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Synthesis of Organochalcogen Propargyl Aryl Ethers and Their Application in the Electrophilic Cyclization Reaction: An Efficient Preparation of 3-Halo-4-Chalcogen-2*H*-Benzopyrans

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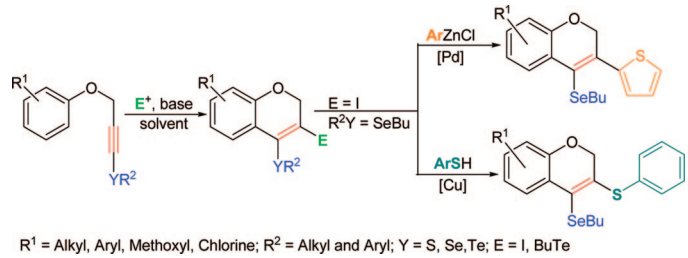

R^1 = Alkyl, Aryl, Methoxyl, Chlorine; R^2 = Alkyl and Aryl; Y = S, Se,Te; E = I, BuTe

We herein described the synthesis of various organochalcogen propargyl aryl ethers via reaction of lithium acetylide intermediate with electrophilic chalcogen (sulfur, selenium, tellurium) species. Various aryl and alkyl groups directly bonded to the chalcogen atom were used as electrophile. The results revealed that the reaction does not significantly depend on the electronic effects of substituents in the aromatic ring bonded to the chalcogen atom of the electrophilic chalcogen species. Additional versatility in this process was demonstrated with respect to a diverse array of functionality in the aromatic ring at propargyl aryl ethers. These propargyl aryl ethers, bearing the chalcogen group, underwent highly selective intramolecular cyclizations when treated with I_2 or ICl affording 3-iodo-4-chalcogen-2H-benzopyrans. The results demonstrated that the cyclization efficiency was significantly influenced by the steric effects of aromatic ring, since the cyclization reaction gave low yields with aromatic rings having a substituent at orto position than those having no substituent. The reactivity of 3-iodo-4-chalcogen-2H-benzopyrans was also studied. 4-Selenobutyl benzopyrans were treated under Neghishi cross-coupling conditions providing the corresponding 3-aryl benzopyran derivatives in good yields. In addition, using the copper catalyzed cross-coupling reactions with thiols, in the absence of any cocatalyst, we were able to introduce a thiol function in 3-iodo-benzopyran derivatives.

Introduction

In recent years, there has been increased interest in the synthesis of heterocycles due to the number of these compounds that show antidepressant, antihypertensive, and hypoglycemic activities as well as other biological effects.[1] The literature contains a variety of synthetic approaches to the heterocycle ring structures, much of which has been compiled into comprehensive reviews,[2] including a special issue in the *Chemical Reviews* journal that was devoted to this field.[3] Among heterocycles, the six-membered oxygenated heterocycles, or pyrans, are probably one of the most common structural motifs spread across natural products, from simple glucose to structur-

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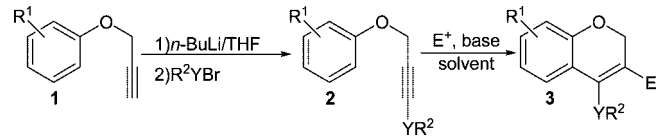
ally complex metabolites present in the structure of several biologically interesting compounds. In particular, 2*H*-benzopyrans are present in a variety of compounds that possess important pharmaceutical and biological applications, such as Daurichromenic acid that exhibits anti-HIV activities[4] and Coutareagenin that is known to present antidiabetic properties.[5] Therefore, the synthesis of 2*H*-benzopyran derivatives and their properties have been thoroughly reported in the literature. The synthetic methods to obtain multiple substituted 2*H*-benzopyran can be basically divided into two classes. The first approach is based on a construction of the 2*H*-benzopyran nucleus after the substituents have been installed and properly functionalized. The second approach is based on a preformed 2*H*-benzopyran to which carbon substituents are attached in successive order. In this context, electrophilic cyclizations of suitable unsaturated systems have been frequently utilized to construct a wide range of carbocycles and heterocycles.[6] Important heterocycles, such as indoles,[7a,b] benzo[*b*]furans,[7c,d] benzo[*b*]thiophenes,[6g,7e] benzo[*b*]selenophenes,[7f] thiophenes,[7g] furans,[6e] pyrroles,[7h] and benzopyrans,[6a] have been accessed using this protocol.

In addition, the introduction of chalcogen group into organic molecules has found such wide utility because their effects on an extraordinary number of very different reactions. They have become attractive synthetic targets because of their chemo-, regio-, and stereoselective reactions,[8] use in a wide variety of functional groups, avoiding protection group chemistry, and useful biological activities.[9] The selenium group can be introduced in an organic substrate via both nucleophile and electrophile reagents. After being introduced in an organic substrate, the organoselenium groups can easily be removed by selenoxide *syn* elimination[10] and [2, 3] sigmatropic rearrangement.[11] The carbon−selenium bond can also be replaced by a carbon−hydrogen,[12] carbon−halogen,[13] carbon−lithium,[14] or carbon−carbon bond.[15]

Heterocycles containing chalcogen play an important role in organic synthesis, especially in the development of methodologies for the synthesis of substituted telluro and selenophenes.[16] There are several reasons for this; they have a widely varied synthetic organochemical potential. The chalcogen atom exercises a stabilizing effect on neighboring positive as well as negative charges. This makes the carbon responsive toward both nucleophilic and electrophilic attack an extremely useful feature for organic synthetic purposes. Recently, Larock and coworkers[6a] reported an elegant synthesis of 2*H*-benzopyrans via electrophilic cyclization of propargylic aryl ethers. In this study, they were able to introduce an alkyl or aryl group at 4-position and the iodine moiety at 3-position of benzopyran. A possible extension of this interesting chemistry envisions that the introduction of chalcogen substituent at 4-position at benzopyrans could provide a versatile synthetic handle for further functionalization as well as lead to increased rates of cyclization. To the best of our knowledge, there is no protocol describing the introduction, at the same time, of both halogen and chalcogen at 3 and 4-positions of benzopyran, respectively, using organochalcogen propargyl aryl ethers as substrate via electrophilic cyclization reactions. The difference of the reactivity between halogen and chalcogen functionality can constitute as a synthetic approach to the preparation of benzopyran compounds. In this study, we optimized the preparation of organochalcogen propargyl aryl ethers **2**, and investigated their applications as substrate in the electrophilic cyclization reactions to obtain 3-halo-4-chalcogen-2*H*-benzopyrans **3** (Scheme 1).

SCHEME 1



Results and Discussion

To the preparation of propargyl aryl ethers **1**, we chose the known reaction of phenol with propargyl bromide in the presence of K_2CO_3 in acetone at reflux for 24 h.[17] To the introduction of selenophenyl group, we first generated the lithium acetylide intermediated by reaction of propargyl aryl ethers **1a**−**i** with 1.1 equiv of *n*-BuLi, in THF at −78 °C for 1 h, followed by the reaction with an electrophilic selenium species. By this way, we prepared a number of novel organochalcogen propargyl aryl ethers, and the generality and scope of the reaction is summarized in Table 1.

Table 1 illustrates the introduction of chalcogen group at terminal triple bond of the propargyl aryl ethers. Various aryl

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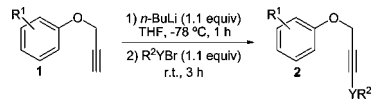
TABLE 1. Synthesis of Organochalcogen Propargyl Aryl Ethers 2[a]



entry	propargyl aryl ether	R^2YBr	product (yield)
1	**1a**	SeBr	**2a** (55%)
2	**1b**	SeBr	**2b** (51%)
3	**1c**	SeBr	**2c** (80%)
4	**1d**	SeBr	**2d** (71%)
5	**1e**	SeBr	**2e** (62%)
6	**1f**	SeBr	**2f** (50%)
7	**1g**	SeBr	**2g** (60%)
8	**1h**	SeBr	**2h** (75%)
9	**1i**	SeBr	**2i** (75%)
10	**1a**	MeO-SeBr	**2j** (65%)
11	**1a**	F_3C-SeBr	**2k** (65%)
12	**1a**	SeBr	**2l** (60%)
13	**1a**	BuSeBr	**2m** (55%)
14	**1a**	PrSeBr	**2n** (50%)
15	**1a**	EtBr	**2o** (55%)
16	**1a**	SBr	**2p** (65%)
17	**1a**	MeSBr	**2q** (64%)
18	**1a**	TeBr	**2r** (75%)
19	**1a**	BuTeBr	**2s** (65%)

[a] Reaction performed in the presence of **1** (5mmol), *n*-BuLi (1.1 equiv), R^2YBr (1.1 equiv) in THF (30 mL).

and alkyl groups directly bonded to the chalcogen atom were used as electrophile, under the same reaction conditions described in Table 1. Interestingly, all entries provided the corresponding organochalcogen propargyl aryl ethers in acceptable yields. Aromatic ring connected to the selenium atom having a neutral (Table 1, entries 1−9), electron-donating (Table 1, entry 10), or electron-withdrawing group (Table 1, entry 11) formed the desired product in similar yields. These results revealed that the reaction does not significantly depend on the electronic effects of substituents in the aromatic ring bonded to the selenium atom of the electrophilic selenium species. The use of a bulky group, such as naphthalene (Table 1, entry 12), proceeded smoothly within 3 h, affording the corresponding organochalcogen propargyl aryl ether in 60% yield. In addition to aromatic rings, the reactions with alkyl group directly bonded to the selenium atom also led to the formation of the desired products (Table 1, entries 13−15). It is also worth noting that this reaction can be performed using tellurium and sulfur groups as electrophile source to functionalize the terminal alkynes under extremely mild conditions (Table 1, entries 16−19). Most importantly, this method turned out to be general with respect to a diverse array of functionality in the aromatic ring at propargyl aryl ethers. Satisfactorily, all propargyl aryl ethers tested were effective in the preparation of the corresponding organochalcogen propargyl aryl ethers. These compounds are yellow oils, odorless, very stable, which can be easily purified and stored in the laboratory. In addition, using this protocol, we were able to prepare the organochalcogen propargyl aryl ethers on a large scale (10 mmol).

After the successful investigation of the preparation of organochalcogen propargyl aryl ethers **2a**−**s**, we then turned our attention to use these compounds in the electrophilic cyclization reactions. The model substrate, arylseleno propargyl aryl ether **2a**, was considered appropriate for studying the scope of the method. Initial experiments focused on the use of I_2 as electrophilic reagent in CH_3NO_2 as solvent in the presence of $NaHCO_3$ as base, using the same reaction conditions described by Larock.[6a] In this way, I_2 (3 equiv)/CH_3NO_2 (3 mL) and subsequently $NaHCO_3$ (2 equiv) were added to a solution of **2a** (0.25mmol) in CH_3NO_2 (2 mL) at room temperature. Unfortunately, these conditions failed to give the desired cyclization product. Indeed, complete recovery of the starting material, even under forcing conditions, led to the conclusion that the solvent was critical for the success of this cyclization reaction. In view of this disappointing result, we further investigated the reaction behavior with different solvents and electrophilic sources aiming to improve the protocol. The outcome of this study and an investigation of other reaction parameters are depicted in Table 2.

The presence of a base was crucial for a clean, high-yielding reaction. It is presumed to neutralize the byproduct HI of the electrophilic cyclization, which can also react with the acetylenic selenide and generate the corresponding vinylic iodide.[18] For this reason, in our experiments, we investigated the influence of some inexpensive bases. As listed in Table 2, when the reaction was carried out using KOH, Na_2CO_3, Cs_2CO_3, and CH_3COONa, the target product was not obtained nor was it obtained in moderated yields, even though a long reaction time was used (24 h). The best result was obtained using $NaHCO_3$, which gave the desired product **3a** in 83% yield (Table 2, entries

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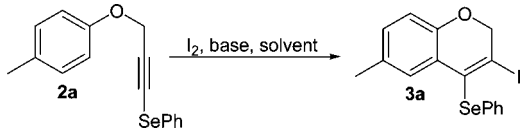
TABLE 2. Influence of Reaction Conditions on the Iodo Cyclization of Arylseleno Propargyl Aryl Ethers 2a



entry	solvent	base (equiv)	I_2 (equiv)	yield (%)
1	CH_3NO_2	$NaHCO_3$ (2)	3.0	traces
2	CH_2Cl_2	$NaHCO_3$ (2)	3.0	–
3	Hexane	$NaHCO_3$ (2)	3.0	–
4	EtOH	$NaHCO_3$ (2)	3.0	25
5	DMF	$NaHCO_3$ (2)	3.0	50
6	THF	$NaHCO_3$ (2)	3.0	83
7	CH_3CN	$NaHCO_3$ (2)	3.0	83
8	THF	$NaHCO_3$ (2)	1.0	23
9	THF	$NaHCO_3$ (2)	1.2	26
10	THF	$NaHCO_3$ (2)	1.5	48
11	THF	$NaHCO_3$ (2)	2.0	68
12	THF	$NaHCO_3$ (2)	3.5	70
13	THF	Na_2CO_3 (2)	3.0	47
14	THF	CH_3COONa (2)	3.0	20
15	THF	Cs_2CO_3 (2)	3.0	5
16	THF	KOH (2)	3.0	23
17	THF	None	3.0	50
18	THF	$NaHCO_3$ (1.2)	3.0	50
19	THF	$NaHCO_3$ (1.5)	3.0	55
20	THF	$NaHCO_3$ (3)	3.0	42

6−7). It is important to note that in the absence (Table 2, entry 17), in excess (Table 2, entry 20), or when the amount of base is reduced from 2.0 to 1.2 equiv (Table 2, entries 18 and 19), a decrease in the yield was also observed. Regarding the influence of the solvent, the best results were achieved using THF and CH_3CN, which furnished the desired product **3a** in 83% yield (Table 2, entries 6−7). We observed that EtOH and DMF were less effective since the product **3a** was obtained in poor yields (Table 2, entries 4−5). The use of CH_2Cl_2 and hexane failed to produce the electrophilic cyclization product (Table 2, entries 2−3). We also studied the influence of the amount of electrophilic source; it was observed that reducing the amount of I_2 from 3 to 1 equiv decreased the yield significantly (Table 2, entries 8−11), while an increase in the number of equivalents of I_2 to 3.5 caused a slight decrease in the yield to 70% (Table 2, entry 12). The large excess of I_2 required for the cyclization can be justified by the initial formation of an organochalcogen (IV) species due to the great affinity of the chalcogen atom for I_2. It is well described that chalcogen alkynes react very fast and quantitatively with halogen to form a species of selenium (IV) known as dihalo organochalcogen.[19] For this reason, different from the mechanism proposed by Larock,[6a] in which the starting materials were free of chalcogen atoms, we believe that the first step of this cyclization involves the usual reaction of organochalcogen propargyl aryl ethers with I_2 to give the selenium (IV) species **a**; after that the cyclization process follows: (i) coordination of the carbon−carbon triple bond to the electrophilic reagent to generate the iodonium intermediate **b**, (ii) attack of the electron from the aromatic ring on the activated triple bond to produce the species **c**, and (iii) the removal of a proton restores the aromatic ring giving the cyclized organochalcogen (IV) species **d** which is reduced to organochalcogen (II) species by sodium thiosulfate (Scheme 2).

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Thus the careful analysis of the optimized reactions revealed that the optimum condition for the I_2 cyclization reactions was the addition of $NaHCO_3$ (0.5 mmol), at room temperature, to a solution of 0.25 mmol of selenophenyl propargyl aryl ether **2a** in 3 mL of THF. After that, 3 equiv of I_2 in 2 mL of THF was gradually added at room temperature.

In the course of our investigation into the eletrophilic cyclization of organochalcogen propargyl aryl ethers, we found that treatment of arylseleno propargyl aryl ether **2a** with the standard conditions using ICl instead of I_2 resulted in the formation of cyclized product **3a** only in 18% yield (Table 3, entry 1). In the Larock's condition[6a] and in our earlier study on the iodocyclization of functionally substituted alkynes,[16g] using ICl as electrophile source, the use of lower temperature (−25 °C) proved to be better than the use of room temperature. In an attempt to obtain an improvement in the yield of this cyclization, the change of the temperature from room temperature to −25 °C and a variety of conditions were investigated, including, solvent and bases. As shown in Table 3, of the bases investigated, Na_2CO_3, CH_3COONa, Cs_2CO_3 and KOH provided similar results giving the products in moderated yields (Table 3, entries 2−5). Interestingly, it was found that in the absence of base, the reaction reached completion in 83% yield (Table 3, entry 6). With regard to the solvent, the reaction worked equally well in THF and DMF giving the cyclized product in 83% and 80% yield respectively (Table 3, entries 6 and 7). We also examined other solvents in place of THF such as DMF, CH_3NO_2, CH_2Cl_2, EtOH, CH_3CN and hexane which gave the desired products in moderate yields (Table 3, entries 7−12). It was pointed out that the amount of ICl also played an important role in the reaction. Not only the increase the amount of ICl to 3.0 equiv (Table 3, entry 16) but also the reduction to 1.0 equiv (Table 3, entry 13) was not better than 1.5 equiv (Table 3, entry 6). Thus, we concluded that our optimized conditions to ICl cyclizations is the addition of a mixture of ICl (1.5 equiv) in THF (2 mL), at −25 °C, to a solution of 0.25 mmol of the selenophenyl propargyl aryl ether **2a** in 3 mL of THF. The reaction mixture was allowed to stir at this temperature for 2 h. After obtaining our best conditions using either I_2 or ICl, we studied the scope of this reaction to various organochalcogen propargyl aryl ethers and the results are summarized in Table 4.

Studies defining the scope and limitations of this reaction led us to a good understanding of this process. First, to determine the real influence of the substituent at aromatic ring of phenol, we keep the selenophenyl group directly bonded to triple bond invariable. The results demonstrated that the cyclization efficiency was significantly influenced by the steric effects of aromatic ring, since the cyclization reaction gave low yields with aromatic rings having a substituent at *ortho* position than those having no substituent (Table 4, entries 3−6). We also observed that the reaction is not sensitive to electronic effects of aromatic ring. For example, phenol with a MeO, an electron-donating group, gave similar yields than phenol with a Cl, an electron-withdrawing group (Table 4, entries 9−10). In addition, the reactions of chalcogen propargyl aryl ethers containing different substituents at aryl group directly bonded to the selenium atom have also been investigated. Our experiments showed that the reaction with selenium having aryl, aryl substituted and alkyl groups gave the benzopyran derivatives in similar yields (Table 4, entries 16−22). By contrast, when the reaction was carried out with chalcogen propargyl aryl ethers

SCHEME 2

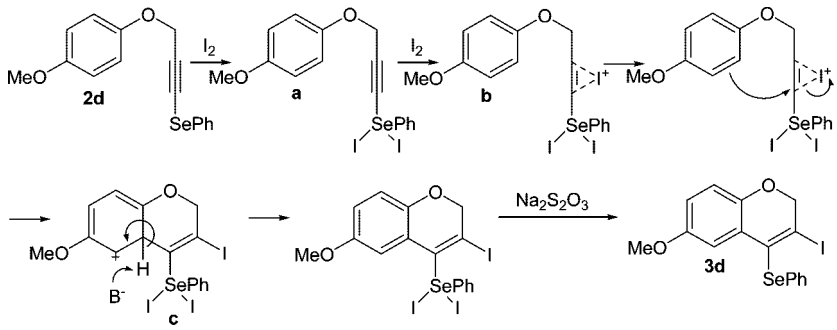
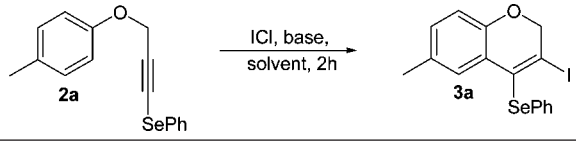


TABLE 3. Influence of Reaction Conditions on the ICl Cyclization of Arylseleno Propargyl Aryl Ethers 2a



entry	solvent	base (equiv)	ICl (equiv)	yield (%)
1	THF	$NaHCO_3$ (2)	1.5	18
2	THF	Na_2CO_3 (2)	1.5	37
3	THF	CH_3COONa (2)	1.5	56
4	THF	Cs_2CO_3 (2)	1.5	35
5	THF	KOH (2)	1.5	52
6	THF	none	1.5	83
7	DMF	none	1.5	80
8	CH_3NO_2	none	1.5	10
9	CH_2Cl_2	none	1.5	45
10	EtOH	none	1.5	60
11	CH_3CN	none	1.5	63
12	Hexane	none	1.5	62
13	THF	none	1.0	40
14	THF	none	1.2	40
15	THF	none	2.0	68
16	THF	none	3.0	60

having a sulfur group a decrease in the yields was observed and the cyclized products were obtained in 50% yields (Table 4, entries 23−25). Meanwhile, with the purpose to evaluate the possibility to introduce one more different function at C-3 of the benzopyran ring, we tested the behavior of chalcogen propargyl aryl ethers using PhSeBr and $BuTeBr_3$ as electrophile source. The reaction of propargyl aryl ethers **2a** with $BuTeBr_3$ in CH_3CN, at room temperature, gave the benzopyran with a BuTe group at C-3 (Table 4, entry 26). This result is significant particularly when one considers that there are many ways to transform the resulting tellurium functionalities into other substituents. Interestingly, although it is known that PhSeBr can act as efficient PhSe+ donors to the alkyne triple bond,[6h,7f] herein under our conditions no cyclized benzopyran derivative was isolated (Table 4, entry 27).

To study the regiochemistry of cyclization, the reaction was carried out with organochalcogen propargyl aryl ethers having Cl (**2f**), 2-naphthalene (**2g**) and MeO (**2e**) substituent at *meta* position to the oxygen moiety. Placing a less bulky Cl in the *meta* position gave two regioisomers **3f** and **3f′** (Table 4, entry 10), which were easily separable by chromatograph column. On the other hand, an electron-donating CH_3O and a stericaly bulky 2-naphthalene substituent gave only the regioisomer **3e** and **3h**, respectively, as sole product (Table 4, entries 9 and 13). These results showed that our method is highly regioselective since, only in the case of **2f**, which has a halogen substituent, was detected a mixture of regioisomers. Regarding the five versus six membered ring, it is important to point out that the unique product obtained during the curse of this cyclization was the six-membered benzopyran, which was determined by X-ray diffraction analysis (see the Supporting Information). This high selectivity is due to the presence of the selenium atom directly bonded to carbon of the triple bond. This selenium atom exerts a high stabilization of the positive charge in the carbon one of the iodonium intermediate **b** (Scheme 2), forcing the subsequent attack into this carbon.

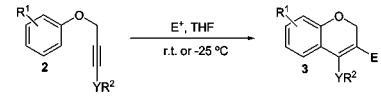
Concerning the tellurium group directly bonded at the triple bond of propargyl aryl ethers **2r** and **2s**, we found some limitations in this methodology. For example no reaction was observed with propargyl aryl ethers bearing an alkyltellurium group (Table 4, entry 30). Unfortunately, all conditions tested were found to be ineffective and neither I_2 nor ICl was effective to produce the cyclized product. In these cases we obtained alkyne iodine **4** (Scheme 3). Based on these results and with the knowledge that the Csp−tellurium bond exhibits an easier heterolytic cleavage than the carbon−sulfur and carbon−selenium bonds, due to the large volume and greater ionic character of the tellurium atom and the easy polarization of the bonds,[20] we assumed that the product **4** was formed via a tellurium IV intermediate **a**. Thus, the great affinity between tellurium and iodine atoms gave the telluride IV **b**;[21] nucleophilic attack of iodide anion on the alkyl group bonded to the tellurium atom[16g] produces a tellurium electrophilic species **c**, which via displacement of the stable tellurium tetraiodide gave the alkynyl iodide **4** (Scheme 3). Concerning the propargyl aryl ether **2s** bearing an arylltellurim group, which has a Csp2−Te bond unable to nucleophilic attack of iodide, we did not observe the formation of alkynyl iodide. In this case, only the starting material was recovered after the reaction quenching with sodium thiosulfate.

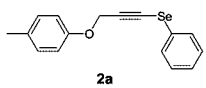
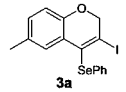
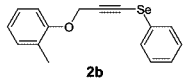
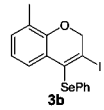
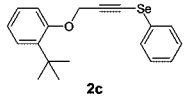
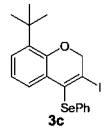
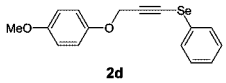
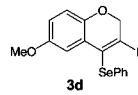
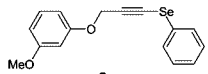
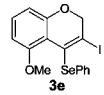
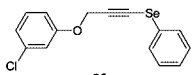
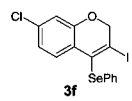
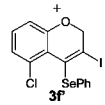
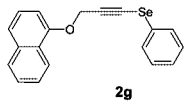
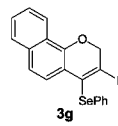
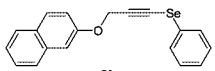
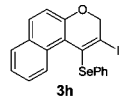
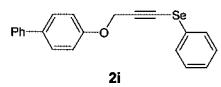
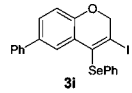
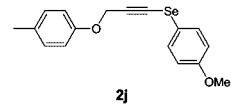
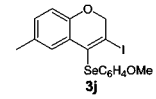
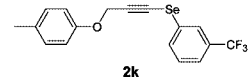
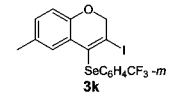
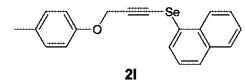
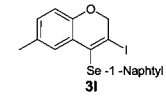
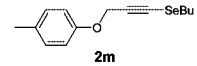
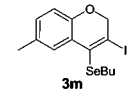
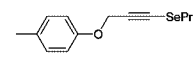
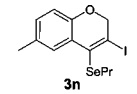
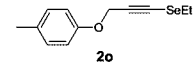
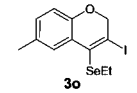
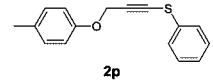
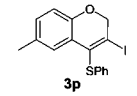
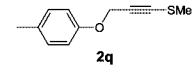
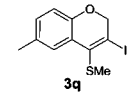
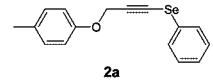
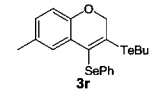
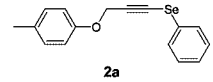
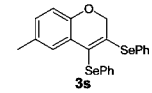
Additional limitation in our method was observed when compound **2e** (Table 4, entry 8), which has a methoxyl group in the *para*-position of aromatic ring, was reacted with I_2 giving as product an almost equimolar mixture of the two compounds, the cyclized **3f** in 50% yield and no cyclized **5** in 45% yield. By contrast, the reaction with propargyl aryl ether having a methoxyl group at *meta*-position of the aromatic ring gave only the expected cyclized product in excellent yield and total stereoselection (Table 4, entry 9). These results are a consequence of the two possible pathways. Mechanistically, we believe that one of them involves the usual cyclization reactions as described in Scheme 2. The second mechanistic hypothesis, involves the formation of hydroxylated uncyclized product **5**, via intermediates **e** and **f** as showed in Scheme 4. The iodonium

(20) *Tellurium in Organic Synthesis*; Petragnani, N., Ed.; Academic Press: London, 1994.

(21) Hope, E. G.; Kemmitt, T.; Levason, W. *Organometallics* **1988**, *7*, 78.

TABLE 4. Synthesis of the 3-Halo-4-chalcogen-2H-benzopyran Derivatives 3 via Electrophilic Cyclization Using I_2 and ICl[a]

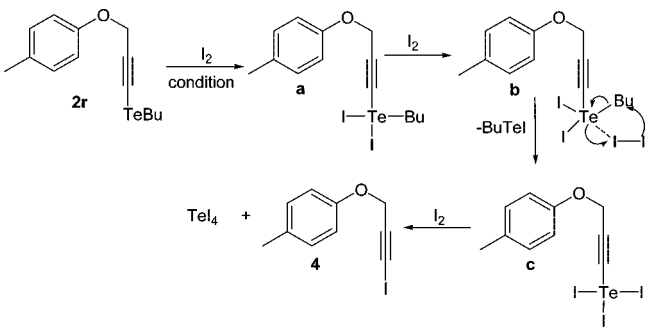


entry	alkynyl chalcogenide 2	E^+	Time (h)	product 3	yield (%)
1	 **2a**	I_2	2.0	 **3a**	83
2	**2a**	ICl	2.0	**3a**	83
3	 **2b**	I_2	1.5	 **3b**	55
4	**2b**	ICl	1.5	**3b**	60
5	 **2c**	I_2	2.0	 **3c**	60
6	**2c**	ICl	1.5	**3c**	63
7	 **2d**	I_2	1.5	 **3d**	50
8	**2d**	ICl	1.0	**3d**	45
9	 **2e**	I_2	1.5	 **3e**	75
10	 **2f**	I_2	2.0	 **3f** +  **3f'**	63 + 26
11	 **2g**	I_2	2	 **3g**	77
12	**2g**	ICl	2	**3g**	67
13	 **2h**	I_2	1.5	 **3h**	82
14	**2h**	ICl	1	**3h**	75
15	 **2i**	I_2	0.75	 **3i**	64
16	 **2j**	I_2	0.75	 **3j**	75
17	 **2k**	I_2	1.5	 **3k**	68
18	 **2l**	I_2	0.75	 **3l**	60
19	 **2m**	I_2	0.75	 **3m**	70
20	**2m**	ICl	0.5	**3m**	70
21	 **2n**	I_2	0.75	 **3n**	77
22	 **2o**	I_2	0.75	 **3o**	70
23	 **2p**	I_2	0.5	 **3p**	52
24	 **2q**	I_2	0.5	 **3q**	50
25	**2q**	ICl	0.5	**3q**	50
26	 **2a**	$BuTeBr_3$	1	 **3r**	40[b]
27	 **2a**	PhSeBr	12	 **3s**	0[c]
28	**2r**	I_2	12	**3t**	0
29	**2r**	ICl	2	**3t**	0
30	**2s**	I_2	12	**3u**	0

[a] I_2 cyclization performed in the presence of **2** (0.25mmol), $NaHCO_3$ (2 equiv), I_2 (3 equiv) in THF (5 mL), at room temperature. The ICl cyclization was performed in the presence of **2** (0.25mmol), ICl (1.5 equiv) in THF, at −25 °C. [b] Reaction performed in the presence of **2a** (0.25mmol), $BuTeBr_3$ (1.1 equiv) in CH_3CN, at room temperature. [c] Reaction performed in the presence of **2a** (0.25mmol), PhSeBr (1.5 equiv) in CH_2Cl_2 (5 mL), at room temperature.

intermediate is formed followed by a nucleophilic attack of iodide anion on the methyl group bonded to the oxygen atom[16g] producing the intermediate **f**, which is impeded to give the cyclized product.

SCHEME 3



Although the intermediates from this mechanism could not be isolated, we carried out a new experiment to get additional observations that support the mechanism described in Scheme 4. We prepared, purified hydroxyled propargyl aryl ether **5** and used as starting material in the I_2 addition reaction, under our standard reaction conditions. After 24 h we recovered only the starting material **5** quantitatively as the product. These results strongly suggest that the reaction of this substrate with iodide does not allow the cyclized product even that using an excess of iodide, reflux and long reaction time (Scheme 5).

We believe that this approach to 3-halo-4-chalcogen-2*H*-benzopyrans should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting functionalities into other substituents. The applicability of the above cyclization product to the synthesis of more functionalized benzopyran can be verified by transition metal-catalyzed processes, such as Sonogashira,[22] Suzuki,[23] Stille,[24] Heck,[25] Negishi[26] and Ullmann[27] cross-couplings. In addition, this reaction associated with the nickel-catalyzed cross-coupling of selenides[15] can also contribute to an interesting alternative route to the preparation of more functionalized benzopyrans. In view of this, the potential of chalcogen−2*H*-benzopyran derivatives as precursors for increasing molecular complexity via palladium and copper catalyzed reactions has been briefly investigated (Scheme 6). For example, compound **3m** under Neghishi cross-coupling with different organozinc species gave the corresponding products **6a**, **6b** and **6c** in 80%, 77% and 70%, respectively. In addition, the reaction of **3m** with aryl thiols, using just CuI as catalyst in dioxane, afforded the resultant products **7a**, **7b** and **7c** in good isolated yields (Scheme 6).

Conclusion

We have shown the synthesis of various organochalcogen propargyl aryl ethers via reaction of the lithium acetylide intermediated with electrophilic chalcogen (sulfur, selenium, tellurium) species. Various aryl and alkyl groups directly bonded to the chalcogen atom were successful used as electrophile. The results revealed that the reaction does not significantly depend on the electronic effects of substituents in the aromatic ring bonded to the selenium atom of the electrophilic chalcogen species. Additional versatility in this process was demonstrated with respect to a diverse array of functionality in the aromatic ring at propargyl aryl ethers. These propargyl aryl ethers, bearing the chalcogen group, underwent highly selective intramolecular cyclizations when treated with I_2 or ICl affording 3-iodo-4-chalcogen-2H-benzopyrans. The results demonstrated that the cyclization efficiency was significantly influenced by the steric effects of aromatic ring, since the cyclization reaction gave low yields with aromatic rings having a substituent at the *orto* position than those having no substituent. The reactivity of 3-iodo-4-chalcogen-2H-benzopyrans was also studied. 4-Selenobutyl benzopyrans were treated under Negishi cross-coupling conditions providing the corresponding 3-aryl benzopyran derivatives in good yields. In addition, using the copper catalyzed cross-coupling reactions with thiols, in the absence of any cocatalyst, we were able to introduce a thiol function in 3-iodo-benzopyran derivatives.

Experimental Section

General Procedure for the Preparation of the Organochalcogen Propargyl Aryl Ethers 2a−s. To a solution of the appropriate propargyl aryl ether (5 mmol) in dry THF (30 mL) at −78 °C, under argon atmosphere was added drop by drop, *n*-BuLi (2.2 mL of a 2.5 M solution in hexane, 5.5 mmol). After 1 h at this temperature, the appropriate organochalcogen electrophile (R^2SBr, R^2SeBr, R^2TeBr; 5.5 mmol) in THF (5 mL) was added. The mixture was stirred at room temperature for 3 h. After this time, the mixture was diluted with ethyl acetate (60 mL) and washed with saturated aq NH_4Cl (30 mL) and water (3 × 30 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum.

4-Methylphenyl 3-Phenylselenylprop-2-yn-1-yl Ether (2a). Purified by flash chromatography and eluted with hexane/ethyl acetate (95:5). Yield: 0.827 g (55%). ^{1}H NMR: $CDCl_3$, 200 MHz, δ(ppm): 7.50−7.45 (m, 2H), 7.34−7.26 (m, 3H), 7.10 (d, J = 8.0 Hz, 2H), 6.93−6.86 (m, 2H), 4.87 (s, 2H), 2.30 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ(ppm): 155.4, 130.7, 129.8, 129.4, 129.2, 127.2, 114.9, 99.8, 98.9, 68.1, 57.0, 20.4. MS (EI, 70 eV) *m*/*z* (relative intensity): 299 (9), 218 (6), 192 (26), 144 (27), 114 (100), 102 (21), 76 (29), 51 (15). Anal. (%) Calcd for $C_{16}H_{14}OSe$: C 63.79, H 4.68. Found: C 63.33, H 4.22.

2-Methylphenyl 3-Phenylselenylprop-2-yn-1-yl Ether (2b). Purified by flash chromatography and eluted with hexane/ethyl acetate (95:5). Yield: 0.767 g (51%). ^{1}H NMR: $CDCl_3$, 200 MHz, δ(ppm): 7.49−7.43 (m, 2H), 7.33−7.07 (m, 5H), 6.98−6.86 (m, 2H), 4.91 (s, 2H), 2.25 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ(ppm): 155.8, 130.8, 129.5, 129.2, 128.1, 127.3, 127.2, 126.6. MS (EI, 70 eV) *m*/*z* (relative intensity): 299 (5), 192 (31), 156 (3), 144 (13), 114 (100), 102 (16), 76 (21). Anal. (%) Calcd for $C_{16}H_{14}OSe$: C 63.79, H 4.68. Found: C 64.12, H 4.91.

General Procedure for the I_2 Cyclization. To a solution of organochalcogen propargyl aryl ethers appropriate (0.25 mmol) in 3 mL of THF, was added at room temperature, $NaHCO_3$ (0.5 mmol). After that, was added gradually I_2 (3 equiv) in 2 mL of THF. The reaction mixture was allowed to stir at room temperature for the time shown in Table 4. Excess I_2 was removed by washing with saturated aq $Na_2S_2O_3$. The product was then extracted by ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product. **3-Iodo-6-methyl-4-phenylselenyl-2*H*-benzopyran (3a):** Purified by flash chromatography and eluted with hexane/ethyl acetate (95:5). Yield: 0.088 g (83%). ^{1}H NMR: $CDCl_3$, 400

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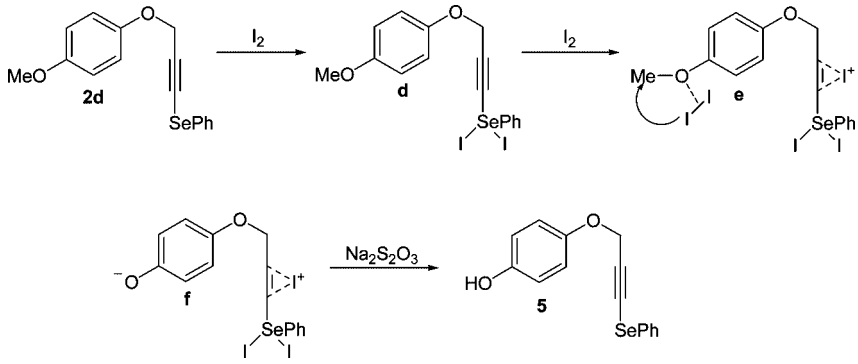
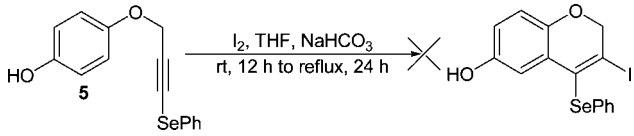
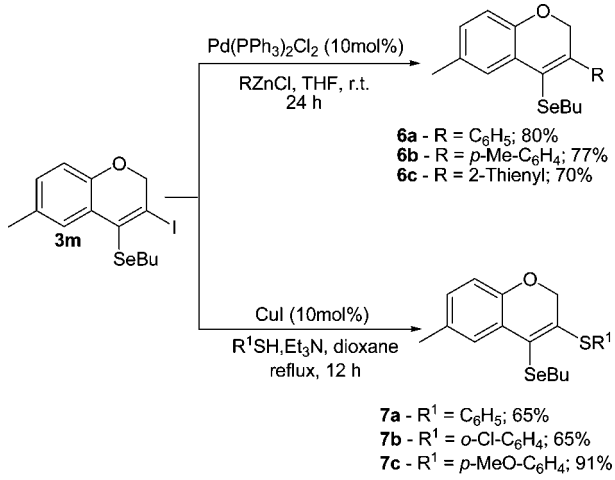
SCHEME 4



SCHEME 5



SCHEME 6



MHz, δ(ppm): 7.36−7.32 (m, 3H), 7.21−7.15 (m, 3H), 6.92−6.89 (m, 1H), 6.70 (d, J = 8.3 Hz, 1H), 4.95 (s, 2H), 2.14 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ(ppm): 151.1, 134.1, 131.4, 131.1, 130.3, 129.8, 129.3, 126.6, 123.2, 115.7, 105.3, 75.8, 20.6. MS (EI, 70 eV) *m/z* (relative intensity): 427 (15), 301 (21), 221 (71), 157 (18), 144 (15), 115 (100), 102 (3), 77 (94), 63 (44), 51 (71). Anal. (%) Calcd for $C_{16}H_{13}IOSe$: C 44.99, H 3.07. Found: C 45.21, H 3.23. **3-Iodo-8-methyl-4-phenylselenyl-2*H*-benzopyran (3b):** Purified by flash chromatography and eluted with hexane/ethyl acetate (95:5). Yield: 0.058 g (55%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ(ppm): 7.42−7.40 (m, 1H), 7.34−7.31 (m, 2H), 7.21−7.13 (m, 3H), 7.00−6.98 (m, 1H), 6.69 (t, J = 7.8 Hz, 1H), 5.00 (s, 2H), 2.18 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ(ppm): 151.3, 134.4, 131.4, 131.2, 130.2, 129.3, 127.2, 126.6, 125.4, 123.1, 121.4, 104.8, 75.7, 15.5. MS (EI, 70 eV) *m/z* (relative intensity): 426 (2), 423 (30), 298 (61), 283 (16), 218 (67), 202 (8), 176 (32), 155 (10), 143 (18), 114 (100), 88 (18), 76 (18). HRMS calcd for $C_{16}H_{13}IOSe$: 427.9176. Found: 427.9190.

General Procedure for the ICl Cyclization. To a solution of appropriate organochalcogen propargyl aryl ethers (0.25 mmol) in 3 mL of THF was added gradually ICl (1.5 equiv) in 2 mL of THF at −25 °C. The reaction mixture was allowed to stir at this temperature for the time shown in Table 4 and washed with saturated aq $Na_2S_2O_3$. The organic product was extracted by ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product. **3-Iodo-8-tert-Butyl-4-phenylselenyl-2*H*-benzopyran (3c):** Purified by flash chromatography and eluted with hexane/ethyl acetate (95:5). Yield: 0.070 g (60%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ(ppm): 7.51−7.49 (m, 1H), 7.35−7.32 (m, 2H), 7.21−7.14 (m, 4H), 6.75 (t, J = 7.8 Hz, 1H), 4.93 (s, 2H), 1.35 (s, 9H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ(ppm): 151.9, 137.9, 134.6, 131.3, 130.2, 129.3, 127.6, 127.4, 126.6, 124.9, 121.5, 104.7, 75.9, 34.5, 29.7. MS (EI, 70 eV) *m/z* (relative intensity): 468 (4), 465 (83), 339 (66), 284 (37), 260 (88), 202 (10), 183 (11), 155 (27), 144 (10), 127 (100), 114 (66), 109 (21), 76 (33), 56 (70), 41 (26). HRMS calcd for $C_{19}H_{19}IOSe$: 469.4696. Found: 469.4692. **3-Iodo-6-methoxyl-4-phenylselenyl-2*H*-benzopyran (3d):** Purified by flash chromatography and eluted with hexane/ethyl acetate (90:10). Yield: 0.055 g (50%). ^{1}H NMR: $CDCl_3$, 200 MHz, δ(ppm): 7.38−7.33 (m, 2H), 7.25−7.17 (m, 3H), 7.09 (d, J = 2.8 Hz, 1H), 6.77−6.62 (m, 2H), 4.93 (s, 2H), 3.57 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ(ppm): 154.5, 147.3, 134.3, 130.8, 130.5, 129.5, 129.4, 126.9, 124.0, 114.2, 105.4, 97.9, 75.9, 55.6. MS (EI, 70 eV) *m/z* (relative intensity): 443 (2), 439 (92), 313 (43), 283 (22), 253 (5), 234 (100), 202 (8), 192 (30), 158 (45), 153 (11), 116 (32), 101 (19), 88 (63), 76 (24). Anal. (%) Calcd for $C_{16}H_{13}IO_2Se$: C 43.37, H 2.96. Found: C 43.45, H 3.02.

Procedure for the $BuTeBr_3$ Cyclization. To a Schlenck tube, under argon, containing a solution of organochalcogen propargyl aryl ethers **2a** (0.25 mmol) in CH_3CN (1.5 mL) was added, at room temperature, the $BuTeBr_3$ (0.28 mmol). The reaction was stirred for 1 h, after that was added 2 mL of EtOH 95% and $NaBH_4$ (0.5 mmol) was added gradually. The reaction mixture was allowed to stir at room temperature for 1 h. After this, the mixture was diluted with ethyl acetate (15 mL) and washed with water (3 × 5 mL) and saturated solution of NaCl (10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. **3-Butyltelluryl-6-methyl-4-phenylselenyl-2*H*-benzopyran (3r):** Purified by flash chromatography and eluted with hexane/ethyl acetate (95:5). Yield: 0.048 g (40%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ(ppm): 7.37−7.14 (m, 6H), 6.90−6.86 (m, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.81 (s, 2H), 2.71 (t, J = 7.4, 2H), 2.16 (s, 3H), 1.79 (quint, J = 7.3 Hz, 2H), 1.40 (sext, J = 7.5 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ(ppm): 151.1, 131.1, 131.0, 129.5, 129.4, 129.3, 128.5, 128.1, 127.6, 126.4, 124.4, 115.4, 70.7, 34.1, 25.2, 20.7, 13.4, 7.6. MS (EI, 70 eV) *m/z* (relative intensity): 481 (2), 424 (19), 337 (46), 278 (62), 250 (40), 204 (100), 189 (13), 154 (8), 146 (26), 134 (27), 114 (8), 72 (56), 43 (34). Anal. (%) Calcd for $C_{20}H_{22}OSeTe$: C 49.53, H 4.21. Found: C 49.29, H 4.31.

General Procedure for the Palladium-Catalyzed Coupling Reaction of 3m with Organozinc Reagents. To a Schlenck tube, under argon, containing a solution of **3m** (0.25 mmol) in THF (3 mL) and $Pd(PPh_3)_2Cl_2$ (10 mol%), was added the organozinc compound (0.75 mmol) in THF (2 mL), previously prepared.[28] The yellow mixture was stirred at room temperature for 24 h. The reaction mixture was then quenched with aqueous NH_4Cl (5 mL),

washed with CH_2Cl_2 (3 × 5 mL), dried with $MgSO_4$ and the solvent removed under vacuum.

3-Phenyl-6-methyl-4-butylselenyl-2H-benzopyran (6a). Purified by flash chromatography and eluted with hexane/ethyl acetate (90:10). Yield: 0.071 g (80%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ(ppm): 7.57 (s, 1H), 7.42−7.29 (m, 5H), 6.98−6.95 (m, 1H), 6.80 (d, J = 8.0 Hz, 1H), 4.86 (s, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.33 (s, 3H), 1.39 (quint, J = 7.6 Hz, 2H), 1.16 (sext, J = 7.6 Hz, 2H), 0.74 (s, 3H). ^{13}C NMR: $CDCl_3$, 50 MHz, δ(ppm): 151.7, 140.7, 139.2, 131.0, 129.4, 128.9, 128.8, 128.0, 124.1, 122.7, 115.7, 70.3, 31.6, 27.2, 22.4, 20.8, 13.4. MS (EI, 70 eV) *m*/*z* (relative intensity): 357 (4), 354 (51), 298 (100), 252 (3), 218 (90), 189 (14), 176 (37), 163 (14), 150 (10), 114 (14), 101 (6), 57 (3). Anal. (%) Calcd for $C_{20}H_{22}OSe$: C 67.22, H 6.21. Found: C 67.45, H 6.47.

General Procedure for the Copper-Catalyzed Coupling Reaction of 3m with Aryl Thiols. To a Schlenck tube, under argon, containing a solution of **3m** (0.25 mmol) in dioxane (2 mL) was added the appropriate aryl thiol (0.3 mmol) in 0.5 mL of dioxane. After that was added the CuI (10 mol%) and Et_3N in 0.5 mL of dioxane. The mixture was kept under reflux for 12 h. After this time, the mixture was diluted with ethyl acetate (10 mL) and washed with saturated brine (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. **3-Phenylsulfuryl-6-methyl-4-butylselenyl-2*H*-benzopyran (7a):** Purified by flash chromatography and eluted with hexane/ethyl acetate (90:10). Yield: 0.063 g (65%). ^{1}H NMR: $CDCl_3$, 200 MHz, δ(ppm): 7.50−7.27 (m, 6H), 6.98−6.94 (m, 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.48 (s, 2H), 2.79 (t, J = 7.1 Hz, 2H), 2.34 (s, 3H), 1.72−1.58 (m, 2H), 1.51−1.33 (sext, J = 7.2 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ(ppm): 151.4, 135.2, 132.9, 131.4, 131.2, 129.4, 129.3, 128.5, 127.7, 126.2, 124.3, 115.7, 68.4, 32.2, 28.0, 22.7, 20.8, 13.5. MS (EI, 70 eV) *m*/*z* (relative intensity): 389 (7), 386 (100), 329 (65), 278 (9), 248 (31), 222 (49), 143 (63), 114 (60), 88 (10), 76 (9), 56 (6). Anal. (%) Calcd for $C_{20}H_{22}OSSe$: C 61.69, H 5.69. Found: C 61.85, H 5.91.

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Supporting Information Available: Experimental procedures, additional experimental details for the preparation of all compounds and ^{1}H and ^{13}C NMR spectra for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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