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Platinum-Catalyzed Multisubstituted Benzo[*b*]selenophene Synthesis

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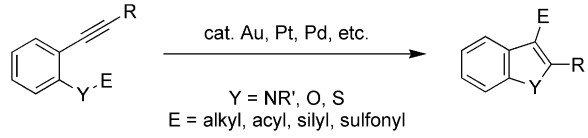
Alkyl *ortho*-alkynylphenyl selenides **1** were efficiently converted into 2,3-disubstituted benzo[*b*]selenophenes **2** in the presence of a catalytic amount of $PtCl_2$. The reactions were shown to proceed via carboselenation, specifically the addition of a C–Se bond to the alkynes.

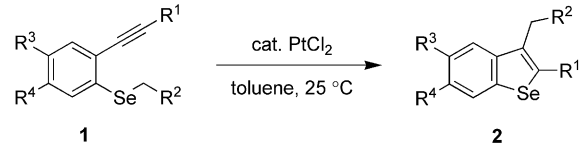
Introduction

Recently, the use of selenaheterocycles has gained increasing attention in organic chemistry. For example, recent studies have revealed that π-conjugated systems that involve selenium is applicable in the field of organic field-effect transistors (OFETs).[1] Moreover, various biologically active selenaheterocycles such as ebselen have been discovered in recent years.[2] Despite these efforts, the properties of benzo[*b*]selenophene (the selenium analog of indole, benzofuran, and benzo[*b*]thiophene) have yet to be investigated in detail, presumably due to the lack of a general synthetic approach for the generation of multisubstituted benzo[*b*]-selenophene derivatives.[3] Recently, Takimiya and Larock reported the synthesis of 2,3-disubstituted benzo[*b*]selenophenes through electrophilic cyclization of *ortho*-alkynylphenyl methyl selenides with stoichiometric amounts of electrophilic reagents.[1c,4] To date, however, the direct synthesis of 2,3-disubstituted benzo[*b*]selenophenes under milder catalytic conditions has remained elusive due to the air-sensitivity of the hydroseleno group (Se–H) and to the poisoning of the metal catalysts by selenium.

In recent years, several groups, including ourselves, have investigated the synthesis of 2,3-disubstituted indoles,[5] benzofurans,[5c,6] and benzo[*b*]thiophenes[7] by using consecutive cyclization–1,3-migration reactions catalyzed by π-acidic transition metals (Scheme 1).[8] Accordingly, our methodology was applicable towards the catalytic synthesis of benzo[*b*]selenophenes − the above-mentioned challenges can be addressed by attaching a carbon-migration group to the selenium atom of the subsrates. Herein, we report the first catalytic synthesis of 2,3-disubstituted benzo[*b*]selenophenes **2** from alkyl *ortho*-alkynylphenyl selenides **1** under very mild conditions (Scheme 2).



Scheme 1. Transition-metal-catalyzed consecutive cyclization–1,3-migration reaction.



Scheme 2. Benzo[*b*]selenophene synthesis by Pt-catalyzed cyclization.

Results and Discussion

In accordance with our previous methodology, we proposed the synthesis of benzo[*b*]selenophene derivatives through a transition-metal-catalyzed cyclization reaction. Prior to the cyclization step, the substrates, alkyl *ortho*-alkynylphenyl selenides **1**, were readily prepared from *o*-iodoaniline (**3**) in three steps (Scheme 3; preparation of **1a**). First, **3** was diazotized, then immediately converted into 2-iodophenyl selenocyanate (**4**) by using aqueous KSeCN. The desired alkyl aryl selenides **1** were obtained through reduction and alkylation of **4** by using KEt_3BH (2 equiv.) and a small excess of the corresponding alkyl halides in a one-pot reaction, followed by either Pd-catalyzed Sonoga-

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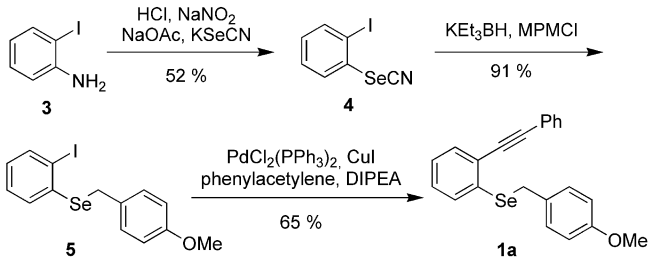
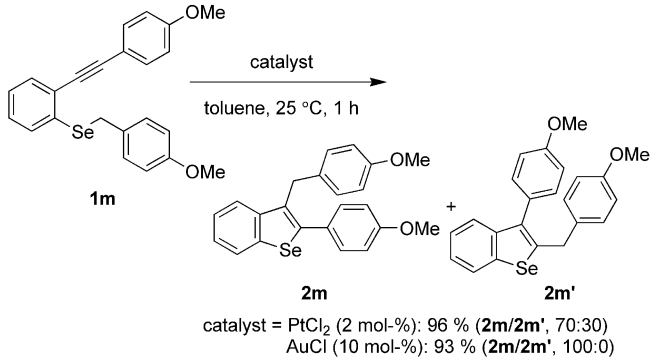
shira coupling with an aryl acetylene, or Stille coupling with an alkyl tributylstannyl acetylene (see Supporting Information).



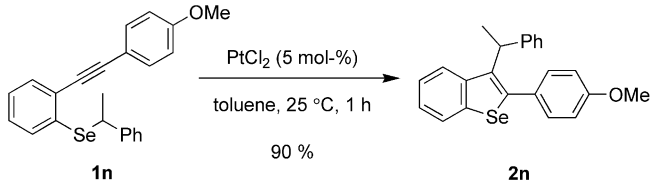
Scheme 3. Representative procedure for the synthesis of **1a**.

Resulting substrates **1** were subjected to a transition-metal-catalyzed cyclization reaction (Scheme 2) to afford desired benzo[*b*]selenophenes **2** (Table 1). In the presence of $PtCl_2$ (2 mol-%), the reaction of **1a** in toluene at 25 °C was complete within 1 h to give the desired 2,3-disubstituted benzo[*b*]selenophene **2a** as a single product in 98% isolated yield (Table 1, Entry 1). Cyclization of **1a** to **2a** was also effectively catalyzed by AuCl, $AuBr_3$, $PtBr_2$, and $PtCl_4$ – their catalytic activities, however, were lower than that of $PtCl_2$ (see the Supporting Information). In contrast, $PdCl_2$ and AgOTf were not effective as catalysts. The reaction of *p*-(triflurometh yl)phenyl substrate **1b** gave product **2b** in an excellent yield (Table 1, Entry 2). Under the conditions described above, even the reactions of **1c**, **1d**, and **1e** (Table 1, Entries 3, 4, and 5, respectively) bearing a primary, a secondary, and a bulky tertiary alkyl group on the alkynyl terminus, respectively, afforded the corresponding products (**2c**, **2d**, **2e**, respectively) in excellent yields; the conversion of **1e** to **2e**, however, required a longer reaction time (18 h). Moreover, the reactions of **1f** and **1g** (Table 1, Entries 6 and 7, respectively) bearing a fluoro group on the tethering benzene ring gave 2,3,5- and 2,3,6-trisubstituted benzo[*b*]selenophene **2f** and **2g**, respectively. In the presence of $PtCl_2$, the reaction of **1h** bearing a 2,6-difluorophenyl group at an alkyne terminus did not undergo cyclization under similar conditions; interestingly, in the presence of AuCl (10 mol-%), and at a slightly elevated temperature, desired product **2h** was obtained in an excellent yield (Table 1, Entry 8). Interestingly, for other substrates, AuCl exhibited lower catalytic activities than $PtCl_2$ (see the Supporting Information). Furthermore, selenoacetal substrates **1i**–**k** (Table 1, Entries 9–11) also underwent cyclization under similar conditions. The reaction, however, was not observed for nonsubstituted benzyl substrate **1l** (Table 1, Entry 12).

It is noteworthy that, in the presence of $PtCl_2$, the reaction of **1m**, which bears a *p*-methoxyphenyl group at the alkyne terminus, gave a 70:30 mixture of regioisomers **2m** and **2m′** (Scheme 4). The abnormal rearrangement resulting in **2m′** was detected only for the reaction of **1m** with the use of $PtCl_2$; in the presence of AuCl (10 mol-%), **2m** was obtained as a single product in good yield. In contrast, the reaction of **1n**, which possess a bulkier 1-phenylethyl group instead of a *p*-methoxybenzyl group, gave **2n** as the sole product, even when $PtCl_2$ was used (Scheme 5).



Scheme 4. Pt- and Au-catalyzed reactions of **1m**.



Scheme 5. Pt-catalyzed reaction of **1n**.

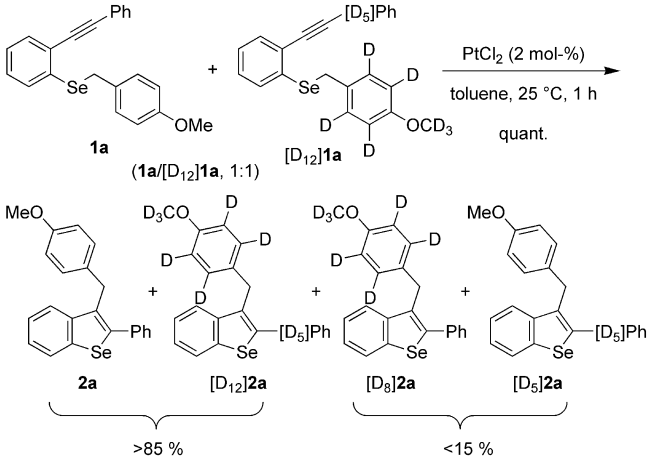
Evidence that the reaction proceeds primarily through an intramolecular process was shown by using a crossover experiment, in which the reaction of a 1:1 mixture of **1a** and

Table 1. Pt-catalyzed cyclization reaction of *ortho*-alkynylphenyl selenides **1**.[a]

Entry	1	R^1	R^2	R^3	R^4	*t* [h]	2, Yield [%]
1	**1a**	Ph	*p*-$MeOC_6H_4$	H	H	1	**2a**, 98
2	**1b**	*p*-$F_3CC_6H_4$	*p*-$MeOC_6H_4$	H	H	1	**2b**, 99
3	**1c**	*n*Pr	*p*-$MeOC_6H_4$	H	H	1	**2c**, 98
4	**1d**	cyclopentyl	*p*-$MeOC_6H_4$	H	H	1	**2d**, quant.
5	**1e**	*t*Bu	*p*-$MeOC_6H_4$	H	H	18	**2e**, 99
6	**1f**	Ph	*p*-$MeOC_6H_4$	F	H	1	**2f**, 99
7	**1g**	Ph	*p*-$MeOC_6H_4$	H	F	1	**2g**, quant.
8[b]	**1h**	2,6-$F_2C_6H_3$	*p*-$MeOC_6H_4$	H	H	48	**2h**, 99
9[c]	**1i**	Ph	MeO	H	H	2	**2i**, 77
10[c]	**1j**	Ph	$Me_3Si(CH_2)_2O$	H	H	2	**2j**, 86
11[c]	**1k**	Ph	TIPSO	H	H	1	**2k**, 77
12	**1l**	Ph	Ph	H	H	24	**2l**, 0[d]

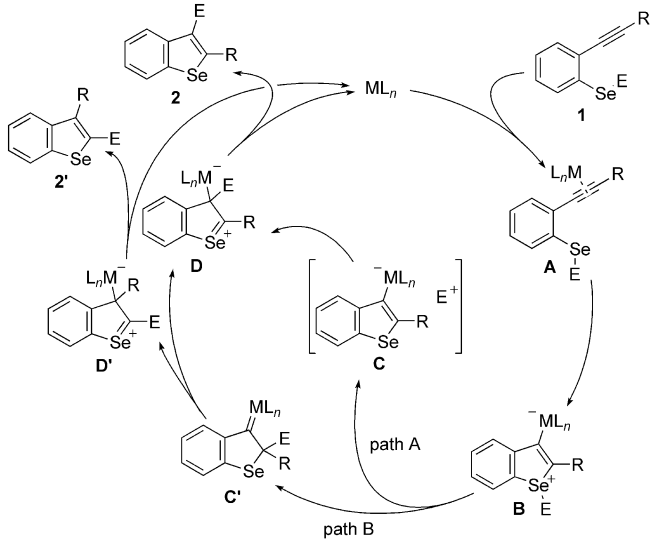
[a] The reaction of **1** was carried out with $PtCl_2$ (2 mol-%) in toluene at 25 °C unless otherwise noted. [b] The reaction was carried out in the presence of AuCl (10 mol-%) at 45 °C. [c] The reaction was carried out in the presence of $PtCl_2$ (5 mol-%). [d] No reaction.

[D_{12}]**1a** afforded a mixture of **2a**, [D_{12}]**2a**, [D_5]**2a**, and [D_8]-**2a** (Scheme 6). By using MS (ESI) analysis, the combined yield of crossover products [D_5]**2a** and [D_8]**2a** was less than 15%.



Scheme 6. Crossover experiment of **1a** with [D_{12}]**1a**.

A plausible mechanism for the Pt- or Au-catalyzed cyclization of **1** is illustrated in Scheme 7. As discussed in a previous study,[7c] the π-acidic metal catalyst is coordinated by the alkynyl group of the substrate to generate π complex **A**.[9] Nucleophilic attack of the selenium atom of **A** to the alkyne moiety results in the formation of cyclized intermediate **B**. In the case of Path A, substituent E of intermediate **B** undergoes direct 1,3-migration to the carbon atom bonded to the metal atom to produce intermediate **D** through ion pair **C** (1,3-migration mechanism). Subsequently, elimination of the catalyst from intermediate **D** results in the formation of product **2**. For the reaction of **1m** in the presence of $PtCl_2$, however, observation of the abnormal rearrangement product **2m′** suggests an alternate reaction pathway. As shown in Path B, **2m′** is formed by two successive 1,2-shift processes: the first 1,2-alkyl shift forms carbene intermediate **C′**, followed by a second 1,2-alkyl or 1,2-aryl shift, leading to intermediate **D** or **D′** (double 1,2-shift mechanism).[10,11] Following this reaction pathway, abnormal rearrangement product **2m′** is formed when the second 1,2-alkyl shift (involving the *p*-methoxybenzyl group) is replaced by a 1,2-aryl shift (involving the *p*-methoxyphenyl group of **1m** at the alkyne moiety). Presumably, the *p*-methoxyphenyl group dramatically facilitates the latter 1,2-aryl shift through a phenonium-like transition state. Moreover, results shown in Schemes 4 and 5 imply strong competition between the 1,3-migration (Path A) and the double 1,2-shift (Path B) reaction pathways.[12] On the basis of our hypothesis, selectivity of the reaction is controlled not only by the competition between the 1,2-alkyl (from **C′** to **D**) and 1,2-aryl (from **C′** to **D′**) shifts, but also by the relative stabilities between carbene intermediate **C′** and ion pair **C** (formed during the heterolytic C–Se bond-cleavage process). Correspondingly, the lack of activity using nonsubstituted benzyl substrate **1l** (Table 1, Entry 12) strongly suggests that ionic C–Se bond cleavage is an essential process. As observed in the reaction of **1n**, the use of a relatively bulky migration group such as 1-phenylethyl decreases the stability of carbene intermediate **C′** by steric repulsion between the migration group itself and the corresponding quaternary carbon (the α-carbon of the carbene).



Scheme 7. Proposed mechanism.

Conclusions

In conclusion, we have developed a novel synthetic protocol for 2,3-disubstituted benzo[*b*]selenophenes that involves Pt-catalyzed cyclization. Our studies indicate that the reaction proceeds through two competing reaction pathways. Furthermore, it should be noted that the cyclization proceeds by carboselenation, specifically the addition of a C–Se bond to the alkynes.[13]

Experimental Section

General Procedure for the Cyclization Reaction of 1: A solution of alkyl *o*-alkynylphenyl selenide **1** (0.25 mmol) and a catalytic amount of $PtCl_2$ (or AuCl) in toluene (1.3 mL) was stirred at 25 °C under an argon atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a short plug of silica gel using ether (ca. 50 mL) as the eluent, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (1–10% ethyl acetate in hexanes) to give benzo[*b*]selenophene **2**.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization of compounds **1** and **2**.

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