

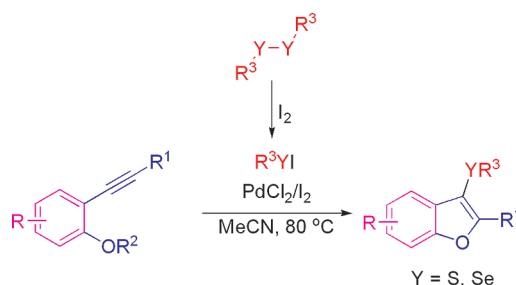
PdCl₂-Promoted Electrophilic Annulation of 2-Alkynylphenol Derivatives with Disulfides or Diselenides in the Presence of Iodine

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An efficient synthesis of 3-chalcogen-benzo[*b*]furans via palladium-promoted annulation reactions of 2-alkynylphenol derivatives with disulfides or diselenides and iodine has been developed. In the presence of I₂ and PdCl₂, both 3-sulfenylbenzofurans and 3-selenenylbenzofurans were selectively prepared from the cyclization of 2-alkynylanisoles with disulfides or diselenides in moderate to excellent yields.

Introduction

Benzofurans, an important class of heterocyclic compounds, are widely presented in a great number of biologically active compounds and natural products,¹ which are identified for their potential in major therapeutic areas such

as anticancer,² antiproliferative,³ antiviral,⁴ antifungal,⁵ and immunosuppressive.⁶ Therefore, the development of efficient strategies for the construction of benzofuran scaffold is a hot topic in organic synthesis.⁷ However, the synthesis of

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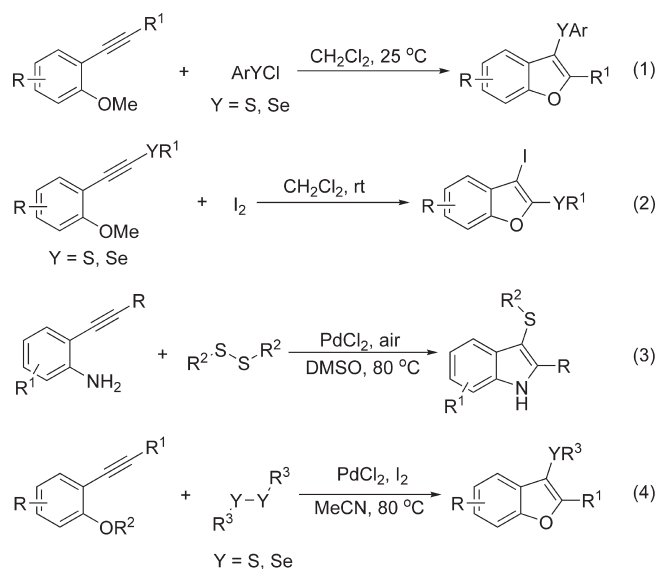
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SCHEME 1



3-chalcogen-benzo[*b*]furans, such as sulfenylbenzo[*b*]furans and selenenylbenzo[*b*]furans, has been scarcely explored,⁸ although these compounds are known to exhibit a broad range of biological activities. Larock and co-workers have reported three examples of 3-chalcogen-benzo[*b*]furans by the electrophilic cyclization of 2-(phenylethynyl)anisole with 4-NO₂C₆H₄SCl or PhSeCl (eq 1 in Scheme 1).⁹ Recently, Zeni and co-workers described a novel approach to 2-chalcogen-benzo[*b*]furans and 2,3-dichalcogenebenzo[*b*]furans via the electrophilic cyclization of 2-chalcogen-alkynylanisoles (eq 2).¹⁰ However, the two methods were restricted to the use of toxic and instable sulfonyl halides as the reaction partners. As a result, the development of direct and concise method for synthesizing 3-chalcogenebenzofurans using the stable and readily available materials remains a challenging area for exploration. Very recently, we reported a novel protocol for the synthesis of 3-sulfenylindoles from the reaction between 2-(1-alkynyl)benzenamines and disulfides in moderate to good yields using the Pd/air catalytic systems (eq 3).¹¹ Unfortunately, the reported standard conditions (PdCl₂/air/DMSO) are incompatible with 1-(2-(2-methoxyphenyl)ethynyl)benzene and PhSSPh (**2a**) for the construction of 2-phenyl-3-(phenylthio)benzofuran (**3**) (entry 1 in Table 1). After a series of trials, we found that in the presence of PdCl₂ and I₂ 2-alkynylphenol derivatives could undergo the annulation reaction with disulfides or diselenides to afford the target 3-chalcogen-benzo[*b*]furans

TABLE 1. Screening Optimal Conditions^a

entry	R	[Pd]	additive (equiv)	<i>T</i> (°C)	yield (%)
1 ^b	H (1a)	PdCl ₂		80	0
2	H (1a)	PdCl ₂		80	trace
3	H (1a)		I ₂ (2)	80	50
4	H (1a)		I ₂ (2)/NaHCO ₃ (2)	80	mixture
5	H (1a)	PdCl ₂	I ₂ (2)	80	77
6	H (1a)	PdCl ₂	I ₂ (1.1)	80	57
7 ^c	H (1a)	PdCl ₂	I ₂ (2)	80	57
8	H (1a)	PdCl ₂	NIS (2)	80	25
9	H (1a)	PdCl ₂	ICl (2)	80	trace
10	H (1a)	PdCl ₂	PhI(OAc) ₂ (2)	80	trace
11	H (1a)	Pd(OAc) ₂	I ₂ (2)	80	46
12	H (1a)	Pd(PPh ₃) ₂ Cl ₂	I ₂ (2)	80	53
13	H (1a)	Pd(PPh ₃) ₄	I ₂ (2)	80	56
14	H (1a)	CuI	I ₂ (2)	80	55
15	H (1a)	AgI	I ₂ (2)	80	49
16	H (1a)	PdCl ₂	I ₂ (2)	100	76
17 ^d	H (1a)	PdCl ₂	I ₂ (2)	100	58
18	H (1a)	PdCl ₂	I ₂ (2)	25	34
19	Ts (1b)	PdCl ₂	I ₂ (2)	80	< 5
20	Bz (1c)	PdCl ₂	I ₂ (2)	80	10
21	Bn (1d)	PdCl ₂	I ₂ (2)	80	44
22	Ac (1e)	PdCl ₂	I ₂ (2)	80	49
23	Me (1f)	PdCl ₂	I ₂ (2)	80	92
24	Me (1f)	—	I ₂ (2)	80	55

^aReaction conditions: **1** (0.2 mmol), **2a** (0.1 mmol), [Pd] (10 mol %), and MeCN (2 mL) under N₂ atmosphere for 36 h. ^bIn DMSO (2 mL) under air atmosphere. ^cPdCl₂ (5 mol %). ^dFor 12 h. The conversion of **1a** is 80% as determined by GC–MS analysis.

in moderate to excellent yields (eq 4). Here, we report our results in detail.¹²

Results and Discussion

We began our study on the reaction between 2-(phenylethynyl)phenol (**1a**) and 1,2-diphenyl disulfide (**2a**) to screen the optimal reaction conditions, and the results are summarized in Table 1. The results demonstrated that no desired product **3** was observed from the reaction of substrate **1a** with disulfide **2a** and PdCl₂ using DMSO or MeCN solvents (entries 1 and 2).¹¹ After checking the results of Zeni and Larock, we envisioned that the generation of PhSX in situ might promote the reaction by adding electrophiles.^{9,10} After a series of failures, we were pleased to find that I₂ could mediate the annulation reaction (entries 3 and 4). Treatment of 2-(phenylethynyl)phenol (**1a**) with 1,2-diphenyl disulfide (**2a**) and 2 equiv of I₂ afforded the target product **3** in 50% yield (entry 3). However, a mixture of products were observed in the presence of NaHCO₃ (entry 4).⁷ⁿ To our delight, the yield of **3** was enhanced to 77% at 10 mol % loading of PdCl₂ (entry 5). It is noteworthy that decreasing amount of either I₂ or PdCl₂ reduces the yield (entries 6 and 7). Encouraged by these results, other iodide reagents, such as NIS, ICl, or PhI(OAc)₂, were investigated in the presence of PdCl₂, and they are less effective than I₂ (entries 8–10). Among the examination of palladium catalysts, other palladium catalysts, including Pd(OAc)₂, Pd(PPh₃)₂Cl₂, and Pd(PPh₃)₄, were inferior to PdCl₂ (entries 11–13). Other transition-metal catalysts, CuI and AgI, were also tested,

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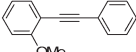
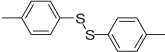
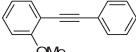
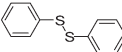
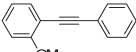
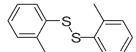
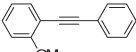
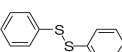
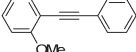
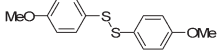
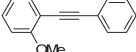
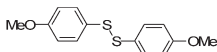
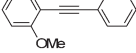
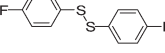
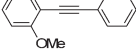
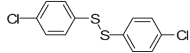
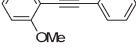
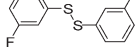
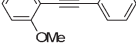
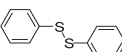
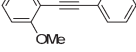
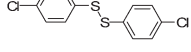
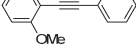
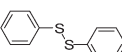
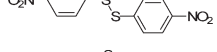
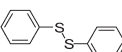
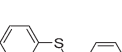
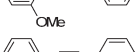
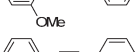
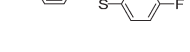
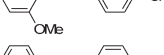
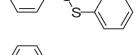
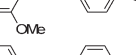
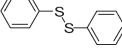
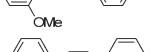
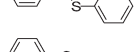
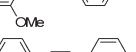
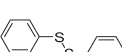
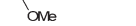
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TABLE 2. PdCl₂-Promoted Electrophilic Annulation Reactions of 2-Alkynylanisoles (**1**) with Disulfides (**2**)^a

R OMe R¹ OMe R² S S R² PdCl₂ I₂ MeCN, 80 °C R OMe R¹ SR²										Entry		Substrate 1		Disulfide 2		T (h)		Yield (%)	
1		(1f)		(2b)	40	92 (4)	14		(1j)		(2a)	36	44 (17)						
2		(1f)		(2c)	48	<10 (5)	15		(1k)		(2a)	36	99 (18)						
3		(1f)		(2d)	36	93 (6)	16		(1k)		(2d)	15	92 (19)						
4		(1f)		(2e)	40	87 (7)	17		(1k)		(2g)	19	85 (20)						
5		(1f)		(2f)	36	60 (8)	18		(1l)		(2a)	24	67 (21)						
6		(1f)		(2g)	36	77 (9)	19		(1m)		(2a)	36	trace (22)						
7		(1f)		(2h)	36	trace (10)	20		(1n)		(2a)	36	90 (23)						
8		(1f)		(2i)	36	74 (11)	21		(1n)		(2a)	36	94 (24)						
9 ^b		(1f)		(2j)	36	<10 (12)	22		(1n)		(2d)	36	75 (25)						
10 ^b		(1f)		(2k)	36	trace (13)	23		(1n)		(2e)	36	75 (25)						
11		(1g)		(2a)	30	65 (14)	24		(1o)		(2a)	36	30 (26)						
12		(1h)		(2a)	36	52 (15)	24		(1p)		(2a)	36	75 (23)						
13		(1i)		(2a)	40	52 (16)													

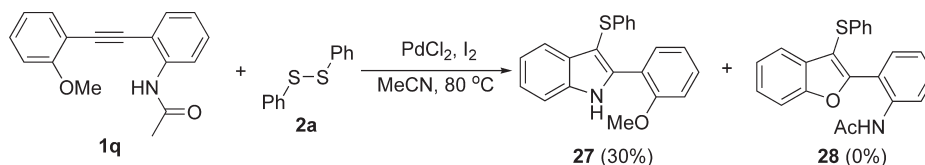
^aReaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), PdCl₂ (10 mol %), I₂ (2 equiv), and MeCN (2 mL) at 80 °C under N₂ atmosphere. ^bA mixture of byproduct was isolated.

and the results showed that they were less active (entries 14 and 15). Screening effect of reaction temperature indicated that results identical to those of 80 °C were observed at 100 °C for 36 h (entries 5 and 16) and at 100 °C shortening reaction time to 12 h resulted in an unsatisfactory yield (entry 17). It was found that room temperature gave a low yield (entry 18). Finally, several *O*-substituted 2-(phenylethynyl)-phenol derivatives were investigated (entries 14–18). We found that three *O*-substituents, acetyl, benzyl, and methyl, were tolerated well, but both Ts (4-methylbenzenesulfonyl) and Bz (benzoyloxy) displayed less activity (entries 19–23). While 2-(2-phenylethynyl)phenyl 4-methylbenzenesulfonate (**1b**), for instance, underwent the reaction with disulfide **2a**, PdCl₂ and I₂ to afford the desired product **3** in less than 5% yield (entry 19), 1-(2-(2-methoxyphenyl)ethynyl)benzene (**1f**) gave 92% yield (entry 23). Noteworthy is that without Pd catalysts only 55% yield is isolated from the reaction of substrate **1f** with I₂ (entry 24).

With the optimal reaction conditions in hand, the scope of both 2-alkynylanisoles and disulfides as the reaction partners was explored for the annulation reaction (Table 2). Initially, a number of disulfides **2b–j** were investigated by reacting

with 2-(2-methoxyphenyl)alkynylanisole (**1f**) (entries 1–9). The results demonstrated that the electronic effect of substituents on the aryl moiety affected the reaction, with the order of the activity being electron-rich disulfides > electron-deficient disulfides (entries 1–7). Disulfide **2b** bearing a *p*-methyl group, for instance, reacted with substrate **1f**, PdCl₂ and I₂ to afford the corresponding product **4** in 92% yield (entry 1), but disulfides **2c** and **2h**, having an *o*-methyl group or a *p*-nitro group, has less activity (entries 2 and 7). Gratifyingly, 1,2-dimethyl disulfide (**2i**), an aliphatic disulfide, was also suitable for the reaction with substrate **1f** under the standard conditions (entry 8). However, the reactions of 1,2-dimethyl disulfide (**2j**) or 1,2-dibenzyl disulfide (**2k**) with alkyne **1f**, PdCl₂, and I₂ were unsuccessful, and a mixture of byproduct, 3-iodo-2-phenylbenzofuran, and 2-phenylbenzofuran was obtained in 70% total yields (entries 9 and 10). Subsequently, a variety of 2-alkynylanisoles **1g–o** were examined (entries 11–23). We found that the standard conditions were compatible with substrates with aromatic groups at the terminal of 1-ethynyl-2-methoxybenzene but inconsistent with alkyl group. For example, treatment of substrate **1g** bearing a *p*-CF₃C₆H₄ group with disulfide **2a**,

SCHEME 2. Selective Annulation Reaction

TABLE 3. Annulation Reactions of 2-Alkynylanisoles (**1**) with Diselenides (**2**)^a

Entry	Substrate 1	Diselenides 2	Time (h)	Yield (%)
1			10	81 (29)
2			6	89 (30)
3			12	83 (31)
4			10	69 (32)
5			10	87 (33)
6			18	78 (34)

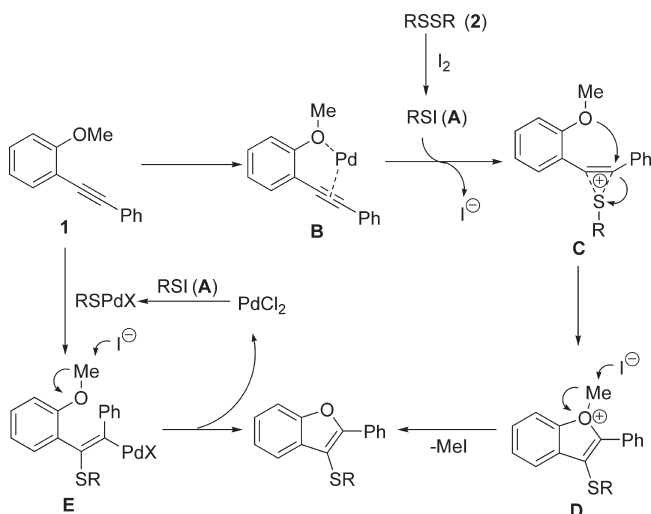
^aReaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), PdCl₂ (10 mol %), I₂ (2 equiv), and MeCN (2 mL) at 80 °C under N₂ atmosphere.

PdCl₂, and I₂ afforded the corresponding product **13** in 65% yield (entry 11). Substrate **1j** having a bulky *o*-methyl group was also successful in 44% yield (entry 14). We were pleased to observe that 2-(2-(2-methoxyphenyl)ethynyl)thiophene (**1l**) was a suitable substrate in moderate yield (entry 18). However, annulation of 1-methoxy-2-(oct-1-ynyl)benzene (**1m**) failed under the same conditions (entry 19). To our delight, methyl and chloro substituents on the anisole moiety were perfectly tolerated (entries 20–23). The reaction of 1-methoxy-4-methyl-2-(2-phenylethynyl)benzene (**1n**), for instance, with disulfides **2a**, **2d**, or **2e**, PdCl₂, and I₂ was conducted successfully in 90%, 94%, and 75% yields, respectively (entries 20–22). It was noted that the reaction of 4-methyl-2-(phenylethynyl)phenol (**1p**) with disulfide **2a** was also conducted smoothly in 75% yield under the standard conditions (entry 24).

The selectivity toward *O*-nucleophile and *N*-nucleophile was also investigated under the standard conditions, and the results are shown in Scheme 2. We found that the selectivity toward *N*-nucleophile, not *O*-nucleophile, was observed for the reaction of substrate **1q** with 1,2-diphenyl disulfide (**2a**), PdCl₂, and I₂.¹¹

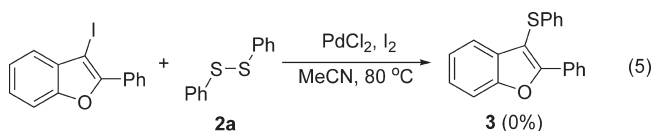
As expected, the reactions of diselenides **2** with 2-alkynylanisoles **1** proceeded successfully to give the desired products in good yields (Table 3). In the presence of PdCl₂ and I₂, substrate **1f** was reacted with diaryl diselenides **2l** or **2m** smoothly to give the target products **29** and **30** in 81% and

SCHEME 3. Possible Mechanism



89% yields, respectively (entries 1 and 2). Good yield was still achieved from the reaction of substrate **1f** with aliphatic diselenide **2n** (entry 3). Gratifyingly, substrate **1i**, bearing a 4-MeC₆H₄ group at the terminal 1-ethynyl-2-methoxybenzene, smoothly underwent the reaction in satisfactory yield (entry 4). Treatment of substrates **1n** or **1o**, bearing a group on the anisole moiety, with 1,2-diphenyldiselenide (**2l**) was also successful in good yields (entries 5 and 6).

To elucidate the mechanism, a controlled reaction between 3-iodo-2-phenylbenzofuran and disulfide **2a** was carried out in the presence of PdCl₂ and I₂ (eq 5). The results showed that no target product **3** was observed by GC–MS analysis, which suggested that the reaction proceeded not via an iodocyclization process. The results of entries 9 and 10 in Table 2 also supported it.



A possible mechanism was proposed as outlined in Scheme 3 on the basis of the reported mechanism^{9,10} and the present results. The reaction could be conducted in the presence of I₂ alone, which suggests that the reaction of disulfide **2** with I₂ yielded PhSI **A** in situ, followed by the electrophilic addition of PhSI (**A**) with intermediate **B** to afford intermediate **C**. Annulation of intermediate **C** gave intermediate **D**. The Me group can be removed from intermediate **D** with aid of an I[−] nucleophile to afford the target product. However, we cannot rule out a sulfonylpalladation process (**1** → **E**) in the present reaction. We deduced that roles of PdCl₂ might be included: (1) complexation of the

triple bond to active the reaction species; (2) as a Lewis acid to stable and active the intermediates; and (3) as a catalyst for the chalcogen-palladation process. Study of the detailed mechanism is in progress.

In summary, we have developed a practical PdCl₂-promoted electrophilic annulation method that allows the reactions between 2-alkynylphenol derivatives and disulfides (or diselenides) for the synthesis of 3-chalcogen-benzo[*b*]furans. The key of the reaction is generation of RYI (Y = S, Se) in situ from the reaction of RYYR with I₂. It is noteworthy that PdCl₂ can improve the reaction. In the presence of PdCl₂ and I₂, a variety of 2-alkynylphenol derivatives underwent the annulation reactions with disulfides or diselenides successfully to afford the corresponding 3-sulphenylbenzofurans and 3-selenenylbenzofuran in moderate to excellent yields.

Experimental Section

Typical Experimental Procedure for the PdCl₂-Promoted Electrophilic Annulation Reaction in the Presence of I₂. A mixture of 2-alkynylphenol derivative **1** (0.2 mmol), disulfide or diselenide **2** (0.1 mmol), I₂ (2 equiv), and PdCl₂ (10 mol %) in MeCN (2 mL) was stirred at 80 °C for the indicated time until complete consumption of starting material as monitored by TLC and GC–MS analysis. After the reaction was finished, the

mixture was poured into ethyl acetate, which was washed with saturated Na₂S₂O₃ and extracted with diethyl ether. The organic layers were dried over anhydrous Na₂SO₄ and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the products.

2-Phenyl-3-(phenylthio)benzofuran (3). White solid. Mp 65.0–66.8 °C (uncorrected). ¹H NMR (300 MHz, CDCl₃) δ: 8.23 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.49–7.33 (m, 5H), 7.24–7.18 (m, 5H), 7.10 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ: 157.5, 154.0, 136.1, 130.8, 129.8, 129.4, 129.0, 128.6, 127.4, 126.5, 125.5, 125.3, 123.5, 120.4, 111.3, 104.7. IR (KBr, cm^{−1}): 1478, 1454, 1439, 737, 686. LRMS (EI, 70 eV) *m/z*: 302 (M⁺, 100), 225 (33), 197 (30), 165 (28). HRMS (APCI): calcd for C₂₀H₁₅OS⁺ ([M + H]⁺) 303.0838, found 303.0825.

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Supporting Information Available: Characterization data for compounds **3**, **4**, **6–9**, **11**, **14–21**, **23–27**, and **29–34** and copies of spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.