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Citation	Organic Letters. 2021, 23(1), p. 49-53
Version Type	AM
URL	https://hdl.handle.net/11094/92812
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Synthesis of Isothiazoles and Isoselenazoles through Rhodium-Catalyzed Oxidative Annulation with Elemental Sulfur and Selenium

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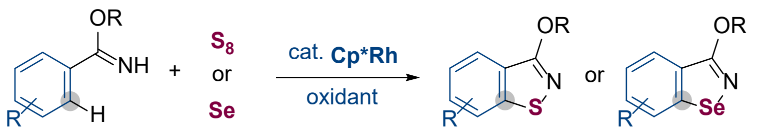
Supporting Information Placeholder



ABSTRACT: A rhodium-catalyzed oxidative annulation of benzimidates with elemental sulfur for the direct construction of isothiazole rings is reported. The proposed reaction mechanism involving Rh(I)/Rh(III) redox is supported by a stoichiometric reaction of metallacycle species as well as DFT calculations. This method is also applicable to the selenium cyclization to produce isoselenazole derivatives. The alkoxy substituent at the C3 position can be used for further functionalization of the azole cores.

Heteroaromatic compounds containing sulfur or selenium atoms constitute the core structures of many functional organic materials and biologically active compounds.[1] In particular, benzisothiazole derivatives have been of vital use in a series of antipsychotic medicines such as tiospirone, ziprasidone, perospirone, and lurasidone.[2] Additionally, oxidized and alkylated analogues of benzisothiazoles occupy an important position for pharmaceutical and agrochemical applications (Figure 1). Ebselen (2-phenyl-1,2-benzoselenazol-3-one) is a well-known oxidized selenium variant with multiple medical uses.[3] It is notable that this molecule exhibits promising inhibitory activity against COVID-19 protease.[4]

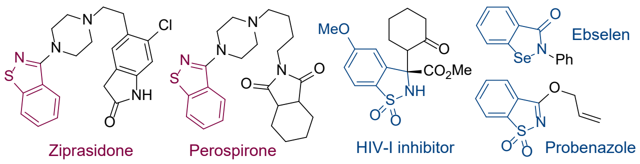
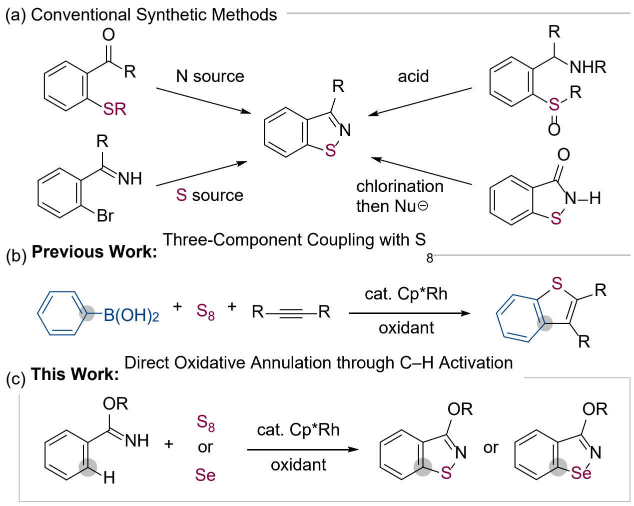


Figure 1. Representative examples of benzisothiazole (benzisoselenazole) derivatives in bioactive compounds.

Conventional synthetic methods for benzisothiazoles involve the cyclization of ortho-disubstituted benzene derivatives,[1,5] which would be prepared via cumbersome multi-step processes (Scheme 1a). The structural diversity in the cyclized products is thus considerably limited by the availability of these precursors, and a similar issue should be addressed for the synthesis of selenium analogues. Moreover, the handling difficulty of organosulfur and organoselenium compounds is usually problematic in practical use. Elemental sulfur (also known as S_8) has been one of the most important raw materials of the modern chemical production due to its low cost and user-friendly nature (stable, non-volatile, non-hygroscopic, non-toxic, and non-odorous). A number of C–S bond forming reactions have been established exploiting this as the sulfur source.[6,7]

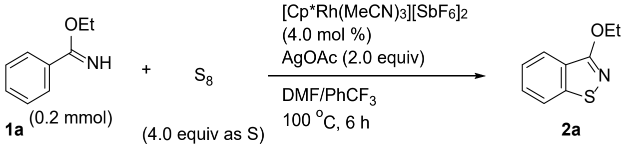
Scheme 1. Representative Synthetic Methods for Isothiazoles



In contrast, the utility of S_8 in direct C−H functionalization[8] has rarely been explored despite the fact that atom transfer of S, Se, and Te from elemental chalcogenides into the metal-carbon bond of Ni(II) metallacycle species has been known for more than 20 years.[9] In 2014, Shi reported a Cu-mediated benzoisothiazolone synthesis using the (pyridin-2-yl)isopropylamine (PIP-amine) bidentate directing group.[10] Recently, Gong and Song developed a catalytic variant of this using Ni with the aid of 2-amino alkylbenzimidazole (MBIP-amine) directing group.[11] As a related example of the selenium annulation, Nishihara achieved a Ni-catalyzed synthesis of benzoisoselenazolones adopting 8-quinolyl auxiliary.[12] We have previously achieved the synthesis of benzo[*b*]thiophenes through a Rh-catalyzed three-component coupling reaction of arylboronic acids, alkynes, and S_8 (Scheme 1b).[13,14] To the best of our knowledge, only these four reports successfully utilized the elemental chalcogenides to the C–H activation strategy. Upon our continuous research interest in this field, we envisioned utilizing this sulfur annulation protocol to the concise assembly of isothiazole derivatives, and herein report a direct oxidative annulation of imidates with elemental sulfur and selenium (Scheme 1c).

Our initial study was conducted to optimize the reaction conditions adopting ethyl benzimidate (**1a**) as a representative substrate (Table 1). To our delight, the desired product **2a** was obtained in 81% yield under the standard conditions using sulfur powder (4.0 equiv as S), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ catalyst (Cp* = pentamethylcyclopentadienyl), and AgOAc oxidant in $DMF/PhCF_3$ solvent (entry 1). No competing polysulfide formation was observed. The reaction did not proceed without the catalyst (entry 2). A chloride complex $[Cp^*RhCl_2]_2$ was moderately productive (entry 3), whereas an analogous cobalt complex was totally inactive even in the presence of $AgSbF_6$ as an anion source (entry 4). A ruthenium complex [Ru(*p*-cymene)$Cl_2]_2$ was also not an active catalyst (entry 5). The product yield significantly dropped when $Cu(OAc)_2$ was used as the oxidant instead of AgOAc (entry 6). The amount of sulfur could be reduced to 2.0 equiv (entry 7) but the yield varied somewhat (66~97%). Thus, 3.0 equiv of sulfur was preferred to be used for the sake of better reproducibility (see Schemes 2 and 3). After further optimization, the target product was obtained in 94% isolated yield employing $PhCF_3$ solely as the solvent (entry 8), whereas DMF was not a suitable solvent (entry 9). This reaction could be conducted in 2.0 mmol scale to give **2a** in 70% isolated yield (Scheme 2).

Table1. Optimization Study [a]

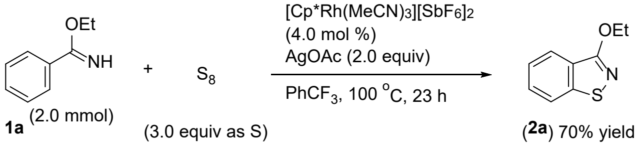


entry	deviation from the standard conditions	yield [b]
1	--	81%
2	without catalyst	n.d.
3	$[Cp^*RhCl_2]_2$ (2.0 mol%) catalyst	51%
4	$Cp^*Co(CO)I_2$ (4.0 mol%) catalyst with $AgSbF_6$ (10 mol%)	n.d.
5	[Ru(*p*-cymene)$Cl_2]_2$ (8.0 mol%) catalyst	trace
6	$Cu(OAc)_2$ (1.0 equiv) instead of AgOAc	7%
7	S (2.0 equiv), average of 3 runs	81%
8	$PhCF_3$ solvent, S (2.0 equiv)	94% (94%)
9	DMF solvent, S (2.0 equiv)	trace

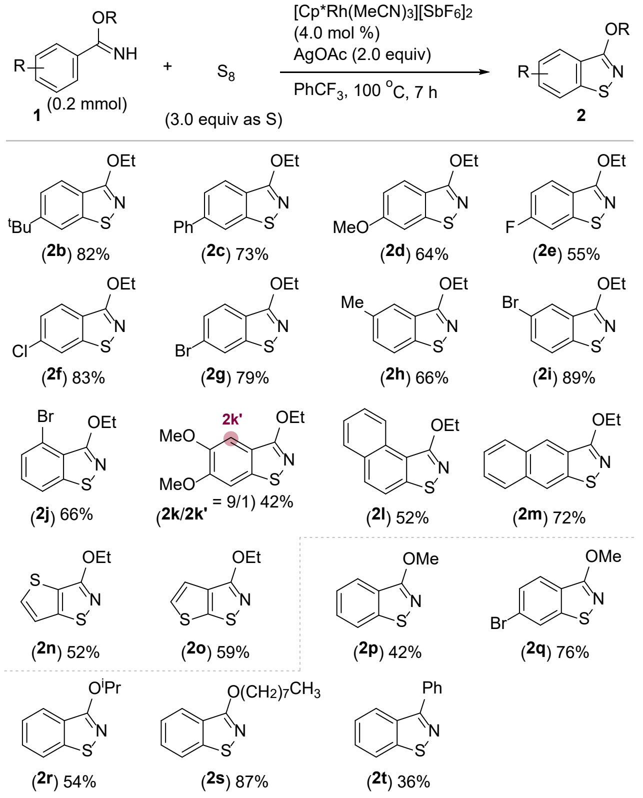
[a] Standard conditions: **1a** (0.2 mmol), S_8 (0.8 mmol as S), AgOAc (0.4 mmol), and $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4.0 mol %) in solvent (DMF 0.1 mL + $PhCF_3$ 0.2 mL). [b] Determined by NMR analysis. Isolated yield is in parentheses. n.d. = Not detected.

Under the optimized reaction conditions, the scope of imidate derivatives was then evaluated (Scheme 3). This protocol was applicable to a series of benzimidates bearing a substituent at the para (**1b**–**1g**), meta (**1h**, **1i**), and ortho (**1j**) positions, producing the corresponding benzisothiazoles in moderate to high yields. For the reaction of meta-substituted substrates, the C–H bond at a sterically more accessible site was preferentially activated to give C5-functionalized products. It is notable that the bromo group (**1g**, **1i**, **1j**), which is hardly tolerate in conventional synthetic methods, remained intact under the present conditions. This is highly beneficial for the post-functionalization of the benzisothiazole scaffold. 3,4-Dimethoxyimidate **1k** afforded a mixture of two isomers (**2k**+**2k'**), whereas naphthyl imidates **1l** and **1m** gave **2l** and **2m**, respectively, as single isomers. The present method was suitable for the reaction of thienyl imidates **1n** and **1o** to give the corresponding products in moderate yields. Additionally, we examined the effect of substituents at the imine carbon. Benzimidates with methyl (**1p**,**1q**), isopropyl (**1r**), and *n*-octyl (**1s**) groups at the oxygen atom were also applicable to the reaction, whereas benzophenone imine (**1t**) was less productive because of the competing hydrolysis. Unfortunately, benzamidine derivatives were not applicable to the present reaction system (not shown).

Scheme 2. A Scale-Up Reaction



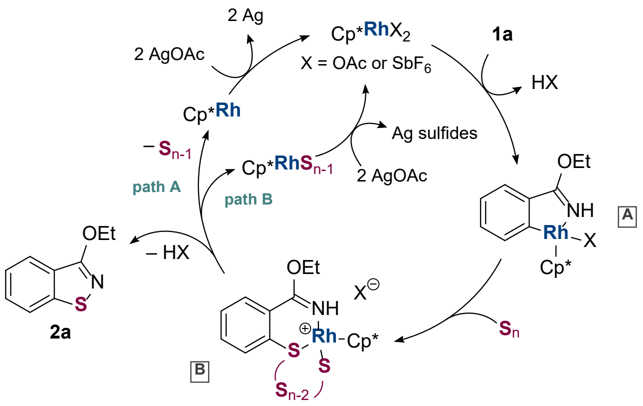
Scheme 3. Substrate Scope [a]



[a] Reaction conditions: **1** (0.2 mmol), S_8 (0.6 mmol as S), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (4.0 mol %), and Ag_2O (0.4 mmol) in $PhCF_3$ (0.3 mL).

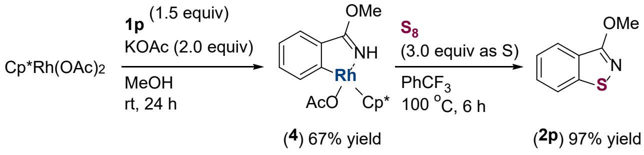
A proposed mechanism of the oxidative annulation is illustrated in Scheme 4. A catalytically active Rh(III) species, assumed to be $Cp^*Rh(OAc)(SbF_6)$, undergoes coordination-assisted C–H activation to afford a five-membered metallacycle **A**. This step would not be rate limiting because no obvious KIE was detected (see the Supporting Information). Insertion of a sulfur atom into the Rh−C bond of the intermediate is effected to form a cationic six-membered complex **B**. The coupling product would be liberated through the N−S reductive elimination and deprotonation, giving Cp*Rh(I) complex (path A) or Cp*Rh(III) sulfide species (path B). The active Rh(III) species is then regenerated through the oxidation (path A) or anion exchange (path B) with AgOAc, closing the catalytic cycle.

Scheme 4. Proposed Reaction Mechanism



Although the mechanistic detail for the sulfur atom migration into metallacycle species has not been established, this process would be experimentally supported by a stoichiometric reaction (Scheme 5). We prepared a Rh complex **4** according to the literature procedure,[15] which is structurally relevant to the proposed reaction intermediate, and treated it with elemental sulfur in $PhCF_3$ solvent. As expected, **2p** was obtained in 97% yield. This result suggested that the silver salt did not participate in the sulfur insertion and the reductive elimination steps, ruling out the occurrence of higher valent Rh(IV) or Rh(V) species within the reaction mechanism.[15,16]

Scheme 5. Preparation and a Stoichiometric Reaction of Rhodacycle Complex **4** with Elemental Sulfur



To gain further insight into the mechanism, we conducted a computational study adopting **1p** as a model compound.[17] Here the composition of elemental sulfur was assumed to be a cyclic S_8 molecule,[18] and dichloromethane (DCM) was employed as the solvent because of its similar electric permittivity value to $PhCF_3$. Figure 2 displays an energy profile relative to a cationic $[Cp^*Rh(OAc)(MeCN)]^+$ complex (**intA**). After the coordination of **1p**, the C–H activation step was calculated as a CMD (concerted metalation-deprotonation) process to output an activation barrier of 19.6 (18.3) kcal/mol (**intB**–**intC**). The AcOH ligand is then replaced by an S_8 molecule to give **intD**. Subsequently, a sulfur atom directly bound to the metal inserts into the Rh–C linkage with an energy barrier of 26.4 (27.2) kcal/mol (**intD**–**intE**). It is noteworthy that the coordinated sulfur atom within **intD** carries a positive APT charge of +0.427, thereby facilitating the nucleophilic attack of the aryl-rhodium species onto it.[19] A negative charge of -1.096 at the “leaving” sulfur atom within **tsDE** also indicates that this process can be seen as an S_N2-type reaction (Figure 3). Unfortunately, all attempts to optimize the transition state structure for the N–S reductive elimination were not successful due to the flexible conformational change of the sulfur chain.

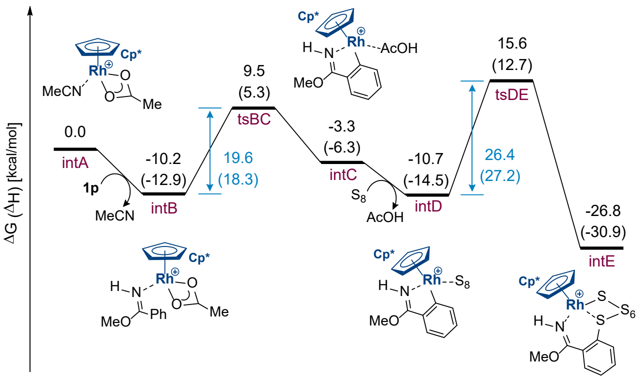


Figure 2. Partial Gibbs free energy profile of the reaction. Values in parentheses are relative enthalpies conducted at the ωB97X-D/6-311+G(d,p)&SDD/PCM(CH_2Cl_2)//ωB97X-D/6-31G+(d,p)&LanL2DZ level.

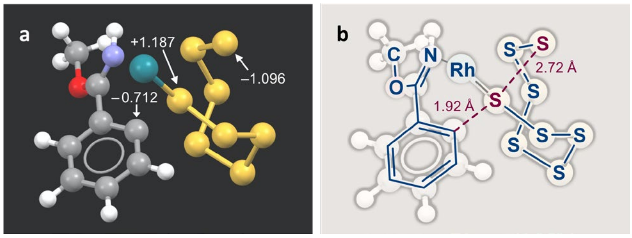


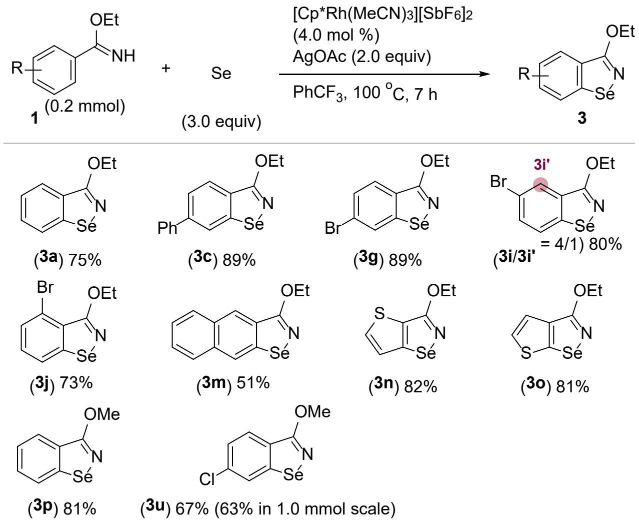
Figure 3. (a) An optimized molecular geometry of the transition state **tsDE** with APT charges: carbon (gray), hydrogen (white), oxygen (red), sulfur (yellow), and rhodium (green). (b) The atom labeling with selected bond lengths. The Cp* ligand was omitted for the sake of clarity.

To our delight, the present method was applicable to the synthesis of isoselenazoles using elemental selenium (Scheme 6). Upon treatment with 3.0 equiv of selenium powder under the standard conditions, imidate **1a** was successfully converted to the desired product **3a** in 75% yield. Para-substituted imidates (**1c**, **1g**) also reacted smoothly. The selenium cyclization exhibited lower regioselectivity as the meta-Br imidate **1i** afforded a mixture of two isomers (**3i**+**3i’**). Imidates bearing ortho-substituent (**1j**), naphtyl ring (**1m**), and thiophene ring (**1n**, **1o**) were applicable as well, producing the corresponding isoselenazoles in high yields. Analogous methoxy imidates **1p** and **1u** were also productive, and the reaction of **1u** could be conducted in 1.0 mmol scale.

Finally, we examined the derivatization of coupling products to highlight the synthetic utility of the developed method (Scheme 7). The alkoxy group at the C3 position of **2a** was a suitable leaving group for the direct substitution with a lithium amide reagent, and the corresponding 3-aminoisothiazole **5** was obtained quantitatively. In addition, hydrolysis of **3u** under acidic conditions afforded an isoselenazolone **6** in 70% yield. This compound would be a useful synthetic intermediate for a series of C3-substituted isoselenazoles as well as ebselen derivatives.[20]

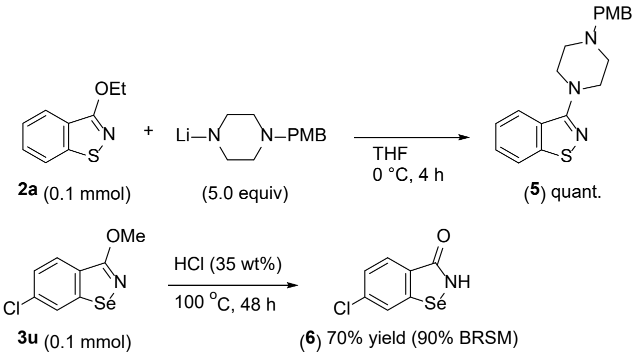
In conclusion, we have developed a Cp*Rh-catalyzed oxidative annulation adopting elemental sulfur/selenium for the direct construction of isothiazole/isoselenazole rings. Considering the easy availability of imidate derivatives, this method is particularly useful for the synthesis of these heterocycles bearing functionalities at the benzene fragment. The proposed catalytic mechanism involving Rh(I)/Rh(III) redox system was supported by a stoichiometric reaction of metallacycle species as well as DFT calculations. Further synthetic application of S_8 under the Rh catalysis is currently studied in our group.

Scheme 6. Direct Annulation with Elemental Selenium [a]



[a] Reaction conditions: **1** (0.2 mmol), Se (0.6 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (4.0 mol %), and AgOAc (0.4 mmol) in $PhCF_3$ (0.3 mL).

Scheme 7. Derivatization of Coupling Products



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

- Experimental procedures, computational method, product identification data, and copy of NMR spectra (PDF)
- Atomic coordinates of all calculated molecules (XYZ)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant No. JP 19K15586 (Grant-in-Aid for Young Scientists) to Y.N. and JP 17H06092 (Grant-in-Aid for Specially Promoted Research) to M.M. The authors thank Dr. Hiroaki Iwamoto (Osaka University) for his assistance with DFT calculations.

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