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Organoselenium-Catalyzed Synthesis of Oxygen- and Nitrogen-Containing Heterocycles

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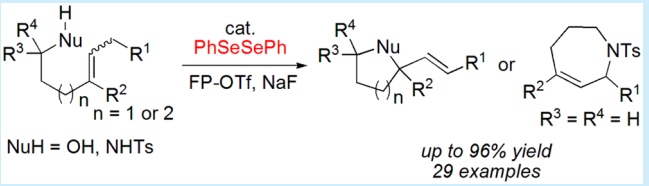
Supporting Information

ABSTRACT: A new and efficient approach for the synthesis of oxygen and nitrogen heterocycles by organoselenium catalysis has been developed. The *exo*-cyclization proceeded smoothly under mild conditions with good functional group tolerance and excellent regioselectivity. Mechanistic studies revealed that 1-fluoropyridinium triflate is key for oxidative cyclization.



For many years, selenium reagents have frequently been applied in organic synthesis.[1] In particular, diselenides, an important class of organoselenium compound, possess unique properties and are readily available. Diselenides as the catalysts or precatalysts have garnered considerable attention in a number of different reactions,[2] e.g., dihydroxylation of alkenes,[3] Baeyer−Villiger oxidation,[4] halogenation,[5] dehydration of aldoximes,[6] amination of alkenes,[7] etc.,[8] due to the mild reaction conditions, good functional group tolerance and excellent regioselectivity. Importantly, some valuable compounds inaccessible by other catalytic methods could be prepared by using catalytic amounts of diselenides. For example, Denmark recently developed an elegant approach to make *syn*-dichlorides with diselenide as the precatalyst.[9] Although some achievements have been made in this area, reactions by using diselenides as the catalysts or precatalysts are not broad, and many others remain unexplored. The study of this area is still in its infancy.

Our group has devoted considerable effort to the development of new and efficient reactions by selenium catalysis,[10] and we noticed that cyclizations with diselenides as the catalysts or precatalysts are rare. In the literature, only some specific heterocycles have been produced. In the 1990s, Tiecco reported synthesis of furans and dihydrofurans with catalytic amounts of diselenide and $(NH_4)_2S_2O_8$ as the oxidant.[11] In these transformations, an electron-withdrawing group such as an ester group had to be installed in the substrates to promote the 5-*endo-trig* cyclizations. Eight years ago, Wirth and coworkers described the cyclization of unsaturated carboxylic acids to afford five- or six-membered intramolecular lactones by a catalytic system PhSeSePh/$PhI(OCOCF_3)_2$.[12] Their methods are efficient for unsaturated carboxylic acid substrates, but they pointed out that the method did not work for cyclizations of γ,δ-unsaturated alcohols at different temperatures in the paper.[12b] Recently, synthesis of isobenzofuranones was demonstrated by Breder using olefinic carboxylic acids as the substrates.[13] Furthermore, we and Breder independently reported synthesis of indole derivatives using catalytic amounts of diselenide and *N*-fluorobenzenesulfonimide (NFSI) as the oxidant.[10c,14] The reported PhSeSePh/NFSI catalytic systems were limited in the synthesis of benzoheterocycles. However, valuable oxygen- and nitrogen-containing heterocycles such as tetrahydrofurans and -pyrans, pyrrolidines, and piperidines have not been synthetically explored with diselenide as the catalyst or precatalyst. The development of an efficient selenium-catalyzed reaction system to prepare them is highly desirable. Herein, we report our discovery that they can be synthesized by a new and efficient catalytic system PhSeSePh/1-fluoropyridinium triflate (FP-OTf)/NaF via *exo-trig* cyclization.

Oxygen- and nitrogen-containing heterocycles exist in a variety of biologically active molecules as well as natural products.[15] Developing new and efficient methods for their synthesis remains a long-standing interest to organic chemists.[16] Cyclization of alkene-tethered nucleophiles, e.g., −OH and −NHTs, as the substrates is a straightforward way to form heterocycles.[17] Thus, we attempted to produce heterocycles by the cyclization with unsaturated alcohol **1a** (E/Z = 4:1) as a model substrate.

The classical oxidants $PhI(OAc)_2$, $PhI(OCOCF_3)_2$, and $(NH_4)_2S_2O_8$ did not result in any desired cyclization product **2a** at room temperature (Table 1, entries 1−3) although they were effective in the synthesis of furans, dihydrofurans,[11] and intramolecular lactones.[12] Only trace amounts of **2a** were generated when the reaction was carried out at 60 °C using $(NH_4)_2S_2O_8$ as the oxidant. The yield improved using a low-cost oxidant hydrogen peroxide−urea adduct (UHP) (Table 1, entry 4). Notably, the use of NFSI as the oxidant selectively furnished the *E*-configured cyclization product **2a** in 59% yield along with the rearrangement product **3a** (Table 1, entry 6). The formation of **3a** was facilitated by HF in the reaction. In this reaction, byproducts other than **3a** were observed.[18] By continuing the search for a more efficient oxidant, FP-OTf

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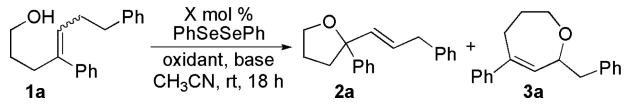
Table 1. Condition Optimization[a]



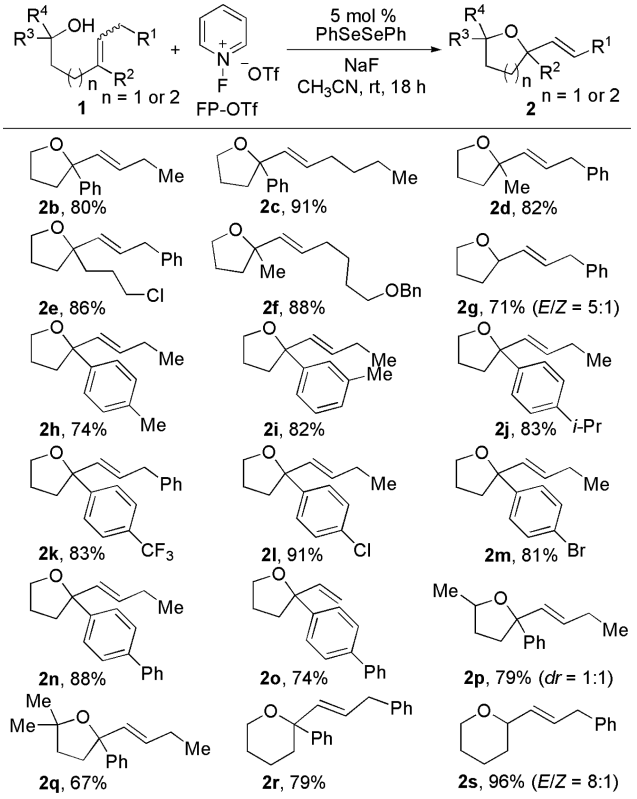
				yield (%)[b]	
entry	X (mol %)	oxidant	base	2a	3a
1	10	$PhI(OAc)_2$	–	–	–
2	10	$PhI(OCOCF_3)_2$	–	–	–
3	10	$(NH_4)_2S_2O_8$	–	–	–
4	10	UHP	–	23	–
5	10	Selectfluor	–	16	–
6	10	NFSI	–	59	19
7	10	FP-OTf	–	64	15
8	10	FP-OTf	NaF	92	–
9	10	FP-OTf	Et_3N	–	–
10	–	FP-OTf	NaF	–	–
11	5	FP-OTf	NaF	92	–
12[c]	5	FP-OTf	NaF	98 (96)	–

[a]Conditions: **1a** (0.1 mmol), oxidant (0.12 mmol), base (1 equiv), CH_3CN (2.0 mL), rt, 18 h. [b]Determined by 400 MHz NMR with 1,3,5-trimethoxybenzene as the internal standard. Isolated yield shown in parentheses. [c]Solvent, 5.0 mL.

resulted in the generation of **2a** in 64% yield (Table 1, entry 7).[19] Due to direct fluorination, only 16% products were formed with Selectfluor as the oxidant (Table 1, entry 5). To eliminate HF in the reaction, the base NaF, an excellent adsorbent of HF, was added. Pleasingly, the yield improved to 92% with FP-OTf (Table 1, entry 8). No seven-membered byproduct **3a** was observed. Other inorganic bases, i.e., Na_2CO_3 and $NaHCO_3$, led to lower yields. Organic base Et_3N inhibited the reaction (Table 1, entry 9). When PhSeSePh was absent or replaced by other chalcogenide catalysts, i.e., PhSePh, BnSeSeBn, and PhSSPh, trace or no desired product was observed (Table 1, entry 10). Product **2a** could eventually be obtained in 96% isolated yield with only 5 mol % catalyst loading (Table 1, entry 12). Importantly, the cyclization proceeded efficiently under mild conditions with the formation of a quaternary center. Additionally, both the *E*- and *Z*-isomers of **1a** were completely converted to the *E*-olefinic tetrahydrofuran.

With the optimal conditions identified, we went on to demonstrate the substrate scope (Scheme 1). The size of the R^1 substituent had little influence on the cyclization. The R^2 substituent could be hydrogen, alkyl, or an aromatic group. Functional groups such as −Cl and −OBn were well tolerated in the cyclization (**2e**, 86%; **2f**, 88%). Interestingly, when R^2 was hydrogen only the *exo*-product (**2g**, *E*/*Z* = 5:1) was formed in 71% yield; the *endo*-cyclization product was not observed. When R^2 were electron-neutral and -deficient aromatic rings, the cyclization proceeded efficiently to produce the desired products (**2h**−**o**, 74−91%). When R^2 were electron-rich aromatic rings, i.e., $(4\text{-MeO})C_6H_4$−, the corresponding tetrahydrofuran products were obtained in low yields and most tetrahydrofuran products were rearranged to **3a** analogues despite of the presence of 1 equiv of NaF. Olefinic secondary and tertiary alcohols underwent cyclization to generate the corresponding products in good yields under similar conditions (**2p**, 79%; **2q**, 67%). Although the diastereoselectivity was poor for **2p**, it was possible to improve it by condition optimization. Furthermore, tetrahydropyran products could be obtained in

Scheme 1. Formation of Tetrahydrofurans and -pyrans from Olefinic Alcohols[a]



[a]Conditions: substrate **1** (0.1 mmol), PhSeSePh (5 mol %), FP-OTf (1.2 equiv), NaF (1 equiv), CH_3CN (5 mL), rt, 18 h.

good to excellent yields by similar cyclization (**2r**, 79%; **2s**, 96%).

This protocol was successfully applied to the cyclization of olefinic sulfonamides. The corresponding five- and six-membered tosyl amines were formed in 54−93% yields (Scheme 2). The reactions were sensitive to solvent and acid. Not only five-membered amines but also their rearrangement products, azepine derivatives, were formed using acetonitrile as the solvent and 1 equiv of base. By simply changing the solvent to 1,2-dichloroethane five-membered amines were generated in the presence of stoichiometric NaF. To afford **5b**, as much as possible, it was essential to replace NaF by $NaHCO_3$. The cyclization reactions using 0.5 equiv of NaF produced seven-membered amines **6a**−**c** in 45−82% yields from the corresponding sulfonamides. The formation of **6a**−**c** can be rationalized via the rearrangement of **5a**−**c**, respectively, facilitated by the HF remaining in the reactions.

When the alcohol **7** was treated with PhSeSePh as the catalyst in the presence of FP-OTf, the hydroxy group selectively added to the double bond to generate tetrahydrofuran **8** (*dr* = 1:1) in 72% yield (Scheme 3).[20] Intriguingly, the protected allylic alcohol moiety was not affected in the cyclization, and no cyclization product was observed where addition of the hydroxyl group to the other double bond had occurred. In contrast, when the alcohol was treated with palladium catalyst, the hydroxy group added to the other double bond to give product **9** (*dr* = 5:1) in almost quantitative yield as one would predict.[21] These results show that selenium catalysis can occur with excellent regioselectivity, in a way complementary to metal catalysis in organic synthesis.

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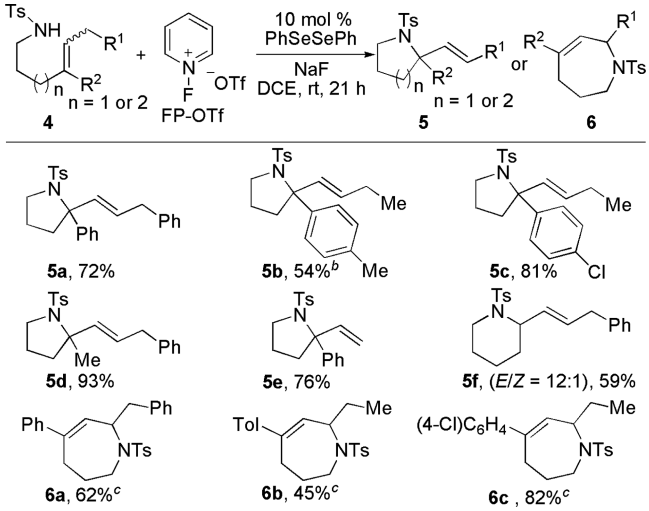
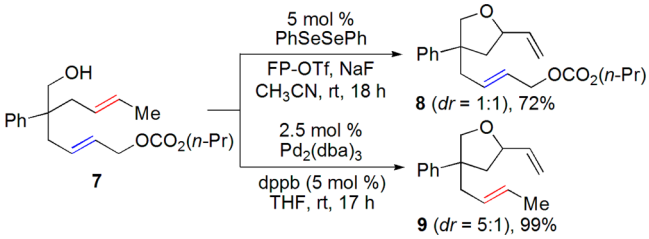
Scheme 2. Formation of *N*-Heterocycles from Olefinic Sulfonamides[a]

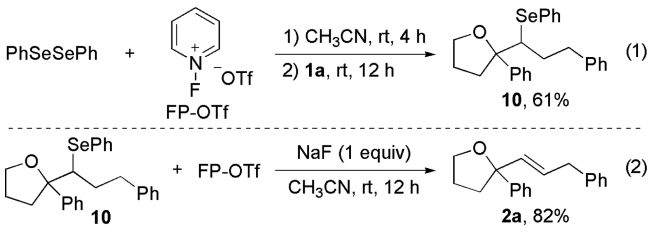


[a]Conditions: substrate **4** (0.1 mmol), PhSeSePh (10 mol %), FP-OTf (1.2 equiv), NaF (1 equiv), DCE (2 mL), rt, 21 h. [b]$NaHCO_3$ (0.8 equiv) instead of NaF. [c]NaF: 0.5 equiv.

Scheme 3. Selenium Catalysis vs Metal Catalysis



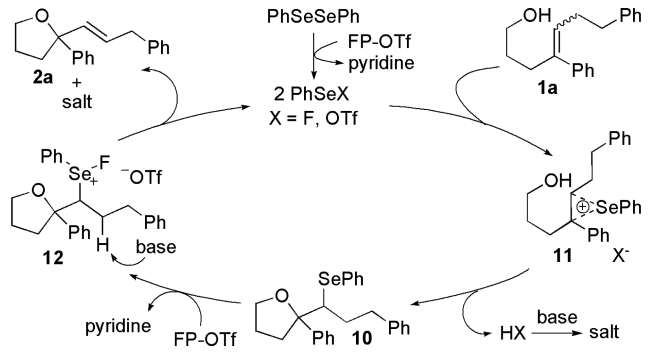
NMR experimental studies in acetonitrile-d_3 were conducted to elucidate the mechanism. First, PhSeSePh was treated with a stoichiometric oxidant FP-OTf in CD_3CN to verify whether it could be oxidized to generate $PhSe^+$.[22] The reaction was monitored by ^1H, ^{19}F, and ^{77}Se NMR (see the Supporting Information). After 4 h, the ^1H NMR spectrum clearly showed that new compounds were formed. A signal at δ = 48.2 ppm assigned to FP-OTf in the ^{19}F NMR spectrum almost disappeared, which revealed that most FP-OTf was decomposed. Meanwhile, a signal at δ = 465.8 ppm assigned to PhSeSePh disappeared and a signal at δ = 1440.6 ppm appeared in ^{77}Se NMR spectrum, which indicated that diselenide was converted to another species. The signal at δ = 1440.6 ppm was assigned to PhSeX (X = F, OTf).[23,24] We attempted to trap it. Another reaction of PhSeSePh with FP-OTf was run, and then **1a** was added after 4 h to see if **1a** could be cyclized (eq 1). As expected, PhSe-functionalized intermediate **10** was observed in 61% NMR yield. This indicated that FP-OTf can oxidize PhSeSePh to form PhSeX.[25] Next, removal of the PhSe group from the intermediate **10** was investigated. The cyclic ether **10** was treated with different oxidants, FP-OTf, pregenerated PhSeF from PhSeBr and AgF, pregenerated PhSeOTf from PhSeBr and AgOTf, and even PhSeBr. Only FP-OTf as the oxidant led to the formation of **2a** in 82% isolated yield (eq 2). The other oxidants only resulted in no or trace **2a**. Thus, the organoselenium catalyzed synthesis of heterocycles is considered to proceed through a PhSe-addition and PhSe-elimination sequence. FP-OTf is key for the transformation.



No or trace **2a** with other conditions:
(a) PhSeBr (1.1 equiv), AgF (1.1 equiv), ultrasound, DCM, 0 °C, 12 h
(b) PhSeBr (1.1 equiv), AgOTf (1.1 equiv), NaF (1.1 equiv), DCM, 0 °C, 11 h
(c) PhSeBr (1.1 equiv), pyridine (1.1 equiv), DCM, 0 °C, 11 h

We have therefore proposed the reaction mechanism depicted in Scheme 4. Reaction of PhSeSePh with fluoropyridium triflate produces PhSeX (X = F, OTf) species. Highly active PhSeX easily interacts with the double bond of olefinic alcohol **1a** to form seleniranium ion **11**, and then intramolecular attack of the hydroxy group leads to three-membered ring opening to yield intermediate **10**. The PhSe group on **10** was oxidized by FP-OTf to generate intermediate **12**. Participation of base assists proton elimination and removal of the selenium moiety to give the desired product **2a** and regenerate the species PhSeX. Acid promotes the rearrangement of **2a** toward **3a**. Based on the aforementioned experiments, the formation of **2a** from **10** is likely through the oxidation of FP-OTf, not by the active species PhSeF and PhSeOTf. At present, it is unclear whether pyridine in the reaction can stabilize $PhSe^+$ or inhibit the oxidation of substrates.

Scheme 4. Proposed Mechanism



In summary, we have developed an efficient approach to the synthesis of *O*- and *N*-hereocycles using organoselenium catalysis. The reactions proceeded smoothly without special care and with good functional group tolerance and excellent regioselectivity. Our mechanistic studies have revealed that FP-OTf is the key for the oxidative cyclization. This method is supplemental to metal catalysis in organic synthesis. Development of an asymmetric version of cyclization is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03543.

Experimental details, characterization data, mechanistic studies, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(24) δ (^{77}Se NMR) for PhSeCl: 1039 ppm; for PhSeBr: 867 ppm. See: Duddeck, H. *Prog. Nucl. Magn. Reson. Spectrosc.* **1995**, *27*, 1.

(25) We could not rule out the formation of Se(IV) species.

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