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Synthesis of 3,4-Disubstituted 2*H*-Benzopyrans through C−C Bond Formation via Electrophilic Cyclization

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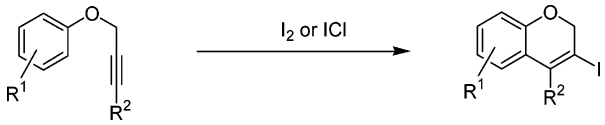

The electrophilic cyclization of substituted propargylic aryl ethers by I_2, ICl, and PhSeBr produces 3,4-disubstituted 2*H*-benzopyrans in excellent yields. This methodology results in vinylic halides or selenides under mild reaction conditions and tolerates a variety of functional groups, including methoxy, alcohol, aldehyde, and nitro groups.

Introduction

2*H*-1-Benzopyrans, commonly known as 2*H*-benzopyrans or 2*H*-chromenes, are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. The 2*H*-benzopyran Daurichromenic acid is known to exhibit anti-HIV properties,[1] while Coutareagenin possesses antidiabetic activity.[2] Derivatives of 3,4-diphenylchromans are known to have estrogenic activity.[3] Numerous derivatives of 2*H*-benzopyrans are useful for the treatment of proliferative skin disorders and microbial infections[4] and show potent antifungal activity.[5] Derivatives of 2*H*-benzopyrans, like 2,4-diphenyl-2*H*-benzopyran and 2,2,4-triphenyl-2*H*-benzopyran, have been studied for their photochromic behavior.[6] Because of their biological and pharmaceutical importance, the isolation and synthesis of 2*H*-benzopyrans has received considerable attention in the literature.

Substituted 2*H*-benzopyrans have been synthesized in our laboratories by the Pd(II)-catalyzed cyclization of allylic aryl ethers,[7] while the palladium-catalyzed cross-coupling of 4-trifluoromethanesulfonyloxy-2*H*-benzopyrans with arylboronic acids has also been reported in the literature.[8] Syntheses of 2*H*-benzopyrans are also known using platinum and gold catalysis,[9] Hg(II)-mediated cyclizations,[10] Grignard reagents,[11] and microwave irradiation.[12]

A wide range of carbocycles and heterocycles have been constructed using the electrophilic cyclization of disubstituted alkynes[13] and transition metal-catalyzed cyclizations.[14,15] Many researchers, including those from our group, have utilized these

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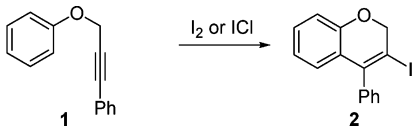
cyclizations for the synthesis of benzofurans,[16] furans,[17] benzo[*b*]thiophenes,[18] thiophenes,[19] naphthols,[20] indoles,[21] quinolines,[22] isoquinolines,[23] isocoumarins,[24] isochromenes,[25] and polycyclic aromatics.[26] Some methods are not compatible with functionality, while some require the use of costly metals as catalysts. Recently, Barluenga and co-workers reported the synthesis of 2*H*-benzopyrans by the cyclization of aryl propargylic ethers using costly IPy_2BF_4 and HBF_4.[27] They also reported two examples of the iodocyclization of propargylic ethers using I_2 in water. We report herein many examples and a general synthesis of 2*H*-benzopyrans in good yields via electrophilic cyclization using the simple, inexpensive electrophiles I_2, ICl, and PhSeBr in nitromethane.

Results and Discussion

Our early studies mainly focused on the iodocyclization of substituted propargylic aryl ethers to give 3,4-disubstituted 2*H*-benzopyrans in excellent yields. Phenyl 3-phenyl-2-propynyl ether (**1**) was used as a model system for optimization of the reaction conditions using I_2 or ICl (eq 1).



(1)

Early in this work, conditions similar to our previous iodocyclization reactions were used. For instance, the reaction was run with 0.25 mmol of **1**, 2 equiv of $NaHCO_3$ as the base, and 3 equiv of I_2 in 5 mL of CH_3CN at 25 °C to obtain a 61% isolated yield of the desired 3-iodo-4-phenyl-2*H*-benzopyran (**2**)[27] (Table 1, entry 1). Solvents, like CH_2Cl_2, CH_3OH, and DMF, resulted in lower yields (entries 2−4), but CH_3NO_2 gave a yield of 77% (entry 5). No reaction was observed at 0 °C after 4 h (entry 6), while the reaction was messy and produced only a 42% yield at 40 °C (entry 7). Reducing the amount of I_2 to 2 equiv decreased the yield significantly to 53% (entry 8), while an increase in the number of equivalents of I_2 caused a slight decrease in the yield to 69% (entry 9). Reducing the reaction time to 12 h lowered the yield to 62% (entry 10), while there was no increase in yield when the reaction time was doubled to 48 h (entry 11). The presence of the base proved to be important for the reaction as the yield was reduced to 58% without the base and only 70% with 1 equiv of the base (entries 12 and 13). Several additional bases were examined in this

TABLE 1. Optimization of the Cyclization of Phenyl 3-Phenyl-2-propynyl Ether Using I_2 as the Electrophile (eq 1)[a]

entry	solvent	I_2 (equiv)	base (equiv)	time (h)	% isolated yield
1	CH_3CN	3	$NaHCO_3$ (2)	24	61
2	CH_2Cl_2	3	$NaHCO_3$ (2)	24	49
3	CH_3OH	3	$NaHCO_3$ (2)	24	41
4	DMF	3	$NaHCO_3$ (2)	24	52
5	CH_3NO_2	3	$NaHCO_3$ (2)	24	77
6	CH_3NO_2	3	$NaHCO_3$ (2)	4	0[b]
7	CH_3NO_2	3	$NaHCO_3$ (2)	24	42[c]
8	CH_3NO_2	2	$NaHCO_3$ (2)	24	53
9	CH_3NO_2	4	$NaHCO_3$ (2)	24	69
10	CH_3NO_2	3	$NaHCO_3$ (2)	12	62
11	CH_3NO_2	3	$NaHCO_3$ (2)	48	76
12	CH_3NO_2	3		24	58
13	CH_3NO_2	3	$NaHCO_3$ (1)	24	70
14	CH_3NO_2	3	NaOMe (2)	24	69
15	CH_3NO_2	3	Na_2CO_3 (2)	24	75
16	CH_3NO_2	3	KOH (2)	24	

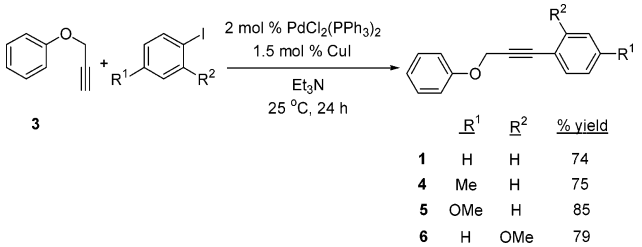
[a] Representative procedure: phenyl 3-phenyl-2-propynyl ether (0.25 mmol), I_2, a base, and the solvent (5 mL) were placed in a four-dram vial and stirred at 25 °C for the indicated time. [b] The reaction was run at 0 °C. [c] The reaction was run at 40 °C.

TABLE 2. Optimization of the Cyclization of Phenyl 3-Phenyl-2-propynyl Ether Using ICl as the Electrophile (eq 1)[a]

entry	solvent	ICl (equiv)	temp (°C)	time (h)	% yield
1	CH_2Cl_2	1.5	−78	2	63[b]
2	ether	1.5	−78	2	51[b]
3	THF	1.5	−78	2	58[b]
4	hexane	1.5	−78	2	49[b]
5	CH_3OH	1.5	−78	2	*b*
6	CH_3NO_2	1.5	−25	2	69[b]
7	CH_2Cl_2	1.5	−25	2	65[b]
8	CH_3NO_2	1.5	−25	0.5	96
9	CH_3NO_2	1.5	0	0.5	<5
10	CH_3NO_2	1.2	−25	2	71
11	CH_3NO_2	2.0	−25	0.5	85

[a] Representative procedure: phenyl 3-phenyl-2-propynyl ether (0.25 mmol), ICl, and the solvent (5 mL) were placed in a four-dram vial and stirred at the indicated temperature for the indicated time. [b] $NaHCO_3$ (0.5 mmol) was added.

SCHEME 1



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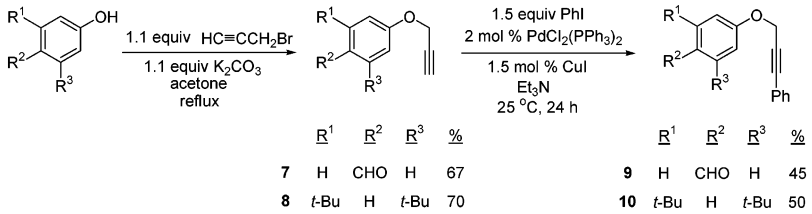
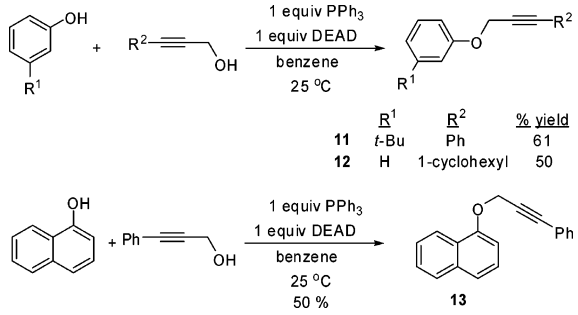
SCHEME 2



SCHEME 3



reaction, but $NaHCO_3$ was found to give the best yield (entries 14−16).

In our previous cyclizations, ICl has proven to be a better electrophile for some substrates. Therefore, with a view of obtaining better yields, the cyclization of phenyl 3-phenyl-2-propynyl ether (**1**) was optimized using ICl as the electrophile, starting with our previously developed conditions. Because of the importance of the solvent in such reactions, the reaction was carried out using CH_2Cl_2, diethyl ether, THF, hexane, CH_3OH, and CH_3NO_2 at low temperatures (Table 2, entries 1−6). The solvent CH_3NO_2 gave the best yield of 69%, but the temperature had to be raised to −25 °C. The reaction was run at −25 °C with the second best solvent for the reaction, namely, CH_2Cl_2, to obtain a slightly lower yield of 65% (entry 7). In all of these reactions, $NaHCO_3$ was used as a base. The yield increased to 96% when the reaction was carried out without $NaHCO_3$ (entry 8). Increasing the temperature to 0 °C gave undetermined side products with the desired compound being formed in less than a 5% yield (entry 9). Decreasing or increasing the amount of ICl gave slightly lower yields (entries 10 and 11). Thus, our optimized conditions using ICl are 0.25 mmol of **1**, 1.5 equiv of ICl, and 5 mL of CH_3NO_2 at −25 °C.

After obtaining our best conditions using either I_2 or ICl, we decided to study the scope of this reaction on various substrates. Ethers **1**, **4**, **5**, and **6** were obtained by standard Sonogashira chemistry[28] using commercially available starting materials (Scheme 1). Ethers **9** and **10** were obtained by a two-step approach, the first step being the synthesis of the substituted aryl propargylic ethers **7** and **8**, followed by Sonogashira chemistry (Scheme 2). Ethers **11**−**13** were synthesized by a Mitsunobu reaction (Scheme 3), while ethers **14**,[29] **15**,[30] **16**,[30] **17**,[27] **18**,[31] **19**,[31] **20**,[31] **21**,[32] and **22**[33] (refer to Table 3) were previously reported in the literature.

Cyclizations were then carried out using our optimized conditions for I_2 (condition A) or ICl (condition B). 3,4-Disubstituted 2*H*-benzopyrans were obtained in good yields using I_2 or ICl when the substituent on the propargylic alkyne was either a simple phenyl or an alkenyl group (Table 3, entries 1, 2, 32, and 33). An alkyl substituent on the alkyne terminus did not give the desired product with I_2 or ICl as the electrophile but worked with PhSeBr (entries 34−36). However, a hydroxymethyl-substituted alkyne gave good yields with I_2, as well as ICl (entries 37 and 38). Simple phenyl propargyl ether (**3**) failed to give any of the desired product with I_2 or ICl (entries 30 and 31).

The introduction of substituents on the aryl groups has a considerable effect on the yield of the reaction. Substituents were first introduced onto the aromatic ring attached to the alkyne. Electron-donating groups, like Me and MeO in the para or ortho positions, gave good yields (entries 4−7, 10, and 11), while an electron-withdrawing group, like a NO_2 group, gave relatively poor yields of 59% with I_2 and 53% with ICl (entries 8 and 9). Introducing substituents onto the aromatic ring attached to the oxygen moiety also has a pronounced effect. Electron-donating groups, like Me, *t*-Bu, and MeO, on the phenyl ring para to the oxygen gave better yields with I_2 as the electrophile (entries 12, 14, and 16) than those obtained using ICl (entries 13, 15, and 17). Compound **30** was thus obtained in improved yields without the use of ion exchange resins as additives, as was reported by Barluenga.[27] The sterically hindered ether **10** also gave good results (entries 23 and 24).

Placing an electron-withdrawing chlorine in the position para to the oxygen gave somewhat lower yields (entries 18 and 19) of the desired isomer. An aldehyde group in the position para to the oxygen gave a mixture of two inseparable regioisomers, the ratio of which depended on the electrophile used and the reaction temperature (entries 20 and 21). The benzopyran isomer was favored when the reaction was carried out at −78 °C with CH_2Cl_2 as the solvent and ICl as the electrophile (entry 22).

To study the regiochemistry of cyclization, the reaction was carried out with substituents meta to the oxygen moiety. A sterically bulky *t*-Bu group in the meta position gave selectively one product **35** (entries 25 and 26). A less bulky Cl in the meta position gave two regioisomers **36** and **37** (entries 27 and 28), while a MeO group gave a similar mixture of two inseparable regioisomers **38** and **39** (entry 29). α-Naphthyl propargylic ether **13** also gave the desired compound **43** in modest yields (entries 39 and 40).

Phenyl 3-phenyl-2-propynyl ether (**3**) gave a 95% yield of the cyclized product **23** when PhSeBr was used as the electrophile (entry 3). Surprisingly, ether **21**, which failed to give the desired product with I_2 or ICl, gave a 79% yield of compound **41** with PhSeBr as the electrophile (entry 36).

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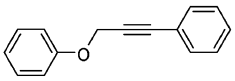
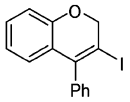
TABLE 3. Synthesis of 3,4-Disubstituted 2*H*-Benzopyrans by Electrophilic Cyclization of Propargylic Aryl Ethers[a]

entry	ether	condition	product(s)	% isolated yield
1		**1** A		**2** 77
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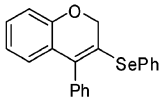
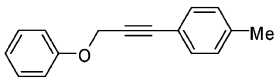
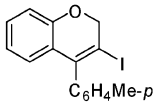
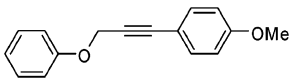
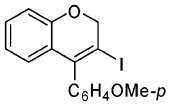
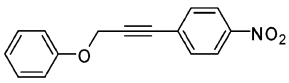
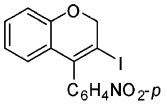
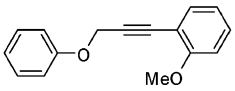
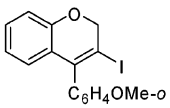
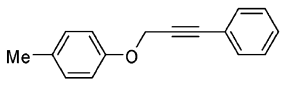
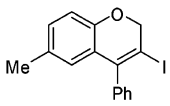
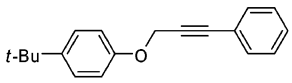
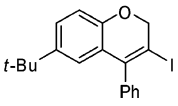
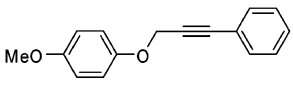
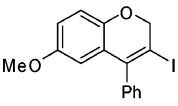
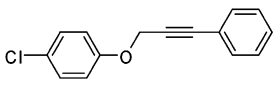
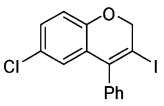
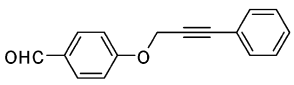
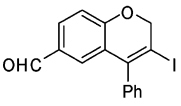
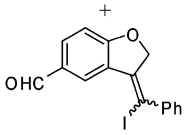
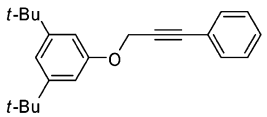
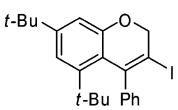
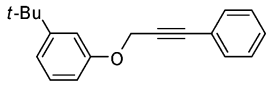
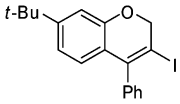
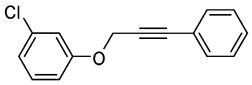
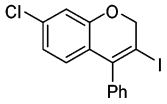
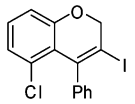
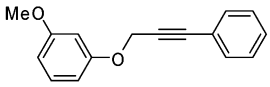
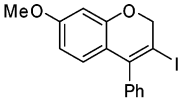
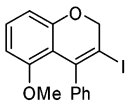
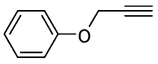
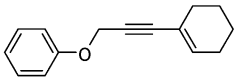
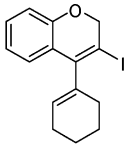
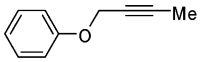
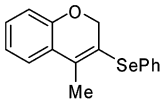
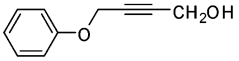
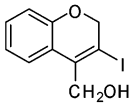
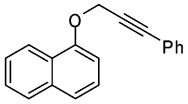
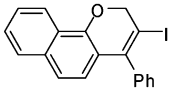
3		**1** C		**23** 95
4		**4** A		**24** 88
5		**4** B		**24** 76
6		**5** A		**25** 89
7		**5** B		**25** 92
8		**14** A		**26** 59
9		**14** B		**26** 53
10		**6** A		**27** 85
11		**6** B		**27** 88
12		**15** A		**28** 79
13		**15** B		**28** 74
14		**16** A		**29** 82
15		**16** B		**29** 77
16		**17** A		**30** 92
17		**17** B		**30** 61
18		**18** A		**31** 52
19		**18** B		**31** 75
20		**9** A	 + 	**32** 76[b] [2:1] **33**
21		**9** B	**32** + **33**	78[b] [1:11]
22		**9** D	**32** + **33**	77[b] [6:1]
23		**10** A		**34** 93
		10 B		**34** 77

Table 3 (Continued)

entry	ether	condition	product(s)	% isolated yield
24		**10** B	**34**	77
25		**11** A	 **35**	72
26		**11** B	**35**	79
27		**19** A	 +  **36** + **37**	21 + 28
28		**19** B	**36** + **37**	27 + 42
29		**20** B	 +  **38** + **39**	82[b] [2:3]
30		**3** A		-
31		**3** B		-
32		**12** A	 **40**	74
33		**12** B	**40**	72
34		**21** A		-
35		**21** B		-
36		**21** C	 **41**	79
37		**22** A	 **42**	79
38		**22** B	**42**	72
39		**13** A	 **43**	61
40		**13** B	**43**	50

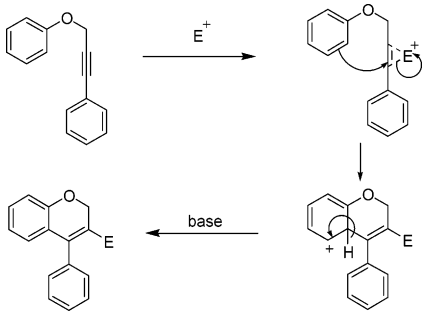
[a] Representative procedure for condition A: ether (0.25 mmol), $NaHCO_3$ (0.50 mmol), I_2 (0.75 mmol), and CH_3NO_2 (5 mL) were placed in a four-dram vial and stirred at 25 °C for 24 h. Condition B: ether (0.25 mmol), ICl (0.375 mmol), and CH_3NO_2 (5 mL) were placed in a four-dram vial and stirred at −25 °C for 30 min. Condition C: ether (0.25 mmol), PhSeBr (1.2 equiv), and CH_2Cl_2 (5 mL) were placed in a four-dram vial and stirred at 25 °C for the indicated time. Condition D: CH_2Cl_2 was used as the solvent for condition B at −78 °C. [b] The ratios were determined by ^1H NMR spectroscopy.

We believe that the mechanism of these cyclizations involves the initial formation of an iodonium or selenonium intermediate by attack of the electrophile on the triple bond, followed by electrophilic attack on the electron cloud of the aromatic ring. Loss of a proton gives the 2*H*-benzopyran (Scheme 4).

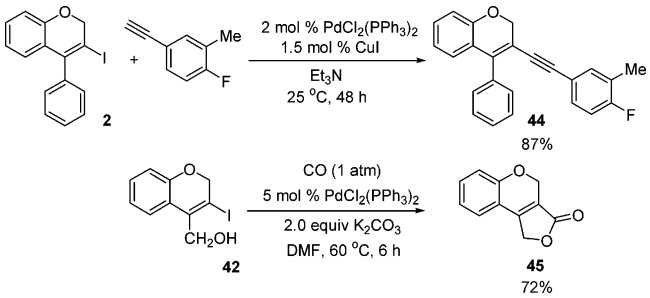
During our cyclization studies, ether **9** gave a mixture of two isomers, one being the expected benzopyran product and the other a possible five-membered ring dihydrofuran product. This encouraged us to confirm the structure of our cyclized product **2** using X-ray crystallography (see the Supporting Information), which indeed proved to be a 2*H*-benzopyran.

The iodo-(*2H*)-benzopyrans obtained by iodocyclization appear highly promising as intermediates for the preparation of more highly substituted benzopyrans. Indeed, 3-iodobenzopy-

SCHEME 4



SCHEME 5



rans, like the ones prepared here, have recently been further elaborated by palladium-catalyzed cross-coupling reactions.[27] To further prove the utility of our methodology, we have carried out the palladium/copper-catalyzed reaction of our product **2** with 5-ethynyl-2-fluorotoluene to obtain **44** in an 87% yield. Palladium-catalyzed CO insertion in our product **42** gave compound **45** in an overall 72% yield (Scheme 5).

Conclusion

3,4-Disubstituted 2*H*-benzopyrans have been obtained from starting materials that are easy to synthesize. The reaction conditions are mild, and the products are easy to isolate in good yields. The iodine moiety in the products provides a useful handle for further functionalization of the resulting heterocycles. A polycyclic Sonogashira product **44** has been obtained in good yield. Our methodology tolerates functional groups, including alcohol, aldehyde, methoxy, and nitro groups. In addition to I_2 and ICl, PhSeBr has also been used as the electrophile. The structure of 3-iodo-4-phenyl-2*H*-benzopyran (**2**) has been confirmed by X-ray crystallography.

Experimental Section

General Procedure for the Palladium/Copper-Catalyzed Reaction of Phenyl Propargyl Ether with Aryl Halides. To a solution of 2.5 mmol of the aryl halide in Et_3N (15 mL) was added $PdCl_2(PPh_3)_2$ (2 mol %), which was then stirred for 5 min. CuI (1.5 mol %) was then added, and the flask was sealed and flushed with Ar. The reaction was stirred for 20 min. A solution of 3.0 mmol of phenyl propargyl ether in 2 mL of Et_3N was then added dropwise, and the reaction mixture was allowed to stir at room temperature for the desired time. After the reaction was over, the resulting solution was diluted with H_2O (10 mL) and extracted with diethyl ether (3 × 15 mL). The combined ether fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

Phenyl 3-*p*-Tolylprop-2-yn-1-yl ether (4). This compound was obtained as a white solid: mp 71−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 4.86 (s, 2H), 6.94−7.08 (m, 5H), 7.18−7.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 56.9, 83.5, 87.5, 115.2, 119.5, 121.6, 129.3, 129.7, 132.0, 139.0, 158.1; IR (neat, cm^{-1}) 3032, 2914, 1598, 1490, 1214, 1029; HRMS *m*/*z* 222.10477 (calcd $C_{16}H_{14}O$, 222.10447).

General Procedure for the Palladium/Copper-Catalyzed Reaction of Terminal Alkynes with Iodobenzene. To a solution of 4.5 mmol of iodobenzene in Et_3N (15 mL) was added $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (1.5 mol %), and the mixture was stirred for 30 min under Ar. A solution of 3.0 mmol of the terminal alkyne in 2 mL of Et_3N was then added dropwise, and the reaction mixture was allowed to stir at room temperature for the desired time. After the reaction was over, the resulting solution was diluted with H_2O (10 mL) and extracted with diethyl ether (3 × 15 mL). The combined ether fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.

4-(3-Phenylprop-2-yn-1-yloxy)benzaldehyde (9). This compound was obtained as a brown solid: mp 86−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (s, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.25−7.32 (m, 3H), 7.41−7.44 (m, 2H), 7.87 (d, J = 8.8 Hz, 2H), 9.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.0, 82.9, 88.1, 115.4, 122.0, 128.5, 129.1, 130.6, 132.0, 132.1, 162.8, 191.0; IR (neat, cm^{-1}) 3078, 2827, 1690, 1598, 1250, 1009; HRMS *m*/*z* 236.08409 (calcd $C_{16}H_{12}O_2$, 236.08373).

General Procedure for the Triphenylphosphine/Diethyl Azodicarboxylate-Promoted Formation of the Substituted Phenyl Propargylic Ethers. To a solution of 1.31 g of PPh_3 (5.0 mmol) in dry benzene (15 mL) was added the substituted propargylic alcohol (5.0 mmol) and the substituted phenol (5.0 mmol) under an inert atmosphere with stirring. Diethyl azodicarboxylate (0.87 g, 5.0 mmol) was then added slowly, and the reaction mixture was stirred at rt for 18−36 h. After the reaction was complete, the solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent.

3-*tert*-Butylphenyl 3-Phenylprop-2-yn-1-y1 Ether (11). This compound was obtained as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 4.86 (s, 2H), 6.83 (dd, J = 8.0, 2.3 Hz, 1H), 6.96−7.02 (m, 1H), 7.08 (t, J = 1.9 Hz, 1H), 7.19−7.25 (m, 4H), 7.39−7.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 34.8, 56.6, 84.3, 87.2, 111.2, 113.1, 118.6, 122.4, 128.4, 128.7, 129.1, 131.9, 153.0, 157.7; IR (neat, cm^{-1}) 3067, 2955, 2868, 1588, 1485, 1270, 1029; HRMS *m*/*z* 264.15187 (calcd $C_{19}H_{20}O$, 264.15142).

General Procedure for Iodocyclization. To a solution of 0.25 mmol of the ether and 3 mL of CH_3NO_2, 2.0 equiv of $NaHCO_3$ and 3.0 equiv of I_2 dissolved in 2 mL of CH_3NO_2 was added gradually. The reaction mixture was allowed to stir at room temperature for the desired time. Alternatively, to a solution of 0.25 mmol of the ether and 3 mL of CH_3NO_2 at −25 to −30 °C, 1.5 equiv of ICl dissolved in 2 mL of CH_3NO_2 was added gradually. The reaction mixture was allowed to stir at −25 to −30 °C for the desired time. The excess I_2 or ICl was removed by washing with saturated aq $Na_2S_2O_3$. The mixture was then extracted by diethyl ether (3 × 10 mL). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent.

3-Iodo-4-phenyl-2*H*-benzopyran (2). This compound was obtained as a pale yellow solid: mp 99−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (s, 2H), 6.61 (dd, J = 7.7, 1.6 Hz, 1H), 6.76 (dt, J = 7.7, 1.1 Hz, 1H), 6.85 (dd, J = 8.0, 1.0 Hz, 1H), 7.14 (dd, J = 7.9, 1.6 Hz, 1H), 7.18−7.22 (m, 2H), 7.39−7.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.1, 91.2, 116.1, 121.7, 124.2, 126.5, 128.3, 128.7, 129.5, 129.7, 140.0, 142.0, 153.3; IR (neat, cm^{-1})

3062, 2904, 1475, 1219, 1029, 994; HRMS *m*/*z* 333.98600 (calcd $C_{15}H_{11}IO$, 333.98547).

General Procedure for the PhSeBr Cyclizations. To a solution of 0.25 mmol of the substituted phenyl propargylic ether and CH_2Cl_2 (3 mL), 0.375 mmol of PhSeBr dissolved in 2 mL of CH_2Cl_2 was added dropwise. The mixture was allowed to stir at room temperature for the desired time. The reaction mixture was washed with 20 mL of water and extracted with diethyl ether (3 × 10 mL). The combined ether layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was further purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent.

4-Phenyl-3-phenylselenyl-2*H*-benzopyran (23). This compound was obtained as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (s, 2H), 6.84−6.87 (m, 2H), 6.94 (t, J = 7.4 Hz, 1H), 7.12−7.25 (m, 5H), 7.27−7.34 (m, 4H), 7.40−7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 71.1, 115.3, 121.4, 124.0, 128.2, 128.4, 128.8, 129.1, 129.2, 129.2, 129.3, 129.6, 134.6, 141.0, 158.4; IR (neat, cm^{-1}) 3052, 2919, 1582, 1480, 1224, 1024; HRMS *m*/*z* 364.03707 (calcd $C_{21}H_{16}OSe$, 364.03664).

3-(4-Fluoro-3-methylphenylethynyl)-4-phenyl-2*H*-benzopyran (44). This compound was prepared by the following procedure. To a solution of 0.17 g of 3-iodo-4-phenyl-2*H*-benzopyran (**2**) (0.5 mmol) in Et_3N (5 mL) was added $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (1.5 mol %), and the mixture was stirred for 30 min under Ar. A total of 0.6 mmol of 5-ethynyl-2-fluorotoluene dissolved in 1 mL of Et_3N was then added dropwise, and the reaction mixture was allowed to stir at room temperature for 24 h. The reaction was monitored by TLC, an additional 0.4 mmol of the 5-ethynyl-2-fluorotoluene dissolved in 1 mL of Et_3N was added slowly under an inert atmosphere, and the reaction mixture was further allowed to stir at room temperature for another 24 h. After the reaction was over, the resulting solution was diluted with H_2O (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined ether fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent to obtain the desired compound **44** in an 87% yield as a pale yellow solid: mp 79−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (d, J = 1.6 Hz, 3H), 4.88 (s, 2H), 6.81−6.93 (m, 4H), 6.97−7.05 (m, 2H), 7.10−7.21 (m, 1H), 7.39−7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (d, J = 3.4 Hz), 68.0, 86.7 (d, J = 1.9 Hz), 95.1 (d, J = 0.8 Hz), 112.4, 115.3 (d, J = 9.4 Hz), 116.4, 118.9 (d, J = 3.8 Hz), 121.8, 124.3, 125.3 (d, J = 18.2 Hz), 126.8, 128.2 (d, J = 10.2 Hz), 129.8, 130.2, 130.8 (d, J = 8.4 Hz), 134.7 (d, J = 5.7 Hz), 136.6, 140.8, 154.6, 160.1, 162.6; IR (neat, cm^{-1}) 3047, 2919, 2192, 1480, 1224, 1106; HRMS *m*/*z* 340.12694 (calcd $C_{24}H_{17}FO$, 340.12634).

1,4-Dihydro-2,5-dioxacyclopenta[*a*]naphthalen-3-one (45). This compound was prepared by the following procedure. To a solution of 0.14 g of 4-hydroxymethyl-3-iodo-2*H*-benzopyran (**42**) (0.5 mmol) in DMF (5 mL) was added $PdCl_2(PPh_3)_2$ (5 mol %) and K_2CO_3 (2 equiv), and the mixture was stirred for 6 h under an atmosphere of CO at 60 °C. The reaction was monitored by TLC and, after completion of the reaction, the resulting solution was cooled to room temperature, diluted with ether (15 mL), and washed with brine (15 mL). The aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined ether fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent to obtain the desired compound **45** in an 72% yield as a brown solid: mp 151−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 5.13−5.15 (m, 4H), 6.92−6.99 (m, 2H), 7.07 (dd, J = 7.5, 1.5 Hz, 1H), 7.34 (dt, J = 8.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.3, 68.8, 116.4, 117.2, 118.3, 122.0, 124.2, 133.8, 154.1, 154.8, 170.7; IR (neat, cm^{-1}) 2361, 1744, 1666, 1449, 1336, 1181, 1052; HRMS *m*/*z* 188.04776 (calcd $C_{11}H_8O_3$, 188.04743).

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Supporting Information Available: General experimental procedures and spectral data for all previously unreported starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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