Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

# Brønsted Acid Mediated Cascade Reaction To Access 3-(2-Bromoethyl)benzofurans

Stefania Porcu,[†] Stefania Demuro,[†] Alberto Luridiana,[†] Andrea Cocco,[†] Angelo Frongia,[†] David J. Aitken,[‡] Florence Charnay-Pouget,[‡] Regis Guillot,[‡] Giorgia Sarais,[§] and Francesco Secci*[,†]

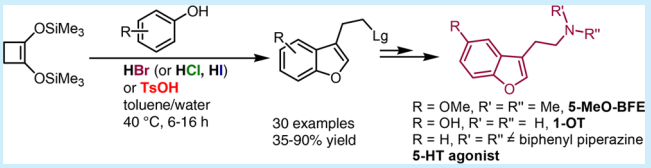
[†]Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Complesso Universitario di Monserrato, S.S. 554, bivio per Sestu, 09042 Monserrato (Ca) Italy

[‡]CP3A Organic Synthesis Group & Services Communs, ICMMO (UMR 8182), CNRS, Université Paris Sud, Université Paris Saclay, 15 rue Georges Clemenceau, 91405 Orsay, Cedex, France

[§]Dipartimento di Scienze della Vita e dell'Ambiente, Università degli Studi di Cagliari, Palazzo delle Scienze, via Ospedale 82, 09124 Cagliari, Italy

Supporting Information

**ABSTRACT:** A unified protocol for the construction of 3-(2-bromoethyl)benzofurans and 2-(benzofuran-3-yl)ethylamines from bis[(trimethylsilyl)oxy]cyclobutene has been developed. This mild and facile strategy was applied for the synthesis of a series of 5-HT serotonin receptor agonists, underlining its potential for the syntheses of bioactive compounds and natural products.




Benzofuran derivatives represent an important class of oxygen-containing heterocycles found in many natural products isolated from plants, sponges, and mushrooms.[1] These compounds exhibit important biological properties, and different derivatives of this family have been investigated as antimicrobial agents,[2] antidepressants,[3] acetylcholine esterase inhibitors,[4] or as pain relief or anesthetic drugs.[5] Moreover, a certain number of 2-(benzofuran-3-yl)ethylamines, such as 5-MeO-BFE and 5-MeO-DiBF, possess strong psychedelic effects leading to their use as recreational drugs, acting as 5-$HT_{1A}$ and 5-$HT_2$ serotonin receptor agonists similar to tryptamine analogues.[6] All of these compounds are characterized by the functionalization of the benzofuran 3-position with an ethylamine fragment (Figure 1). For this reason, several synthetic strategies have been developed for the preparation of 2-(benzofuran-3-yl)ethylamines and their precursors, 3-(2-halogenoethyl)benzofurans: these include multistep functionalization of benzofuran-3-ones,[6a,7] photoredox 1,4-addition,[8] base-mediated Michael addition of acrylates,[9] Ru-catalyzed 3-alkylation of 2-arylbenzofurans,[10] and Pd-catalyzed intramolecular cyclization of 2-bromobenzene ethers.[11] In contrast, the direct construction of 3-(2-halogenoethyl)benzofuran moieties has not been reported before. Considering that multistep approaches generally require the preparation of prefunctionalized substrates, significant efforts for purification, the production of large amount of waste, and a consequential increase in operational costs, the development of a simple and practical method to access these functionalized heterocycles is still highly desirable. To continue our work on exploration of the reactivity of 2-hydroxycyclobutanone,[12] we now report that 3-(2-bromoethyl)benzofurans can be readily obtained from commercially available bis[(trimethylsilyl)oxy]cyclobutene **1a**

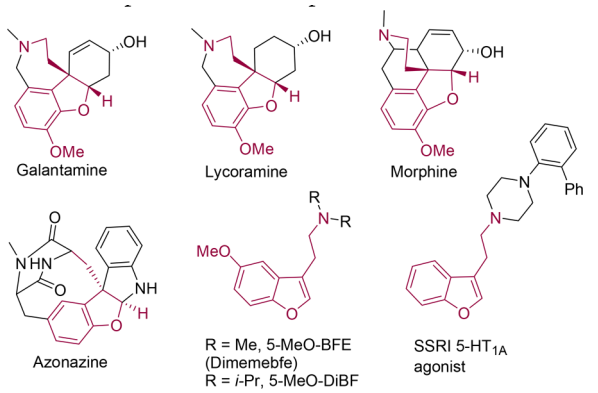



**Figure 1.** Representative natural products: galantamine, lyco-ramine, morphine, azonazide, and bioactive compounds as 5-MeO-BFE, 5-MeO-DiBF, and a biphenylpiperazine 5-HT receptor agonist, bearing a 2-(benzofuran-3-yl)ethylamine structural unit.

and various phenols **2** via a Brønsted acid mediated nucleophilic addition−carbocyclic rearrangement cascade reaction; this is a one-pot, metal-free process that operates under mild conditions.

Recently, our research group reported some important advances in the use of 2-hydroxycyclobutanone for the rapid synthesis of functionalized tryptamines[13] and tricyclic dioxins.[14] In the presence of a Brønsted acid, 2-hydroxycyclobutanone **1b** and its precursor bis[(trimethylsilyl)oxy]cyclobutene **1a** can behave as electrophilic acceptors for intermolecular nucleophilic addition followed by a ring closure−ring fission process.[13] These

**Received:** October 26, 2018



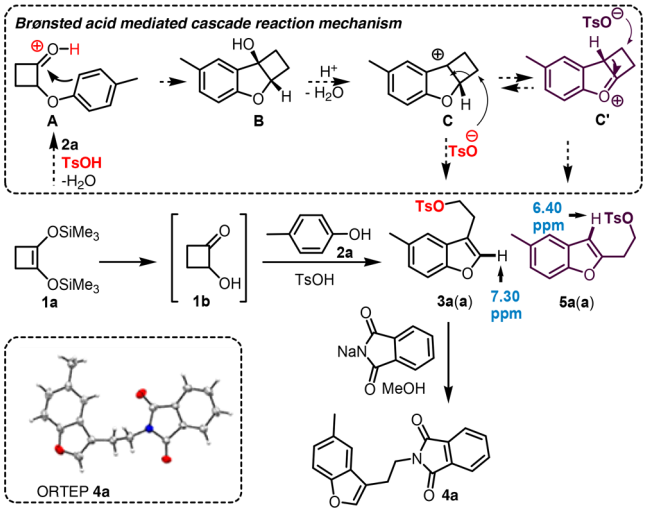



DOI: 10.1021/acs.orglett.8b03429
Org. Lett. XXXX, XXX, XXX−XXX

observations led us to speculate that the reaction of **1a** or **1b** with a phenol **2** might deliver a one-pot cascade-reaction assembly of the benzofuran molecular scaffold.

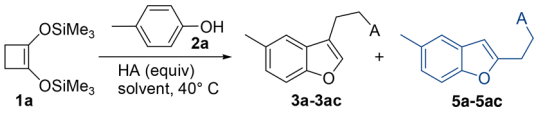
According to our hypothesis (Scheme 1), a Brønsted acid should promote the formation of the corresponding 2-aryloxycyclobutanone **A** from **1a** (or **1b**) and **2a**. Subsequent acid-mediated intramolecular ring closure should furnish the corresponding dihydrocyclobutabenzofuran **B**. Finally, acid-induced generation of carbocationic species **C** and nucleophilic attack should lead to the formation of a benzofuran **3** or **5**.

**Scheme 1. Rational Design for the Synthesis of 3-Substituted Benzofurans via a Brønsted Acid-Catalyzed Cascade Reaction and ORTEP Representation of Compound 4a**




To test our hypothesis, we first examined the reaction between **1a** and *p*-cresol **2a**, at 40 °C and in the presence of TsOH (1.0 equiv). We were encouraged to find that under solvent-free conditions, the desired benzofuran product **3a**(**a**) could be isolated from the reaction mixture in 30% yield accompanied by traces (<7%) of the compound **5a**(**a**) (Table 1, entry 1). Tosylate **3a**(**a**) was also reacted with Na-phthalimide in order to achieve the crystalline solid **4a** (characterized by NMR and X-ray diffraction analysis). The use of toluene (entry 2) or dichloromethane (entry 3) as a solvent provided a significant improvement since the isolated yield of **3a**(**a**) almost doubled in each case. However, the reaction did not proceed at all when THF, EtOAc, or 1,4-dioxane was employed as solvent (entries 4–6). Retaining a toluene solution at 40 °C as standard conditions, the activity of other Brønsted acids (as concentrated aqueous solutions) was evaluated: HI provided a 3:1 mixture of the corresponding 3-(2-iodoethyl)benzofuran **3a**(**b**) (2-CH, 7.49 ppm) and 2-(2-iodoethyl)benzofuran **5a**(**b**) (3-CH, 6.45 ppm) in 70% isolated overall yield (entry 7), while HBr and HCl performed better, leading to the corresponding benzofuran adducts **3a** and **3a**(**c**) in 78% and 84% yields, respectively, and higher regioselectivity (entries 8–9 and Scheme 2).[15] HF and TFA, however, appeared to be largely unreactive (entries 10–11). Further evaluation of the preparation of **3a** was carried out using excess acid loading (entries 12–13), which led to an optimum yield (89%) in the presence of 2.0 equiv of the acid. Moreover, the same results were obtained when **1b** was used as the functionalized cyclobutanone source in the place of **1a** (entry 14). With the optimized reaction conditions in hand, we next examined the substrate scope using a series of phenols **2a–w**. The results are summarized in Scheme 2. A reasonable substituent tolerance in the phenols emerged, allowing access to a variety of highly functionalized benzofurans with diverse ring-substituent patterns. Phenols **2a–f**, bearing *m*- or *p*-alkoxy substituents, furnished the corresponding adducts **3a–f**[16] in good chemical yields and high regioselectivity.

**Table 1. Initial Screening Studies**[a]




| entry | HA (equiv) | solvent | **3** yield %[b] | **3**/**5** ratio[c] |
|---|---|---|---|---|
| 1 | TsOH (1) | | 30 (**3aa**) | 15:1 |
| 2 | TsOH (1) | toluene | 59 (**3aa**) | 17:1 |
| 3 | TsOH (1) | $CH_2Cl_2$ | 57 (**3aa**) | 17:1 |
| 4 | TsOH (1) | THF | | |
| 5 | TsOH (1) | 1,4-dioxane | | |
| 6 | TsOH (1) | EtOAc | | |
| 7 | HI (1)[d] | toluene | 70 (**3ab**) | 3:1 |
| 8 | HBr (1)[e,f] | toluene | 79 (**3a**) | 20:1 |
| 9 | HCl (1)[g] | toluene | 84 (**3ac**) | 25:1 |
| 10 | HF (1)[h] | toluene | *n.d.* (**3ad**) | |
| 11 | TFA (1) | toluene | | |
| 12 | HBr (1.5) | toluene | 82 (**3a**) | 23:1 |
| 13 | HBr (2) | toluene | 89 (**3a**) | 27:1 |
| 14 | HBr (2)[i] | toluene | 88 (**3a**) | 25:1 |

[a]Reactions were performed with 50 mg (0.2 mmol) of **1a**, **2a** (1.1 equiv), acid (0.2–0.4 mmol), solvent (1.0 mL), 16 h, 40 °C. [b]Isolated yield after the flash chromatography. [c]A 3:5 ratio was determined by GC–MS analysis. [d]HI (57% in water). [e]HBr (47% in water). [f]Reactions conducted in the presence of HBr (in AcOH) furnished the adduct **3a** in 18% yield. [g]HCl (37% in water). [h]HF (48% in water). [i]**1b** was used as the substrate instead of **1a**.

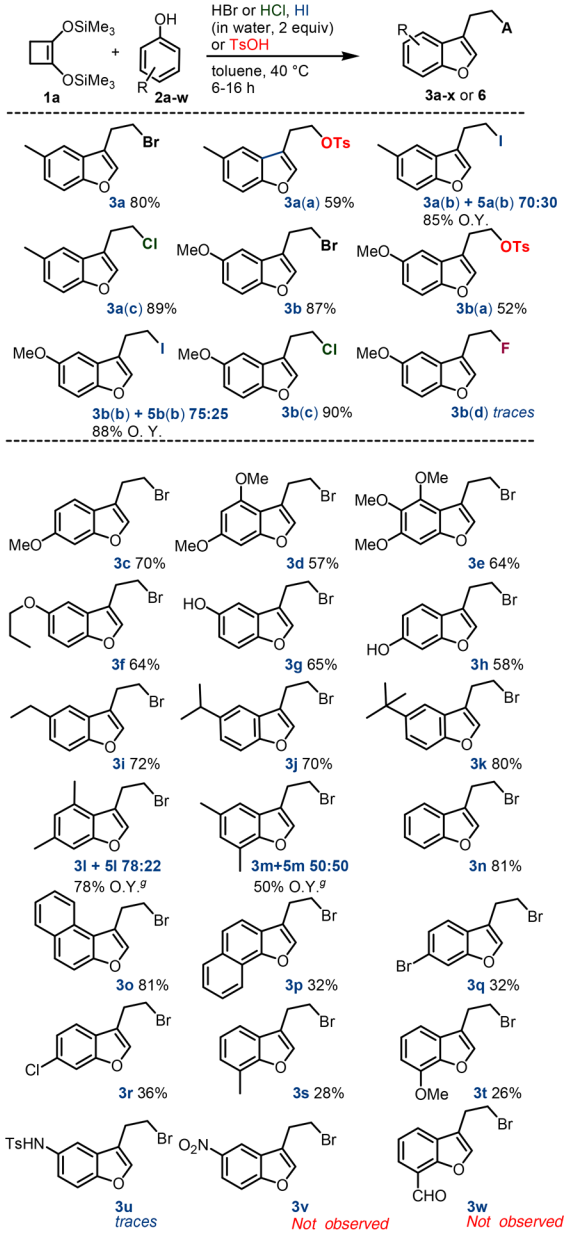
Similar results were achieved when reactions were carried out with, *m*- or *p*-hydroxyphenols **2g–2h** affording the 3-(2-bromoethyl)benzofuran derivatives **3g–3h** in 58–65% yield. Good tolerance of alkyl substituents was also observed, allowing the isolation of the adducts **3i–3k** in satisfactory yields. However, the reaction of 3,5-dimethyl- and 2,4-dimethylphenols **2l–2m** with **1a** afforded the corresponding derivatives **3l–3m** as a mixture of regioisomeric benzofurans. When *o*-substituted phenols **2s** and **2t** were employed in this reaction, compounds **3s** and **3t** were afforded in only moderate yields (26 to 28%) after 4 days. Unsubstituted phenol **2n** and *β*-naphthols **2o** yielded benzofuran **3n** and the parent naphtho[1,2-*b*]furan **3o** in good yields. However, compound **3p** was isolated in 32% yield. Also, phenols bearing halogen atoms (*m*-Br **2q**, *m*-Cl **2r**) gave the adducts **3q** and **3r** in moderate yields. In contrast, electron-withdrawing groups, such as *p*-nitrophenol **2v** or *o*-hydroxybenzaldehyde **2w**, failed to provide the corresponding 3-(2-bromoethyl)benzofuran adducts, probably due to electronic effects. In a further extension of this methodology, hydroquinone **2g**, resorcinol **2h**, and pyrocatechol **2x** were reacted with 2 equiv of **1a**, and we isolated the related bis(2-bromoethyl)-benzodifurans (Figure 2) in respective 40–57% yields. Moreover, compound **6h** and **6h′** were collected as a 70:30 mixture of regioisomers.

Moved by the large number of bioactive compounds that might be accessible using this methodology,[2−7] we set out to explore the reactions of the 3-(2-bromoethyl)benzofurans **3b**, **3g**, and **3l** with selected amines, as shown in Scheme 3. The



DOI: 10.1021/acs.orglett.8b03429
Org. Lett. XXXX, XXX, XXX–XXX

**Scheme 2. Exploration of the Substrate Scope**[a,b,c,d,e,f]




[a]Reactions were performed with 0.2 mmol of **1a**, 0.2 mmol of **2a**, 0.4 mmol of acid, toluene (1.0 mL); [b]0.2 mmol of TsOH; [c]HBr (47% in water), 40 °C; [d]HI (57% in water), 40 °C; [e]HCl (37% in water), 40 °C; [f]Isolated yield after flash chromatography are given. [g]O.Y. (overall yield).

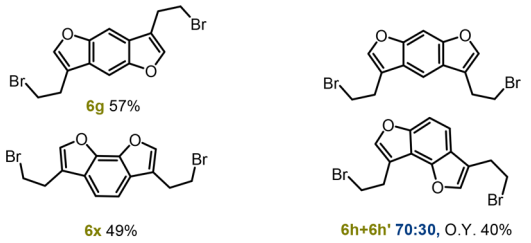
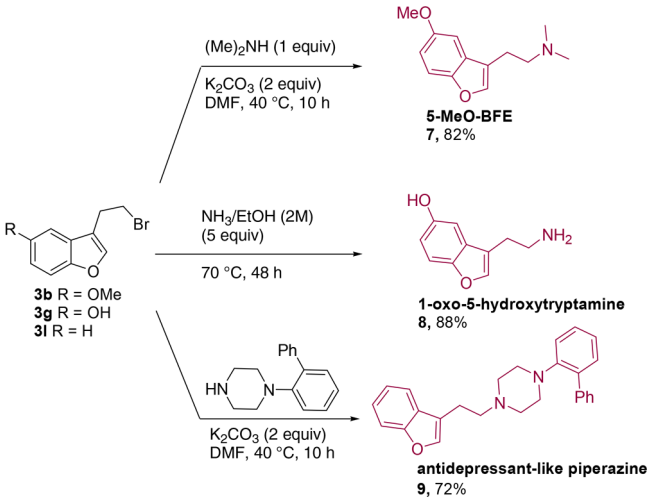



**Figure 2.** Synthesis of benzo[1,2-b;4,5-b′]difuran **6g**, benzo[1,2-b;5,4-b′]difuran **6h**, and benzo[2,1-b;3,4-b′]difuran **6x**.

reaction of compound **3g** with an ethanolic solution of ammonia at 40 °C furnished the 5-$HT_3$ serotonin receptor agonist 1-oxo-5-hydroxytryptamine **8**[17] in 88% yield.

**Scheme 3. Synthesis of 5-MeO-BFE 7, 1-Oxo-5-hydroxytryptamine 8, and Antidepressant-Like Piperazine SSRI/5-HT1A 9**




In a third example, the reaction of **3l** with 1-(biphenyl-2-yl)piperazine[18] in DMF afforded the SSRI-piperazine-like bioactive compound **9**[19] in 72% yield.

In summary, a new Brønsted acid mediated regioselective cascade reaction has been established, allowing access to highly substituted benzofurans from simple starting materials under mild conditions. To the best of our knowledge, there are no literature reports of the construction of a 3-(2-haloethyl)- or other 3-functionalized benzofuran skeleton using a similar strategy. This methodology can be expected to serve as a practical tool for the synthesis and for the elaboration of libraries of bioactive compounds. Future work will be dedicated to the specific applications of the developed method for the total synthesis of complex benzofuran-containing natural products.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03429.

Complete experimental, NMR, and X-ray crystallographic data (PDF)

### Accession Codes

CCDC 1852863−1852864 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: fsecci@unica.it.

### ORCID

David J. Aitken: 0000-0002-5164-6042

Francesco Secci: 0000-0003-0443-2890



DOI: 10.1021/acs.orglett.8b03429
Org. Lett. XXXX, XXX, XXX−XXX

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was partially supported by the Fondazione di Sardegna under the project "Innovative antioxidant molecules for the food and health industry" (CUP F71I17000180002). The authors gratefully acknowledge R.A.S. "Sardinia Regional Government" (FIR 2017). C.I.N.M.P.I.S. (Consorzio Interuniversitario Nazionale di Ricerca in Metodologie e Processi Innovativi di Sintesi) is also acknowledged.

## ■ REFERENCES

(1) For examples, see: (a) Radadiya, A.; Shah, A. *Eur. J. Med. Chem.* **2015**, *97*, 356. (b) Khanam, H.; Shamsuzzaman. *Eur. J. Med. Chem.* **2015**, *97*, 483. (c) Chand, K.; Hiremathada, A.; Singh, M. M.; Santos, A.; Keri, R. S. *Pharmacol. Rep.* **2017**, *67*, 281. (d) Heravi, M. M.; Zadsirjan, V.; Hamidi, H.; Amiri, P. H. T. *RSC Adv.* **2017**, *7*, 24470.

(2) (a) Koca, M.; Servi, S.; Kirilmis, C.; Ahmedzade, M.; Kazaz, C.; Ozbek, B.; Ötük, G. *Eur. J. Med. Chem.* **2005**, *40*, 1351. (b) Rao, G. K.; Venugopala, K. N.; Pai, P. N. S. *J. Pharmacol. Toxicol.* **2007**, *2*, 481.

(3) (a) Artigas, F. *ACS Chem. Neurosci.* **2013**, *4*, 5. (b) Hu, B.; Song, Q.; Xu, Y. *Org. Process Res. Dev.* **2012**, *16*, 1552. (c) Rickli, A.; Kopf, S.; Hoener, M. C.; Liechti, M. E. *Br. J. Pharmacol.* **2015**, *172*, 3412.

(4) (a) Rizzo, S.; Riviere, C.; Piazzi, L.; Bisi, A.; Gobbi, S.; Bartolini, M.; Andrisano, V.; Morroni, F.; Tarozzi, A.; Monti, J.-P.; Rampa, A. *J. Med. Chem.* **2008**, *51*, 2883. (b) Kumar, A.; Pintus, F.; Di Petrillo, A.; Medda, R.; Caria, P.; João Matos, M.; Viña, D.; Pieroni, E.; Delogu, F.; Era, B.; Delogu, G. L.; Fais, A. *Sci. Rep.* **2018**, *8*, 4424. (c) Kodama, S.; Hamashima, Y.; Nishide, K.; Node, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2659. (d) Fan, C.-A.; Tu, Y.-Q.; Song, Z.-L.; Zhang, E.; Shi, L.; Wang, M.; Wang, B.; Zhang, S.-Y. *Org. Lett.* **2004**, *6*, 4691.

(5) Stork, G.; Yamashita, A.; Adams, J.; Schulte, G. R.; Ches-worth, R.; Miyazaki, Y.; Farmer, J. J. *J. Am. Chem. Soc.* **2009**, *131*, 11402.

(6) (a) Tomaszewski, Z.; Johnson, M. P.; Huang, X.; Nichols, D. E. *J. Med. Chem.* **1992**, *35*, 2061. (b) Landagaray, E.; Ettaoussi, M.; Leclerc, V.; Traoré, B.; Perez, V.; Nosjean, O.; Boutin, J. A.; Caignard, D.-H.; Delagrange, P.; Berthelot, P.; Yous, S. *Bioorg. Med. Chem.* **2014**, *22*, 986. (c) Casale, J. F.; Hays, P. A. *Microgram J.* **2012**, *9*, 39.

(7) Venkatesan, A. M.; Dos Santos, O.; Ellingboe, J.; Evrard, D. A.; Harrison, B. L.; Smith, D. L.; Scerni, R.; Hornby, G. A.; Schechter, L. E.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 824.

(8) Alpers, D.; Gallhof, M.; Witt, J.; Hoffmann, F.; Brasholz, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 1402.

(9) Srinivas, K.; Sharma, R.; Ramana, C. V. *J. Org. Chem.* **2017**, *82*, 9816.

(10) Srinivas, K.; Dangat, Y.; Kommagalla, Y.; Vanka, K.; Ramana, C. V. *Chem. - Eur. J.* **2017**, *23*, 7570.

(11) (a) Choi, J.; Kim, H.; Park, S.; Tae, J. *Synlett* **2013**, *24*, 379. (b) Aechtner, T.; Barry, D. A.; David, E.; Ghellamallah, C.; Harvey, D. F.; de la Houpliere, A.; Knopp, M.; Malaska, M. J.; Pérez, D.; Schärer, K. A. B.; Siesel, A.; Vollhardt, K. P. C.; Zitterbart, R. *Synthesis* **2018**, *50*, 1053. (c) Furstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760.

(12) (a) Aitken, D. J.; Capitta, F.; Frongia, A.; Gori, D.; Guillot, R.; Ollivier, J.; Piras, P. P.; Secci, F.; Spiga, M. *Synlett* **2011**, *2011*, 712. (b) Aitken, D. J.; Capitta, F.; Frongia, A.; Ollivier, J.; Piras, P. P.; Secci, F. *Synlett* **2012**, *23*, 727. (c) Aitken, D. J.; Caboni, P.; Eijsberg, H.; Frongia, A.; Guillot, R.; Ollivier, J.; Piras, P. P.; Secci, F. *Adv. Synth. Catal.* **2014**, *356*, 941. (d) Melis, N.; Ghisu, L.; Guillot, R.; Caboni, P.; Secci, F.; Aitken, D. J.; Frongia, A. *Eur. J. Org. Chem.* **2015**, *2015*, 4358. (e) Ghisu, L.; Melis, N.; Secci, F.; Caboni, P.; Arca, M.; Guillot, R.; Boddaert, T.; Aitken, D. J.; Frongia, A. *Org. Biomol. Chem.* **2017**, *15*, 9779.

(13) Melis, N.; Secci, F.; Boddaert, T.; Aitken, D. J.; Frongia, A. *Chem. Commun.* **2015**, *51*, 15272.

(14) Martis, A.; Luridiana, A.; Frongia, A.; Arca, M.; Sarais, G.; Aitken, D. J.; Guillot, R.; Secci, F. *Org. Biomol. Chem.* **2017**, *15*, 10053.

(15) A plausible mechanism for the acid-catalyzed synthesis of 3- and 2-substituted benzofurans **3** and **5** is proposed in the Supporting Information.

(16) When phenol **3b** was reacted with **1a**, under the operational reaction conditions we observed the formation of a solid side product **3b′** (8% yield), which was characterized by X-ray diffractometric analysis. This compound is fully described in the Supporting Information (CCDC 1852863).

(17) (a) Hallmann, G.; Hagele, K. *Leibigs. Ann. Chem.* **1963**, *662*, 147. (b) Pinder, R. M.; Green, D. M.; Thompson, P. B. *J. Med. Chem.* **1971**, *14*, 626. (c) Kedrowski, S. M. A.; Bower, K. S.; Dougherty, D. A. *Org. Lett.* **2007**, *9*, 3205.

(18) 1-(Biphenyl-2-yl)piperazine was synthesized as described in the following reference: Lacivita, E.; Patarnello, D.; Stroth, N.; Caroli, A.; Niso, M.; Contino, M.; De Giorgio, P.; Di Pilato, P.; Colabufo, N. A.; Berardi, F.; Perrone, R.; Svenningsson, P.; Hedlund, P. B.; Leopoldo, M. *J. Med. Chem.* **2012**, *55*, 6375.

(19) Gu, Z.-S; Zhou, A.-N.; Xiao, Y.; Zhang, Q.-W.; Li, J.-Q. *Eur. J. Med. Chem.* **2018**, *144*, 701.



DOI: 10.1021/acs.orglett.8b03429
*Org. Lett.* XXXX, XXX, XXX−XXX