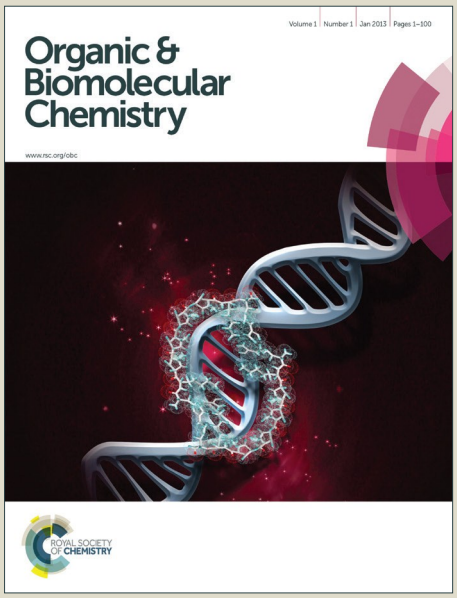
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Y. Jung and I. Kim, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB01941B.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C6OB01941B

Chemoselective Reduction of Quinols As an Alternative to Sonogashira Coupling: Synthesis of Polysubstituted Benzofurans

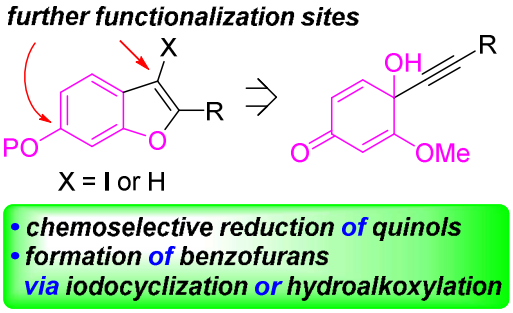
Youngeun Jung and Ikyon Kim*

College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University

85 Songdogwahak-ro, Yeonsu-gu, Incheon, 21983, Republic of Korea

* Corresponding author. Tel.: +82 32 749 4515; fax: +82 32 749 4105; e-mail: ikyonkim@yonsei.ac.kr

Table of Contents



Abstract: An efficient synthetic approach to polysubstituted benzofurans is described by using 2-methoxyquinone as a benzofuran backbone. Nucleophilic addition of terminal alkynes to 2-methoxy-1,4-benzoquinone afforded the corresponding quinols containing an alkyne unit, which were converted to phenols via mild Zn-mediated reduction. After proper protection of the free phenolic OH, 5-endo-dig iodocyclization allowed facile access to a number of 3-iodobenzofurans. In addition, it was demonstrated for the first time that *o*-methoxyarylalkynes underwent intramolecular hydroalkoxylation under the influence of

View Article Online
DOI: 10.1039/C6OB01941B

AgOTf furnishing the corresponding benzofurans.

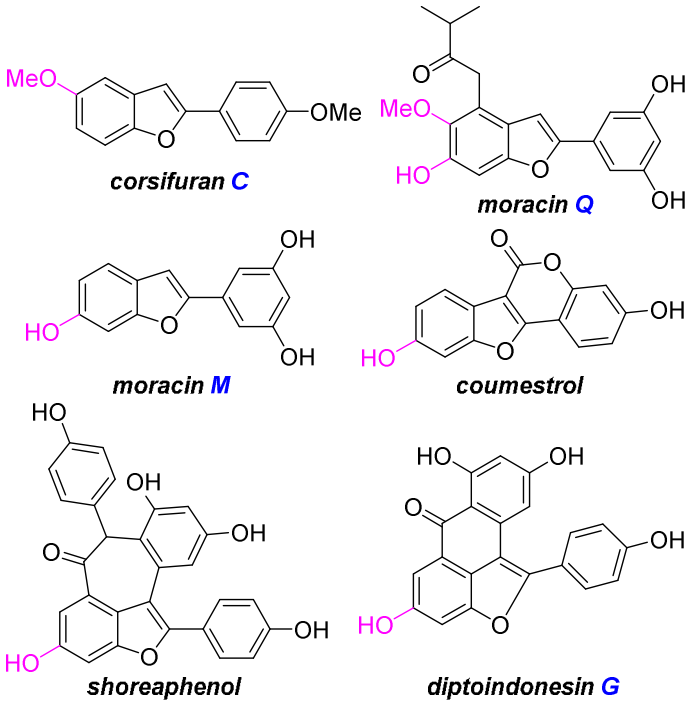
Keywords: Benzofuran; Quinol; Reduction; Cyclization; Iodine; Silver Triflate; Natural Product Synthesis.

Introduction

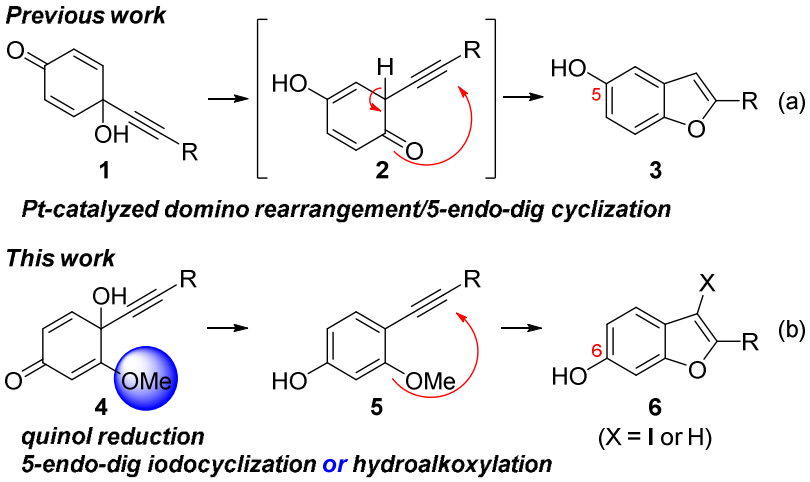
Many naturally occurring or synthetic benzofurans with important biological activities have hydroxyl group(s) at 5 and/or 6 positions (Figure 1).[1] Previously, we have reported the synthesis of 5-hydroxybenzofuran **3** from quinol **1** bearing an alkyne via **2** through a domino cyclohexadienone-phenol rearrangement/intramolecular 5-endo-dig cyclization sequence (Scheme 1a).[2] As an extension of our continued study on benzofurans,[3] we envisioned that quinol having a methoxy group (highlighted in blue) **4** might be used for the synthesis of 6-hydroxybenzofuran **6** (Scheme 1b). We expected that if chemoselective reduction of quinol **4** to phenol **5** would be viable, subsequent electrophilic cyclization would lead to 6-hydroxybenzofuran. Typically, arylalkyne **4** could be accessed by Sonogashira cross-coupling of aryl halide and terminal alkyne.[4] Despite tremendous advances in these metal-catalyzed coupling reactions, however, electron-rich aryl halides tend to give a relatively low yield of the desired cross-coupling product. In some cases, alkyne homodimer is often produced as a major product as a result of competitive Glaser-Eglington-Hay type reaction. As an alternative to Sonogashira coupling, we decided to evaluate a reaction sequence consisting of nucleophilic addition of terminal alkyne to quinone and chemoselective quinol reduction in the course of our approach to 6-hydroxybenzofuran, which is a topic of this paper.

Figure 1. Some Benzofuran Natural Products

View Article Online
DOI: 10.1039/C6OB01941B



Scheme 1. Synthetic Plans



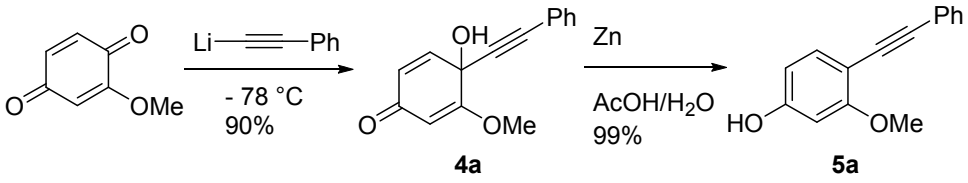
Results and discussion

To test the feasibility of our idea, we first prepared quinol **4a** by nucleophilic addition of phenylacetylide to 2-methoxy-1,4-benzoquinone (Scheme 2). Several examples of quinol reduction appeared in the literature.[5] To the best of our knowledge, however, chemoselective

View Article Online
DOI: 10.1039/C6OB01941B

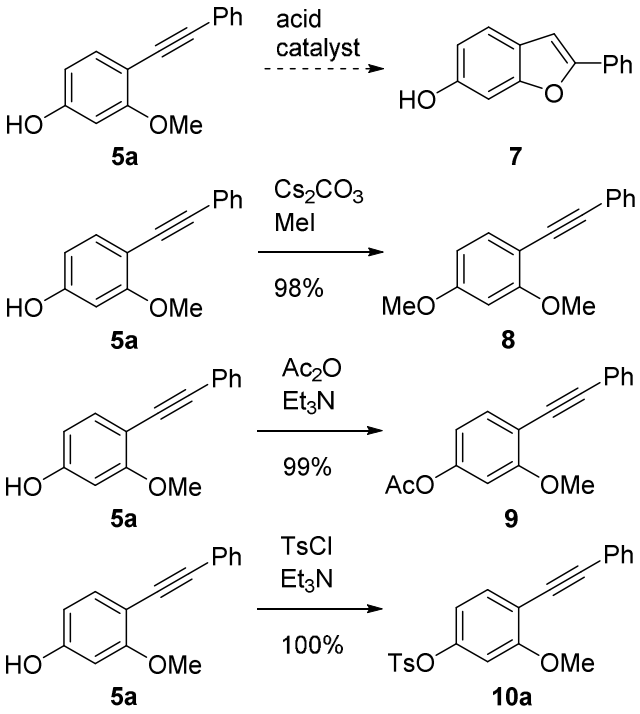
reduction of quinol possessing an alkyne to the corresponding phenol has not been disclosed yet. After screening several reductants, we were pleased to find that Zn-mediated reduction of **4a** in AcOH/H_2O at room temperature provided the desired phenol **5a** in 99% yield.

Scheme 2. Synthesis of 5a



At this point, we initially examined the direct cyclization of **5a** to **7**. Reactions under several acid catalysts (PTSA, $Cu(OTf)_2$, AgOTf, $InCl_3$, $FeCl_3$, or $AuCl_3$) at elevated temperature gave a complex mixture, which might result from the unprotected phenolic OH group (Scheme 3). Thus, we decided to protect the hydroxyl in **5a** with several protecting groups. For this purpose, **5a** was converted to the methyl ether **8**, acetate **9**, and sulfonate **10a**, respectively.[6]

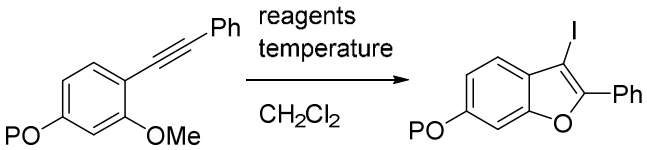
Scheme 3. Direct Cyclization Attempts and Protection



View Article Online
DOI: 10.1039/C6OB01941B

Since 2-alkoxyarylalkynes are good substrates for iodocyclization,[7,8] **8**, **9**, and **10a** were treated under several different iodocyclization conditions (Table 1). While **8** was reacted with I_2 and $NaHCO_3$ to afford the corresponding 3-iodobenzofuran **11** in 49% yield, use of ICl provided the impure mixture of products (entries 1 and 2). Exposure of **9** to either I_2/$NaHCO_3$ or ICl led to the desired product **12** in similar yields (entries 3 and 4). When **10a** was used as a cyclization substrate, 87% of the cyclized product **13a** was obtained by treatment with I_2 and $NaHCO_3$ (entry 5). Again, ICl-mediated cyclization of **10a** at -20 °C resulted in the desired product contaminated with unidentified inseparable compound (entry 6). Subjection of **10a** to I_2 (3 equiv) delivered **13a** in 79% yield (entry 7). These data clearly revealed that the protecting group of the phenolic OH in **5a** plays a crucial role in iodine-mediated cyclization reactions.

Table 1. Iodocyclization[a]



8 (P = Me)
9 (P = Ac)
10a (P = Ts)

11 (P = Me)
12 (P = Ac)
13a (P = Ts)

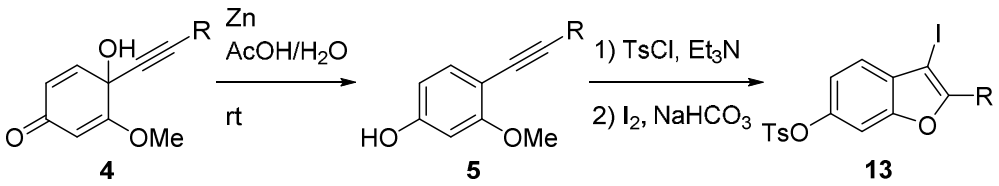
entry	starting material	reagents	temperature (°C)	yield (%)[b]	
1	**8**	I_2 (5 equiv), $NaHCO_3$ (5 equiv)	0 to rt	**11**	49
2	**8**	ICl (1.5 quiv)	-20	*c*	
3	**9**	I_2 (5 equiv), $NaHCO_3$ (5 equiv)	0	**12**	55
4	**9**	ICl (1.5 equiv)	-20	**12**	52
5	**10a**	I_2 (5 equiv), $NaHCO_3$ (5 equiv)	0 to rt	**13a**	87
6	**10a**	ICl (1.5 equiv)	-20	*c*	
7	**10a**	I_2 (3 equiv)	0 to rt	**13a**	79

[a] A solution of starting material (0.1 mmol) in CH_2Cl_2 (2 mL) was treated with reagents as noted above at the indicated temperature. [b] Isolated yield (%). [c] The desired product was contaminated with unidentified inseparable impurity.

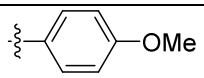
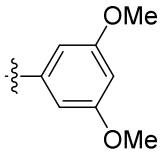
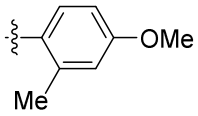
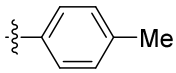
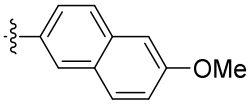
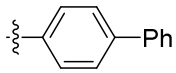
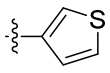
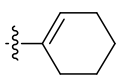
View Article Online
DOI: 10.1039/C6OB01941B

With these optimized conditions in hand, generality of this sequence was investigated (Table 2). The required quinols **4b-4j** were readily accessed by nucleophilic addition reactions of various terminal alkynes to 2-methoxy-1,4-benzoquinone at -78 °C.[9] The corresponding phenols **5b-5j** were obtained in good to excellent yields upon reduction of **4** with Zn in AcOH/H_2O. With respect to R moiety, alkyl as well as (hetero)aryl groups in **4** seemed to exhibit good tolerance under these conditions. Tosylation followed by iodine-mediated cyclization led to various 3-iodobenzofurans in good overall yields.

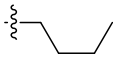
Table 2. Synthesis of 13[a]



4 **5** **13**

entry	R	**4**[b]	**5**[b]	**10**[b]	**13**[b]
1		**4b** (87)	**5b** (85)	**10b** (100)	**13b** (100)
2		**4c** (96)	**5c** (72)	**10c** (91)	**13c** (94)
3		**4d** (84)	**5d** (83)	**10d** (97)	**13d** (93)
4		**4e** (94)	**5e** (86)	**10e** (98)	**13e** (92)
5		**4f** (93)	**5f** (100)	**10f** (83)	**13f** (91)
6		**4g** (93)	**5g** (64)	**10g** (86)	**13g** (95)
7		**4h** (73)	**5h** (89)	**10h** (83)	**13h** (87)
8		**4i** (65)	**5i** (73)	**10i** (58)	**13i** (56)

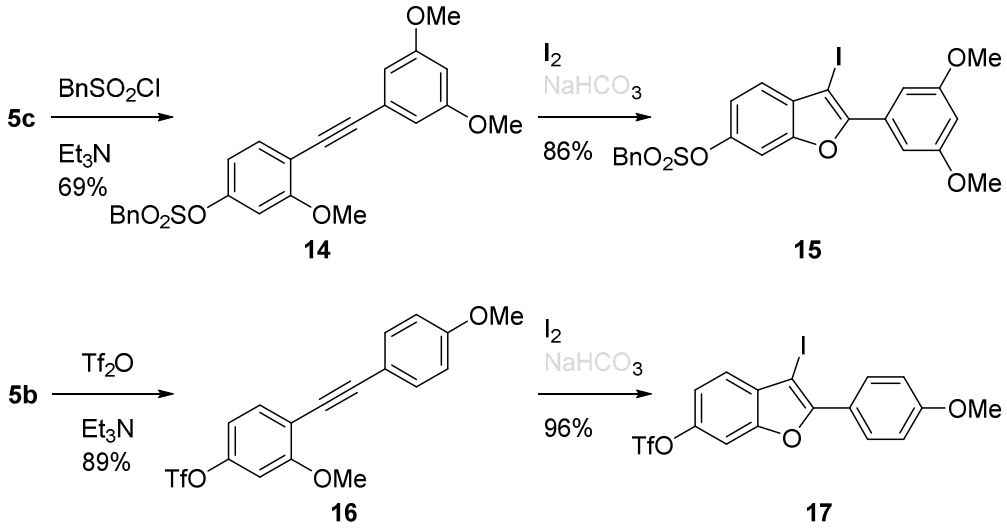
View Article Online
DOI: 10.1039/C6OB01941B

9		**4j** (80)	**5j** (62)	**10j** (99)	**13j** (89)

[a] A solution of **4** (1.18 mmol) and Zn (2.0 equiv) in AcOH/EtOH/H_2O (4:1:1, 3 mL) was stirred at 0 °C for 18 h. A mixture of **5** (0.22 mmol), TsCl (1.2 equiv), and Et_3N (2.0 equiv) in CH_2Cl_2 (5 mL) was stirred at 0 °C to rt for 1 h. A mixture of **10** (0.1 mmol), I_2 (5.0 equiv), and $NaHCO_3$ (5.0 equiv) in CH_2Cl_2 (2 mL) was stirred at 0 °C to rt for 3 h. [b] Isolated yield (%).

Not only *p*-toluenesulfonyl group but also benzylsulfonyl or trifluoromethanesulfonyl groups were used to protect the free hydroxyl in **5** (Scheme 4). The resulting sulfonates, **14** and **16**, were also successfully converted to the corresponding 3-iodobenzofurans, **15** and **17**, under similar conditions.

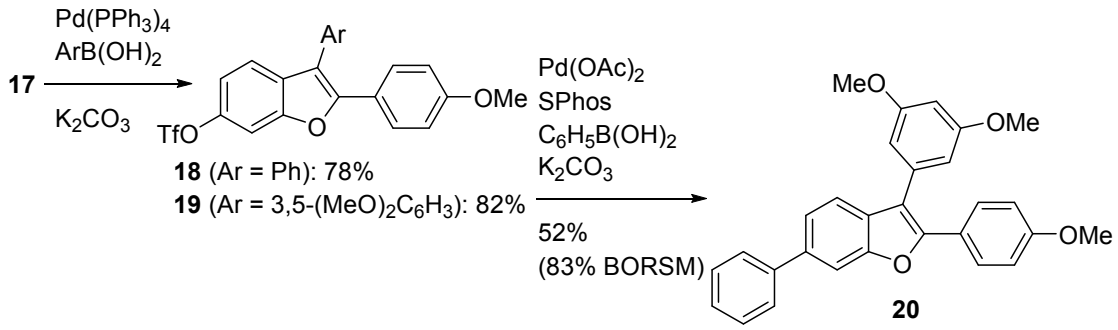
Scheme 4.



Further functionalization of the resulting product **17** was examined (Scheme 5). Due to the different reactivity of the two sites (I and TfO) in **17** toward Pd-catalyzed cross-coupling reactions, selective installation of different groups was realized to deliver 2,3,6-trisubstituted benzofuran **20**.

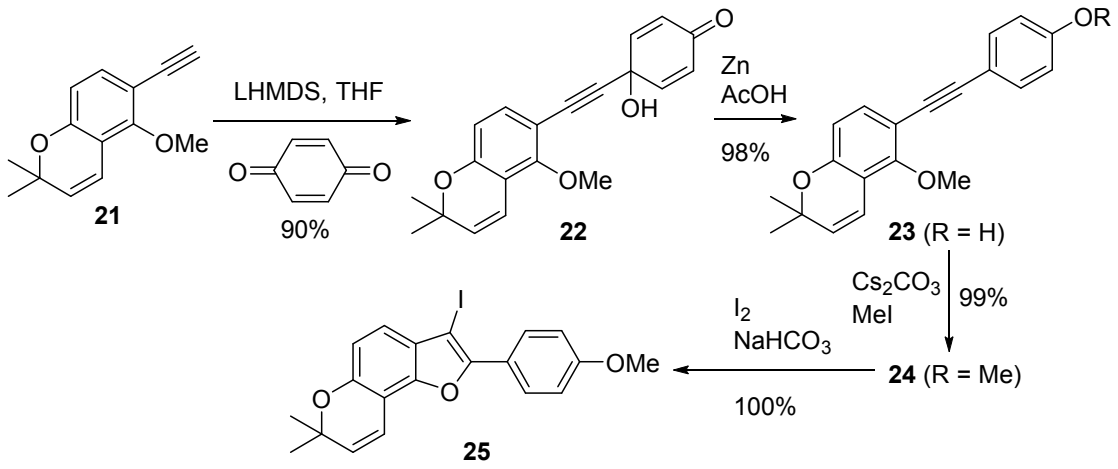
Scheme 5. Further Elaborations

View Article Online
DOI: 10.1039/C6OB01941B



In the meantime, we decided to test the viability of assembling benzofurans by switching the roles of alkyne and quinone of the approach mentioned above (Scheme 6). Thus, nucleophilic addition of lithium acetylide derived from **21**[10] to benzoquinone resulted in quinol **22**, which was subjected to Zn in AcOH to furnish **23** in excellent yield. Methylation and subsequent iodocyclization cleanly afforded the desired 3-iodobenzofuran **25**, demonstrating that 1,4-benzoquinone could be used as a 4-alkoxyphenyl surrogate.

Scheme 6. Synthesis of 25

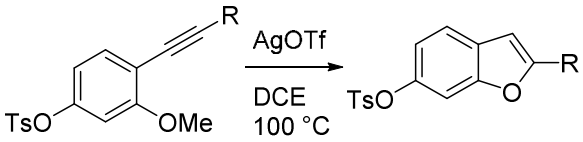


Finally, we also investigated the intramolecular 5-endo-dig hydroalkoxylation of **10** (Table 3). Among the catalysts screened, we were pleased to find that treatment of **10b** with silver triflate[11] afforded the cyclized product **26a** in 83% yield. Examples on the hydroalkoxylation of *o*-alkoxyarylalkynes leading to the formation of benzofurans have been disclosed in the literature.[12] However, use of silver salts as catalysts for the synthesis of benzofuran via

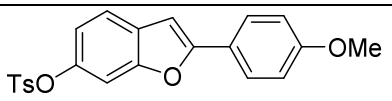
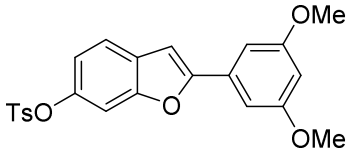
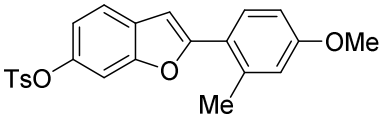
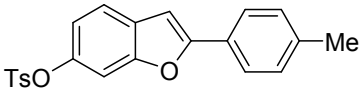
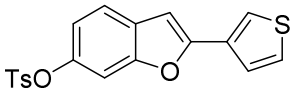
View Article Online
DOI: 10.1039/C6OB01941B

intramolecular hydroalkoxylation have not been reported. Triflic acid did not give rise to the desired product. Other silver salts such as $AgSbF_6$ were not effective in this transformation, either. Worthy of note is that the amount of silver triflate is highly dependent on the substrates; some needed a catalytic amount of AgOTf whereas others required stoichiometric amount of catalyst. Exposure of **10j** to AgOTf (2 equiv) at 100 °C resulted in a complex mixture although the reason is unclear at this point (entry 6).

Table 3. Intramolecular Hydroalkoxylation of 10[a]



10 **26**

entry	**10**	AgOTf (equiv)	time (hr)	**26**		yield (%)[b]
1	**10b**	1	72		**26a**	83
2	**10c**	0.2	10		**26b**	69
3	**10d**	0.6	48		**26c**	74
4	**10e**	1.2	48		**26d**	99
5	**10h**	2	72		**26e**	86
6	**10j**	2	72	*c*		

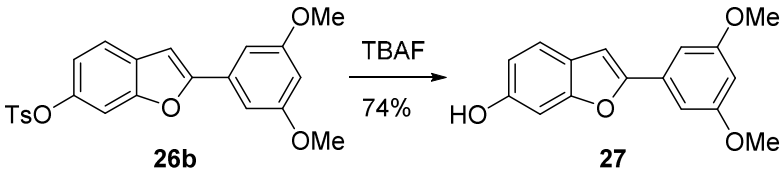
[a] A solution of **10** (0.08 mmol) and AgOTf in DCE (1 mL) was stirred at 100 °C. [b] Isolated yield (%). [c] The starting material was decomposed.

For the synthesis of 6-hydroxybenzofurans from **13** and **26**, deprotection of the Ts group in **13** and **26** was required. The tosyl group in **26b** was easily removed by TBAF treatment to give a dimethylether analogue **27** of moracin M, a basic skeleton of many moracin family

View Article Online
DOI: 10.1039/C6OB01941B

natural products (Scheme 7).[13]

Scheme 7. Synthesis of Dimethylether 27 of Moracin M



In summary, we have developed a highly efficient strategy for the synthesis of polysusbstituted benzofurans by utilizing 2-methoxy-1,4-benzoquinone as a benzofuran core. Quinols containing an alkyne easily prepared by nucleophilic addition of terminal alkynes to 2-methoxy-1,4-benzoquinone were chemoselectively reduced to the corresponding phenols under the influence of Zn in AcOH/H_2O. We are confident that this nucleophilic addition-quinol reduction sequence could be a good alternative to Sonogashira coupling reactions in some difficult situations. After protection of the free hydroxyls with sulfonyl groups, 5-endo-dig iodocyclization provided 3-iodobenzofurans in good to excellent yields. Further diversification via introduction of different functional moieties onto this skeleton was conducted by Pd-catalyzed cross-coupling reactions. Intramolecular hydroalkoxylation of 2-methoxyarylalkynes facilitated by AgOTf was also demonstrated for the first time. Currently underway in our laboratory is the application of this route to the natural product synthesis.

Experimental Section

General Methods

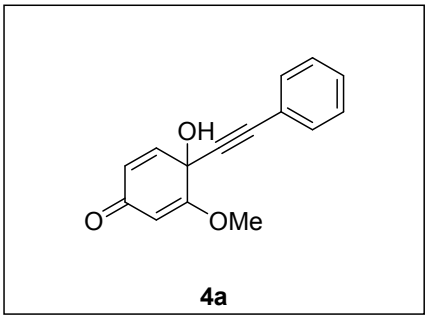
Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. “Concentrated” refers to the removal of volatile solvents via distillation using a rotary evaporator. “Dried” refers to pouring onto, or passing through, anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230−400 mesh) with hexanes, ethyl acetate, and dichloromethane

View Article Online
DOI: 10.1039/C6OB01941B

as eluent. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualizing with UV light. Melting points were measured using a capillary melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. HRMS were measured with electrospray ionization (ESI) and Q-TOF mass analyzer.

General Procedure for the Synthesis of 4

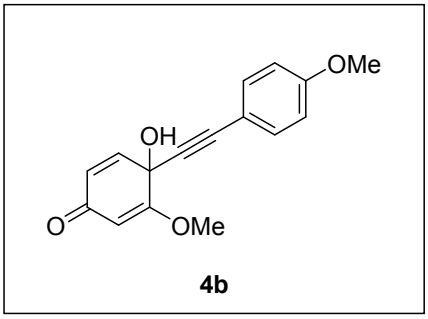
To a stirred solution of alkyne (3.76 mmol, 1.3 equiv) in anhydrous THF (10 mL) at -78 °C was added 2.5 M n-BuLi (1.39 mL, 1.2 equiv). After the mixture was stirred for 5 min under nitrogen atmosphere, a solution of 2-methoxy-1,4-benzoquinone (400 mg, 2.89 mmol) in anhydrous THF (15 mL) was added at -78 °C. After 15 min, the reaction mixture was quenched with saturated aq. NH_4Cl, warmed to rt, and concentrated under reduced pressure to give the crude residue, which was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 3:1:2) to give **4**.



4a

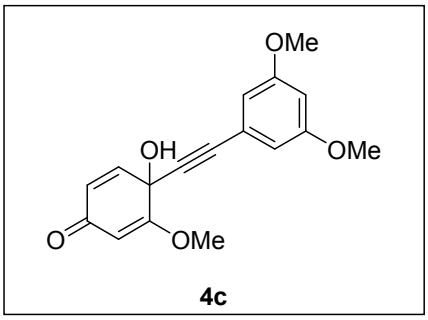
4-Hydroxy-3-methoxy-4-(phenylethynyl)cyclohexa-2,5-dien-1-one (4a). Pale brown solid, mp: 144.0-145.2 °C (624.9 mg, 90%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, J = 6.8 Hz, 2H), 7.41-7.28 (m, 3H), 6.80 (d, J = 9.6 Hz, 1H), 6.19 (d, J = 9.6 Hz, 1H), 5.55 (s, 1H), 3.87 (s, 3H), 3.52 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.9, 171.4, 142.2, 132.1, 129.4, 128.5, 126.9, 121.4, 100.5, 85.6, 85.5, 64.3, 56.6; **HRMS** (ESI-QTOF) m/z $[M+H]^+$ calcd for $C_{15}H_{13}O_3$ 241.0859 found 241.0858.

View Article Online
DOI: 10.1039/C6OB01941B



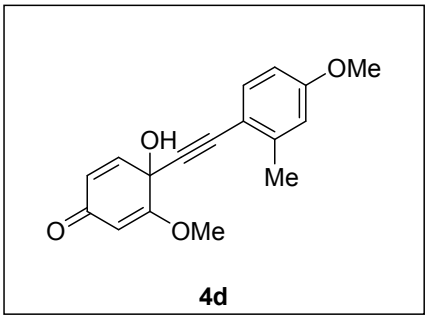
4b

4-Hydroxy-3-methoxy-4-((4-methoxyphenyl)ethynyl)cyclohexa-2,5-dien-1-one (4b). Pale brown solid, mp: 152.6-153.4 °C (679.6 mg, 87%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 9.6 Hz, 1H), 6.18 (d, *J* = 9.6 Hz, 1H), 5.54 (s, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.28 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.8, 171.4, 160.4, 142.3, 133.7, 126.8, 114.1, 113.4, 100.5, 85.7, 84.3, 64.4, 56.6, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_4$ 271.0965 found 271.0968.



4c

4-((3,5-Dimethoxyphenyl)ethynyl)-4-hydroxy-3-methoxycyclohexa-2,5-dien-1-one (4c). Pale brown solid, mp: 190.0-190.6 °C (833 mg, 96%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 10.0 Hz, 1H), 6.59 (s, 1H), 6.58 (s, 1H), 6.47 (s, 1H), 6.19 (d, *J* = 10.0 Hz, 1H), 5.55 (s, 1H), 3.88 (s, 3H), 3.78 (s, 6H), 3.30 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.7, 171.2, 160.7, 142.0, 127.1, 122.6, 109.9, 102.8, 100.6, 85.5, 85.1, 64.3, 56.6, 55.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}O_5$ 301.1071 found 301.1072.

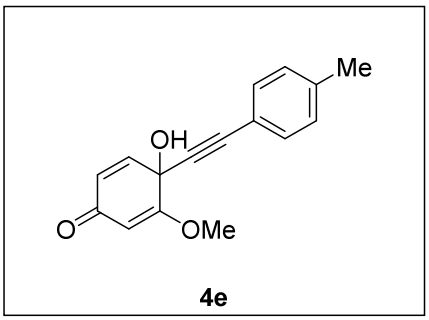


4d

4-Hydroxy-3-methoxy-4-((4-methoxy-2-methylphenyl)ethynyl)cyclohexa-2,5-dien-1-one (4d). Brown solid, mp: 120.7-121.8 °C (690.2 mg, 84%); **^{1}H**

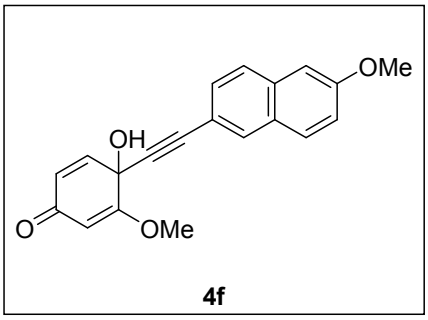
View Article Online
DOI: 10.1039/C6OB01941B

NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 9.6 Hz, 1H), 6.72 (s, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.17 (d, *J* = 10.0 Hz, 1H), 5.54 (s, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 187.0, 171.8, 160.3, 142.9, 142.6, 133.8, 126.6, 115.3, 113.3, 111.4, 100.3, 88.2, 84.7, 64.4, 56.5, 55.4, 20.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}O_4$ 285.1121 found 285.1120.



4e

4-Hydroxy-3-methoxy-4-(*p*-tolylethynyl)cyclohexa-2,5-dien-1-one (4e). Brown solid, mp: 125.2-126.8 °C (690.8 mg, 94%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 6.8 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 2H), 6.79 (d, *J* = 9.6 Hz, 1H), 6.18 (d, *J* = 9.6 Hz, 1H), 5.54 (s, 1H), 3.86 (s, 3H), 3.56 (s, 1H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.9, 171.6, 142.4, 139.7, 132.0, 129.2, 126.7, 118.3, 100.4, 85.7, 84.9, 64.3, 56.6, 21.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_3$ 255.1016 found 255.1017.

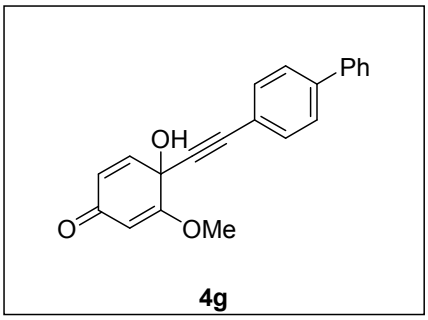


4f

4-Hydroxy-3-methoxy-4-((6-methoxynaphthalen-2-yl)ethynyl)cyclohexa-2,5-dien-1-one (4f). Pale brown solid, mp: 189.4.6-190.2 °C (861.0 mg, 93%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.72-7.63 (m, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.10 (s, 1H), 6.83 (d, *J* = 10.0 Hz, 1H), 6.21 (d, *J* = 9.6 Hz, 1H), 5.57 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.37 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.8, 171.4, 158.8, 142.2, 134.7, 132.3, 129.5, 128.9, 128.3, 127.0, 126.9, 119.8, 116.2, 105.9, 100.5, 86.2, 85.2, 64.4, 56.6, 55.5;

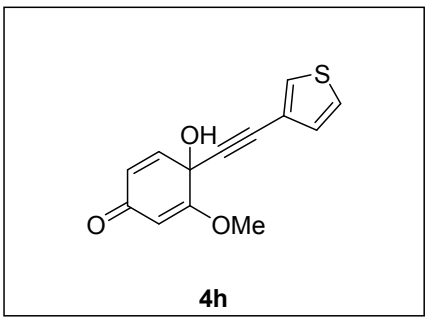
View Article Online
DOI: 10.1039/C6OB01941B

HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}O_4$ 321.1121 found 321.1120.



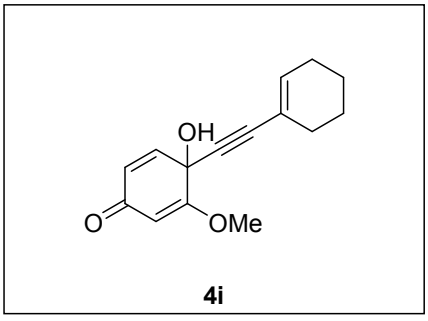
4g

4-([1,1'-Biphenyl]-4-ylethynyl)-4-hydroxy-3-methoxycyclohexa-2,5-dien-1-one (4g). Pale brown solid, mp: 152.4-154.0 °C (850.3 mg, 93%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65-7.48 (m, 6H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 10.0 Hz, 1H), 6.20 (t, *J* = 10.0 Hz, 1H), 5.56 (s, 1H), 3.99 (s, 1H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.9, 171.6, 142.5, 142.0, 140.1, 132.5, 129.0, 128.0, 127.1, 127.1, 126.7, 120.3, 100.5, 86.3, 85.3, 64.3, 56.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}O_3$ 317.1172 found 317.1170.



4h

4-Hydroxy-3-methoxy-4-(thiophen-3-ylethynyl)cyclohexa-2,5-dien-1-one (4h). Pale yellow solid, mp: 123.5-124.1 °C (519.6 mg, 73%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.27 (s, 1H), 7.11 (d, *J* = 4.8 Hz, 1H), 6.78 (d, *J* = 9.6 Hz, 1H), 6.18 (d, *J* = 10.0 Hz, 1H), 5.54 (s, 1H), 3.87 (s, 3H), 3.45 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.8, 171.3, 142.2, 130.6, 130.0, 126.9, 125.8, 120.5, 100.5, 85.3, 80.8, 64.3, 56.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}O_3S$ 247.0423 found 247.0425.

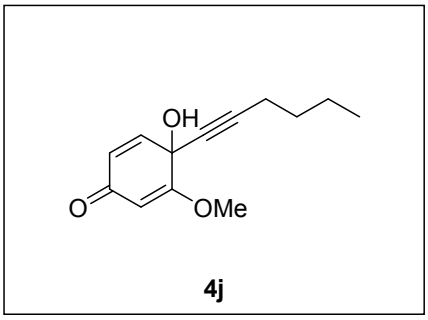


4i

4-(Cyclohex-1-en-1-ylethynyl)-4-hydroxy-3-

View Article Online
DOI: 10.1039/C6OB01941B

methoxycyclohexa-2,5-dien-1-one (4i). Yellow gum, (458.9 mg, 65%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 10.0 Hz, 1H), 6.19 (s, 1H), 6.13 (d, *J* = 9.6 Hz, 1H), 5.49 (s, 1H), 3.84 (s, 3H), 3.39 (s, 1H), 2.17-2.02 (m, 4H), 1.69-1.48 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 187.0, 171.7, 142.7, 137.8, 126.5, 119.4, 100.3, 87.4, 82.9, 64.2, 56.5, 28.8, 25.8, 22.2, 21.4; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}O_3$ 245.1172 found 245.1171.



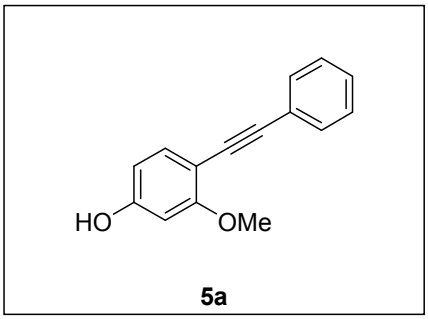
4j

4-(Hex-1-yn-1-yl)-4-hydroxy-3-methoxycyclohexa-2,5-dien-1-one (4j). Yellow solid, mp: 77.5-78.2 °C (509.3 mg, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 10.0 Hz, 1H), 6.11 (dd, *J* = 1.2, 10.0 Hz, 1H), 5.48 (d, *J* = 1.2 Hz, 1H), 3.84 (s, 3H), 3.12 (s, 1H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.55-1.44 (m, 2H), 1.44-1.31 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 187.0, 171.7, 142.8, 126.4, 100.2, 87.3, 63.9, 56.5, 30.3, 22.0, 18.6, 13.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}O_3$ 221.1172 found 221.1173.

General Procedure for the Synthesis of 5

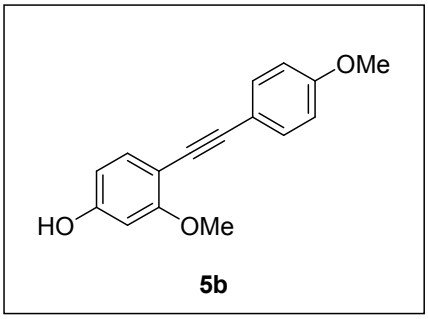
To a stirred solution of **4** (1.18 mmol) in AcOH/EtOH/H_2O (4:1:1, 3 mL) was added Zn powder (154.2 mg, 2.0 equiv) at 0 °C. After being stirred at rt for 18 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford the crude residue. Purification by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 20:1:2) furnished compound **5**.

View Article Online
DOI: 10.1039/C6OB01941B



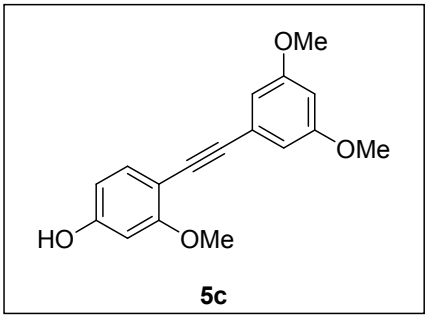
5a

3-Methoxy-4-(phenylethynyl)phenol (5a). Red gum, (262.0 mg, 99%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 1.6, 8.0 Hz, 2H), 7.37-7.27 (m, 4H), 6.45-6.36 (m, 2H), 3.86 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5, 157.4, 134.6, 131.6, 128.3, 128.0, 123.9, 107.6, 105.0, 99.2, 92.3, 85.8, 56.0; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}O_2$ 225.0910 found 225.0911.



5b

3-Methoxy-4-((4-methoxyphenyl)ethynyl)phenol (5b). Brown gum, (255.1 mg, 85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 2.0 Hz, 1H), 6.39 (dd, *J* = 2.0, 8.0 Hz, 1H), 5.05 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 157.1, 134.4, 133.1, 116.1, 114.0, 108.1, 107.5, 105.4, 99.1, 92.1, 84.2, 56.0, 55.4; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_3$ 255.1016 found 255.1017.

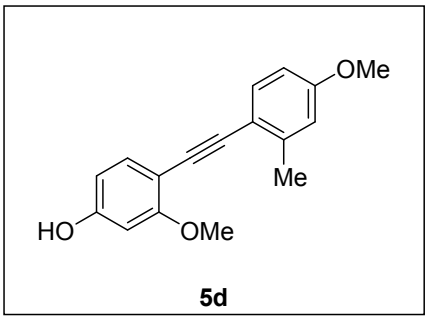


5c

4-((3,5-Dimethoxyphenyl)ethynyl)-3-methoxyphenol (5c). Yellow gum, (241.5 mg, 72%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 1H), 6.69 (s, 2H), 6.45-6.36 (m, 3H), 5.42 (s, 1H), 3.86 (s, 3H), 3.76 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5, 160.5, 157.6, 134.7, 125.2, 109.4, 107.7, 104.7, 101.7, 99.2, 92.2, 85.5, 56.0, 55.6; **HRMS** (ESI-

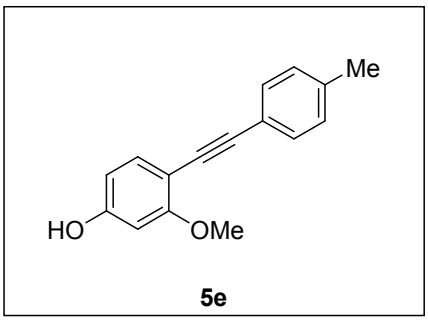
View Article Online
DOI: 10.1039/C6OB01941B

QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}O_4$ 285.1121 found 285.1120.



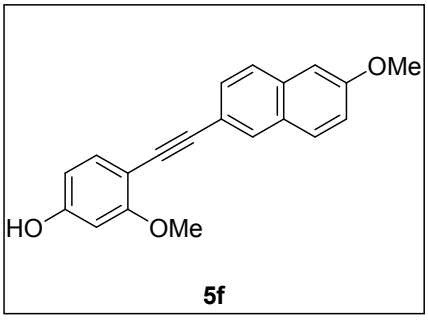
5d

3-Methoxy-4-((4-methoxy-2-methylphenyl)ethynyl)phenol (5d). White solid, mp: 100.9-102.7 °C (262.8 mg, 83%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.69 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.41 (d, *J* = 10.0 Hz, 1H), 6.38 (dd, *J* = 2.4, 8.4 Hz, 1H), 5.15 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.49 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.3, 159.3, 157.0, 142.0, 134.1, 133.0, 116.1, 115.2, 111.2, 107.5, 105.7, 99.2, 91.3, 88.2, 56.0, 55.4, 21.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}O_3$ 269.1172 found 269.1171.



5e

3-Methoxy-4-(*p*-tolylethynyl)phenol (5e). Pale brown solid, mp: 115.8-118.0 °C (241.8 mg, 86%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 2H), 6.48-6.34 (m, 2H), 5.23 (s, 1H), 3.86 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.4, 157.2, 138.0, 134.5, 131.5, 129.1, 120.8, 107.6, 105.2, 99.2, 92.4, 85.0, 56.0, 21.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_2$ 239.1067 found 239.1068.

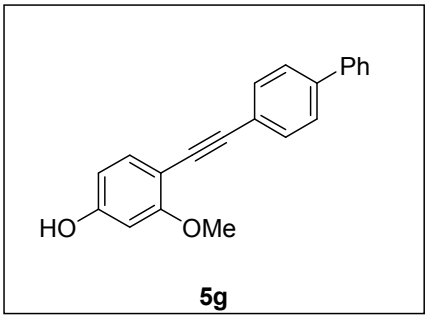


5f

3-Methoxy-4-((6-methoxynaphthalen-2-

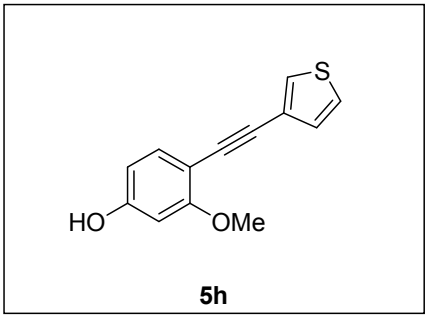
View Article Online
DOI: 10.1039/C6OB01941B

yl)ethynyl)phenol (5f). Brown solid, mp: 150.9-152.1 °C (359.0 mg, 100%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97(s, 1H), 7.69 (t, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 2.0, 9.2 Hz, 1H), 7.11 (d, *J* = 1.6 Hz, 1H), 6.44 (s, 1H), 6.41 (dd, *J* = 1.2, 8.4 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5, 158.3, 157.2, 134.6, 134.0, 131.1, 129.5, 129.3, 128.7, 126.8, 119.4, 118.9, 107.6, 106.0, 105.3, 99.2, 92.8, 85.4, 56.1, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}O_3$ 305.1172 found 305.1170.



5g

4-([1,1'-Biphenyl]-4-ylethynyl)-3-methoxyphenol (5g). White solid, mp: 178.6-188.9 °C (226.8 mg, 64%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68-7.54 (m, 6H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.40-7.31 (m, 2H), 6.43 (s, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.17 (s, 1H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6, 157.4, 140.6, 134.6, 132.1, 129.0, 127.7, 127.1, 127.0, 122.9, 107.6, 105.1, 99.2, 92.1, 86.5, 56.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}O_2$ 301.1223 found 301.1222.

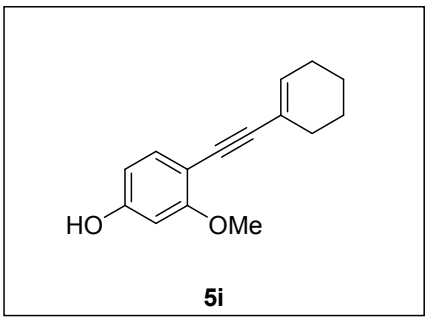


5h

3-Methoxy-4-(thiophen-3-ylethynyl)phenol (5h). Yellow gum, (241.8 mg, 89%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 1.2, 3.2 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.28-7.24 (m, 1H), 7.18 (dd, *J* = 1.2, 4.8 Hz, 1H), 6.44-6.37 (m, 2H), 5.54 (s, 1H), 3.83 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.4, 157.4, 134.5, 130.1, 128.3, 125.2, 122.7, 107.7, 104.8,

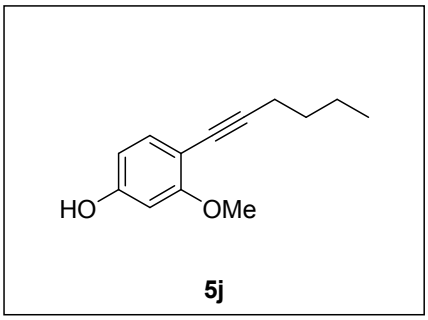
View Article Online
DOI: 10.1039/C6OB01941B

99.2, 87.3, 85.1, 56.0; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}O_2S$ 231.0474 found 231.0475.



5i

4-(Cyclohex-1-en-1-ylethynyl)-3-methoxyphenol (5i). Red gum, (196.6 mg, 73%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.0 Hz, 1H), 6.42-6.31 (m, 2H), 6.22-6.13 (m, 1H), 5.34 (s, 1H), 3.80 (s, 3H), 2.26-2.18 (m, 2H), 2.16-2.07 (m, 2H), 1.70-1.54 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.1, 157.0, 134.7, 134.3, 121.0, 107.5, 105.4, 99.1, 94.2, 82.8, 55.9, 29.5, 25.9, 22.5, 21.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}O_2$ 229.1223 found 229.1222.



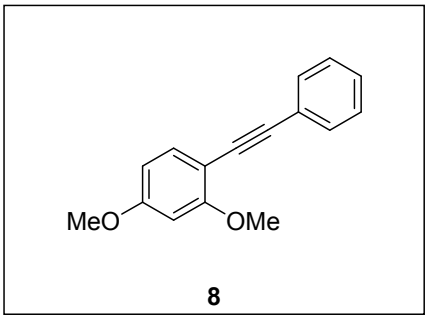
5j

4-(Hex-1-yn-1-yl)-3-methoxyphenol (5j). Red gum, (149.4 mg, 62%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 1H), 6.38 (d, *J* = 2.0 Hz, 1H), 6.35 (dd, *J* = 2.0, 8.4 Hz, 1H), 3.81 (s, 3H), 2.43 (t, *J* = 7.2 Hz, 2H), 1.65-1.53 (m, 2H), 1.53-1.41 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.2, 156.6, 134.5, 107.4, 105.6, 99.1, 93.3, 76.4, 55.9, 31.1, 22.2, 19.6, 13.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}O_2$ 205.1223 found 205.1223.

Synthesis of 8

View Article Online
DOI: 10.1039/C6OB01941B

To a solution of **5a** (50 mg, 0.22 mmol) in CH_3CN (3 mL) were added Cs_2CO_3 (145 mg, 2.0 equiv) and MeI (0.021 mL, 1.5 equiv). After being stirred at rt for 1 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was diluted with H_2O. The water layer was extracted with CH_2Cl_2 (5 mL x 2) two more times. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford **8**.

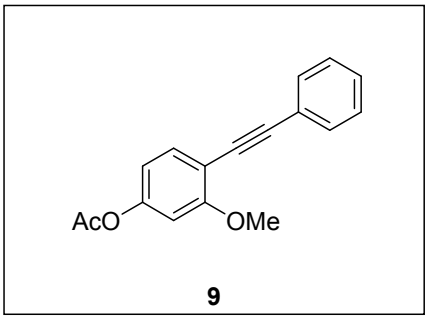


8

2,4-Dimethoxy-1-(phenylethynyl)benzene (8). Colorless gum, (51.4 mg, 98%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58-7.45 (m, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.37-7.22 (m, 3H), 6.51-6.43 (m, 2H), 3.88(s, 3H), 3.81 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.3, 161.3, 134.4, 131.6, 128.3, 127.9, 124.0, 105.1, 105.0, 98.6, 92.1, 85.9, 56.0, 55.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_2$ 239.1067 found 239.1066.

Synthesis of 9

To a solution of **5a** (50 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (0.062 mL, 2.0 equiv) and Ac_2O (0.032 mL, 1.5 equiv) at 0 °C. After being stirred at rt for 1 h, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and washed with 10% aq. HCl and aq. $NaHCO_3$, successively. The water layer was extracted with CH_2Cl_2 (5 mL x 2) two more times. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford **9**.



9

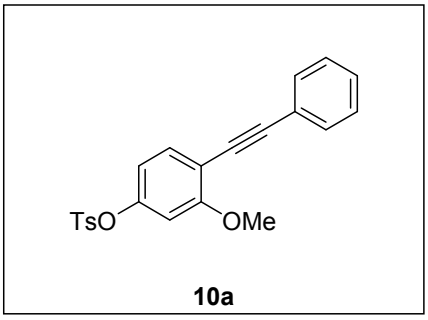
3-Methoxy-4-(phenylethynyl)phenyl acetate (9). Colorless gum, (58.0 mg, 99%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58-7.52 (m, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.37-7.29 (m, 3H), 6.70 (dd, J = 2.0, 8.4 Hz, 1H), 6.67

View Article Online
DOI: 10.1039/C6OB01941B

(d, J = 2.0 Hz, 1H), 3.89 (s, 3H), 2.30 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 160.8, 151.8, 134.0, 131.8, 128.4, 128.3, 123.6, 113.7, 110.3, 105.1, 93.5, 85.1, 56.2, 21.3; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{15}O_3$ 267.1016 found 267.1018.

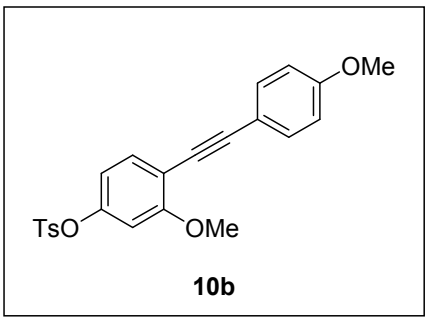
General Procedure for the Synthesis of 10

To a solution of **5** (0.99 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (0.28 mL, 2.0 equiv) and TsCl (227 mg, 1.2 equiv) at 0 °C. After being stirred at rt for 1 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexanes/ethyl acetate = 50:1) to give **10**.



10a

3-Methoxy-4-(phenylethynyl)phenyl 4-methylbenzenesulfonate (10a). White solid, mp: 98.7-100.1 °C (374.6 mg, 100%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.58-7.47 (m, 2H), 7.40-7.28 (m, 6H), 6.58 (d, J = 2.0 Hz, 1H), 6.50 (dd, J = 2.0, 8.4 Hz, 1H), 3.79 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 150.4, 145.7, 133.9, 132.2, 131.8, 129.9, 128.8, 128.5, 128.4, 123.2, 114.3, 111.7, 105.9, 94.4, 84.5, 56.2, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}O_4S$ 379.0999 found 379.0998.

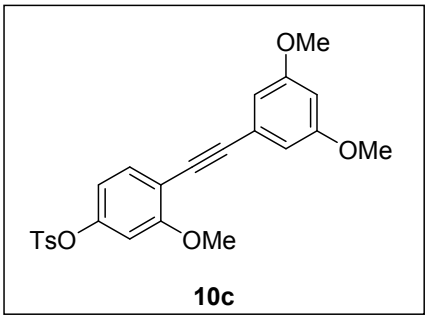


10b

3-Methoxy-4-((4-methoxyphenyl)ethynyl)phenyl 4-methylbenzenesulfonate (10b). White solid, mp: 105.1-106.5 °C (404.4 mg, 100%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, J = 6.4 Hz, 2H), 7.46 (d, J = 6.8 Hz,

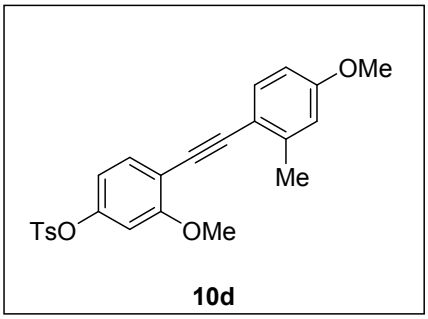
View Article Online
DOI: 10.1039/C6OB01941B

2H), 7.37-7.27 (m, 3H), 6.86 (d, J = 6.8 Hz, 2H), 6.57 (s, 1H), 6.49 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.6, 159.9, 150.1, 145.7, 133.8, 133.3, 132.3, 129.9, 128.8, 115.4, 114.3, 114.1, 112.0, 105.9, 94.5, 83.2, 56.2, 55.4, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}O_5S$ 409.1104 found 409.1104.



10c

4-((3,5-Dimethoxyphenyl)ethynyl)-3-methoxyphenyl 4-methylbenzenesulfonate (10c). White solid, mp: 84.6-86.1 °C (395.0 mg, 91%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2H), 7.334 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 6.66 (s, 1H), 6.65 (s, 1H), 6.56 (s, 1H), 6.48 (dd, J = 1.6, 8.4 Hz, 1H), 6.43 (s, 1H), 3.77 (s, 9H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 160.6, 150.4, 145.7, 134.0, 132.2, 129.9, 128.7, 124.5, 114.3, 111.5, 109.5, 105.9, 102.0, 94.4, 84.1, 56.2, 55.6, 21.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}O_6S$ 439.1210 found 439.1212.

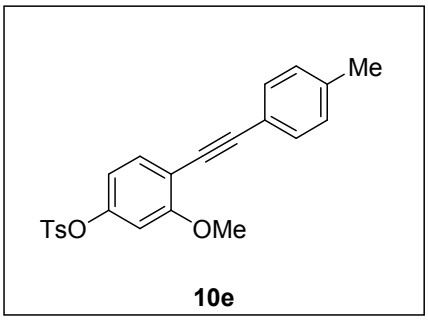


10d

3-Methoxy-4-((4-methoxy-2-methylphenyl)ethynyl)phenyl 4-methylbenzenesulfonate (10d). White solid, mp: 96.9-98.5 °C (405.7 mg, 97%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.8 Hz, 1H), 7.36-7.29 (m, 3H), 6,76 (d, J = 2.4 Hz, 1H), 6.70 (dd, J = 2.4, 8.4 Hz, 1H), 6.58 (d, J = 2.0 Hz, 1H), 6.49 (dd, J = 2.0, 8.0 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.48 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.5, 159.8, 150.0, 145.7, 142.3, 133.4, 133.3, 132.3, 129.9,

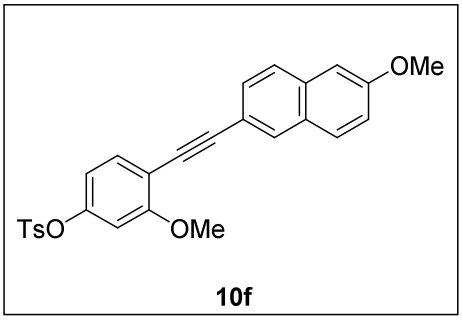
View Article Online
DOI: 10.1039/C6OB01941B

128.8, 115.4, 115.2, 114.2, 112.4, 111.4, 105.9, 93.7, 87.1, 56.2, 55.4, 21.9, 21.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}O_5S$ 423.1261 found 423.1264.



10e

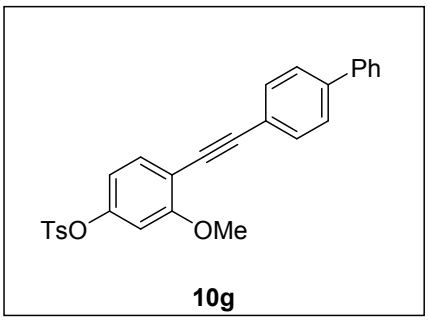
3-Methoxy-4-(*p*-tolylethynyl)phenyl 4-methylbenzenesulfonate (10e). White solid, mp: 108.6-109.4 °C (380.8 mg, 98%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.38-7.28 (m, 3H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.58 (s, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 3.79 (s, 3H), 2.45 (s, 3H), 2.36 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.6, 150.3, 145.7, 138.7, 133.9, 132.2, 131.7, 129.9, 129.2, 128.8, 120.2, 114.3, 111.9, 105.9, 94.7, 83.9, 56.2, 21.9, 21.7.; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}O_4S$ 393.1155 found 393.1153.



10f

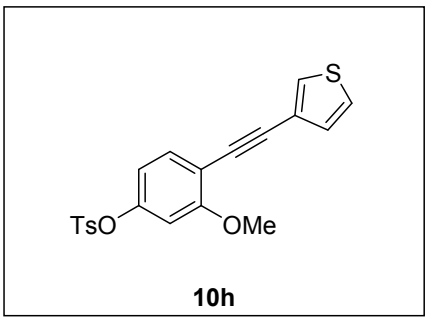
3-Methoxy-4-((6-methoxynaphthalen-2-yl)ethynyl)phenyl 4-methylbenzenesulfonate (10f). White solid, mp: 131.8-133.1 °C (376.8 mg, 83%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.79-7.63 (m, 4H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.10 (s, 1H), 6.59 (s, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 158.5, 150.3, 145.7, 134.3, 133.9, 132.2, 131.4, 129.9, 129.5, 129.1, 128.7, 128.5, 126.9, 119.5, 118.1, 114.3, 111.9, 105.9, 105.9, 95.0, 84.2, 56.2, 55.4, 21.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{23}O_5S$ 459.1261 found 459.1260.

View Article Online
DOI: 10.1039/C6OB01941B



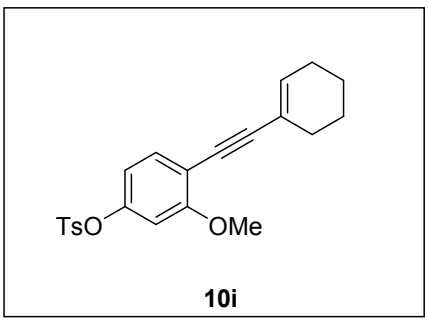
10g

4-([1,1'-Biphenyl]-4-ylethynyl)-3-methoxyphenyl 4-methylbenzenesulfonate (10g). White solid, mp: 121.8-123.0 °C (387.0 mg, 86%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.63-7.51 (m, 6H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.39-7.26 (m, 4H), 6.58 (d, *J* = 1.6 Hz, 1H), 6.50 (dd, *J* = 1.6, 8.0 Hz, 1H), 3.79 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 150.4, 145.7, 141.2, 140.4, 133.9, 132.3, 132.2, 129.9, 129.0, 128.8, 127.8, 127.1, 127.1, 122.2, 114.3, 111.7, 105.9, 94.3, 85.3, 56.2, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{28}H_{23}O_4S$ 455.1312 found 455.1312.



10h

3-Methoxy-4-(thiophen-3-ylethynyl)phenyl 4-methylbenzenesulfonate (10h). Pale yellow solid, mp: 105.2-106.7 °C (315.9 mg, 83%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.52 (dd, *J* = 1.2, 3.2 Hz, 1H), 7.38-7.26 (m, 4H), 7.18 (dd, *J* = 1.2, 5.2 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 6.50 (dd, *J* = 2.0, 8.4 Hz, 1H), 3.78 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 150.3, 145.7, 133.9, 132.2, 130.0, 129.9, 129.0, 128.7, 125.4, 122.2, 114.3, 111.6, 105.9, 89.5, 84.0, 56.2, 21.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}O_4S_2$ 385.0563 found 385.0565.

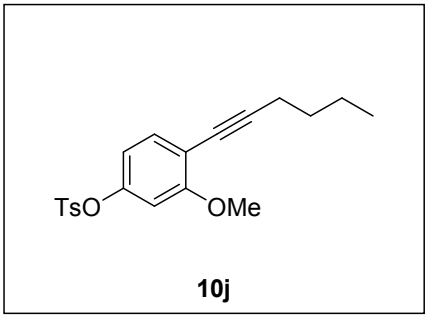


10i

4-(Cyclohex-1-en-1-ylethynyl)-3-methoxyphenyl 4-

View Article Online
DOI: 10.1039/C6OB01941B

methylbenzenesulfonate (10i). White solid, mp: 110.8-112.5 °C (219.6 mg, 58%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.38-7.20 (m, 3H), 6.53 (s, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 6.22 (s, 1H), 3.75 (s, 3H), 2.44 (s, 3H), 2.27-2.18 (m, 2H), 2.18-2.09 (m, 2H), 1.73-1.57 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.4, 150.0, 145.6, 135.8, 133.7, 132.3, 129.9, 128.8, 120.8, 114.2, 112.2, 105.8, 96.4, 81.8, 56.2, 29.3, 25.9, 22.4, 21.9, 21.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{23}O_4S$ 383.1312 found 383.1311.



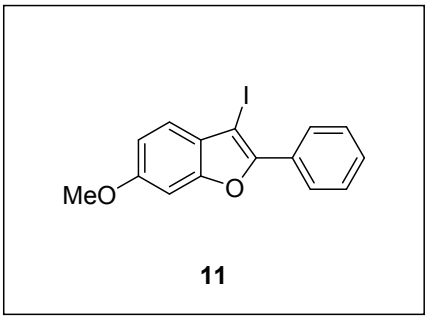
10j

4-(Hex-1-yn-1-yl)-3-methoxyphenyl 4-methylbenzenesulfonate (10j). White solid, mp: 53.8-54.6 °C (351.3 mg, 99%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 6.44 (dd, *J* = 2.4, 8.4 Hz, 1H), 3.74 (s, 3H), 2.48-2.38 (m, 2H), 2.43 (s, 3H), 1.64-1.53 (m, 2H), 1.53-1.40 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H),; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.5, 149.7, 145.6, 133.9, 132.2, 129.8, 128.7, 114.1, 112.3, 105.7, 95.8, 75.6, 56.1, 30.9, 22.1, 21.8, 19.5, 13.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}O_4S$ 359.1312 found 359.1311.

General Procedure for the Synthesis of 11, 12, and **13**

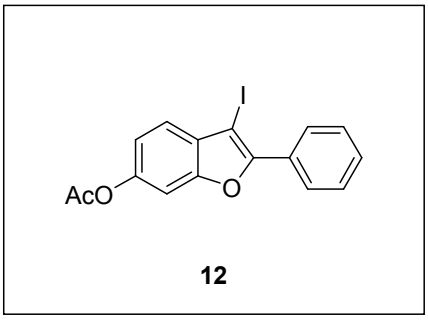
To a solution of **8**, **9**, or **10** (0.1 mmol) in CH_2Cl_2 (2 mL) were added $NaHCO_3$ (42 mg, 5.0 equiv) and I_2 (127 mg, 5.0 equiv) at 0 °C. After being stirred at rt for 3 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexane to hexanes/ethyl acetate = 50:1) to give **11**, **12**, or **13**, respectively.

View Article Online
DOI: 10.1039/C6OB01941B



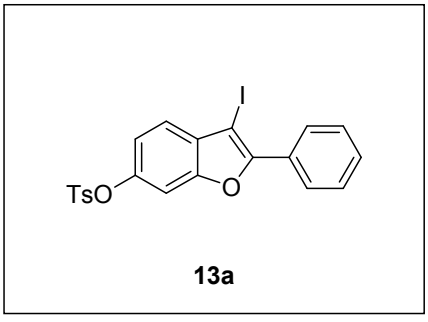
11

3-Iodo-6-methoxy-2-phenylbenzofuran (11). Yellow solid, mp: 55.6-56.9 °C (17.2 mg, 49%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 2.0, 8.4 Hz, 1H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 154.8, 152.3, 130.3, 128.9, 128.6, 127.2, 126.1, 122.1, 112.7, 95.7, 61.0, 56.0; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}IO_2$ 350.9876 found 350.9877.



12

3-Iodo-2-phenylbenzofuran-6-yl acetate (12). Pale yellow solid, mp: 117.8-118.9 °C (20.8 mg, 55%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.47-7.40 (m, 2H), 7.30 (d, *J* = 1.2 Hz, 1H), 7.07 (dd, *J* = 2.0, 8.4 Hz, 1H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.7, 154.2, 153.6, 149.1, 130.5, 129.9, 129.5, 128.7, 127.5, 122.1, 117.9, 105.2, 60.7, 21.3; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}IO_3$ 378.9826 found 378.9823.

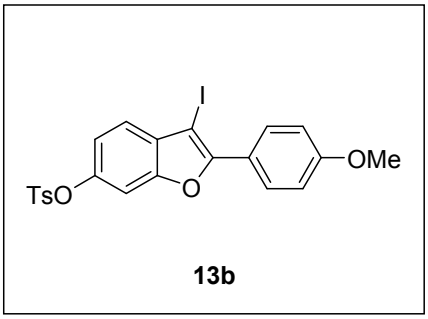


13a

3-Iodo-2-phenylbenzofuran-6-yl 4-methylbenzenesulfonate (13a). White solid, mp: 107.9-110.1 °C (42.7 mg, 87%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15-8.09 (m, 2H), 7.72 (d, *J* = 8.4 Hz, 2H),

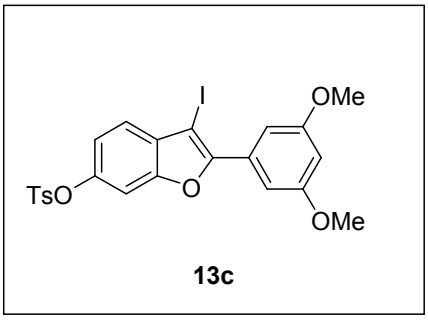
View Article Online
DOI: 10.1039/C6OB01941B

7.54-7.40 (m, 3H), 7.31 (dd, J = 1.6, 8.0 Hz, 3H), 7.22 (d, J = 2.0 Hz, 1H), 6.92 (dd, J = 2.0, 8.8 Hz, 1H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.9, 153.2, 147.9, 145.7, 132.3, 131.6, 130.0, 129.7, 129.6, 128.7, 127.6, 122.1, 118.5, 106.2, 60.5, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}IO_4S$ 490.9808 found 490.9808.



13b

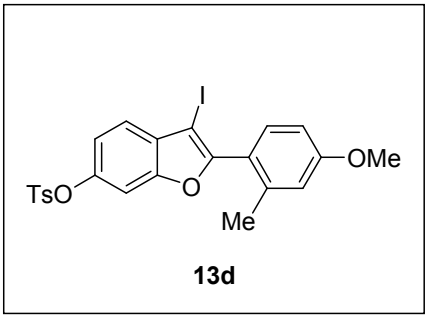
3-Iodo-2-(4-methoxyphenyl)benzofuran-6-yl 4-methylbenzenesulfonate (13b). White solid, mp: 110.2-111.8 °C (52.0 mg, 100%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.36-7.22 (m, 3H), 7.19 (d, J = 1.6 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.89 (dd, J = 1.6, 8.4 Hz, 1H), 3.87 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 155.1, 153.0, 147.5, 145.6, 132.3, 131.7, 130.0, 129.1, 128.7, 122.2, 121.7, 118.4, 114.2, 106.1, 58.8, 55.5, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}IO_5S$ 520.9914 found 520.9912.



13c

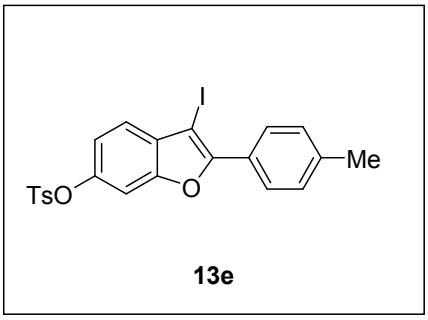
2-(3,5-Dimethoxyphenyl)-3-iodobenzofuran-6-yl 4-methylbenzenesulfonate (13c). Yellow solid, mp: 133.1-134.6 °C (51.7 mg, 94%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.35-7.26 (m, 5H), 7.23 (d, J = 1.6 Hz, 1H), 6.91 (dd, J = 1.6, 8.4 Hz, 1H), 6.55(s, 1H), 3.87 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.9, 154.5, 153.1, 148.0, 145.7, 132.3, 131.6, 131.1, 130.0, 128.7, 122.2, 118.6, 106.2, 105.6, 102.3, 61.0, 55.7, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}IO_6S$ 551.0020 found 551.0021.

View Article Online
DOI: 10.1039/C6OB01941B



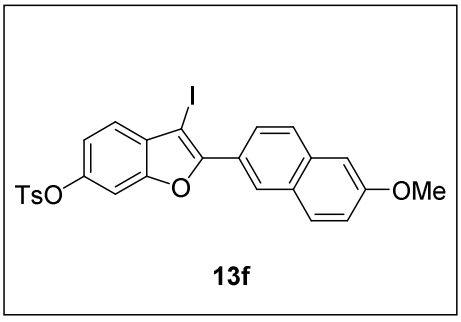
13d

3-Iodo-2-(4-methoxy-2-methylphenyl)benzofuran-6-yl 4-methylbenzenesulfonate (13d). White solid, mp: 65.7-67.0 °C (49.7 mg, 93%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 8.4 Hz, 3H), 7.19 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.87-6.80 (m, 2H), 3.86 (s, 3H), 2.45 (s, 3H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.0, 158.2, 153.7, 147.5, 145.6, 140.2, 132.6, 132.4, 130.6, 130.0, 128.7, 121.7, 121.4, 118.3, 116.2, 111.2, 106.3, 64.1, 55.4, 21.9, 20.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}IO_5S$ 535.0071 found 535.0070.



13e

3-Iodo-2-(*p*-tolyl)benzofuran-6-yl 4-methylbenzenesulfonate (13e). Pale yellow solid, mp: 115.7-116.9 °C (46.4 mg, 92%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.35-7.26 (m, 5H), 7.20 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 2.45 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.2, 153.2, 147.7, 145.6, 140.0, 132.3, 131.7, 130.0, 129.4, 128.7, 127.5, 126.8, 121.9, 118.4, 106.1, 59.8, 21.9, 21.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}IO_4S$ 504.9965 found 504.9966.

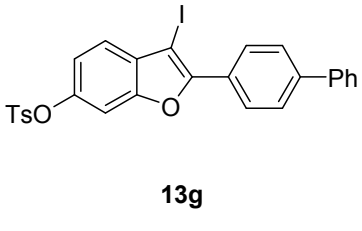


13f

3-Iodo-2-(6-methoxynaphthalen-2-yl)benzofuran-6-yl 4-methylbenzenesulfonate (13f). White solid, mp: 146.1-147.6 °C (51.9 mg, 91%); **^{1}H NMR** (400

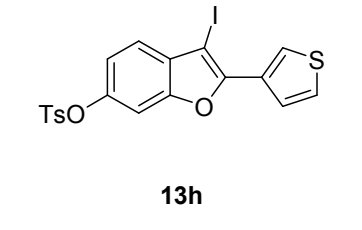
View Article Online
DOI: 10.1039/C6OB01941B

MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.15 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.80 (t, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.35-7.25 (m, 3H), 7.22 (d, *J* = 1.6 Hz, 1H), 7.18 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 2.0, 8.8 Hz, 1H), 3.93 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.9, 155.1, 153.2, 147.8, 145.7, 135.0, 132.3, 131.8, 130.3, 130.0, 128.7, 128.5, 127.3, 127.2, 124.9 124.7, 122.0, 119.8, 118.5, 106.1, 105.9, 60.0, 55.5, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{20}IO_5S$ 571.0071 found 571.0073.



13g

2-([1,1'-Biphenyl]-4-yl)-3-iodobenzofuran-6-yl 4-methylbenzenesulfonate (13g). White solid, mp: 170.6-171.1 °C (53.8 mg, 95%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 2H), 7.77-7.70 (m, 4H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 3H), 7.24 (d, *J* = 1.2 Hz, 1H), 6.93 (dd, *J* = 1.2, 8.4 Hz, 1H), 2.46 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.6, 153.3, 147.9, 145.7, 142.4, 140.3, 132.3, 131.7, 130.0, 129.1, 128.7, 128.5, 128.0, 127.9, 127.4, 127.2, 122.1, 118.6, 106.2, 60.6, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{27}H_{20}IO_4S$ 567.0121 found 567.0122.

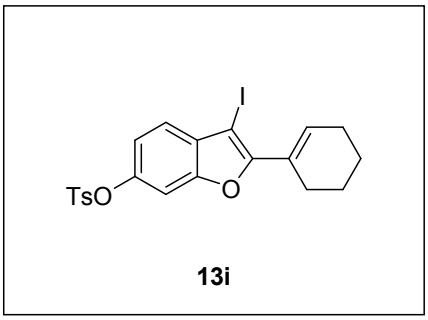


13h

3-Iodo-2-(thiophen-3-yl)benzofuran-6-yl 4-methylbenzenesulfonate (13h). Yellow gum, (43.2 mg, 87%); **^{1}H NMR** (400 MHz, $CDCl_3$) 8.15 (dd, *J* = 1.2, 3.2 Hz, 1H), 7.86 (dd, *J* = 1.2, 5.2 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.43 (dd, *J* = 3.2, 5.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J* = 2.0, 8.8 Hz, 1H),

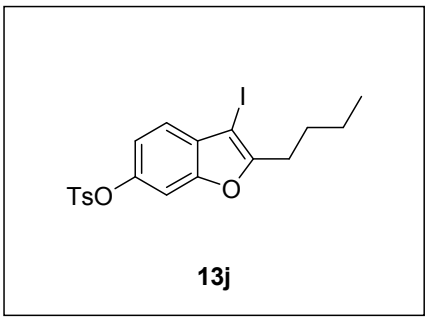
View Article Online
DOI: 10.1039/C6OB01941B

2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.8, 152.5, 147.7, 145.7, 132.2, 131.3, 130.8, 130.0, 128.7, 126.3, 126.2, 125.2 121.7, 118.5, 106.1, 59.8, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{14}IO_4S_2$ 496.9373 found 496.9374.



13i

2-(Cyclohex-1-en-1-yl)-3-iodobenzofuran-6-yl 4-methylbenzenesulfonate (13i). Yellow gum (27.7 mg, 56%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.12 (s, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.77 (s, 1H), 2.64-2.54 (m, 2H), 2.45 (s, 3H), 2.33-2.23 (m, 2H), 1.89-1.73 (m, 2H), 1.73-1.65 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.9, 152.6, 147.5, 145.6, 132.6, 132.3, 131.5, 130.0, 128.7, 127.8, 121.7, 118.1, 105.8, 58.3, 26.7, 25.9, 22.6, 21.9, 21.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}IO_4S$ 495.0121 found 495.0121.



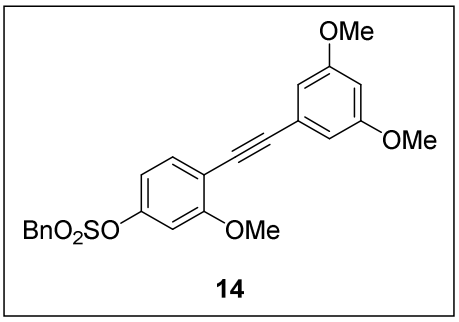
13j

2-butyl-3-iodobenzofuran-6-yl 4-methylbenzenesulfonate (13j). Yellow solid, mp: 92.5-93.4 °C (41.9 mg, 89%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 2.85-2.72 (m, 2H), 3.29 (s, 3H), 1.70-1.55 (m, 2H), 1.52-1.36 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 150.5, 145.6, 135.7, 132.3, 130.3, 129.8, 128.8, 114.4, 107.8, 106.8, 89.4, 56.1, 49.4, 30.8, 21.9, 21.6, 14.3; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}IO_4S$ 471.0121 found 471.0123.

View Article Online
DOI: 10.1039/C6OB01941B

Synthesis of 14

To a solution of **5c** (0.99 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (0.28 mL, 2.0 equiv) and benzylsulfonyl chloride (227 mg, 1.19 mmol, 1.2 equiv) at 0 °C. After being stirred at rt for 1 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 20:1:2) to give **14**.

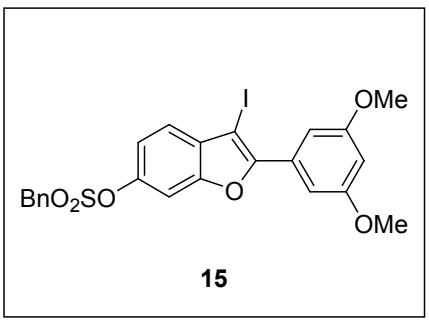


14

4-((3,5-Dimethoxyphenyl)ethynyl)-3-methoxyphenyl phenylmethanesulfonate (14). White solid, mp: 112.7-114.1 °C (299.5 mg, 69%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57-7.36 (m, 6H), 6.69 (s, 3H), 6.59 (s, 1H), 6.46 (s, 1H), 4.54 (s, 2H), 3.83 (s, 3H), 3.80 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.0, 160.6, 150.0, 134.2, 131.1, 129.5, 129.2, 127.2, 124.6, 113.8, 111.7, 109.6, 105.5, 102.1, 94.4, 84.1, 57.2, 56.3, 55.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}O_6S$ 439.1210 found 439.1211.

Synthesis of 15

15 was synthesized by following the same procedure for the synthesis **11-13**.



15

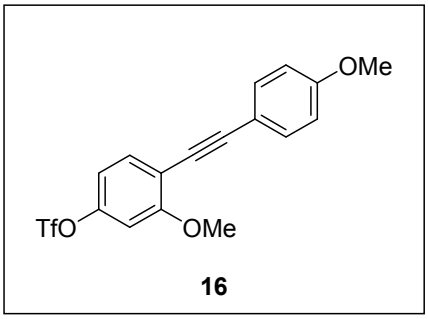
2-(3,5-Dimethoxyphenyl)-3-iodobenzofuran-6-yl phenylmethanesulfonate (15). White solid, mp: 80.2-

View Article Online
DOI: 10.1039/C6OB01941B

89.3 °C (47.3 mg, 86%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.36 (m, 6H), 7.36-7.27 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.56 (s, 1H), 4.56 (s, 2H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.9, 154.7, 153.2, 147.4, 131.7, 131.0, 129.5, 129.2, 127.2, 122.5, 118.2, 106.0, 105.6, 102.3, 61.0, 56.9, 55.7; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}IO_6S$ 551.0020 found 551.0023.

Synthesis of 16

To a solution of **5b** (0.91 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (0.255 mL, 2.0 equiv) and Tf_2O (0.229 mL, 1.5 equiv) at 0 °C. After being stirred at rt for 2 h, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and washed with 10% aq. HCl and aq. $NaHCO_3$, successively. The water layer was extracted with CH_2Cl_2 (5 mL x 2) two more times. The combined organic layers were dried over $MgSO_4$ and purified by silica gel column chromatography (hexanes/ethyl acetate = 50:1) to give **16**.



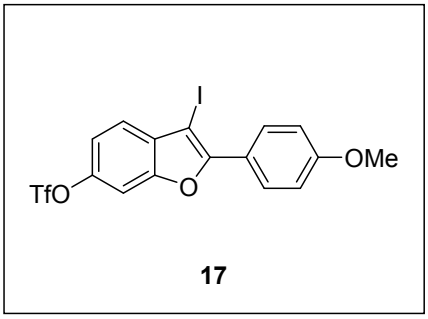
16

3-Methoxy-4-((4-methoxyphenyl)ethynyl)phenyl trifluoromethanesulfonate (16). Yellow gum, (312.9 mg, 89%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57-7.45 (m, 3H), 6.93-6.82 (m, 3H), 6.79 (s, 1H), 3.93 (s, 3H), 3.83 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.9, 160.0, 149.6, 134.2, 133.4, 115.1, 114.1, 113.8, 113.2, 104.8, 95.3, 82.7, 56.5, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}F_3O_5S$ 387.0509 found 387.0508.

Synthesis of 17

View Article Online
DOI: 10.1039/C6OB01941B

17 was synthesized by following the same procedure for the synthesis of **11-13**.

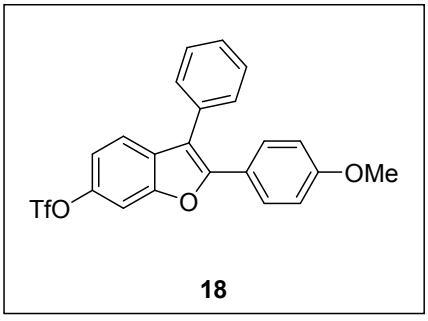


17

3-Iodo-2-(4-methoxyphenyl)benzofuran-6-yl trifluoromethanesulfonate (17). Yellow solid, mp: 78.2-79.2 °C (47.8 mg, 96%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.51-7.42 (m, 2H), 7.23 (s, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.0, 156.0, 153.0, 147.2, 133.0, 129.3, 126.8, 122.4, 121.9, 117.2, 114.3, 105.2, 58.5, 55.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{11}F_3IO_5S$ 498.9318 found 498.9316.

Synthesis of 18

A mixture of **17** (50 mg, 0.1 mmol), $Pd(Ph_3P)_4$ (11.6 mg, 0.1 equiv), K_2CO_3 (27.7 mg, 2 equiv), and phenylboronic acid (18.4 mg, 1.5 equiv) in toluene/EtOH/H_2O (4:2:1, 1.4 mL) was heated at 100 °C for 6 h. The reaction mixture was concentrated in vacuo and extracted with CH_2Cl_2 (3 mL) and water (3 mL). The water layer was extracted with CH_2Cl_2 (3 mL) twice more. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 50:1) to give **18**.



18

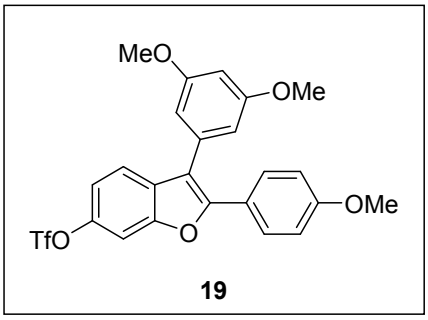
2-(4-Methoxyphenyl)-3-phenylbenzofuran-6-yl trifluoromethanesulfonate (18). Yellow gum (35.1 mg, 78%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.8 Hz, 2H), 7.52-7.37 (m, 7H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H); **^{13}C NMR** (100

View Article Online
DOI: 10.1039/C6OB01941B

MHz, $CDCl_3$) δ 160.3, 153.3, 153.2, 146.5, 132.2, 130.7, 129.8, 129.3, 128.7, 128.1, 122.5, 120.5, 116.6, 115.8, 114.2, 105.2, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{16}F_3O_5S$ 449.0665 found 449.0665.

Synthesis of 19

A mixture of **17** (240 mg, 0.48 mmol), $Pd(Ph_3P)_4$ (55.7 mg, 0.1 equiv), K_2CO_3 (133.2 mg, 2 equiv), and 3,5-dimethoxyphenylboronic acid (131.5 mg, 1.5 equiv) in toluene/EtOH/H_2O (4:2:1, 3.5 mL) was heated at 100 °C for 7 h. The reaction mixture was concentrated in vacuo and extracted with CH_2Cl_2 (10 mL) and water (10 mL). The water layer was extracted with CH_2Cl_2 (10 mL) twice more. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 50:1) to give **19**.



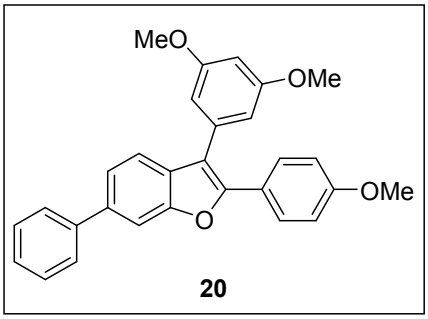
19

3-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)benzofuran-6-yl trifluoromethanesulfonate (19). Yellow gum, (200.8 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.55-7.44 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.61 (s, 1H), 6.60 (s, 1H), 6.53 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5, 160.3, 153.3, 153.1, 146.5, 134.0, 130.7, 128.7, 122.4, 120.5, 117.4, 116.6, 115.7, 114.2, 107.7, 105.1, 100.3, 55.6, 55.4; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}F_3O_7S$ 509.0876 found 509.0878.

Synthesis of 20

View Article Online
DOI: 10.1039/C6OB01941B

A mixture of **19** (27 mg, 0.05 mmol), $Pd(OAc)_2$ (2.4 mg, 0.1 equiv), K_2CO_3 (22.0 mg, 3 equiv), SPhos (6.5 mg, 0.3equiv) and phenylboronic acid (14.2 mg, 2.2 equiv) in benzene/EtOH/H_2O (10:5:1 mL) was heated at 100 °C for 17 h. The reaction mixture was concentrated in vacuo and extracted with CH_2Cl_2 (3 mL) and water (3 mL). The water layer was extracted with CH_2Cl_2 (3 mL) twice more. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 50:1) to give **20**.



20

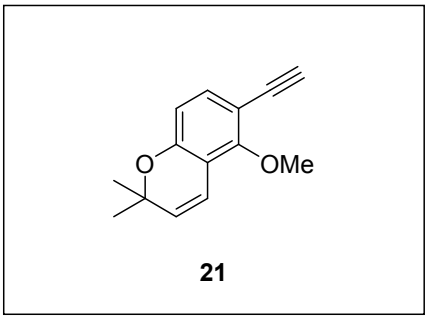
3-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-6-phenylbenzofuran (20). Colorless gum (12.1 mg, 52%, 83% BORSM); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 4H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.53-7.42 (m, 3H), 7.36 (t, *J* = 6.8 Hz, 1H), 6.88 (d *J* = 8.0 Hz, 2H), 6.68 (s, 2H), 6.52 (s, 1H), 3.83 (s, 3H), 3.79 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.4, 159.9, 154.5, 151.4, 141.5, 138.1, 135.1, 129.7, 129.0, 128.7, 127.5, 127.3, 123.3, 122.6, 120.0, 116.0, 114.1, 109.6, 107.8, 100.1, 55.6, 55.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}O_4$ 437.1747 found 437.1746.

Synthesis of 22

To a stirred solution of **21** (380.1 mg, 1.5 equiv) in anhydrous THF (5 mL) at -78 °C was added 1.0 M LHMDS (1.18 mL, 1.3 equiv). After the mixture was stirred for 5 min under nitrogen atmosphere, 1,4-benzoquinone (128.0 mg, 1.18 mmol) dissolved in anhydrous THF (3 mL) was added at -78 °C. After 15 min, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was extracted with CH_2Cl_2 (2 x 5 mL). The

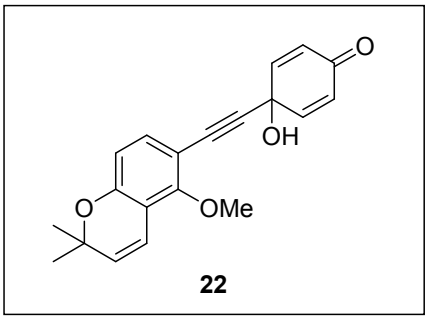
View Article Online
DOI: 10.1039/C6OB01941B

combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 3:1:2) to give **22**.



21

6-Ethynyl-5-methoxy-2,2-dimethyl-2*H*-chromene (21). Yellow gum; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 10.0 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 3.93 (s, 3H), 3.20 (s, 1H), 1.43 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.0, 154.8, 134.1, 130.7, 116.7, 114.9, 112.5, 107.6, 80.4, 80.0, 76.6, 61.9, 28.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}O_2$ 215.1067 found 215.1067.



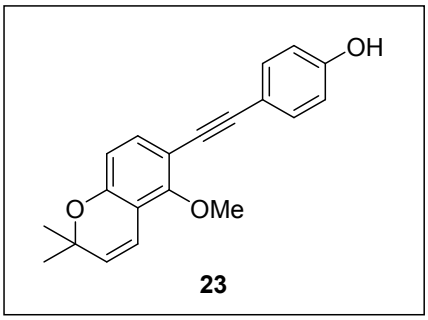
22

4-Hydroxy-4-((5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethynyl)cyclohexa-2,5-dien-1-one (22). Yellow solid, mp: 106.3-107.1 °C (343.6 mg, 90%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 10.0 Hz, 2H), 6.56 (d, *J* = 10.0 Hz, 1H), 6.51 (d, *J* = 8.8 Hz, 1H), 6.21 (d, *J* = 10.0 Hz, 2H), 5.64 (d, *J* = 10.0 Hz, 1H), 3.87 (s, 3H), 3.17 (s, 1H), 1.42 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.9, 157.8, 155.4, 146.9, 133.7, 130.9, 127.0, 116.4, 115.0, 112.7, 106.6, 87.7, 83.2, 63.0, 61.9, 28.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}O_4$ 323.1278 found 323.1277.

Synthesis of 23

View Article Online
DOI: 10.1039/C6OB01941B

23 was synthesized by following the same procedure for the synthesis of **5**.

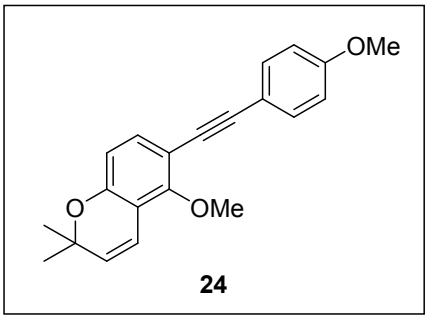


23

4-((5-Methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethynyl)phenol (23). White solid, mp: 156.0-157.2 °C (93.1 mg, 98%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 10.0 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 4.95 (s, 1H), 4.00 (s, 3H), 1.43 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.0, 155.6, 154.2, 133.3, 133.1, 130.6, 116.9, 116.3, 115.6, 115.0, 112.5, 109.0, 92.1, 84.6, 76.6, 61.7, 28.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}O_3$ 307.1329 found 307.1330.

Synthesis of 24

24 was synthesized by following the same procedure for the synthesis of **8**.



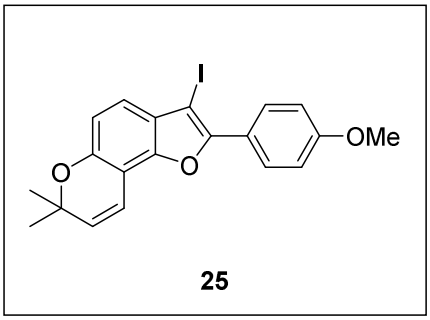
24

5-Methoxy-6-((4-methoxyphenyl)ethynyl)-2,2-dimethyl-2*H*-chromene (24). White solid, mp: 70.5-72.2 °C (61.0 mg, 99%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 10.0 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 5.63 (d, *J* = 10.0 Hz, 1H), 4.00 (s, 3H), 3.81 (s, 3H), 1.43 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 157.1, 154.2, 133.3, 132.8, 130.6, 116.9, 116.1, 114.9, 114.1, 112.4, 109.0, 92.2, 84.7, 76.5, 61.6, 55.4, 28.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{21}O_3$ 321.1485 found 321.1484.

View Article Online
DOI: 10.1039/C6OB01941B

Synthesis of 25

25 was synthesized by following the same procedure for the synthesis of **11-13**.

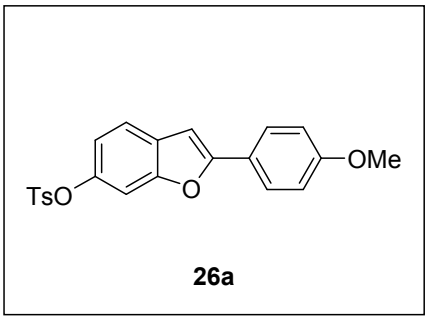


25

3-Iodo-2-(4-methoxyphenyl)-7,7-dimethyl-7*H*-furo[2,3-*f*]chromene (25). Pale brown solid, mp: 133.0-134.2 °C (43.1 mg, 100%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.2 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 10.4 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 5.72 (d, *J* = 10.0 Hz, 1H), 3.87 (s, 3H), 1.48 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.1, 152.5, 151.5, 149.7, 131.0, 128.8, 126.3, 123.0, 120.8, 115.8, 114.0, 113.4, 106.2, 76.7, 59.9, 55.5, 27.8; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}IO_3$ 433.0295 found 433.0296.

General Procedure for the Synthesis of 26

To a solution of **10** (0.08 mmol) in DCE (1 mL) was added AgOTf. After being stirred at 100 °C, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 50:1:2) to give **26a** to **26e**.

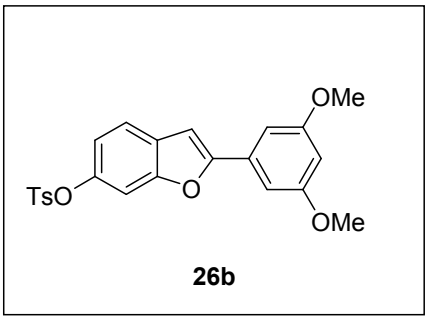


26a

2-(4-Methoxyphenyl)benzofuran-6-yl 4-methylbenzenesulfonate (26a). White solid, mp: 174.2-174.7 °C (26.1 mg, 83%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82-7.68 (m, 4H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.18 (s, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.87-6.80 (m, 2H), 3.86 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.4,

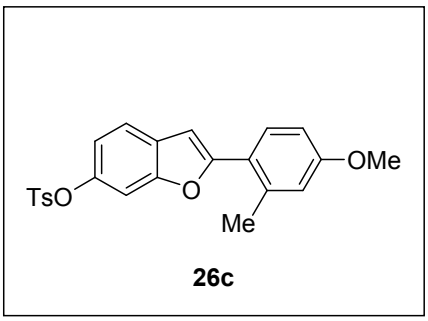
View Article Online
DOI: 10.1039/C6OB01941B

157.9, 154.1, 146.4, 145.5, 132.4, 129.9, 128.7, 128.6, 126.6, 122.8, 120.5, 117.8, 114.4, 106.0, 99.4, 55.5, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}O_5S$ 395.0948 found 395.0948.



26b

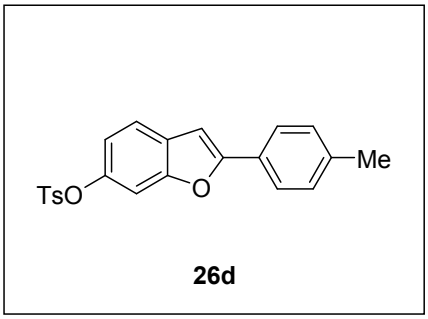
2-(3,5-Dimethoxyphenyl)benzofuran-6-yl 4-methylbenzenesulfonate (26b). White solid, mp: 130.9-132.2 °C (23.4 mg, 69%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.22 (s, 1H), 6.96 (s, 3H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.48 (s, 1H), 3.86 (s, 6H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.3, 157.6, 154.3, 146.9, 145.5, 132.4, 131.8, 129.9, 128.7, 128.2, 121.0, 118.0, 106.2, 103.2, 101.6, 101.4, 55.7, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}O_6S$ 425.1053 found 425.1055.



26c

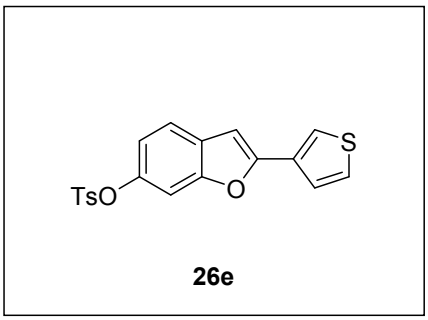
2-(4-Methoxy-2-methylphenyl)benzofuran-6-yl 4-methylbenzenesulfonate (26c). White solid, mp: 128.6-130.1 °C (24.1 mg, 74%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79-7.67 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.19 (s, 1H), 6.89-6.78 (m, 3H), 6.73 (s, 1H), 3.85 (s, 3H), 2.53 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.0, 157.6, 153.7, 146.5, 145.5, 137.8, 132.5, 129.9, 129.7, 128.7, 128.5, 122.4, 120.6, 117.7, 116.8, 111.7, 106.0, 103.5, 55.4, 22.2, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}O_5S$ 409.1104 found 409.1102.

View Article Online
DOI: 10.1039/C6OB01941B



26d

2-(*p*-Tolyl)benzofuran-6-yl 4-methylbenzenesulfonate (26d). White solid, mp: 189.8-191.0 °C (17.8 mg, 99%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79-7.64 (m, 4H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.24 (s, 1H), 7.19 (s, 1H), 6.90 (s, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 2.45 (s, 3H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.0, 154.2, 146.6, 145.5, 139.2, 132.4, 129.9, 129.7, 128.7, 128.4, 127.3, 125.0, 120.8, 117.9, 106.1, 100.3, 21.9, 21.5; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}O_4S$ 379.0999 found 379.1000.



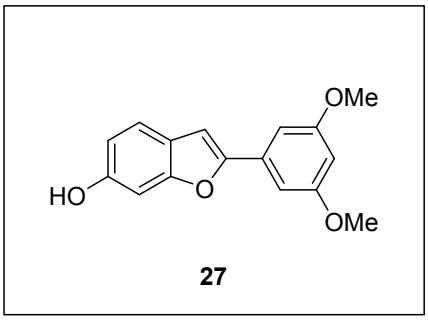
26e

2-(Thiophen-3-yl)benzofuran-6-yl 4-methylbenzenesulfonate (26e). White solid, mp: 174.8-176.2 °C (14.8 mg, 86%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79-7.67 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.19 (s, 1H), 6.90-6.78 (m, 3H), 6.73 (s, 1H), 3.85 (s, 3H), 2.53 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.0, 157.6, 153.7, 146.5, 145.5, 137.8, 132.5, 129.9, 129.7, 128.7, 128.5, 122.4, 120.6, 117.7, 116.8, 111.7, 106.0, 103.5, 55.4, 22.2, 21.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}O_4S_2$ 371.0406 found 371.0405.

Synthesis of 27

View Article Online
DOI: 10.1039/C6OB01941B

To a solution of **26b** (0.05 mmol) in DMF (1 mL) was added 1M n-Bu_4NF. After being stirred at 100 °C for 4 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 5:1:2) to give **27**.



27

2-(3,5-Dimethoxyphenyl)benzofuran-6-ol (27). White solid, mp: 105.7-106.3 °C (10.0 mg, 74%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 6.97 (s, 2H), 6.93 (s, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.45 (s, 1H), 5.01 (s, 1H), 3.87 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.2, 155.8, 155.2, 153.9, 132.5, 122.9, 121.4, 112.3, 102.8, 101.8, 100.8, 98.4, 55.6; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_4$ 271.0965 found 271.0966.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (2014R1A2A1A11050491). We thank Mr. Seok Hyun Yoon for conducting preliminary experiments of this study.

Electronic Supplementary Information

^{1}H and ^{13}C NMR spectra of synthesized compounds.

References

View Article Online
DOI: 10.1039/C6OB01941B

[1] (a) Dat, N. T.; Jin, X.; Hong, Y.-S.; Kim, Y. H.; Lee, J. J. *J. Nat. Prod.* **2009**, *72*, 39. (b) Kuete, V.; Fozing, D. C.; Kapche, W. F. G. D.; Mbaveng, A. T.; Kuiate, A. T.; Ngadjui, B. T.; Abegaz, B. M. *J. Ethnopharmacol.* **2009**, *124*, 551. (c) He, Y.; Xu, J.; Yu, Z.-H.; Gunawan, A. M.; Wu, L.; Wang, L.; Zhang, Z.-Y. *J. Med. Chem.* **2013**, *56*, 832. (d) Hao, H.; Chen, W.; Zhu, J.; Lu, C.; Shen Y. *Eur. J. Med. Chem.* **2015**, *102*, 277. (e) Li, X.; Li, C.; Xuan, B.; Du, X.; Xia, L.; Shen, Z. *Tetrahedron* **2016**, *72*, 2464. (f) Ha, M. T.; Tran, M. H.; Kim, J. A.; Jo, K.-J.; Kim, J.; Kim, W. D.; Cheon, W. J.; Woo, M. H.; Ryu, S. H.; Min, B. S. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2788. (g) Pahari, P.; Saikia U. P.; Das, T. P.; Damodaran C.; Rohr, J. *Tetrahedron* **2016**, *72*, 3324.

[2] Kim, I.; Kim, K.; Choi, J. *J. Org. Chem.* **2009**, *74*, 8492.

[3] (a) Kim, I.; Lee, S.-H.; Lee, S. *Tetrahedron Lett.* **2008**, *49*, 6579. (b) Kim, I.; Choi, J. *Org. Biomol. Chem.* **2009**, *7*, 2788. (c) Kim, K.; Kim, I. *Org. Lett.* **2010**, *12*, 5314. (d) Lee, J. H.; Kim, M.; Kim, I. *J. Org. Chem.* **2014**, *79*, 6153. (e) Nayak, M.; Jung, Y.; Kim, I. *Org. Biomol. Chem.* **2016**, *14*, 8074.

[4] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (d) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

[5] (a) Iyoda, M.; Yamauchi, T.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 303. (b) Capparelli, M. P.; DeSchepper, R. E.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 4953. (c) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 5547. (d) Miller, L. A.; Marsini, M. A.; Pettus, T. R. R. *Org. Lett.* **2009**, *11*, 1955. (e) Miki, K.; Fujita, M.; Inoue, Y.; Senda, Y.; Kowada, T.; Ohe, K. *J. Org. Chem.* **2010**, *75*, 3537. (f) Kayahara, E.; Patel, V. K.; Yamago, S. *J. Am.*

View Article Online
DOI: 10.1039/C6OB01941B

Chem. Soc. **2014**, *136*, 2284.

[6] For alkyl protection, see: (a) Yang, L.-Y.; Chang, C.-F.; Huang, Y.-C.; Lee, Y.-J.; Hu, C.-C.; Tseng, T.-H. *Synthesis* **2009**, 1175. (b) Vang, T.; Xie, Y.; Liu, W. H.; Vidović, D.; Liu, Y.; Wu, S.; Smith, D. H.; Rinderspacher, A.; Chung, C.; Gong, G.; Mustelin, T.; Landry, D. W.; Rickert, R. C.; Schürer, S. C.; Deng, S.-X.; Tautz, L. *J. Med. Chem.* **2011**, *54*, 562. (c) Bang, H. B.; Han, S. Y.; Choi, D. H.; Hwang, J. W.; Jun, J.-G. *ARKIVOC* **2008**, 112. For acetyl protection, see: (d) Massue, J.; Benelhadj, K.; Chibani, S.; Le Guennic, B.; Jacquemin, D.; Retailleau, P.; Ulrich, G.; Ziessel, R. *Tetrahedron Lett.* **2014**, *55*, 4136. For p-toluenesulfonyl protection, see: (e) Ahmed, N.; Dubuc, C.; Rousseau, J.; Bénard, F.; van Lier, J. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3212. (f) Yao, T.; Yue, D.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985.

[7] For recent reviews, see: (a) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Chem. · Eur. J.* **2012**, *18*, 5460. (b) Gabriele, B.; Mancuso, R.; Larock, R. C. *Curr. Org. Synth.* **2014**, *18*, 341. (c) Aggarwal, T.; Kumar, S.; Verma, A. K. *Org. Biomol. Chem.* **2016**, *14*, 7639.

[8] (a) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (b) Wang, J.; Zhu, H.-T.; Li, Y.-X.; Wang, L.-J.; Qiu, Y.-F.; Qiu, Z.-H.; Zhong, M.-j.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2014**, *16*, 2236. (c) Aurelio, L.; Volpe, R.; Halim, R.; Scammells, P. J.; Flynn, B. L. *Adv. Synth. Cat.* **2014**, *356*, 1974. (d) Danilkina, N. A.; Kulyashova, A. E.; Khlebnikov, A. F.; Bräse, S.; Balova, I. A. *J. Org. Chem.* **2014**, *79*, 9018. (e) Zhang, X.; Feng, C.; Jiang, T.; Li, Y.; Pan, L.; Xu, X. *Org. Lett.* **2015**, *17*, 3576. (f) Jung, Y.; Kim, I. *Asian J. Org. Chem.* **2016**, *5*, 147. and references cited therein.

[9] See the Experimental Section for details.

View Article Online
DOI: 10.1039/C6OB01941B

[10] Nayak, M.; Kim, I. *J. Org. Chem.* **2015**, *80*, 11460.

[11] For a recent review on silver-catalyzed reactions of alkynes, see: Fang, G.; Bi, X. *Chem. Soc. Rev.* **2015**, *44*, 8124.

[12] (a) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218. (b) Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2443. (c) Pinhey, J. T.; Stoermer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2455. (d) Hiroya, K.; Hashimura, K.; Ogasawara, K. *Heterocycles* **1994**, *38*, 2463. (e) Ishibashi, K.; Nakajima, K.; Sugioka, Y.; Sugiyama, M.; Hamada, T.; Horikoshi, H.; Nishi, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 561. (f) Kao, C.-L.; Chern, J.-W. *J. Org. Chem.* **2002**, *67*, 6772. (g) Colobert, F.; Castanet, A.-S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334. (h) Le Bras, G.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2006**, *47*, 5497. (i) Jacubert, M.; Hamze, A.; Provot, O.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2009**, *50*, 3588. (j) Hamze, A.; Rasolofonjatovo, E.; Provot, O.; Mousset, C.; Veau, D.; Rodrigo, J.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *ChemMedChem* **2011**, *6*, 2179. (k) Thévenin, M.; Thoret, S.; Grellier, P.; Dubois, J. *Bioorg. Med. Chem.* **2013**, *21*, 4885.

[13] Naik, R.; Harmalkar, D. S.; Xu, X.; Jang, K.; Lee, K. *Eur. J. Med. Chem.* **2015**, *90*, 379.