



Title	Synthesis of Benzoisoselenazolones via Rh(III)-Catalyzed Direct Annulative Selenation by Using Elemental Selenium
Author(s)	Xu-Xu, Qing Feng; Nishii, Yuji; Uetake, Yuta et al.
Citation	Chemistry - A European Journal. 2021, 27(71), p. 17952-17959
Version Type	AM
URL	https://hdl.handle.net/11094/92779
rights	© 2021 Wiley-VCH GmbH
Note	

The University of Osaka Institutional Knowledge Archive : OUKA

<https://ir.library.osaka-u.ac.jp/>

The University of Osaka

Synthesis of Benzoisoselenazolones via Rh(III)-Catalyzed Direct Annulative Selenation Using Elemental Selenium

Qing-Feng Xu-Xu,^[a] Yuji Nishii,^{*[b]} Yuta Uetake,^[a,b] Hidehiro Sakurai,^[a,b] and Masahiro Miura^{*[a]}

Dedication ((optional))

[a] Dr. Q.-F. Xu-Xu, Dr. Y. Uetake, Prof. Dr. H. Sakurai, Prof. Dr. M. Miura
Innovative Catalysis Science Division, Institute for Open and Transitionary Research Initiative (ICS-OTRI), Osaka University
Suita, Osaka 565-0871, Japan
E-mail: miura@chem.eng.osaka-u.ac.jp

[b] Dr. Y. Nishii, Dr. Y. Uetake, Prof. Dr. H. Sakurai
Department of Applied Chemistry, Graduate School of Engineering, Osaka University
Suita, Osaka 565-0871, Japan
E-mail: y_nishii@chem.eng.osaka-u.ac.jp

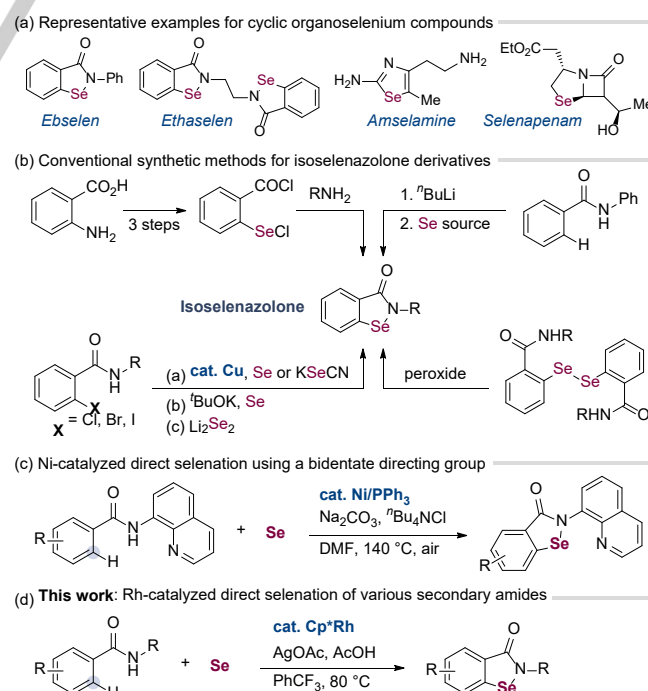
Supporting information for this article is given via a link at the end of the document. ((Please delete this text if not appropriate))

Abstract: Isoselenazolone derivatives have attracted significant research interest because of their potent therapeutic activities and indispensable applications in organic synthesis. Efficient construction of functionalized isoselenazolone scaffolds is still challenging, and thus new synthetic approaches with improved operational simplicity have been of particular interest. In this manuscript, we introduce a rhodium-catalyzed direct selenium annulation using stable and tractable elemental selenium. A series of benzamides as well as acrylamides were successfully coupled with selenium under mild reaction conditions, and the obtained isoselenazolones could be pivotal synthetic precursors for several organoselenium compounds. Based on the designed control experiments and X-ray absorption spectroscopy measurements, we propose an unprecedented selenation mechanism involving a highly electrophilic Se(IV) species as the reactive selenium donor. The reaction mechanism was further verified by a computational study.

Introduction

Organoselenium compounds have attracted significant research interests because of their unique biological activities and indispensable applications in organic synthesis (Scheme 1a).^{1,2} In particular, 1,2-benzoisoselenazol-3-(2H)-ones, especially Ebselen derivatives,^{3,4} have been extensively studied for their interesting therapeutic properties on bipolar disorder,⁵ stroke disease,⁶ inflammatory,⁷ cancer,⁸ neurodegeneration,⁹ etc. More recently, a fascinating effect on inhibition of COVID-19 protease in cell-based assays was reported.¹⁰ Upon screening the bioactivity of isoselenazolone analogues, superior performance is often found with modifications of the substituent on the nitrogen atom as well as the benzene rings.^{3g,8b,9,11} The most common synthetic method is annulation of primary amines with *o*-chloroselanylbenzoyl chloride, which is prepared from anthranilic acid by sequential diazotization, selenation, and chlorination. (Scheme 1b).¹² Another conventional strategy is *ortho*-lithiation of benzamides and subsequent double substitution reaction with electrophilic selenium reagents.¹³ Recently, Kumar¹⁴ and Sucheck¹⁵ developed Cu-catalyzed annulative selenation

protocols of *o*-halobenzamides with selenium powder and KSeCN, respectively. The *o*-halobenzamides can be converted to the corresponding benzoisoselenazolones under the transition-metal-free conditions utilizing ^tBuOK/Se^{14c} or lithium diselenide¹⁶ as the selenium source. In addition, radical cyclization of diselenides or their analogues has been a well-established synthetic approach.¹⁷ The existing methodologies mentioned above have suffered from the use of highly reactive lithium reagents and/or the cumbersome multistep preparation of the starting *ortho*-disubstituted benzene derivatives, thereby limiting the structural diversity in the cyclized products. The construction of derivatized isoselenazolone scaffolds is still challenging, and thus more effective approaches which operate under mild conditions would be highly appreciated.



Scheme 1. Synthetic approaches to isoselenazolone derivatives.

FULL PAPER

Over the past few decades, transition-metal-catalyzed C–H functionalization has emerged as a powerful toolbox in synthetic chemistry because of its step-economical fashion.¹⁸ To the best of our knowledge, only one example for the direct catalytic selenium annulation was reported by Nishihara in 2017.¹⁹ This elegant work achieved the annulation of various benzamides as well as acrylamides with elemental selenium adopting a Ni catalyst (Scheme 1c). The inevitability of using an 8-aminoquinoline bidentate directing group^{18d} considerably narrowed the generality of this transformation, and the reaction condition was relatively harsh. It is obvious that new synthetic methodologies with broad scope and mild conditions are highly in demand for the efficient construction of isoselenazolone derivatives.²⁰ As part of our continuous interests in construction of heterocycles with element chalcogen,²¹ we herein introduce a Rh-catalyzed direct oxidative annulation of readily available secondary benzamides with elemental selenium (Scheme 1d). Furthermore, an unprecedented selenation mechanism involving an electrophilic Se(IV) species which acts as the reactive selenium donor is presented.

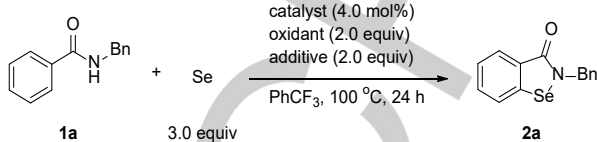
Results and Discussion

As an initial attempt, we examined the reaction of *N*-benzylbenzamide (**1a**) with metallic (gray) selenium powder (Table 1, see the Supporting Information for additional data). Under the standard conditions using a cationic [Cp*Rh(MeCN)₃][SbF₆]₂ as a catalyst (4.0 mol%) and AgOAc (2.0 equiv) in PhCF₃ solvent at 100 °C, the target selenazolone **2a** was obtained in 72% yield (entry 1). AgOBz was less effective (entry 2), and the product was not detected when Cu(OAc)₂ was used in place of AgOAc (entry 3). The reaction was significantly retarded by the addition of base (entry 5), whereas the presence of AcOH exerted a positive influence on this transformation (entry 6). With a slightly increased amount of AgOAc (2.2 equiv), the yield of **2a** was improved to 91% (83% isolated, entry 7). A control experiment confirmed that the Rh catalyst was essential in this reaction (entry 8). A chloride complex [Cp*RhCl₂]₂ exhibited comparable activity only when combined with AgSbF₆ as a non-coordinating anion source (entries 9 and 10). Analogous Cp*Co(III) and Cp*Ir(III) complexes were not effective catalysts (entries 11 and 12). The temperature could be decreased to 80 °C without affecting the reaction efficiency (entry 13). Furthermore, the catalyst loading could be reduced to 2.0 mol%, affording **2a** in 95% yield (86% isolated, entry 14). This reaction was successfully performed in gram scale to produce 1.2 g of **2a** (83% yield) with a mere 1.0 mol% Rh catalyst (Scheme 2).

With the optimized conditions employed in Table 1, entry 14, we evaluated the scope with respect to the substituent on the nitrogen atom of benzamide derivatives (Scheme 3a). A series of *N*-benzylbenzamides bearing functional groups on the benzyl moiety **1b–1f** reacted smoothly to give the corresponding annulated products **2b–2f** in high yields. The structure of **2d** was determined by an X-ray crystallographic analysis (CCDC 2103646). Substrates with a tertiary (**1g**) or a quaternary (**1h**) carbon atom adjacent to the amide nitrogen were also applicable to the present protocol. An *N*-(1-naphthyl)methyl amide (**1i**) was converted to the product **2i** in 80% yield. Rather simple *N*-alkyl amides **1j–1m** were also well tolerated. To our delight, glycine- and phenylalanine-derived benzamides **1n** and **1o** were

successfully coupled with selenium to afford **2n** and **2o** in 75% and 73% yields, respectively. Unfortunately, attempted selenium annulation of *N*-phenylbenzamide produced small amount of the target product Ebselen (8% yield, see the Supporting Information).²²

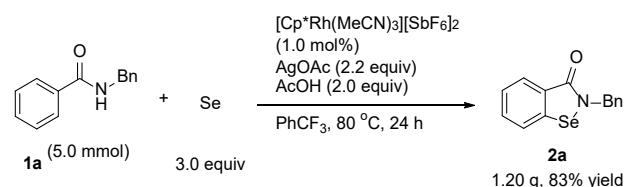
Table 1. Optimization of the reaction conditions.^[a]



Reaction scheme showing the conversion of **1a** (N-benzylbenzamide) to **2a** (isoselenazolone) using Se (3.0 equiv) in PhCF₃ at 100 °C for 24 h, with catalyst (4.0 mol%), oxidant (2.0 equiv), and additive (2.0 equiv).

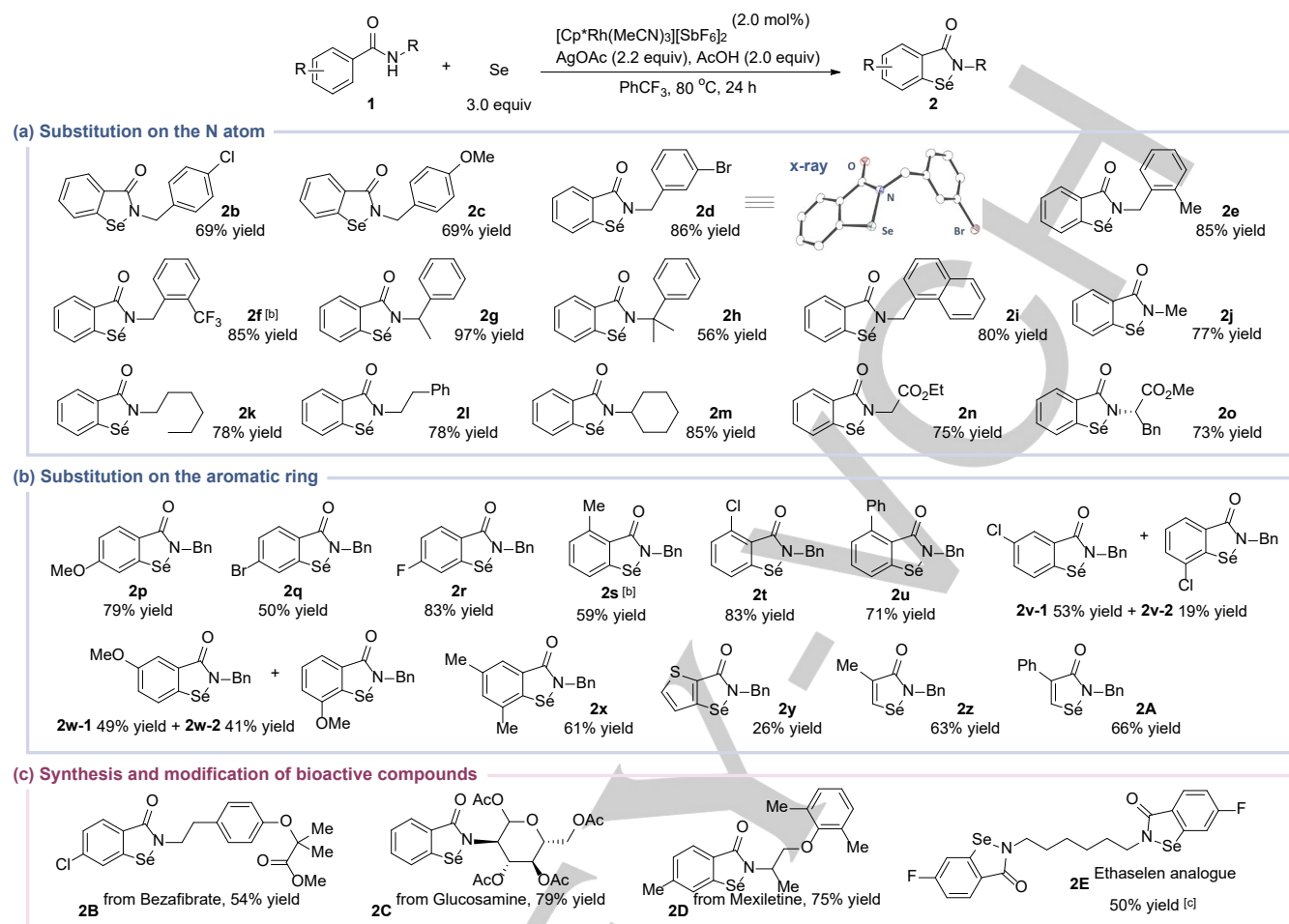
Entry	Catalyst	Oxidant	Additive	Yield ^[b]
1	[Cp [*] Rh(MeCN) ₃][SbF ₆] ₂	AgOAc	-	72%
2	[Cp [*] Rh(MeCN) ₃][SbF ₆] ₂	AgOBz	-	51%
3	[Cp [*] Rh(MeCN) ₃][SbF ₆] ₂	Cu(OAc) ₂	-	n.d.
4	[Cp [*] Rh(MeCN) ₃][SbF ₆] ₂	AgOAc	NaOAc	trace
5	[Cp [*] Rh(MeCN) ₃][SbF ₆] ₂	AgOAc	AcOH	83%
6 ^[c]	[Cp [*] Rh(MeCN) ₃][SbF ₆] ₂	AgOAc	AcOH	91%(83%)
7 ^[c]	-	AgOAc	AcOH	trace
8 ^[c]	[Cp [*] RhCl ₂] ₂	AgOAc	AcOH	5%
9 ^[c,d]	[Cp [*] RhCl ₂] ₂	AgOAc	AcOH	83%
10 ^[c,d]	Cp [*] Co(CO) ₂ I ₂	AgOAc	AcOH	trace
11 ^[c,d]	[Cp [*] IrCl ₂] ₂	AgOAc	AcOH	trace
12 ^[c,e]	[Cp [*] Rh(MeCN) ₃][SbF ₆] ₂	AgOAc	AcOH	89%(85%)
13 ^[c,e,f]	[Cp [*] Rh(MeCN) ₃][SbF ₆] ₂	AgOAc	AcOH	95%(86%)

[a] Reaction conditions: catalyst (4 mol%, calc. by metal), **1a** (0.2 mmol), Se (0.6 mmol), oxidant (0.4 mmol), and additive (0.4 mmol) in PhCF₃ (0.3 mL) at 100 °C for 24 h under N₂. [b] Determined by ¹H NMR analysis. The values in parentheses are isolated yield. [c] Conducted with AgOAc (2.2 equiv) and PhCF₃ (0.4 mL). [d] Conducted with AgSbF₆ (20 mol%). [e] Conducted at 80 °C. [f] Conducted with [Cp*Rh(MeCN)₃][SbF₆]₂ (2.0 mol%).



Scheme 2. Gram-scale reaction.

We also tested the selenium cyclization with a series of *N*-benzyl carboxamides (Scheme 3b). For the *para*- and *ortho*-substituted benzamides (**1p–1u**), the desired products were obtained in moderate to good yields (50–83%). It was notable that the halogen functionalities were compatible under the developed catalytic system. Both of two possible regioisomers formed when *meta*-substituted benzamides **1v** and **1w** were employed, and sterically

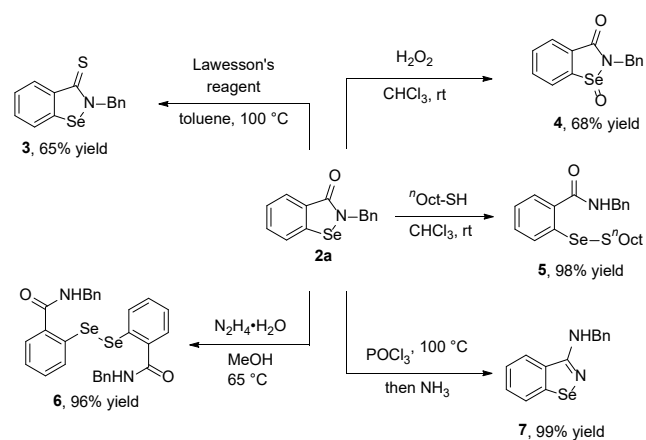


Scheme 3. Substrate scope. [a] Reaction condition: $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ (2.0 mol%), **1** (0.2 mmol), Se (0.6 mmol), AgOAc (0.44 mmol), and AcOH (0.4 mmol) in PhCF_3 (0.4 mL) at 80 °C for 24 h under N_2 . Isolated yields are shown. [b] Conducted with PhCF_3 (0.8 mL). [c] Isolated after two cycles of the standard procedure.

more accessible position tended to react faster. A disubstituted benzamide **1x** as well as a 2-thiophenecarboxamide **1y** could be coupled with selenium to give the corresponding selenazolonones in 61% and 26% yields, respectively. Intriguingly, this reaction was applicable to the more challenging vinylic C–H activation. 2-Methyl and 2-phenyl acrylamides **1z** and **1aa** were successfully converted to the desired coupling products **2z** and **2aa** in good yields.

In order to highlight the generality of the developed reaction system, we examined the synthesis and modification of some bioactive compounds (Scheme 3c). A methyl ester of Bezafibrate (cholesterol-lowering drug) **1B** was successfully annulated under the standard conditions to afford **2B** in 54% yield. Glucosamine-modified isoselenazolonones were previously prepared through the multistep process,²³ whereas our method could achieve the efficient synthesis of **2C** in three steps involving protection and selenation. Mexiletine, which is used for the treatment of arrhythmias, was readily converted to the corresponding isoselenazolonone **2D** in high yield. Diamine-based benzoisoselenazolonone derivatives have attracted considerable attention because of their potent pharmaceutical applications.²⁴ A particular example is Ethaselen derived from ethylenediamine. The present catalytic system was also applicable to the double

cyclization to give **2E** in 50% yield after two cycles of the standard procedure.



Scheme 4. Derivatization of the product **2a**.

FULL PAPER

The isoselenazolone derivatives have also been of pivotal synthetic precursors for a variety of organoselenium compounds. Thus, we conducted some derivatization of a representative coupling product **2a** (Scheme 4). The carbonyl group could be converted to thiocarbonyl upon treatment with Lawesson's reagent (**3**, 65% yield). The selenium atom within the selenazolone fragment was selectively oxidized by H_2O_2 (**4**, 68% yield). Ring-opening of **2a** was prompted by the nucleophilic addition of a thiol to give **5** in 98% yields. The corresponding diselenide **6** was obtained in 96% yield via the reductive Se–N bond cleavage adopting hydrazine monohydrate. Notably, **2a** was quantitatively transformed to the corresponding 3-aminobenzisoselenazolone **7** after reacting with POCl_3 and NH_3 . To gain an insight into the reaction mechanism, we plotted the time-course profile in an early stage of the reaction of **2a** with selenium (Fig. 1). During the initial 2 h, the reaction hardly proceeded, indicating the existence of the induction period to generate reactive species. Thereafter, the amide **1a** began to be consumed rapidly, and the yield of **2a** reached more than 80% at 4 h. It is notable that up to 33% yield of an oxidized selenazolone **4** was observed, indicating its intermediacy within the catalytic transformation (see below).

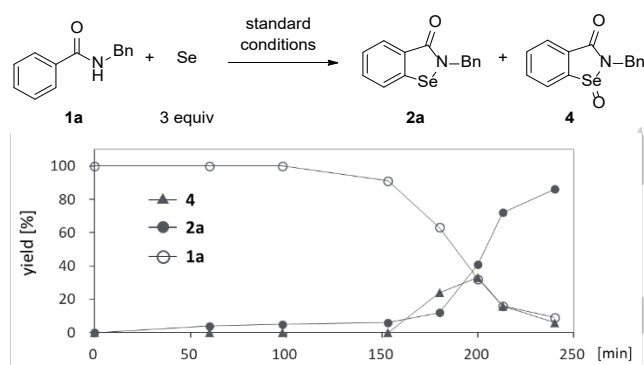
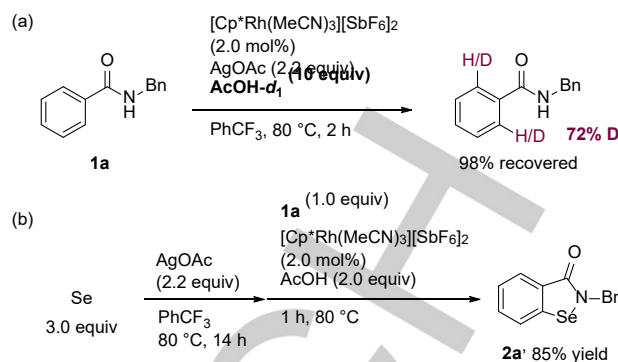


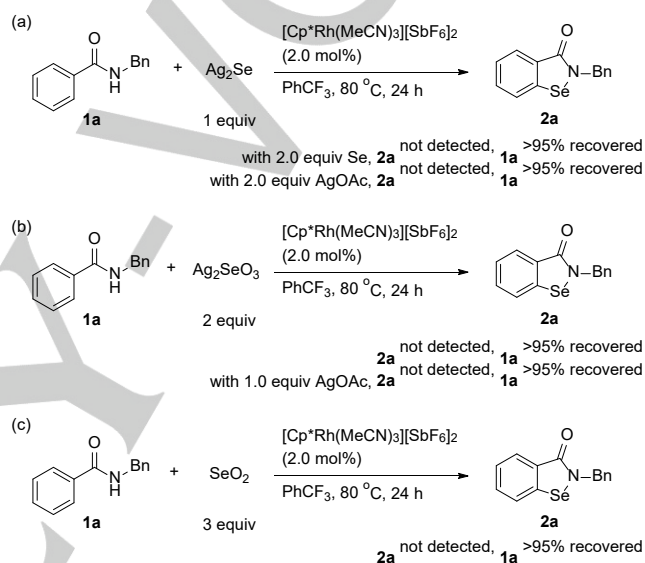
Figure 1. Reaction time course under the standard reaction conditions.

We then examined the deuterium incorporation into the aromatic ring of **1a** using AcOH-d_1 as the deuterium source under the conditions (Scheme 5a). The recovered starting material was considerably deuterated at the *ortho* positions (72% D) after 2 h. This result suggests that the cleavage of C–H bond is a reversible process and not involved in the induction period. We assumed that the induction period was required for the formation of an active selenium species. Indeed, when selenium powder was treated with AgOAc in heating PhCF_3 solvent for 14 h prior to the catalysis, the product **2a** was obtained in 85% yield only within 1 h (Scheme 5b).

These observations prompted us to examine the reactivity of several selenium compounds which were expected to be produced in situ. It has been known that selenium undergoes disproportionation in the presence of Ag(I) salt to afford silver selenide (Ag_2Se) and silver selenite (Ag_2SeO_3) in aqueous media.²⁵ These selenium compounds were employed to the reaction instead of elemental selenium; however, the desired product **2a** was not obtained even in the presence of additional AgOAc (Schemes 6a and 6b). The use of SeO_2 also did not work under the catalytic conditions, resulting in the recovery of the starting material **1a** (Scheme 6c).



Scheme 5. Deuterium incorporation and pre-heating experiment



Scheme 6. Control experiments using other selenium sources.

To identify the reactive selenium species generated in situ, X-ray absorption spectroscopy (XAS) measurements were carried out. On the basis of the result shown in Scheme 5b, the sample containing reactive selenium species was prepared by mixing an equimolar amount of selenium and AgOAc at 80 °C in PhCF_3 . Se–K edge X-ray absorption near edge structure (XANES) spectrum of this sample showed two peaks at 12662 eV and 12665 eV, which correspond to the electric dipole transition from 1s to 4p orbital (Fig. 2a). In the case of selenium, it is known that the energy at the absorption edge tends to shift to higher energy regions as the valency of the selenium species increases.²⁶ The peak observed at 12665 eV is characteristic of Se(IV) species. Meanwhile, the other peak at 12662 eV could be assigned as Se(0) and/or Se(–II) species; these two oxidation states are hardly distinguishable by XANES. Considering this result, the reactive selenium species generated in situ was composed of the mixture of Se(IV) and Se(0/–II) species, that was consistent with the reported result.²⁴ The extended X-ray absorption fine structure (EXAFS) oscillations were Fourier transformed in the k -range of 3–16 \AA^{-1} , and thus-obtained FT-EXAFS of this sample showed a new peak at 2.5 \AA which can be assigned as Se–Ag scattering, suggesting the presence of Ag_2Se (Fig. 2b). The peaks which are

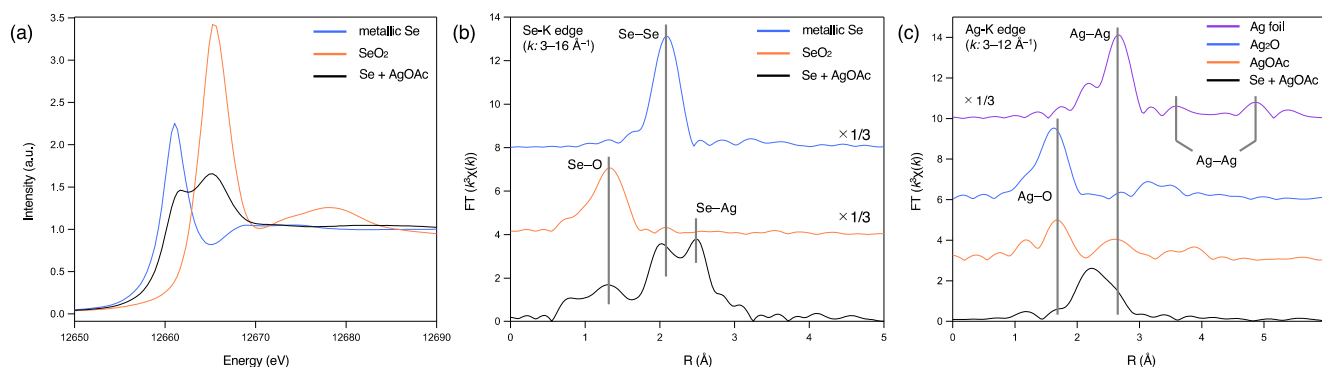


Figure 2. XAS analyses of the residue after mixing AgOAc and Se. (a) Se-K edge XANES spectra, (b) Se-K edge FT-EXAFS, and (c) Ag-K edge FT-EXAFS.

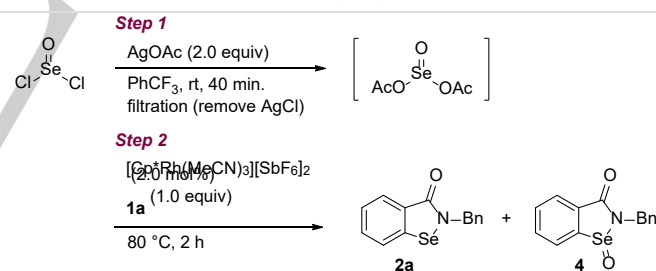
derived from the scattering of Se–O (1.3 Å) and Se–Se (2.0 Å) were also detected, indicating the existence of selenite and unreacted selenium. Ag–K edge XAS measurements were also carried out. Although it is difficult to fully analyze the EXAFS of mixture, the peak corresponding to Ag–O scattering seems to be disappeared, suggesting the absence of species having Ag–O bond, such as Ag_2SeO_3 and Ag_2O , under the reaction conditions (Fig. 2c). Considering the results of XAS analyses, we currently assume that $\text{SeO}(\text{OAc})_2$ is most plausible active Se(IV) species. This is consistent with the fact that the Se(IV) intermediate **4** was detected as a transient intermediate under the catalytic conditions (Fig. 1). The peak originated from the scattering of silver atoms located at the second and third proximities (3.6 Å and 4.9 Å) did not appear, implying the absence of metallic silver (Fig. 2c). Hence, the shoulder peak (2.6 Å) would correspond to the Ag–Se scattering of Ag_2Se .

Additional experimental support was obtained from a catalytic reaction of **1a** with $\text{SeO}(\text{OAc})_2$, which was prepared from SeOCl_2 and AgOAc in situ (Table 2). As expected, the annulated product **2a** was obtained in 23% yield along with its oxidized analog **4** (48% yield) even in the absence of stoichiometric AgOAc (entry 1). A similar result was obtained when the reaction was conducted with 1.0 equiv of Ac_2O (entry 2). To facilitate the conversion of **4** to **2a**, the reaction mixture was treated with 1.0 equiv of Se and 2.1 equiv of AgOAc (see also Table 3), and the target product **2a** was obtained in 92% yield (entry 3). We then carried out a deuterium experiment under these conditions. An excess amount of AcOH-d_1 (10 equiv) was used in the step 2, and the resulting mixture was heated at 80 °C for 2 h in the presence of Se and AgOAc (entry 4). No significant deuterium incorporation was observed at the carbonyl ortho position within **2a** (up to 3%D), indicating that the selenium annulation with $\text{SeO}(\text{OAc})_2$ is much faster than the C–H activation step. This result is consistent with the computational analysis (see below).

Next, we investigated the reduction process of the possible intermediate **4** observed in Figure 1. This compound was quantitatively converted to its reduced form **2a** upon treatment with selenium, AgOAc, and AcOH in PhCF_3 solvent (Table 3, entry 1). Almost no reaction proceeded in the absence of selenium (entry 2) or AgOAc (entry 3). The role of silver salt in this

process is not yet clear since the use of LiOAc gave a considerably high 79% yield (entry 4), whereas $\text{Zn}(\text{OAc})_2$ did not promote the reduction (entry 5). AcOH was not essential for this transformation (entry 6). The amount of selenium could be reduced to 1.0 equiv without drop of the product yield (entry 7). The reaction rate was considerably retarded with 0.5 equiv of selenium (entry 8); however, it reached completion after prolonged reaction time of 96 h (entry 9). A similar trend was observed regarding the amount of AgOAc (entries 10–12). We concluded that selenium powder is also acting as the oxygen scavenger because **4** was completely reduced using only a catalytic amount of AgOAc even though rather sluggishly (entry 13).

Table 2. Selenium annulation with $\text{SeO}(\text{OAc})_2$.^[a]



Entry	Deviation from the standard conditions	1a ^[b]	2a ^[b]	4 ^[b]
1	--	13%	23%	48%
2	Step 2: with Ac_2O (1.0 equiv)	trace	31%	53%
3	After Step 2: Se (1.0 equiv), AgOAc (2.1 equiv), 80 °C, 2 h	5%	92%	n.d.
4	Step 2: with AcOH-d_1 (10 equiv) After Step 2: Se (1.0 equiv), AgOAc (2.1 equiv), 80 °C, 2 h	6%	89% (<3%D)	trace

[a] Step 1: SeCl_2 (0.2 mmol) and AgOAc (0.42 mmol) in PhCF_3 (0.5 mL) at rt for 40 min. under N_2 . Step 2: **1a** (0.2 mmol) and $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$ (2.0 mol%) at 80 °C for 2 h under N_2 . [b] Determined by ^1H NMR analysis.

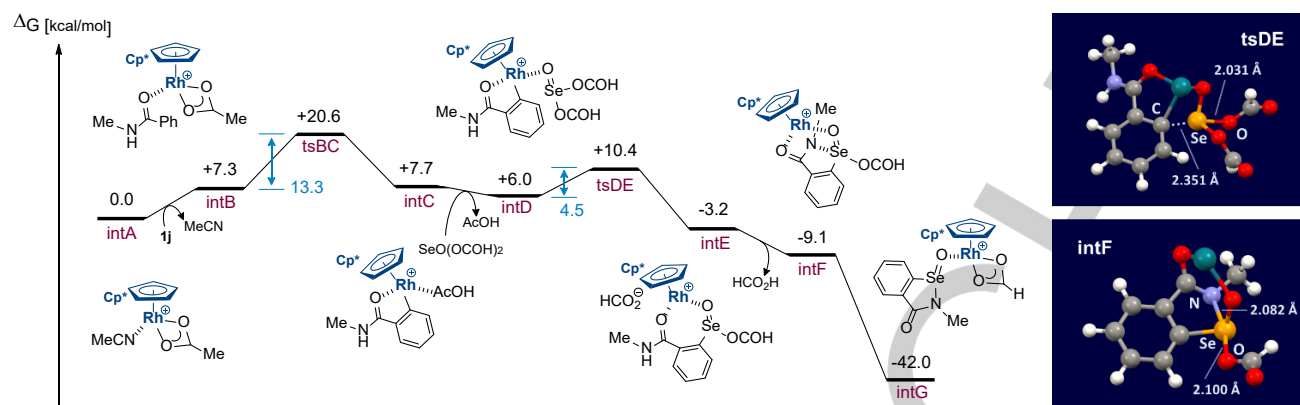
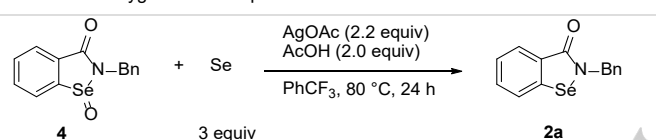


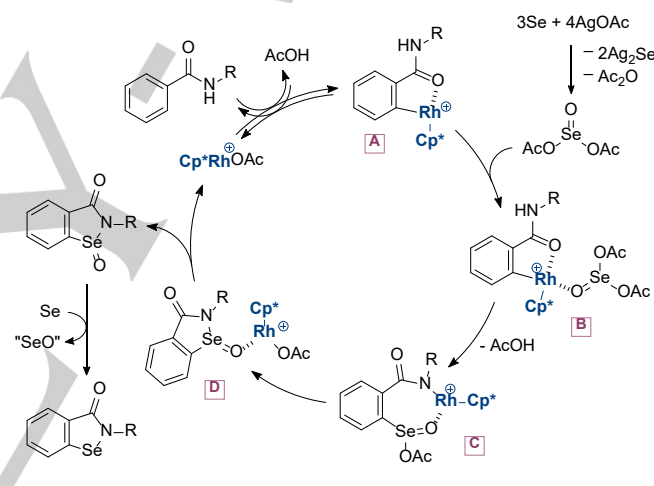
Figure 3. Partial Gibbs free energy profile of the reaction conducted at the ωB97X-D/6-311+G(d,p)&SDD//ωB97X-D/6-311+G(d,p)&LanL2DZ level with IEF-PCM(CH₂Cl₂) solvation (left). Optimized molecular geometries of **tsDE** and **intF** (right): carbon (gray), hydrogen (white), oxygen (red), selenium (yellow), and rhodium (green). Cp* ligands were omitted for clarity.

Table 3. Deoxygenation of a possible intermediate **4**.^[a]



Entry	Se (eq.)	AgOAc (eq.)	AcOH (eq.)	Yield ^[b]
1	3.0	2.2	2.0	99%
2	--	2.2	2.0	trace
3	3.0	--	2.0	7%
4	3.0	LiOAc (2.2)	2.0	79%
5	3.0	Zn(OAc) ₂ (1.1)	2.0	5%
6	3.0	2.2	--	99%
7	1.0	2.2	--	93%
8	0.5	2.2	--	67%
9 ^[c]	0.5	2.2	--	97%
10	1.0	1.0	--	97%
11	1.0	0.5	--	64%
12 ^[c]	1.0	0.5	--	92%
13 ^[d]	1.0	0.2	--	93%

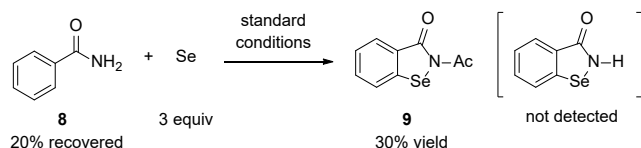
[a] Reaction condition: **4** (0.1 mmol), Se (0.3 mmol), AgOAc (0.22 mmol), and AcOH (0.2 mmol) in PhCF₃ (0.4 mL) for 24 h under N₂. [b] Determined by ¹H NMR analysis. [c] Conducted for 96 h. [d] Conducted for 120 h.



Scheme 7. A proposed reaction mechanism.

Based on the experimental results, we propose a reaction mechanism as illustrated in Scheme 7. A catalytically active Rh complex, which is assumed to be Cp*Rh(OAc)(SbF₆), undergoes the coordination-assisted C–H activation to give a five-membered metallacycle **A**. This step would be reversible and not be involved in the turnover-limiting step according to the control experiment (Scheme 5). Meanwhile, SeO(OAc)₂ is generated along with Ag₂Se as proposed from XAS experiments. In addition, we observed the formation of an *N*-acetylated selenazolone **9** when a primary benzamide **8** was subjected to the standard reaction conditions (Scheme 8), suggesting the formation of Ac₂O as well. These results are consistent with the mass balance depicted in the proposed reaction pathway. The Se(IV) species then coordinates to the Rh complex (**A** → **B**), and formal double nucleophilic substitution at the selenium atom produces the intermediate **D**. The coupling product would be dissociated and further reduced by an extra selenium to afford the target selenazolone.

FULL PAPER



Scheme 8. Attempted selenium annulation with a primary benzamide.

The proposed mechanism was further verified by computational study. Here the structure of reactive Se(IV) species was simplified as formate $\text{SeO}(\text{OCOH})_2$ and *N*-methylbenzamide (**1j**) was employed as the model compound. Dichloromethane was involved as the solvent because its electric permittivity is similar to that of PhCF_3 used for the catalysis. An energy profile relative to a cationic $[\text{Cp}^*\text{Rh}(\text{OAc})(\text{MeCN})]^+$ complex (**intA**) is summarized in Fig. 3. After the coordination of **1j**, the proximal C–H bond is activated via the concerted metalation-deprotonation (CMD) process with an activation barrier of 13.3 kcal/mol (**intB**→**intC**). The AcOH ligand is then replaced by a $\text{SeO}(\text{OCOH})_2$ molecule to form **intD**.²⁶ Nucleophilic attack of the arylrhodium species to the selenium atom is triggered to give **intE** with an activation barrier of 4.5 kcal/mol (**tsDE**). Deprotonation of the amide moiety (**intE**→**intF**) and the subsequent intramolecular substitution (**intF**→**intG**) deliver the annulated intermediate. The second nucleophilic addition is assumed to be an essentially barrierless process. Indeed, the N–Se bond is partially formed (2.082 Å) and the Se–O bond is considerably elongated (2.100 Å) within **intF**. The largest energy barrier for this reaction profile is 20.6 kcal/mol, which is consistent with the fact that the reaction proceeded even at 40 °C (see the Supporting Information).

Conclusion

In conclusion, we have developed an effective Rh(III)-catalyzed C–H oxidative selenation of benzamides with stable and tractable elemental selenium, and various 1,2-benzoisoselenazol-3(2H)-ones of potent interest in medicinal chemistry have been obtained through this protocol in good yields. By demonstrating a gram-scale reaction and the diverse elaborations of a representative product, potential synthetic utility of the methodology has been proved. We also have proposed a novel catalytic cycle involving an electrophilic Se(VI) species as the active selenium donor to the key rhodacycle intermediate formed via C–H activation based on a series of designed control experiments, X-ray absorption spectroscopy, and computational study. This work appears to show a new, significant aspect of organic chalcogen chemistry, and we thereby are developing related catalytic synthetic reactions in our laboratories.

Acknowledgements

This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grants JP 19K15586 and 21K14627 (Grant-in-Aid for Young Scientists) to Y.N., JP 17H06092 (Grant-in-Aid for Specially Promoted Research) to M.M., 20K15279 (Grant-in-Aid for Young Scientists) to Y.U., Mitsubishi Gas Chemical Award in Synthetic Organic Chemistry, Japan to Y.U., and RIKEN-Osaka University Science and Technology Hub

Collaborative Research Program from RIKEN and Osaka University to Y.U. XAS measurements were performed at the BL14B2 of SPring-8 with the approval of the Japan Synchrotron Radiation Research Institute (JASRI) (Proposal No. 2021A1630). We thank Dr. Tetsuo Honma (JASRI) for the support of XAS experiments in SPring-8.

Conflict of Interest

The authors declare no conflict of interest.

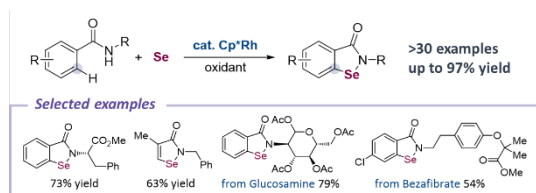
Keywords: rhodium catalysis • C–H functionalization • selenium • benzoisoselesenzolone • annulation

- [1] a) G. Mugesh, W.-W. du Mont, H. Sies, *Chem. Rev.* **2001**, *101*, 2125–2180; b) C. W. Nogueira, G. Zeni, J. B. T. Rocha, *Chem. Rev.* **2004**, *104*, 6255–6286; c) C. W. Nogueira, J. B. T. Rocha, *Arch. Toxicol.* **2011**, *85*, 1313–1359; d) H. Chuai, S.-Q. Zhang, H. Bai, J. Li, Y. Wang, J. Sun, E. Wen, J. Zhang, M. Xin, *Eur. J. Med. Chem.* **2021**, *223*, 113621.
- [2] a) G. Mugesh, W.-W. du Mont, *Chem. - Eur. J.* **2001**, *7*, 1365–1370; b) R. Masuda, R. Kimura, T. Karasaki, S. Sase, K. Goto, *J. Am. Chem. Soc.* **2021**, *143*, 6345–6350.
- [3] a) A. Müller, E. Cadenas, P. Graf, H. Sies, *Biochem. Pharmacol.* **1984**, *33*, 3235–3239; b) M. J. Parnham, H. Sies, *Biochem. Pharmacol.* **2013**, *86*, 1248–1253; c) L. Orian, S. Toppo, *Free Radic. Biol. Med.* **2014**, *66*, 65–74; d) D. Bhowmick, G. Mugesh, *Org. Biomol. Chem.* **2015**, *13*, 10262–10272; e) N. Noguchi, *Arch. Biochem. Biophys.* **2016**, *595*, 109–112; f) N. V. Barbosa, C. W. Nogueira, P. A. Nogueira, A. F. de Bem, M. Aschner, J. B. T. Rocha, *Metallomics* **2017**, *9*, 1703–1734; g) C. Santi, C. Scimmi, L. Sancineto, *Molecules* **2021**, *26*, 4230.
- [4] a) B. K. Sarma, G. Mugesh, *J. Am. Chem. Soc.* **2005**, *127*, 11477–11485; b) K. N. Sands, T. G. Back, *Tetrahedron* **2018**, *74*, 4959–4967.
- [5] a) N. Singh, A. C. Halliday, J. M. Thomas, O. V. Kuznetsova, R. Baldwin, E. C. Y. Woon, P. K. Aley, I. Antoniadou, T. Sharp, S. R. Vasudevan, G. C. Churchill, *Nat. Commun.* **2013**, *4*, 1332; b) F. Mota, T. Sementa, V. Taddei, N. Moses, J. Bordoloi, S. Hader, T. Eykyn, D. Cash, F. Turkheimer, M. Veronese, N. Singh, *Synapse* **2020**, *74*, e22151.
- [6] T. Yamaguchi, K. Sano, K. Takakura, I. Saito, Y. Shinohara, T. Asano, H. Yasuhara, *Stroke* **1998**, *29*, 12–17.
- [7] F. Petronilho, D. Florentino, F. Silvestre, L. G. Danielski, D. Z. Nascimento, A. Vieira, L. A. Kanis, J. J. Fortunato, M. Badawy, T. Barichello, J. Quevedo, *Inflammation* **2015**, *38*, 1394–1400.
- [8] a) H. Zeng, G. F. Combs Jr, *J. Nutr. Biochem.* **2008**, *19*, 1–7; b) J. Yan, Y. Guo, Y. Wang, F. Mao, L. Huang, X. Li, *Eur. J. Med. Chem.* **2015**, *95*, 220–229.
- [9] A. D. Landgraf, A. S. Alseghiani, S. Alaql, S. Thanna, Z. A. Shah, S. J. Sucheck, *ACS Chem. Neurosci.* **2020**, *11*, 3008–3016.
- [10] a) Z. Jin, X. Du, Y. Xu, Y. Deng, M. Liu, Y. Zhao, B. Zhang, X. Li, L. Zhang, C. Peng, Y. Duan, J. Yu, L. Wang, K. Yang, F. Liu, R. Jiang, X. Yang, T. You, X. Liu, X. Yang, F. Bai, H. Liu, X. Liu, L. W. Guddat, W. Xu, G. Xiao, G. Qin, Z. Shi, H. Jiang, Z. Rao, H. Yang, *Nature* **2020**, *582*, 289–293; b) K. Sargsyan, C.-C. Lin, T. Chen, C. Grauffel, Y.-P. Chen, W.-Z. Yang, H. S. Yuan, C. Lim, *Chem. Sci.* **2020**, *11*, 9904–9909; c) H. Sies and M. J. Parnham, *Free Radic. Biol. Med.* **2020**, *156*, 107–112; d) C. Ma, Y. Hu, J. A. Townsend, P. I. Lagarias, M. T. Marty, A. Kolocouris, J. Wang, *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 1265–1277.
- [11] E. Węglarz-Tomczak, M. Burda-Grabowska, M. Giurg, A. Mucha, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5254–5259.
- [12] For selected recent examples, see: a) M. Giurg, A. Gołab, J. Suchodolski, R. Kaleta, A. Krasowska, E. Piasecki, M. Piętko-Ottlik, *Molecules* **2017**, *22*, 974; b) Y. Tang, S. Zhang, Y. Chang, D. Fan, A. De Agostini, L. Zhang and T. Jiang, *J. Med. Chem.* **2018**, *61*, 2937–2948; c) W. B. Jin, C. Xu, Q. Cheng, X. L. Qi, W. Gao, Z. Zheng, E. W. C. Chan, Y.-C. Leung, T. H. Chan, K.-Y. Wong, S. Chen, K.-F. Chan, *Eur. J. Med. Chem.* **2018**, *155*, 285–302; d) A. C. Ruberte, D. Plano, I. Encio, C. Aydllo, A. K. Sharma, C. Sanmartin, *Eur. J. Med. Chem.* **2018**, *157*, 14–27.

- [13] a) L. Engman, *J. Org. Chem.* **1989**, *54*, 2964-2966; b) T.-C. Chang, M.-L. Huang, W.-L. Hsu, J.-M. Hwang, L.-Y. Hsu, *Chem. Pharm. Bull.* **2003**, *51*, 1413-1416; c) S. S. Zade, S. Panda, H. B. Singh, G. Wolmershäuser, *Tetrahedron Lett.* **2005**, *46*, 665-669.
- [14] a) S. J. Balkrishna, B. S. Bhakuni, D. Chopra, S. Kumar, *Org. Lett.* **2010**, *12*, 5394-5397; b) S. J. Balkrishna, B. S. Bhakuni, S. Kumar, *Tetrahedron* **2011**, *67*, 9565-9575; c) S. J. Balkrishna, S. Kumar, G. K. Azad, B. S. Bhakuni, P. Panini, N. Ahalawat, R. S. Tomar, M. R. Dettly, S. Kumar, *Org. Biomol. Chem.* **2014**, *12*, 1215-1219.
- [15] S. Thanna, C. M. Goins, S. E. Knudson, R. A. Slayden, D. R. Ronning, S. J. Sucheck, *J. Org. Chem.* **2017**, *82*, 3844-3854.
- [16] A. J. Pacula, J. Ścianowski, K. B. Aleksandrak, *RSC Adv.* **2014**, *4*, 48959-48962.
- [17] a) M. C. Fong and C. H. Schiesser, *J. Org. Chem.* **1997**, *62*, 3103-3108; b) S. S. Zade, S. Panda, S. K. Tripathi, H. B. Singh, G. Wolmershäuser, *Eur. J. Org. Chem.* **2004**, 3857-3864; c) B. K. Sarma, G. Mugesh, *Chem. - Eur. J.* **2008**, *14*, 10603-10614.
- [18] For selected recent reviews on C-H functionalization, see: a) C. Sambiagio, D. Schönbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. A. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603-6743; b) S. Rej, N. Chatani, *Angew. Chem. Int. Ed.* **2019**, *58*, 8304-8329; *Angew. Chem.* **2019**, *131*, 8390-8416; c) D. Chandra, A. K. Dhiman, D. Parmar, U. Sharma, *Catal. Rev.* **2020** (doi: 10.1080/01614940.2020.1839849); d) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788-1887; e) S. Nunewar, S. Kumar, S. Talakola, S. Nanduri, V. Kanchupalli, *Chem. Asian J.* **2021**, *16*, 443-459.
- [19] M. Iwasaki, N. Miki, Y. Tsuchiya, K. Nakajima, Y. Nishihara, *Org. Lett.* **2017**, *19*, 1092-1095.
- [20] For related examples with elemental sulfur, see: a) F. J. Chen, G. Liao, X. Li, J. Wu, B.-F. Shi, *Org. Lett.* **2014**, *16*, 5644-5647; b) J.-R. Guo, J.-F. Gong, M.-P. Song, *Org. Biomol. Chem.* **2019**, *17*, 5029-5037.
- [21] a) S. Moon, M. Kato, Y. Nishii, M. Miura, *Adv. Synth. Catal.* **2020**, *362*, 1669-1673; b) S. Moon, Y. Nishii, M. Miura, *Org. Lett.* **2021**, *23*, 49-53.
- [22] A possible reason for this is the byproduct formation. Ebselen derivatives may act as electrophilic selenium reagents under the catalytic conditions (for example, see: H. Xu, Y. Gu, S. Zhang, H. Xiong, F. Ma, F. Lu, Q. Ji, L. Liu, P. Ma, W. Hou, G. Yang, R. A. Lerner, *Angew. Chem. Int. Ed.* **2020**, *59*, 13273-13280; *Angew. Chem.* **2020**, *132*, 13375-13382). The primary product i.e., Ebselen would be coupled with another *N*-phenylbenzamide molecule to give a diaryselenide derivative.
- [23] Z. Zhang, S. Ren, S. Wan, W. Li, T. Jiang, *Synth. Commun.* **2010**, *40*, 3438-3446.
- [24] J. He, D. Li, K. Xiong, Y. Ge, H. Jin, G. Zhang, M. Hong, Y. Tian, J. Yin, H. Zeng, *Bioorg. Med. Chem.* **2012**, *20*, 3816-3827.
- [25] a) B. Gates, B. Mayers, Y. Wu, Y. Sun, B. Cattle, P. Yang, Y. Xia, *Adv. Funct. Mater.* **2002**, *12*, 679-686; b) Y. Jiang, B. Xie, J. Wu, S. Yuan, Y. Wu, H. Huang, Y. Qian, *J. Solid State Chem.* **2002**, *167*, 28-33.
- [26] A. L. Ryser, D. G. Strawn, M. A. Marcus, J. L. Johnson-Maynard, M. E. Gunter, G. Möller, *Geochem. Trans.* **2005**, *6*, 1.
- [27] C. Weilbeer, D. Selent, K. M. Dyballa, R. Franke, A. Spannenberg, A. Börner, *ChemistrySelect* **2016**, *1*, 5421-5429.

Entry for the Table of Contents

Insert graphic for Table of Contents here. ((Please ensure your graphic is in **one** of following formats))



A Rh(III)-catalyzed direct selenium annulation using stable and tractable elemental selenium is developed. A series of benzamides as well as acrylamides were successfully coupled with selenium under mild reaction conditions to give isoselenazolone derivatives. An unprecedented selenation mechanism involving an electrophilic Se(IV) species as the reactive selenium donor is proposed based on the designed control experiments, X-ray absorption spectroscopy, and computational study.

Institute and/or researcher Twitter usernames: ((optional))