.5 (OC=CH), 154.9 (ArCO), 141.5 (ArC), 135.9 (CH=CH2), 128.7 (2 × ArCH), 128.2 (2 × ArCH), 127.0 (ArCH), 123.6 (ArCH), 122.6 (ArCH), 120.6 (ArCH), 117.0 (CH=CH_2), 111.1 (ArCH), 103.0 (OC=CH), 45.9 ($CHCH_2$), 38.9 (CH_2); HRESIMS calcd for $C_{18}H_{17}O$ $(M + H)^+$ 249.1279; found 249.1275.

Method B: Using Allyl Tributylstannane. To a solution of **5a** (100 mg, 0.34 mmol) and allyltributylstanane (316 μL, 1.02 mmol) in anhydrous acetonitrile (5 mL) at rt was added $BF_3{\cdot}Et_2O$ (62 μL, 0.51 mmol) dropwise under N_2. After stirring for 2 h at rt, the reaction mixture was treated with saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined CH_2Cl_2 extract was washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude reaction mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) to give **6a** (26 mg, 26%) and **15a** (61 mg, 73%).

*Method C: From Allylation of 1-(2-Benzylidene-2,3-dihydrobenzofuran-3-yl)piperidine (**5b**) with Allyltributylstannane.* The title compound was prepared according to method B above from **5b** (100 mg, 0.34 mmol) and allyltributylstannane (316 μL, 1.02 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (63 μL, 0.51 mmol). After stirring the solution at rt for 18 h, the reaction mixture was worked up as described above. The crude reaction mixture was purified using flash column chromatography (5% EtOAc/petrol (1:23)) to give **15a** (73 mg, 87%) as a colorless oil.

*Method D: From Allylation of 1-(2-Benzylidene-2,3-dihydrobenzofuran-3-yl)pyrrolidine (**5c**) with Allyltributylstannane.* The title compound was prepared according to method B above from **5c** (105 mg, 0.38 mmol) and allyltributylstannane (353 μL, 1.14 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (70 μL, 0.57 mmol). After stirring the solution at rt for 18 h, the reaction mixture was worked up as described above. The crude reaction mixture was purified using flash column chromatography (5% EtOAc/petrol (1:23)) to give **15a** (36 mg, 38%), **6c** (4 mg, 3.8%), and recovered starting material (**5c**) (60 mg, 57%).

2-(1-(4-Fluorophenyl)but-3-en-1-yl)benzofuran (15d). The title compound was prepared according to method B above from **5d** (99 mg, 0.32 mmol) and allyltributylstannane (298 μL, 0.96 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (59 μL, 0.48 mmol). After stirring the solution at rt for 2 h, the reaction mixture was worked up as described above. The crude reaction mixture was purified using flash column chromatography (EtOAc/petrol (1:23)) to give **6d** (30 mg, 30%) and **15d** (59 mg, 69%). Compound **15d** was obtained as a colorless viscous oil: R_f = 0.50 (EtOAc/petrol (1:23)); IR (neat) ν_{max} 3070, 2925, 1641, 1602, 1507, 1452, 1253, 1224, 1161, 917, and 744 cm^{-1}; ^1H NMR (300 MHz) δ 7.50−7.47 (1H, m, ArH), 7.41−7.38 (1H, m, ArH), 7.27−7.17 (4H, m, ArH), 7.04−6.96 (2H, m, ArH), 6.45 (1H, s, C=CH), 5.80−5.68 (1H, m, CH=CH_2), 5.10−4.97 (2H, m, CH=CH_2), 4.13 (1H, t, J = 8.1 Hz, $CHCH_2$), 3.00−2.91

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(1H, m, $CHCH_2$), 2.75−2.67 (1H, m, $CHCH_2$); ^{13}C NMR (75 MHz) δ 161.9 (d, J = 244 Hz, ArCF), 160.2 (OC=CH), 154.9 (ArCO), 137.2 (d, J = 3.2 Hz, ArC), 135.6 ($CH_2CH=CH_2$), 129.7 (d, J = 7.7 Hz, ArCH), 128.6 (ArC), 123.7 (ArCH), 122.7 (ArCH), 120.7 (ArCH), 117.3 ($CH_2CH=CH_2$), 115.5 (d, J = 21.2 Hz, ArCH), 111.1 (C=CCO), 103.0 (CHAr), 45.1 ($CHCH_2$), 38.9 ($CH_2CH=CH_2$); HRESIMS calcd for $C_{18}H_{16}OF$ $(M + H)^+$ 267.1185; found 267.1187.

2-(1-(4-Methoxyphenyl)but-3-en-1-yl)benzofuran (15e). The title compound was prepared according to method B above from **6e** (80 mg, 0.25 mmol) and allyltributylstannane (233 μL, 0.75 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (47 μL, 0.38 mmol). After stirring the solution at rt for 18 h, the reaction mixture was worked up as described above. The crude reaction mixture was purified using flash column chromatography (EtOAc/petrol (1:23)) to give **15e** (25 mg, 36%) as a colorless viscous oil: R_f = 0.35 (EtOAc/petrol (1:23)); IR (neat) ν_{max} 3069, 3034, 2931, 2835, 1610, 1582, 1510, 1453, 1248, 1175, 1034, 915 803 and 745 cm^{-1}; ^1H NMR (300 MHz) δ 7.47 (1H, d, J = 8.0 Hz, ArH), 7.39 (1H, d, J = 8.0 Hz, ArH), 7.23−7.13 (4H, m, ArH), 6.85 (2H, d, J = 8.7 Hz, ArH), 6.43 (1H, s, OC=CH), 5.82−5.68 (1H, m, $CH=CH_2$), 5.07 (1H, d, J = 17.1 Hz), 4.98 (d, J = 10.2 Hz), 4.10 (1H, t, J = 7.8 Hz, $CHCH_2$), H4), 3.77 (3H, s, OCH_3), 3.00−2.91 (1H, m), 2.78−2.66 (1H, m); ^{13}C NMR (75 MHz) δ 160.9 (OC=CH), 158.6 (ArCO), 154.9 (ArCO), 136.0 ($CH=CH_2$), 133.6 (ArC), 129.1 (2 × ArCH), 128.7 (ArC), 123.5 (ArCH), 122.6 (ArCH), 120.6 (ArCH), 117.0 ($CH=CH_2$), 114.0 (2 × ArCH), 111.1 (ArCH), 102.7 (OC=CH), 55.4 (OCH_3), 45.0 ($CHCH_2$), 39.0 (CH_2); HRESIMS calcd for $C_{19}H_{19}O_2$ $(M + H)^+$ 279.1385; found 279.1376.

2-(Non-1-en-4-yl)benzofuran (15f). The title compound was prepared according to method B above from **5f** (101 mg, 0.35 mmol) and allyltributylstannane (326 μL, 1.05 mmol) using CH_2Cl_2 (5 mL) and $BF_3{\cdot}Et_2O$ (65 μL, 0.53 mmol). After stirring the solution at rt for 2 h, the reaction mixture was worked up as described above. The crude reaction mixture was purified using flash column chromatography (100% petrol) to give **15f** (74 mg, 87.1%) as a colorless oil: R_f = 0.60 (5% EtOAc/petrol (1:23)); IR (neat) ν_{max} 3072, 2926, 2857, 1641, 1586, 1451, 1251, 1171, 913, 798, and 742 cm^{-1}; ^1H NMR (300 MHz) δ 7.50−7.41 (2H, m, ArH), 7.23−7.17 (2H, m, ArH), 6.38 (1H, s, C=CH), 5.81−5.67 (1H, m, $CH=CH_2$), 5.06−4.95 (2H, m, $CH=CH_2$), 2.95−2.83 (1H, m, $CH(CH_2)_2$), 2.58−2.38 (2H, m, $CH_2CH=CH_2$), 1.80−1.60 (2H, m, CH_2), 1.27 (6H, brs, 3 × CH_2), 0.85 (3H, brs, CH_2CH_3); ^{13}C NMR (75 MHz) δ 161.9 (OC=C), 154.7 (ArCO), 136.4 ($CH=CH_2$), 128.9 (ArC), 123.1 (ArCH), 122.5 (ArCH), 120.4 (ArCH), 116.5 ($CH=CH_2$), 111.0 (ArCH), 102.3 (CH=CO), 39.6 ($CH(CH_2)_2$), 38.3 ($CH_2CH=CH_2$), 33.3 (CH_2), 31.9 (CH_2), 27.0 (CH_2), 22.7 (CH_2), 14.2 (CH_2CH_3); HRESIMS calcd for $C_{17}H_{22}O$ $(M + H)^+$ 243.1749; found 243.1741.

2-(Furan-2-yl(phenyl)methyl)benzofuran (16). To a solution of **5a** (101 mg, 0.34 mmol) and furan (248 μL, 3.40 mmol) in anhydrous acetonitrile (5 mL) at rt was added $BF_3{\cdot}Et_2O$ (62 μL, 0.51 mmol) dropwise under N_2. After stirring for 2 h at rt, the reaction mixture was treated with saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined CH_2Cl_2 extract was washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude reaction mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) to give **6a** (54 mg, 54%) and **16** (40 mg, 43%). Compound **16** was obtained as a brown viscous oil; R_f = 0.60 (EtOAc/petrol (1:5)); IR (neat) ν_{max} 3062, 3030, 1583, 1499, 1452, 1165, 1009, 736, and 697 cm^{-1}; ^1H NMR (300 MHz) δ 7.56−7.18 (9H, m, ArH), 6.41 (1H, m, furanyl-H), 6.35 (1H, brs, furanyl-H), 6.11 (1H, brs, furanyl-H), 5.59 (1H,s, CH); ^{13}C NMR (75 MHz) δ 157.6 (OC=CH), 155.1 (ArCO), 153.8 (furanyl-C), 142.3 (OC=CH), 138.9 (ArC), 128.8 (2 × ArCH), 128.6 (2 × ArCH), 128.5 (ArC), 127.6 (ArCH), 124.0 (ArCH), 122.8 (ArCH), 120.9 (ArCH), 111.3 (ArCH), 110.5 (furanyl-C), 108.1 (furanyl-C), 104.9 (furanyl-C), 45.6 (CH); HRESIMS calcd for $C_{19}H_{15}O_2$ $(M + H)^+$ 275.1072; found 275.1064.

2-(Methoxy(phenyl)methyl)benzofuran (17). To a solution of **5a** (100 mg, 0.34 mmol) and methanol (139 μL, 3.40 mmol) in anhydrous acetonitrile (5 mL) at rt was added $BF_3{\cdot}Et_2O$ (62 μL, 0.51 mmol) dropwise under N_2. The mixture was stirred at rt for 2 h and then treated with saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined CH_2Cl_2 extract was washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude reaction mixture was purified using flash column chromatography (EtOAc/petrol (1:9)) to give **6a** (48 mg, 48%) and **17** (42 mg, 52%). Compound **17** was obtained as a light yellow oil: R_f = 0.58 (EtOAc/petrol (1:4)); IR (neat) ν_{max} 3062, 3032, 2931, 1822, 1600, 1451, 1252, 1087, 745, and 698 cm^{-1}; ^1H NMR (300 MHz) δ 7.50−7.14 (9H, m, ArH), 6.52 (1H, s, C=CH), 5.39 (1H, s, $Ar(OCH_3)CH$), 3.45 (3H, s, OCH_3); ^{13}C NMR (75 MHz) δ 157.1 (C=CO), 155.3 (ArCO), 138.6 (ArC), 128.6 (2 × ArCH), 128.4 (ArCH), 128.1 (ArC), 127.4 (2 × ArCH), 124.4 (ArCH), 122.8 (ArCH), 121.2 (ArCH), 111.5 (ArCH), 105.1 (C=CH), 79.5 [$(OCH_3)CAr$], 57.4 (OCH_3); HRESIMS calcd for $C_{16}H_{15}O_2$ $(M + H)^+$ 239.1072; found 239.1092.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of all synthesized compounds and the X-ray crystallographic details of compound **12** (CCDC no 911817). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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