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Communication

Preparation of selenofunctionalized heterocycles *via* iodosobenzene-mediated intramolecular selenocyclizations of olefins with diselenides

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ABSTRACT

An intramolecular selenocyclizations of olefins mediated by a commercially available hypervalent iodine (III) reagent, PhIO, was developed. This method provided access to a wide range of selenenylated heterocycles under ambient conditions. The striking advantages of this protocol over all previous methods include mild reaction conditions, easy operation, good yields, high levels of functional group compatibility, large-scale application and suitability for the late-stage functionalization of complex molecules of biological importance.

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Selenenylated molecules have widespread applications in the fields of pharmaceuticals and materials science because of their interesting biological activities [1] and suitable fluorescence properties [2]. Furthermore, organoselenium compounds have been widely used as convenient intermediates or reagents and catalysts in organic synthesis [3]. Thus, significant efforts have been made to develop various strategies for the incorporation of selenium functional groups into organic molecules [4].

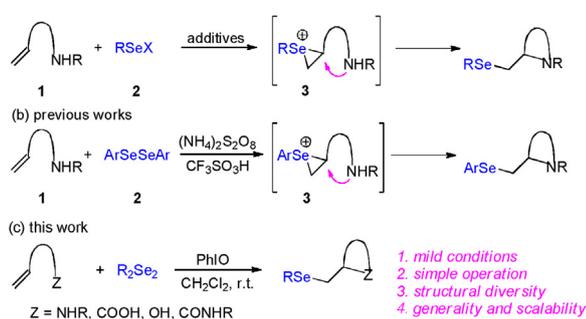
On the other hand, the difunctionalization of readily accessible alkenes has become a powerful tool for the construction of highly functionalized skeletons in organic synthesis [5]. In this context, selenocyclizations of unsaturated amines are a useful concept for the preparation of selenenylated and nitrogenated heterocycles, which could provide an excellent opportunity for medicinal chemists in drug discovery. Additionally, the simultaneous incorporation of synthetically versatile seleno and nitro moieties has enabled further elaboration of these products as intermediates in syntheses of structurally diverse molecules. Accordingly, over the years, substantial efforts have been devoted to advance this topic, and numerous elegant procedures have been developed as a result. Early reports on these reactions usually involved electrophilic selenium species-induced cyclizations with organoselenium

reagents, e.g., phenylselenenyl halides have been reported with olefinic amines [6], (sulfon)amides [7], oximes [8], thiazolines [9], carbamates [10], imines [11], imidates [12], hydrazines [13] and hydrazine [14] (Scheme 1a). Typically, this selenoamination of olefins occurs *via* intramolecular nucleophilic attack onto seleniranium ion **3** to form nitrogen-containing heterocycles with the aid of additives, such as Lewis acids [8a], Brønsted acids [7a,13], or silica gel [7e,10b–10e]. However, the presence of nucleophilic halides often causes some undesirable processes, such as the incorporation of halogens, which decrease the selectivity [15]. Additionally, the addition adducts sometimes can further react with phenylselenenyl halides to afford the deselenenylated products [16]. Furthermore, these procedures are usually incompatible with a large number of important functional groups due to the formation of hydrogen halide as a side-product during the course of the reaction.

Diselenide is preferable as an alternative selenylation agent in this transformation because it is bench-stable, readily available and easy to handle during the synthesis process. For example, Tiecco *et al.* reported the reaction of unsaturated amines with phenylselenenyl sulfate, generated from the oxidation of diphenyl diselenide with ammonium persulfate in the presence of trifluoromethanesulfonic acid, to afford phenylseleno-substituted *N*-heterocyclics (Scheme 1b) [17]. Again, these cyclization reactions were carried out in acidic conditions, and substrates bearing acid-sensitive functional group, such as silyl ethers or ketones, were not tolerated under these reaction conditions.

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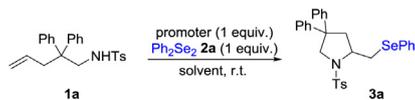


Scheme 1. Intramolecular selenoamination.

Despite these advances, general methods for the preparation of various arylselenopyrrolidines and alkylselenopyrrolidines in particular are still limited. Our goal was to develop an efficient and operationally simple selenoamination, in which readily available, inexpensive, and easy-to-handle reagents were employed. In continuation of our interest in hypervalent iodine chemistry [18], we conjectured that diselenides would be oxidized in the presence of a commercially available hypervalent iodine(III) reagent to form electrophilic selenium species (RSe^+), which would participate in the electrophilic selenocyclization of olefins (Scheme 1c).

We started our investigation with the optimization of the reaction conditions using *N*-(2,2-diphenylpent-4-en-1-yl)-4-methylbenzenesulfonamide (**1a**) as a model substrate due to its ease of preparation and UV-absorption property, which facilitates the monitoring of the reaction progress. The preliminary results are summarized in Table 1.

Based on our previous results [18a], we first employed iodine pentoxide (I_2O_5) as reaction promoter and diphenyl diselenide (Ph_2Se_2) (**2a**) as selenium source. However, only a trace amount of selenoamination product **3a** was obtained (Table 1, entry 1). Other promoters, such as oxone, $K_2S_2O_8$, O_2 , $PhI(OAc)_2$ and PhIO were tested to further improve the yield, and PhIO produced the best result (entries 2–6). The effect of the solvents on the course of the reaction was also noteworthy (entries 7–10), and CH_2Cl_2 was the most suitable solvent for the reaction. Decreasing the amount of Ph_2Se_2 to 0.5 equiv. led to a decrease in the conversion (entry 11). Control experiments indicated that PhIO played an important role

Table 1
Optimization of the reaction conditions.^a

Entry	Promoter	Solvent	Yield (%) ^b
1	I_2O_5	CH_2Cl_2	trace
2	oxone	CH_2Cl_2	80
3	$K_2S_2O_8$	CH_2Cl_2	43
4	O_2	CH_2Cl_2	NR
5	$PhI(OAc)_2$	CH_2Cl_2	85
6	PhIO	CH_2Cl_2	91
7	PhIO	hexane	46
8	PhIO	MeOH	53
9	PhIO	DMF	63
10	PhIO	DMSO	31
11 ^c	PhIO	CH_2Cl_2	44
12		CH_2Cl_2	–

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), promoter (0.2 mmol), solvent (2 mL), r.t., 20 h.

^b Isolated yields.

^c 0.1 mmol of **2a** was used.

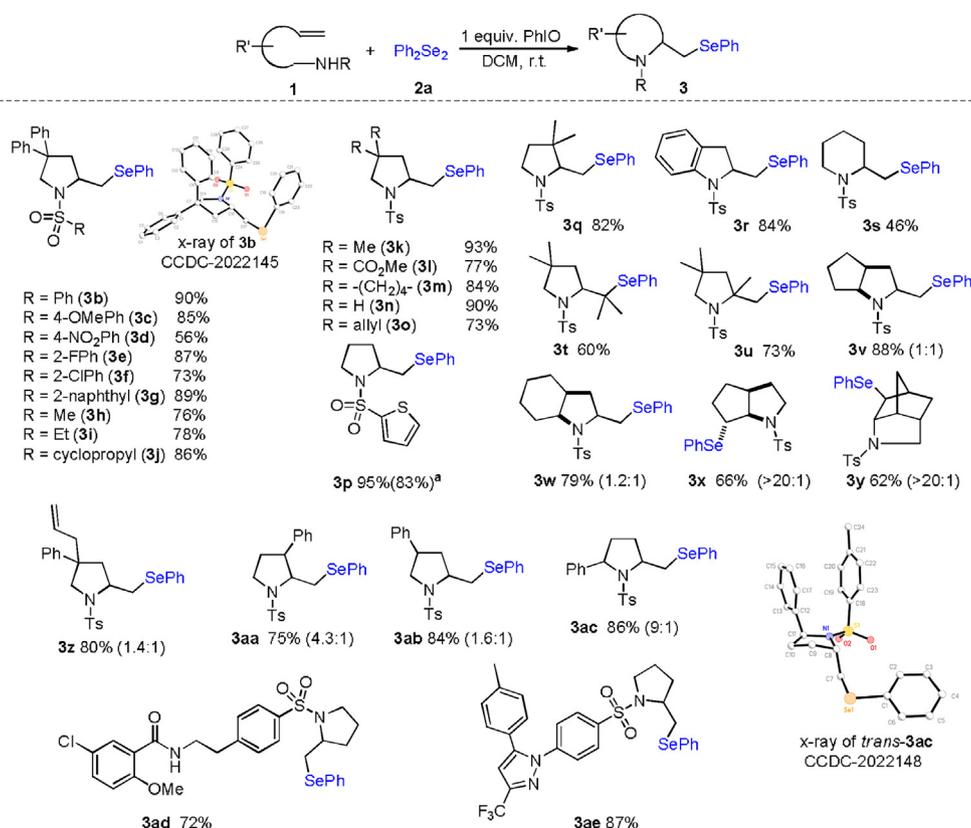
in this transformation, as no reaction occurred in the absence of PhIO (entry 12).

With these optimized reaction conditions, we turned our attention to investigating the substrate scope of the title transformation with a diverse range of *N*-alkenyl sulfonamides using **2a** as the selenium source. As indicated in Scheme 2, both *N*-aryl and *N*-alkylsulfonamides produced the corresponding 2-phenylselenomethylpyrrolidines with good to excellent isolated yields (**3b–3j**). The structural skeleton of 2-phenylselenomethylpyrrolidine was confirmed by an X-ray diffraction experiment performed with compound **3b** (CCDC: 2022145). As shown in the ORTEP drawing, **3b** bore an envelope chair conformation with two phenyl groups at both axial and equatorial positions, the phenyl-seleno moiety and Ts group also stayed at equatorial positions. Notably, *p*-nitrobenzenesulfonamide resulted in the corresponding pyrrolidine derivative **3d** with moderate yield. This is most likely because of the low nucleophilicity of sulfonamide caused by the strong electron-withdrawing nitro group at the *para* position of the benzene ring. Reactions of substrates bearing different substituents on the main chain proceeded well to produce their corresponding products **3k–3q** with good yields. It is noteworthy that the Thorpe–Ingold effect was not required in the current cyclization, and selenoaminated products **3n** and **3p** were isolated with 90% and 95% yields, respectively.

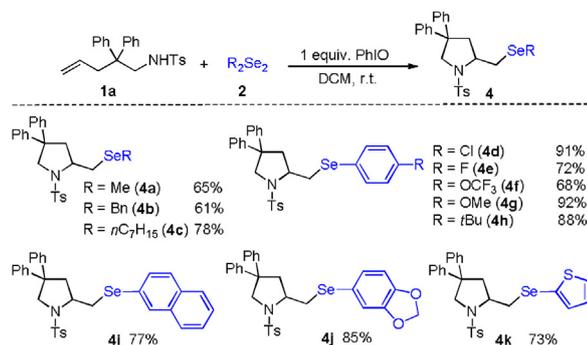
Importantly, the protocol of the present reaction was very simple: the alkene, PhIO and diselenide were stirred in simple glassware under ambient conditions. Thus, this reaction could be applied to a large-scale synthesis without any difficulties. For instance, when the reaction of **1p** (1.16 g, 5 mmol) was performed with Ph_2Se_2 (1.56 g, 5 mmol) and PhIO (1.10 g, 5 mmol) under the optimized reaction conditions, the desired product **3p** was obtained with 83% yield (1.60 g) after recrystallization.

N-Tosyl *o*-allyl aniline **1r** worked well in this transformation, and the corresponding indoline **3r** was obtained with good yield. Reaction of 1-sulfonamido-5-hexene substrate gave lower isolated yield of seleno piperidine (**3s**), although a lower yield was obtained, possibly due to unfavorable entropy of the current cyclization [19]. Substituents on the C=C double bonds showed a low impact on the reaction. Di- and trisubstituted terminal alkenes, such as **1t** and **1u**, were efficiently converted into their corresponding pyrrolidines with satisfactory yields. More complex bicyclic and bridged ring systems were also accessible using this protocol (**3v–3y**). The relative configuration of the phenylseleno unit and amino group in **3x** and **3y** was assigned to *trans*, as expected for a selenoamination via an intermediate seleniranium ion. The desymmetrization of diene **1z** delivered seleno-pyrrolidine **3z** with 80% yield as a mixture of diastereomers. Substrates bearing one substitute on the main chain also underwent high cyclization to produce the corresponding pyrrolidines **3aa–3ac** with a good isolated yield but low diastereoselectivity. The resulting disubstituted pyrrolidines can serve as useful precursors for the synthesis of biological hexahydro-1*H*-pyrrolizines and octahydroindolizines [20]. The relative stereochemistry of *trans*-**3ac** was established by an X-ray diffraction experiment (CCDC: 2022148). Finally, we further applied this methodology to architecturally complex sulfonamide substrates. In this regard, a glibenclamide precursor-derived sulfonamide smoothly engaged in this selenoamination and afforded acceptable yields of **3ad**. The sulfonamide **1ae** derived from celecoxib, which is a nonsteroidal anti-inflammatory drug, worked well under the standard conditions, delivering the corresponding products **3ae** with good yields.

Next, we examined the generality of this transformation with respect to different diselenides, and the results are summarized in Scheme 3. As depicted in Scheme 3, the dialkyl diselenides were suitable reaction partners under the reaction conditions, and provided



Scheme 2. Scope of the intramolecular selenoamination. Reaction conditions: **1** (0.2 mmol, 1.00 equiv.), **2a** (0.2 mmol, 1.00 equiv.), PhIO (0.2 mmol, 1.00 equiv.), DCM (2 mL), r. t., the numbers in the parentheses are the diastereomeric ratios determined by ¹H NMR. ^a 5 mmol scale.

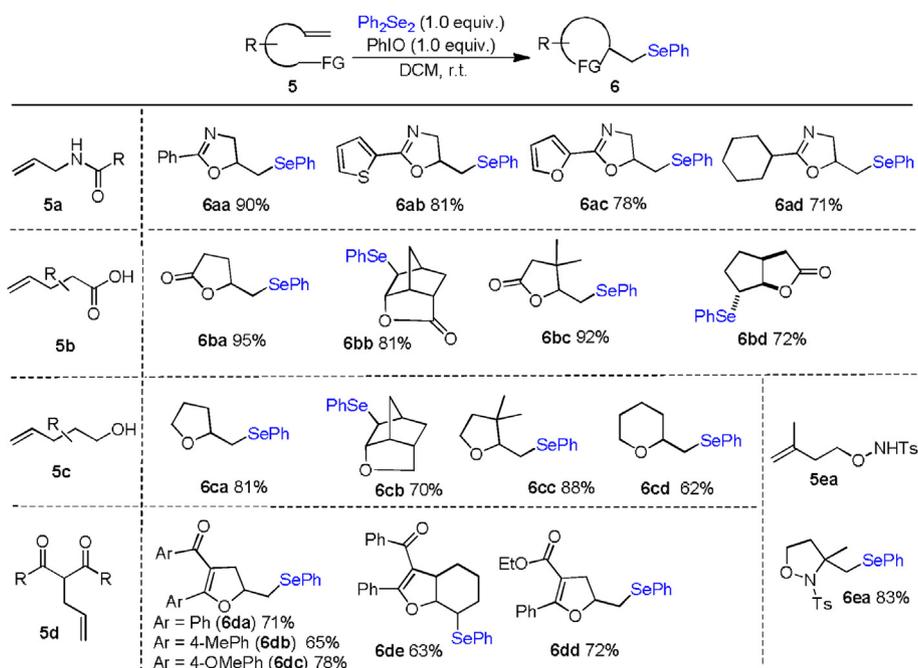


Scheme 3. Scope of diselenides. Reaction conditions: **1a** (0.2 mmol, 1.00 equiv.), **2** (0.2 mmol, 1.00 equiv.), PhIO (0.2 mmol, 1.00 equiv.), DCM (2 mL), r. t.

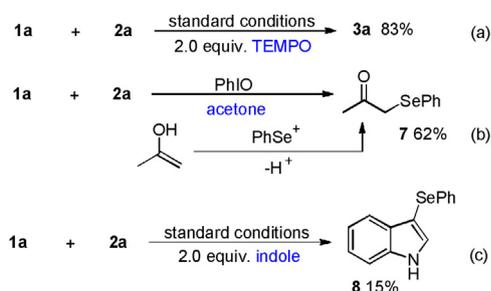
the corresponding products with good yields (**4a–4c**). Thus, this newly developed PhIO-promoted selenoamination provides, for the first time, a feasible way to access alkylselenopyrrolidines. Different diaryl diselenides with an electron-withdrawing group or electron-donating group at the *para* position all showed good reactivity in the procedure (**4d–4h**). Additionally, naphthyl diselenide was successfully reacted with **1a** to produce the respective 2-selenomethylpyrrolidine **4i** with 77% yield. Finally, heteroaryl diselenides, such as dithienyl diselenide were subjected to the procedure, and the selenation product (**4k**) was isolated with 73% yields. Unfortunately, other dichalcogenides, such as diphenyl disulfide (Ph_2S_2) and diphenyl ditelluride (Ph_2Te_2), failed to produce the desired products in this transformation, presumably because Ph_2S_2 and Ph_2Te_2 cannot be oxidized to the corresponding electrophilic species under the present conditions.

In consideration of the remarkably broad substrate scope accessible from this transformation, the current procedure was applied to the preparation of other seleno-containing heterocycles. As shown in **Scheme 4**, a series of seleno oxazolines were produced successfully under optimal conditions (**6aa–6ad**). The generality of the title procedure has also been demonstrated by a series of unsaturated carboxylic acids furnishing the corresponding phenylselenolactones in good yield (**6ba–6bd**). Additionally, using the alkenoic alcohols as substrates, we observed the construction of five- and six-membered cyclic ethers in high yields (**6ca–6cd**). Subsequently, we continued to investigate the generality of this transformation with respect to different olefinic dicarbonyl compounds. As we expected, different seleno dihydrofurans (**6da–6de**) could be obtained in acceptable isolated yields under standard conditions. Finally, preparation of isoxazolidine **6ea** was also possible using *N*-alkenoxy sulfonamide derivative **5ea** as the starting material.

Mechanistic studies were then performed to gain knowledge regarding the reaction pathway. Initially, no dramatic decline in the yield was observed after the addition of 2.0 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the reaction mixture (**Scheme 5a**), which indicated that a radical process likely did not occur. PhIO was insoluble in CH_2Cl_2 because it displays a zigzag polymeric chain structure according to X-ray powder diffraction and EXAFS studies [21]. It, however, could be mostly dissolved when Ph_2Se_2 was added to the CH_2Cl_2 solution (Fig. S1 in Supporting information). This result indicated that PhIO can react with Ph_2Se_2 to generate new reactive species in the current reaction system. This phenomenon was in accordance with NMR observations, which showed that the signal pattern for the aromatic protons of Ph_2Se_2 changed significantly after the addition of PhIO, indicating the mutual interaction between Ph_2Se_2 and



Scheme 4. Selenocyclization of different olefins. Reaction conditions: **5** (0.2 mmol, 1.00 equiv.), Ph_2Se_2 (0.2 mmol, 1.00 equiv.), PhIO (0.2 mmol, 1.00 equiv.), DCM (2 mL), r.t.

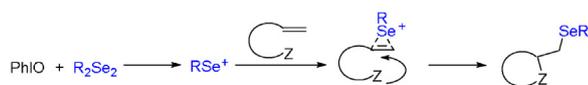


Scheme 5. Experiments for mechanistic studies.

PhIO and, thus, resulting in changes in the electronic environment surrounding the phenyl groups in Ph_2Se_2 (Fig. S2 in Supporting information).

When the reaction was performed in acetone under otherwise identical conditions, α -phenylselenenylated ketone **7** was obtained unexpectedly instead of the selenoamination product (Scheme 5b). Compound **7** was probably a result of an electrophilic attack of the phenylselenenyl cation (PhSe^+) to the enol form of acetone [22]. Furthermore, 2 equiv. of indole was added to the reaction mixture under optimal conditions to capture any possible PhSe^+ formed during the reaction. Indole was employed as a competitive substrate based on the fact that it could be easily selenenylated by PhSe^+ [23]. As expected, indolyl selenide **8** was detected with 15% isolated yield (Scheme 5c).

According to the aforementioned information and previous reports [24], a possible reaction pathway for this transformation is outlined in Scheme 6. First, diselenide is oxidized by PhIO to generate RSe^+ , which serves as a reactive electrophilic intermediate to induce the title selenocyclization.



Scheme 6. Tentative reaction pathway.

In summary, we developed an iodosobenzene-mediated intramolecular selenocyclization of olefins, which produced selenenylated heterocycles with good yields and excellent functional group compatibility. Preliminary mechanistic studies indicate that the title reaction takes place *via* an active electrophilic selenium intermediate generated *in situ* from PhIO and diselenide. We believe that the developed methodology can be applied to potential operational procedures for the synthesis of nitrogen- and selenium-containing molecules due to its good isolated yields, high functional group tolerance, mild conditions and operational simplicity. Efforts are in progress to elucidate the mechanistic details of this reaction by means of DFT-calculations and to disclose its scope and limitations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.cclet.2021.02.050>.

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