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The Staudinger reaction with 2-imino-1,3-thiaselenanes toward the synthesis of C4 spiro-β-lactams†

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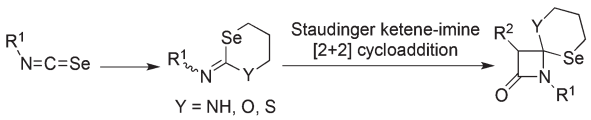
The Staudinger ketene–imine [2 + 2] cycloaddition reaction for conversion of α-heteroatom-substituted exocyclic imines to C4 heterocyclic spiro-β-lactams has rarely been investigated due to their instability. Herein, we describe the Staudinger reaction between ketenes and α-selenium-substituted exocyclic imines to synthesize C4 spiro-β-lactams.

Introduction

The Staudinger ketene–imine [2 + 2] cycloaddition reaction (the Staudinger reaction) was first reported in 1907.[1] This process took on interest after the discovery of penicillin in 1928 and still remains a general and effective method for the synthesis of β-lactam (2-azetidinone) derivatives.[2] Recently, spiro-β-lactams have received much attention because they are relatively unexplored compared with mono- and bicyclic β-lactams,[2,3] are found in biologically active natural compounds such as chartelline,[4] and behave as β-turn mimetics which is one of the major molecular recognition events for receptor–ligand interactions.[5] There are two types of spiro-β-lactams, C3 and C4 spiro-β-lactams. Several methods have been described for the synthesis of C3 spiro-β-lactams using the Staudinger reaction; in contrast, there are few reports on the synthesis of C4 spiro-β-lactams.[3] Especially the Staudinger reactions with α-heteroatom-substituted imines, which form C4 heterocyclic spiro-β-lactams, were limited because of their instability caused by the bridgehead C4 heteroatom.[6,7]

On the other hand, the synthesis and the biological evaluation of selenium-containing heterocycles have been developed because of their unique reactivities and potential biological activities such as anti-oxidant, anti-inflammatory, anti-viral, anti-microbial, *etc*.[8] Recently, our group and other groups reported the synthesis of selenium-containing heterocycles bearing an exocyclic imine from isoselenocyanates.[9–12] Also, we have established the synthesis of the bicyclic seleno-β-lactams starting from a selenium-modified 2-azetidinone skeleton.[13] However, the syntheses of seleno-β-lactams *via* the Staudinger reaction were limited.[14] To the best of our knowledge, the Staudinger reaction for the conversion of α-selenium-substituted exocyclic imines to C4 spiro-β-lactams has never been reported. Herein, we investigated the synthesis of C4 spiro-β-lactams *via* the Staudinger reaction using α-selenium-substituted exocyclic imines (Scheme 1).



Scheme 1 A strategy to synthesize C4 spiro-β-lactams in this study.

Results and discussion

First, we examined the Staudinger reaction of α-nitrogen- and α-oxygen-substituted exocyclic imines such as 2-imino-1,3-selenazine **1**[9a] and 2-imino-1,3-oxaselenane **3**,[15] with methoxyketene generated *in situ* from the reaction of methoxyacetyl chloride with Et_3N. In the case of 2-imino-1,3-selenazine **1**, the lone pair on nitrogen in selenazine attacked the carbonyl group of the acyl chloride to form *N*-methoxyacetyl-substituted 2-imino-1,3-selenazine **2**. When 2-imino-1,3-oxaselenane **3** was reacted with methoxyketene, carbamoselenoate **4** was obtained (Scheme 2).

Next, we investigated the Staudinger reaction with the α-thiaseleno-exocyclic imine. To this end, we examined the

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†Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra for all new compounds. CCDC 911411 (**6c**), 911412 (**8b**) and 911413 (**9a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob00073g

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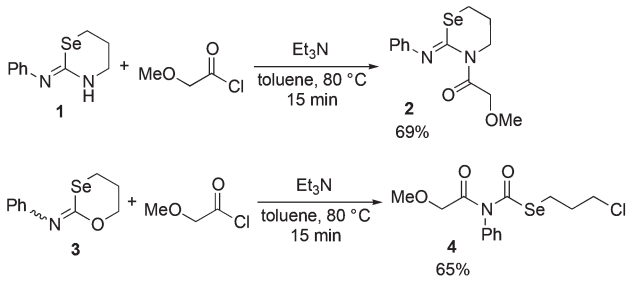
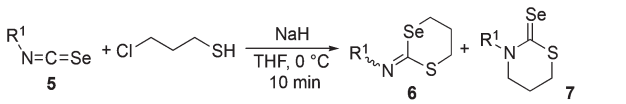


Scheme 2 The Staudinger reaction with 2-imino-1,3-selenazine **1** and 2-imino-1,3-oxaselenane **3**.

Table 1 Synthesis of 2-imino-1,3-thiaselenanes **6** and 2-selenoxoperhydro-1,3-thiazines **7**



	5	6		7
Entry	R^1	Yield[a] (%)	Z/E[b]	Yield (%)
1	C_6H_5 (**5a**)	88 (**6a**)	77 : 23	6 (**7a**)
2	*p*-MeC_6H_4 (**5b**)	68 (**6b**)	77 : 23	5 (**7b**)
3	*o*-MeC_6H_4 (**5c**)	64 (**6c**)	85 : 15	5 (**7c**)
4	*p*-ClC_6H_4 (**5d**)	71 (**6d**)	77 : 23	20 (**7d**)
5	*p*-$MeOC_6H_4$ (**5e**)	76 (**6e**)	75 : 25	14 (**7e**)
6	2-Naphthyl (**5f**)	75 (**6f**)	80 : 20	2 (**7f**)
7	Benzyl (**5g**)	44 (**6g**)	67 : 33	17 (**7g**)
8	*cyclo*-Hexyl (**5h**)	37 (**6h**)	68 : 32	Trace (**7h**)

[a] Isolated yield. [b] The ratio was calculated by ^{13}C NMR.

synthesis of the α-thiaseleno exocyclic imine by the reaction of isoselenocyanates.[12] Phenylisoselenocyanate **5a** was reacted with 3-chloro-1-propanethiol in the presence of NaH in THF at 0 °C, yielding 2-imino-1,3-thiaselenane **6a** in 88% yield and the by-product 1,3-thiazinane-2-selenone **7a** in 6% yield (Table 1, entry 1). Since **6a** has not enough purity as a yellow oil by silica gel column chromatography, **6a** was further purified by alumina column chromatography and obtained as a colorless solid. In the NMR spectra, **6a** was confirmed to be an inseparable mixture of *Z* and *E* isomers at the exocyclic imine position. Recently, we reported a similar *Z*/*E* isomerization for 2-imino-1,3-oxaselenepanes by the reaction of isoselenocyanates with 4-bromobutanol,[10] and for 2-imino-1,3-thiaselenolanes *via* the iodocyclization reaction of *S*-allylthioselenocarbamates.[11]

Then we examined the reactions using various isoselenocyanates **5**, and the corresponding exocyclic imines **6** and by-products **7** were obtained (Table 1). The higher nucleophilicity of selenium compared with nitrogen gave **6** as the predominant product in higher yield than **7**. All 2-imino-1,3-thiaselenanes **6** were confirmed to be inseparable *Z*/*E* isomer mixtures. The yields by the reactions with aliphatic isoselenocyanates (entries 7 and 8) were lower compared to those of the aromatic isoselenocyanates (entries 1–6) owing to instability of the

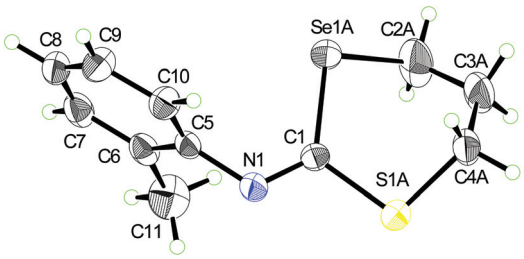


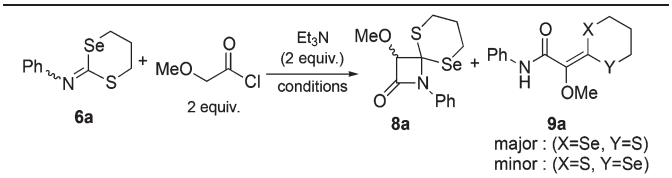
Fig. 1 ORTEP drawing of 2-(2-methylphenylimino)-1,3-thiaselenane (**6c**). In the structure of **6c**, S and Se atoms were disordered and refined as Se1A/S1B (Se 0.830(2), S 0.170(2)) and S1A/Se1B (Se 0.170(2), S 0.830(2)). Carbon atoms in the ring (C2, C3, and C4) were also disordered as Se1A–C2A–C3A–C4A–S1B and S1B–C2B–C3B–C4B–Se1B.

aliphatic group. In the ^{77}Se NMR spectra of **6**, two ^{77}Se signals were observed at 339.0–386.7 ppm for the *Z* isomer and at 371.1–397.2 ppm for the *E* isomer, respectively. Most of the ^{77}Se signals of the *Z* isomers of **6** were observed at higher fields than those of the *E* isomers.[10,11] On the other hand, the ^{77}Se signals of compounds **7** were observed at 525.9–639.2 ppm. In the ^{13}C NMR spectrum of benzyl-thiaselenane **6g**, we found an interesting spectral feature at the benzylic carbon. The selenium coupling $^3J(^{77}Se–^{13}C)$ with the (*Z*)-benzylic carbon was observed exclusively ($^3J(^{77}Se–^{13}C)$ = 26.9 Hz), while this coupling with the (*E*)-benzylic carbon was not observed. Furthermore, **6c** was examined by single-crystal X-ray diffraction (Fig. 1). The structure of **6c** showed disorder of S and Se atoms in the heterocyclic moiety. This means that the crystal included two isomers with an isomeric ratio of *Z*/*E* = 83 : 17.

Subsequently, the Staudinger reactions of the resulting exocyclic imine **6a** with methoxyketene were performed. Table 2 lists several reaction conditions. In entry 1, the reaction of **6a** with methoxyacetyl chloride (1.2 equiv.) in the presence of Et_3N (1.2 equiv.) in toluene at 80 °C gave C4 spiro-β-lactam **8a** in 69% yield. The diastereomer ratio (dr) of **8a** was calculated by ^1H NMR spectra. When we used 2 equiv. of both methoxyacetyl chloride and Et_3N, the reaction proceeded immediately to form spiro-β-lactam **8a** in excellent yield (98%, entry 2). However, the reaction at room temperature gave **8a** in a lower yield (49%, entry 3). When CH_2Cl_2 was used under reflux conditions for 2 h, **8a** was obtained in 90% yield (entry 4). In contrast, when THF was used as a solvent for 30 h, enamide **9a**, a ring opening product from **8a**, was obtained as stereoisomers; the major and minor isomers of **9a** were isolated in 51% and 23% yields, respectively (entry 6).[7] The structure of **9a** was determined by single crystal X-ray diffraction analysis (Fig. 2).[16] In this structure, there were two isomers that showed disorder of S and Se with an isomer ratio of 84/16. In the ^1H NMR of crystal **9a**, the ratio of the isomers was determined as 84/16. As a result, the conditions of entry 2 were optimal to give the desired product **8a** in a short time (10 min) in excellent yield (98%).

We next examined the Staudinger reactions using various imines **6** with methoxyacetyl chloride under the optimized

Table 2 Effect of solvent and temperature on the Staudinger reaction of **6a** with methoxyketene



		8a		9a	
Entry	Conditions	Yield[b] (%)	dr[c,d]	Yield[b] (%)	dr[c,d]
1[a]	Toluene, 80 °C, 5 h	69[e]	73 : 27	—	—
2	Toluene, 80 °C, 10 min	98	73 : 27	—	—
3	Toluene, rt, 48 h	49[e]	73 : 27	—	—
4	CH_2Cl_2, reflux, 2 h	90	74 : 26	—	—
5	CH_2Cl_2, 0 °C to rt, 45 h	52	75 : 25	29	—
6	THF, reflux, 3 h	—[e]	—	74	69 : 31

[a] **6a** : acylchloride : Et_3N = 1 : 1.2 : 1.2. [b] Isolated yield. [c] The ratio was calculated by ^{1}H NMR. [d] The ratio was calculated by isolated yield. [e] **6a** was recovered in 23%, 47%, and 21% yields, respectively.

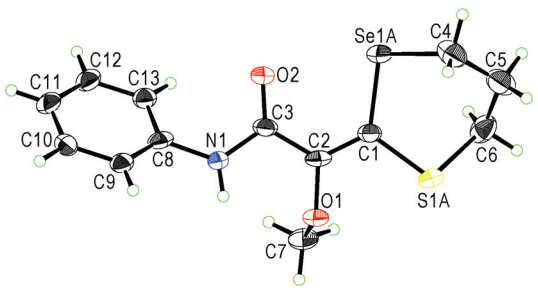
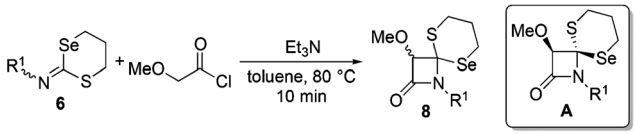


Fig. 2 ORTEP drawing of 2-methoxy-*N*-phenyl-2-(1,3-thiaselenan-2-ylidene)-acetamide (**9a**). In the structure of **9a**, S and Se atoms were disordered and refined as Se1A/S1B (Se 0.839(4), S 0.161(4)) and S1A/Se1B (Se 0.161(4), S 0.839(2)).

conditions. All imines **6** readily gave the corresponding spiro-β-lactams **8** in excellent yields (Table 3). Spiro-β-lactams **8** were obtained as a stereoisomer mixture. Among them, *p*-tolyl-spiro-β-lactam **8b** was determined by X-ray structure analysis (Fig. 3).[17] There are two independent structures of **8b** in a unit cell. Both of them showed disorder of chalcogen atoms in the spirocycle and one of them also had a disordered methoxy domain. The occupancy factor of each site and the ratio of isomers (68/32) in the crystal suggest that a *cis* conformation such as **A** shown in Table 3 is predominant.

We next investigated the Staudinger reactions of **8a** with various types of acyl chlorides, such as chloro-, propionyl-, phenyl-, cyclohexyl-, phenoxy-, and *p*-chlorophenoxyacetyl chloride. When chloroacetyl chloride was used, the reaction yielded decomposed materials; on the other hand, when propionyl chloride, phenylacetyl chloride, and cyclohexylacetyl chloride were used, the starting materials were recovered even after long reaction times and under reflux conditions. When phenoxyacetyl chloride was used, the corresponding enamide

Table 3 Synthesis of spiro-β-lactams **8** with various imines **6**



	6	8	
Entry	R^1	Yield[a] (%)	dr[b]
1	C_6H_5 (**6a**)	98 (**8a**)	73 : 27
2	*p*-MeC_6H_4 (**6b**)	95 (**8b**)	71 : 29
3	*o*-MeC_6H_4 (**6c**)	97 (**8c**)	73 : 27
4	*p*-ClC_6H_4 (**6d**)	88 (**8d**)	73 : 27
5	*p*-$MeOC_6H_4$ (**6e**)	99 (**8e**)	69 : 31
6	2-Naphthyl (**6f**)	93 (**8f**)	72 : 28
7	Benzyl (**6g**)	88 (**8g**)	80 : 20
8	*cyclo*-Hexyl (**6h**)	99 (**8h**)	78 : 22

[a] Isolated yield. [b] The ratio was calculated by ^{1}H NMR.

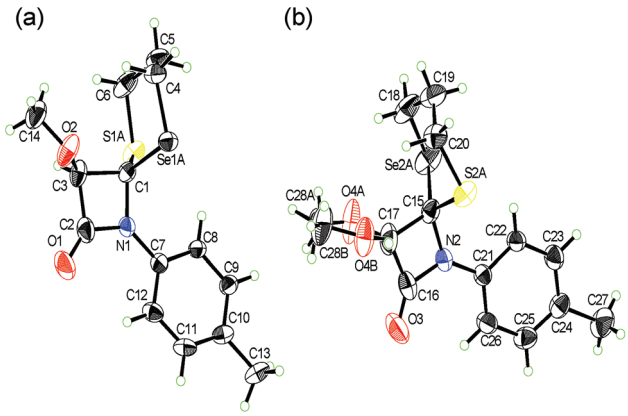
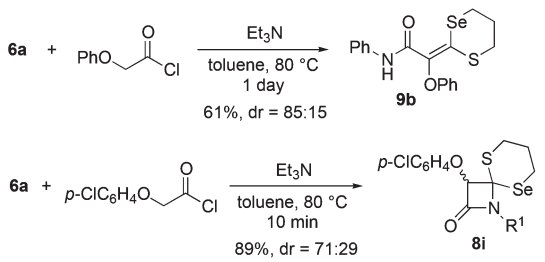


Fig. 3 ORTEP drawing of two independent structures of 3-methoxy-5-selena-9-thia-1-(4-tolyl)-1-azaspiro[3.5]nonan-2-one (**8b**). The crystal of **8b** had two independent molecules in a unit cell. In one molecule (a), S and Se atoms are disordered and refined as Se1A/S1B (Se 0.627(2), S 0.373(2)) and S1A/Se1B (Se 0.373(2), S 0.627(2)). In the other molecule (b), S and Se atoms are also disordered and refined as Se2A/S2B (Se 0.542(3), S 0.458(3)) and S2A/Se2B (Se 0.458(3), S 0.542(3)), and the methoxy group is disordered over two sites (O4A and C28A 0.678(11), O4B and C28B 0.322(11)).

9b was obtained in 61% yield after 24 h. However, when *p*-chlorophenoxyacetyl chloride was used, the desired spiro-β-lactam **8i** was obtained in 89% yield after 30 min (Scheme 3). These results would be explained by the previous report that the reactivity of the Staudinger reaction is highly dependent on the electronic effect of substituents of ketenes.[18]

Conclusions

In conclusion, we have reported the syntheses of 2-imino-1,3-thiaselenanes **6**, and confirmed the formation of *Z*/*E* isomers at the exocyclic imine position *via* the reaction of isoselenocyanates **5** with 3-chloro-1-propanethiol. In addition, we obtained C4 spiro-β-lactams **8** *via* the Staudinger reaction of **6** with



Scheme 3 The Staudinger reactions between **6a** and *O*-aryl ketenes.

methoxyketene in excellent yields and the structure of **8c** was determined by X-ray crystal diffraction analysis. Furthermore, the Staudinger reactions of several acetyl chlorides or various types of exocyclic imines were investigated.

Experimental section

General information

All solvents and commercially available reagents were purchased from the suppliers and used without further purification. All reactions were performed under argon or nitrogen. Evaporation and condensation were carried out *in vacuo*. TLC analysis was performed on Merck silica gel $60F_{254}$ on glass plates. Silica gel (Kanto Chemical Co. Inc., 60N, spherical, neutral) and alumina (Merck, aluminium oxide 90 active basic) were used for flash column chromatography. Melting points were measured by a Yanagimoto micromelting point apparatus (uncorrected). IR spectra were measured on a JASCO FT/IR-410 Fourier Transform Infrared Spectrometer. The ^{1}H NMR spectra, ^{13}C NMR spectra and ^{77}Se NMR spectra were measured on JEOL:JNM ECX-400P, JEOL:JNM ECA-600 spectrometers in $CDCl_3$. The chemical shifts of protons are reported in δ values referred to TMS as an internal standard. The ^{77}Se chemical shifts were expressed in δ values deshielded with respect to neat Me_2Se. The mass spectra (MS) and high resolution mass spectra (HRMS) were measured on a JEOL JMS-700.

Isoselenocyanates (**5**) were prepared according to the literature.[19]

(*Z*)-Perhydro(2-phenylimino)-1,3-selenazine (1). **1** was prepared according to the literature.[9a] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (2H, quint, J = 5.9 Hz, CH_2), 2.92 (2H, t, J = 6.5 Hz, ^2J(^{77}Se–^{1}H) = 29.5 Hz, CH_2), 3.28 (2H, t, J = 5.2 Hz, CH_2), 6.97–7.03 (3H, m, Ar), 7.24 (2H, t, J = 7.9 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7 (^1J (^{77}Se–^{13}C) = 54.9 Hz), 24.1, 44.1, 122.3, 122.9, 128.6, 148.0, 149.8. ^{77}Se NMR (75 MHz, $CDCl_3$): δ 250.1. MS (EI): m/z = 239 $[M]^+$.

2-Methoxy-1-(2-(phenylimino)-1,3-selenazan-3-yl)ethanone (2). **2** was prepared by the same method of synthesis of spiro-β-lactams **6** as described below. Colorless oil; IR (KBr): 1118, 1621, 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (2H, tt, J = 6.2 Hz, CH_2), 2.97 (2H, t, J = 6.8 Hz, ^2J(^{77}Se–^{1}H) = 30.6 Hz, CH_2), 3.49 (3H, s, Me), 4.02 (2H, t, J = 6.2 Hz, CH_2), 4.56 (2H, s, CH_2), 6.89 (2H, d, J = 7.4 Hz, Ar), 7.17 (1H, t, J = 7.5 Hz, Ar), 7.37 (2H, t, J = 7.8 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 23.1, 43.4, 59.3, 72.6, 120.0, 125.0, 129.2, 147.8, 151.2, 169.5; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 327.8; MS (FAB): m/z = 313 $[M + H]^+$; Anal. Calcd for $C_{13}H_{16}N_2O_2Se$: C, 50.17; H, 5.18; N, 9.00. Found: C, 50.10; H, 5.44; N, 8.92.

2-Phenylimino-1,3-oxaselenane (3). **3** was prepared by a modified procedure of the previous report.[15] To a stirred suspension of NaH (60%, 71.6 mg, 1.79 mmol) in dry THF (2.0 mL) was added phenylisoselenocyanate **5a** (181.2 mg, 1.00 mmol) in dry THF (2.0 mL) at 0 °C. After 3-bromo-1-propanol (97%, 140 μl, 1.50 mmol) was added dropwise, stirring was continued for 1 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate, and washed with water and brine. The combined organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography (SiO_2: hexane–ethyl acetate = 3 : 1) to give **3** (184 mg, 77%, Z/E = 86 : 14). Colorless oil; IR (KBr): 1675 cm^{-1}; *Z*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.11–2.16 (2H, m, CH_2), 2.96 (2H, t, J = 6.9 Hz, ^2J(^{77}Se–^{1}H) = 31.0 Hz, CH_2), 4.30 (2H, t, J = 5.2 Hz, CH_2), 6.83 (2H, d, J = 7.5 Hz, Ar), 7.03 (1H, t, J = 7.4 Hz, Ar), 7.23 (2H, t, J = 7.6 Hz, Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.3, 23.3, 70.1, 121.4, 124.1, 129.0, 146.8, 152.7; ^{77}Se NMR (114 MHz, $CDCl_3$): δ 249.8; *E*-isomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.11–2.16 (2H, m, CH_2), 2.96 (2H, t, J = 6.9 Hz, ^2J(^{77}Se–^{1}H) = 31.0 Hz, CH_2), 4.30 (2H, t, J = 5.2 Hz, CH_2), 6.83 (2H, d, J = 7.5 Hz, Ar), 7.03 (1H, t, J = 7.4 Hz, Ar), 7.23 (2H, t, J = 7.6 Hz, Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.5, 23.1, 70.8, 122.6, 123.5, 128.4, 146.2, 151.0; ^{77}Se NMR (114 MHz, $CDCl_3$): δ 266.9; MS (EI): m/z = 241 $[M]^+$; HRMS (EI): Calcd for $C_{10}H_{11}NOSe$: 241.0006, Found: 240.9995.

Se-(3-Chloropropyl) (2-methoxyacetyl)(phenyl)carbamoselenoate (4). **4** was prepared by the same method of synthesis of spiro-β-lactams **8** as described below. Colorless oil; IR (KBr): 1105, 1186, 1686, 1722 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.14 (2H, tt, J = 6.9 Hz, CH_2), 2.92 (2H, t, J = 7.2 Hz, ^2J(^{77}Se–^{1}H) = 30.3 Hz, CH_2), 3.46 (3H, s, Me), 3.57 (2H, t, J = 6.9 Hz, CH_2), 4.38 (2H, s, CH_2), 7.23–7.26 (2H, m, Ar), 7.47–7.53 (3H, m, Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 24.8, 32.5, 44.4, 59.4, 73.5, 129.6, 130.0, 130.1, 135.6, 169.6, 171.2; ^{77}Se NMR (114 MHz, $CDCl_3$): δ 487.4; MS (EI): m/z = 349 $[M]^+$; Anal. Calcd for $C_{13}H_{16}ClNO_3Se$: C, 44.78; H, 4.63; N, 4.02. Found: C, 45.03; H, 4.85; N, 3.70.

Typical procedure for the preparation of 2-imino-1,3-thiaselenanes (6) and 1,3-thiazinane-2-selenone (7). To a stirred suspension of NaH (60%, 96 mg, 2.40 mmol) in dry THF (2.0 mL) was added phenylisoselenocyanate **5a** (365.0 mg, 2.00 mmol) in dry THF (2.0 mL) at 0 °C. After 3-chloro-1-propanethiol (98%, 218.6 μl, 2.20 mmol) was added dropwise, stirring was continued for 10 min at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with diethyl ether, and washed with water and brine. The combined organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography (SiO_2: hexane–diethyl ether = 10 : 1→2 : 1→hexane–ethyl acetate = 2 : 1) (alumina: hexane–

diethyl ether = 10 : 1) to give **6a** (449.5 mg, 88%) and **7a** (28.6 mg, 6%).

2-Phenylimino-1,3-thiaselenane (6a). Colorless solid; mp: 101–103 °C; IR (KBr): 1551 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 2.10–2.20 (2H, m, CH_2), 2.98 (minor 2H, t, J = 6.2 Hz, CH_2), 3.02 (2H, t, J = 6.9 Hz, CH_2), 3.11 (2H, t, J = 6.6 Hz, CH_2), 3.17 (minor 2H, t, J = 6.8 Hz, CH_2), 6.86 (2H, d, J = 8.3 Hz, Ar), 7.11 (1H, t, J = 7.2 Hz, Ar), 7.30 (2H, t, J = 7.5 Hz, Ar); ^{13}C NMR (150 MHz, $CDCl_3$): major: δ 22.2, 24.2, 32.1, 119.6, 124.4, 128.7, 150.1, 162.0; minor: δ 22.0, 24.5, 32.8, 119.8, 124.1, 128.6, 149.4, 160.9; ^{77}Se NMR (114 MHz, $CDCl_3$): major: δ 379.2; minor: δ 391.6; MS (EI): m/z = 257 $[M]^+$; Anal. Calcd for $C_{10}H_{11}NSSe$: C, 46.88; H, 4.33; N, 5.47. Found: C, 46.58; H, 4.30; N, 5.44.

3-Phenyl-1,3-thiazinane-2-selenone (7a). Yellow solid; mp: 110–111 °C; IR (KBr): 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.48 (2H, tt, J = 5.8 Hz CH_2), 3.01 (2H, t, J = 6.0 Hz, CH_2), 3.77 (2H, t, J = 5.4 Hz, CH_2), 7.29 (2H, d, J = 7.5 Hz, Ar), 7.38 (1H, t, J = 7.5 Hz, Ar), 7.46 (2H, t, J = 7.5 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 33.0, 54.6, 126.3, 128.2, 129.6, 148.2, 193.2; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 624.1; MS (EI): m/z = 257 $[M]^+$; Anal. Calcd for $C_{10}H_{11}NSSe$: C, 46.88; H, 4.33; N, 5.47. Found: C, 46.87; H, 4.38; N, 5.36.

2-(4-Methylphenylimino)-1,3-thiaselenane (6b). Colorless solid; mp: 72–73 °C; IR (KBr): 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (2H, tt, J = 6.6 Hz, CH_2), 2.31 (3H, s, Me), 3.03 (2H, t, J = 6.8 Hz, CH_2), 3.11 (2H, t, J = 6.4 Hz, CH_2), 3.18 (minor 2H, t, J = 7.1 Hz, CH_2), 6.76 (2H, d, J = 7.7 Hz, Ar), 7.11 (2H, d, J = 7.8 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 20.8, 22.4, 24.2, 32.2, 119.5, 129.3, 134.0, 147.7, 161.3; minor: δ 20.8, 22.1, 24.4, 32.9, 119.8, 129.2, 133.6, 146.9, 160.2; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 378.1; minor: δ 390.8; MS (EI): m/z = 271 $[M]^+$; Anal. Calcd for $C_{11}H_{13}NSSe$: C, 48.89; H, 4.85; N, 5.18. Found: C, 49.11; H, 5.01; N, 5.08.

3-(4-Methylphenyl)-1,3-thiazinane-2-selenone (7b). Yellow solid; mp: 144–145 °C; IR (KBr): 1028, 1319, 1479 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (3H, s, Me), 2.48 (2H, tt, J = 5.8 Hz, CH_2), 3.00 (2H, t, J = 6.1 Hz, CH_2), 3.75 (2H, t, J = 5.5 Hz, CH_2), 7.16 (2H, d, J = 8.2 Hz, Ar), 7.26 (2H, d, J = 8.2 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 22.7, 33.0, 54.7, 126.0, 130.3, 138.3, 145.8, 193.2; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 618.1; MS (FAB): m/z = 272 $[M + H]^+$; Anal. Calcd for $C_{11}H_{13}NSSe$: C, 48.89; H, 4.85; N, 5.18. Found: C, 48.79; H, 5.16; N, 4.80.

2-(2-Methylphenylimino)-1,3-thiaselenane (6c). Colorless solid; mp: 62–63 °C; IR (KBr): 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.11–2.21 (2H, m, CH_2), 2.13 (3H, s, Me), 3.03 (2H, t, J = 6. 6 Hz, CH_2), 3.11 (2H, t, J = 6.2 Hz, CH_2), 6.72 (1H, d, J = 7.8 Hz, Ar), 7.02 (1H, t, J = 7.1 Hz, Ar), 7.11 (1H, t, J = 6.3 Hz, Ar) 7.16 (1H, d, J = 7.3 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 17.5, 22.3, 24.1, 32.2, 118.7, 124.4, 126.0, 127.9, 130.4, 149.3, 160.8; minor: δ 17.5, 22.3, 24.4, 32.7, 118.9, 124.1, 126.0, 127.6, 130.4, 148.8, 159.5; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 386.7; minor: δ 385.9; MS (EI): m/z = 271 $[M]^+$; Anal. Calcd for $C_{11}H_{13}NSSe$: C, 48.89; H, 4.85; N, 5.18. Found: C, 48.67; H, 5.01; N, 5.02.

3-(2-Methylphenyl)-1,3-thiazinane-2-selenone (7c). Yellow solid; mp: 182–183 °C; IR (KBr): 1323, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.28 (3H, s, Me), 2.40–2.58 (2H, m, CH_2), 2.91–2.99 (1H, m, CH_2) 3.03–3.11 (1H, m, CH_2), 3.58–3.72 (2H, m, CH_2) 7.15 (1H, d, J = 8.2 Hz, Ar), 7.26–7.32 (3H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 22.7, 32.9, 53.5, 126.2, 127.6, 128.7, 131.4, 133.9, 146.9, 192.3; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 613.9; MS (FAB): m/z = 272 $[M + H]^+$; Anal. Calcd for $C_{11}H_{13}NSSe$: C, 48.89; H, 4.85; N, 5.18. Found: C, 49.26; H, 5.07; N, 4.78.

2-(4-Chlorophenylimino)-1,3-thiaselenane (6d). Colorless solid; mp: 70–71 °C; IR (KBr): 1560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.21 (2H, tt, J = 6.6 Hz, CH_2), 3.03 (minor 2H, t, J = 6.2 Hz, CH_2), 3.08 (2H, t, J = 6.7 Hz, CH_2), 3.14 (2H, t, J = 6.4 Hz, CH_2), 3.21 (minor 2H, t, J = 6.9 Hz, CH_2), 6.80 (2H, d, J = 8.7 Hz, Ar), 7.27 (2H, d, J = 8.7 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 22.4, 24.5, 32.3, 121.2, 128.9, 129.7, 148.7, 163.2; minor: δ 22.1, 24.6, 33.0, 121.5, 128.8, 129.4, 147.9, 162.1; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 382.5; minor: δ 397.2; MS (EI): m/z = 291 $[M]^+$; Anal. Calcd for $C_{10}H_{10}ClNSSe$: C, 41.32; H, 3.47; N, 4.82. Found: C, 41.22; H, 3.50; N, 4.78.

3-(4-Chlorophenyl)-1,3-thiazinane-2-selenone (7d). Yellow solid; mp: 109–110 °C, IR (KBr): 1024, 1321, 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.49 (2H, tt, J = 5.9 Hz, CH_2), 3.02 (2H, t, J = 5.8 Hz, CH_2), 3.75 (2H, t, J = 5.5 Hz, CH_2), 7.23 (2H, d, J = 8.7 Hz, Ar), 7.42 (2H, d, J = 8.7 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 33.1, 54.6, 127.9, 134.0, 146.6, 194.0; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 639.2; MS (EI): m/z = 291 $[M]^+$; Anal. Calcd for $C_{10}H_{10}ClNSSe$: C, 41.32; H, 3.47; N, 4.82. Found: C, 41.39; H, 3.69; N, 4.48.

2-(4-Methoxyphenylimino)-1,3-thiaselenane (6e). Yellow oil, IR (KBr): 1563 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.15 (2H, tt, J = 6.6 Hz, CH_2), 3.01 (2H, t, J = 6. 8 Hz, CH_2), 3.09 (2H, t, J = 6.4 Hz, CH_2), 3.15 (minor 2H, t, J = 6.8 Hz, CH_2), 3.73 (3H, s, MeO), 6.77–6.88 (4H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 22.2, 24.0, 31.9, 54.9, 113.6, 120.6, 143.2, 156.3, 160.8; minor: δ 21.9, 24.3, 32.7, 54.9, 113.5, 121.1, 142.2, 156.1, 159.6, ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 379.5; minor: δ 390.9; MS (FAB): m/z = 288 $[M + H]^+$; Anal. Calcd for $C_{11}H_{13}NOSSe$: C, 46.15; H, 4.58; N, 4.89. Found: C, 46.24; H, 4.64; N, 4.84.

3-(4-Methoxyphenyl)-1,3-thiazinane-2-selenone (7e). Yellow solid; mp: 180 °C; IR (KBr): 1247, 1321, 1480, 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (2H, tt, J = 5.8 Hz, CH_2), 3.00 (2H, t, J = 6.1 Hz, CH_2), 3.75 (2H, t, J = 5.5 Hz, CH_2), 3.82 (3H, s, MeO), 6.95 (2H, d, J = 8.8 Hz, Ar), 7.20 (2H, d J = 8.8 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 33.0, 54.9, 55.3, 114.6, 127.3, 141.2, 158.9, 193.5; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 616.1; MS (EI): m/z = 287 $[M]^+$; HRMS (FAB): Calcd for $C_{11}H_{13}NOSSe$: 286.9883, Found: 286.9880 $[M]^+$.

2-(2-Naphthylimino)-1,3-thiaselenane (6f). Colorless solid; mp: 99–101 °C; IR (KBr): 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.09–2.22 (2H, m, CH_2), 3.02 (2H, t, J = 6. 8 Hz, CH_2), 3.13 (2H, t, J = 6.6 Hz, CH_2), 3.19 (2H, t, J = 6.6 Hz, CH_2), 7.08 (1H, dd, J = 2.1, 8.5 Hz, Ar), 7.25 (1H, s, Ar), 7.28 (minor 1H, s, Ar), 7.34–7.46 (2H, m, Ar), 7.72–7.82 (3H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 22.5, 24.4, 32.3, 116.0, 120.6,

124.9, 126.2, 127.5, 127.6, 128.9, 131.0, 133.7, 148.0, 162.5; minor: δ 22.2, 24.6, 33.0, 116.4, 120.8, 124.8, 126.2, 127.5, 127.6, 128.7, 130.8, 133.7, 147.2, 161.4; ^{77}Se NMR (75 MHz, $CDCl_3$): δ major: 384.2; minor: 393.6; MS (EI): m/z = 307 $[M]^+$; Anal. Calcd for $C_{14}H_{13}NSSe$: C, 54.90; H, 4.28; N, 4.57. Found: C, 55.21; H, 4.43; N, 4.52.

3-(2-Naphthyl)-1,3-thiazinane-2-selenone (7f). Yellow solid; mp: 149–150 °C; IR (KBr): 1311, 1480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (2H, tt, J = 5.8 Hz, CH_2), 2.96 (2H, t, J = 5.9 Hz, CH_2), 3.76 (2H, t, J = 5.5 Hz, CH_2), 7.39 (1H, dd, J = 2.1, 8.3 Hz, Ar), 7.44–7.52 (2H, m, Ar), 7.71 (1H, s, Ar), 7.75–7.90 (3H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 33.0, 54.8, 124.4, 124.5, 126.4, 126.6, 127.7, 127.9, 129.3, 132.4, 133.4, 145.6, 193.1; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 628.3; MS (EI): m/z = 307 $[M]^+$; HRMS (FAB): Calcd for $C_{14}H_{14}NSSe$: 308.0007, Found: 308.0046 $[M + H]^+$.

2-Benzylimino-1,3-thiaselenane (6g). Yellow oil; IR (KBr): 1574 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (2H, tt, J = 6.7 Hz, CH_2), 3.02 (2H, t, J = 6.6 Hz, CH_2), 3.09 (2H, t, J = 6.6 Hz, CH_2), 4.59 (2H, s, CH_2), 4.60 (minor 2H, s, CH_2), 7.21 (1H, t, J = 6.9 Hz, Ar), 7.26–7.36 (4H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 22.4, 24.3, 31.7, 59.8 (^3J(^{77}Se–^{13}C) = 26.9 Hz), 126.6, 127.6, 128.1, 138.5, 158.9; minor: δ 22.2, 24.0, 32.7, 57.8, 126.5, 127.6, 128.0, 138.9, 157.2; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 350.4; minor: δ 378.4; MS (EI): m/z = 271 $[M]^+$; Anal. Calcd for $C_{11}H_{13}NSSe$: C, 48.89; H, 4.85; N, 5.18. Found: C, 49.12; H, 5.00; N, 5.02.

3-Benzyl-1,3-thiazinane-2-selenone (7g). Yellow solid; mp: 148–149 °C; IR (KBr): 1343, 1504 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (2H, tt, J = 5.8 Hz, CH_2), 2.88 (2H, t, J = 5.9 Hz, CH_2), 3.40 (2H, t, J = 5.5 Hz, CH_2), 5.51 (2H, s, CH_2), 7.30–7.43 (5H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 33.1, 49.2, 61.4, 127.9, 128.1, 128.8, 134.4, 191.9; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 525.9; MS (EI): m/z = 271 $[M]^+$; Anal. Calcd for $C_{11}H_{13}NSSe$: C, 48.89; H, 4.85; N, 5.18. Found: C, 48.97; H, 5.10; N, 4.81.

2-Cyclohexylimino-1,3-thiaselenane (6h). Colorless solid; mp: 55–57 °C; IR (KBr): 1572 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15–1.38 (3H, m, ringCH_2), 1.38–1.53 (2H, m, ringCH_2) 1.63 (2H, d, J = 12.4 Hz, Ar)1.69–1.82 (4H, m, ringCH_2), 2.20 (2H, tt, J = 6.6 Hz, CH_2), 3.05–3.18 (4H, m, CH_2), 3.23–3.42 (1H, m, CH), 3.51–3.60 (minor 1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 22.7, 23.9, 24.5, 25.4, 31.8, 32.9, 65.5, 154.4; minor: δ 22.5, 24.1, 24.6, 25.5, 32.7, 32.8, 63.2, 153.4; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 339.0; minor: δ 371.1; MS (EI): m/z = 263 $[M]^+$; Anal. Calcd for $C_{10}H_{17}NSSe$: C, 45.79; H, 6.53; N, 5.34. Found: C, 45.64; H, 6.50; N, 5.21.

Typical procedure for the preparation of 2, 4, 8, 9, 11 and 12. To a stirred solution of **6a** (54.0 mg, 0.200 mmol) in 1 ml of dry toluene was added methoxyacetyl chloride (97%, 37.6 µl, 0.400 mmol) at 80 °C. Then triethylamine (55.5 µl, 0.400 mmol) in 0.5 ml of toluene was added dropwise, and stirring was continued for 10 min at 80 °C. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate, and washed with water and brine. The combined organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography (SiO_2: hexane–ethyl acetate = 10 : 1) to give **8a** (64.0 mg, 98%, major : minor = 73 : 27).

3-Methoxy-1-phenyl-5-selena-9-thia-1-azaspiro[3.5]nonan-2-one (8a). Colorless oil; IR (KBr): 1363, 1495, 1763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95–2.20 (2H, m, CH_2), 2.85–3.23 (4H, m, CH_2), 3.75 (3H, s, Me), 3.77 (minor 3H, s, Me), 4.67 (1H, s, CH), 4.99 (minor 1H, s, CH), 7.18–7.22 (1H, m, Ar), 7.37 (2H, t, J = 7.9 Hz, Ar), 7.77 (2H, d, J = 7.5 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 22.1 (^1J(^{77}Se–^{13}C) = 60.7 Hz), 22.8, 31.1, 59.9, 69.2, 95.9, 120.1, 125.6, 129.0, 135.4, 161.8; minor: δ 23.0, 23.3, 30.5, 59.7, 65.9, 96.8, 119.6, 125.6, 129.0, 135.6, 162.2; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 310.0; minor: δ 394.1; MS (EI): m/z = 329 $[M]^+$; Anal. Calcd for $C_{13}H_{15}NO_2SSe$: C, 47.56; H, 4.61; N, 4.27. Found: C, 47.71; H, 4.72; N, 4.21.

3-Methoxy-5-selena-9-thia-1-(4-tolyl)-1-azaspiro[3.5]nonan-2-one (8b). Colorless oil; IR (KBr): 1364, 1513, 1751 cm^{-1}, major-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00–2.13 (2H, m, CH_2), 2.33 (3H, s, Me), 2.85–3.14 (4H, m, CH_2), 3.74 (3H, s, Me), 4.65 (1H, s, CH), 7.17 (1H, d, J = 8.2 Hz, Ar), 7.63 (1H, d, J = 8.7 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 21.9, 22.7, 31.1, 59.9, 69.4, 95.8, 120.6, 129.6, 132.8, 135.8, 161.8; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 311.7; minor-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96–2.20 (2H, m, CH_2), 2.33 (3H, s, Me), 2.85–3.22 (4H, m, CH_2), 3.77 (3H, s, Me), 4.97 (1H, s, CH), 7.17 (1H, d, J = 8.3 Hz, Ar), 7.66 (1H, d, J = 8.7 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 23.1, 23.3, 30.5, 59.8, 66.3, 96.8, 120.1, 129.6, 133.1, 135.7, 162.1; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 391.5; MS (EI): m/z = 343 $[M]^+$; Anal. Calcd for $C_{14}H_{17}NO_2SSe$: C, 49.12; H, 5.01; N, 4.09. Found: C, 49.33; H, 5.22; N, 3.87.

3-Methoxy-5-selena-9-thia-1-(2-tolyl)-1-azaspiro[3.5]nonan-2-one (8c). Colorless oil; IR (KBr): 1363, 1774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93–2.00 (2H, m, CH_2), 2.41 (3H, s, Me), 2.70–2.96 (4H, m, CH_2), 3.72 (3H, s, Me), 3.74 (minor 3H, s, Me), 4.56 (1H, s, CH), 4.81 (minor 1H, s, CH), 7.14–7.33 (3H, m, Ar), 7.62 (minor 1H, d, J = 7.8 Hz, Ar), 7.66 (1H, d, J = 7.3 Hz, Ar), ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 18.9, 20.4, 22.9, 30.0, 60.2, 69.7, 93.5, 126.4, 126.9, 129.1, 131.0, 132.9, 137.1, 162.4; minor: δ 18.9, 22.5, 22.7, 28.7, 60.2, 69.7, 94.5, 126.4, 126.7, 129.1, 131.0, 132.9, 137.0, 162.7; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 346.4; minor: δ 368.5; MS (EI): m/z = 343 $[M]^+$; HRMS (FAB): Calcd for $C_{14}H_{17}NO_2SSe$: 343.0145, Found: 343.0190 $[M]^+$.

1-(4-Chlorophenyl)-3-methoxy-5-selena-9-thia-1-azaspiro[3.5]-nonan-2-one (8d). Colorless oil; IR (KBr): 1492, 1764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95–2.20 (2H, m, CH_2), 2.86–3.23 (4H, m, CH_2), 3.74 (3H, s, Me), 3.77 (minor 3H, s, Me), 4.67 (1H, s, CH), 4.99 (minor 1H, s, CH), 7.33 (2H, d, J = 8.7 Hz, Ar), 7.74 (2H, d, J = 8.7 Hz, Ar), ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 22.2, 22.5, 31.2, 60.0, 69.4, 96.2, 121.2, 129.1, 130.9, 134.0, 161.7; minor: δ 22.9, 23.4, 30.6, 59.8, 66.0, 97.1, 120.8, 129.1, 130.8, 134.2, 162.1; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 305.4; minor: δ 392.3; MS (EI): m/z = 364 $[M]^+$; HRMS (EI): Calcd for $C_{13}H_{14}ClNO_2SSe$: 362.9599, Found: 362.9581.

3-Methoxy-1-(4-methoxyphenyl)-5-selena-9-thia-1-azaspiro-[3.5]nonan-2-one (8e). Colorless oil; IR (KBr): 1510, 1759 cm^{-1},

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95–2.20 (2H, m, CH_2), 2.80–3.15 (4H, m, CH_2), 3.73 (3H, s, Me), 3.75 (minor 3H, s, Me), 3.80 (3H, s, Me), 4.62 (1H, s, CH), 4.94 (minor 1H, s, CH), 6.91 (2H, d, J = 9.1 Hz, Ar), 7.64 (2H, d, J = 8.7 Hz, Ar), ^{13}C NMR (100 MHz, $CDCl_3$): major; δ 21.6, 22.6, 30.8, 55.4, 60.0, 69.6, 95.4, 114.2, 123.1, 128.0, 157.9, 161.8, minor: δ 22.9, 23.1, 30.2, 55.4, 59.8, 66.6, 96.4, 114.2, 122.4, 128.3, 157.6, 162.0, ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 313.7; minor: δ 384.9; MS (EI): m/z = 359 $[M]^+$; Anal. Calcd for $C_{14}H_{17}NO_3SSe$: C, 46.93; H, 4.78; N, 3.91. Found: C, 46.58; H, 4.97; N, 3.55.

3-Methoxy-1-(naphthalen-2-yl)-5-selena-9-thia-1-azaspiro[3.5]-nonan-2-one (8f). Colorless oil; IR (KBr): 1761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00–2.20 (2H, m, CH_2), 2.87–3.25 (4H, m, CH_2), 3.77 (3H, s, Me), 3.79 (minor 3H, s, Me), 4.71 (1H, s, CH), 5.04 (minor 1H, s, CH), 7.42–7.50 (2H, m, Ar) 7.77–7.85 (3H, m, Ar), 7.95–8.05 (1H, m, Ar), 8.15–8.20 (1H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 22.1, 22.6, 31.2, 60.0, 69.4, 96.0, 117.7, 119.1, 125.7, 126.6, 127.6, 127.8, 128.9, 131.1, 133.0, 133.2, 162.0; minor: δ 23.0, 23.4, 30.6, 59.8, 60.0, 96.9, 117.2, 118.8, 125.7, 126.6, 127.8, 128.9, 131.0, 133.0, 133.2, 162.4; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 311.6; minor: δ 396.7; MS (EI): m/z = 380 $[M]^+$; HRMS (EI): Calcd for $C_{17}H_{17}NO_2SSe$: 379.0145, Found: 379.0130.

1-Benzyl-3-methoxy-5-selena-9-thia-1-azaspiro[3.5]nonan-2-one (8g). Colorless solid; mp: 76–77 °C; IR (KBr): 1385, 1755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87–2.00 (2H, m, CH_2), 2.70 (2H, t, J = 6.0 Hz, CH_2), 2.80 (2H, t, J = 6.4 Hz, CH_2), 2.89 (minor 2H, t, J = 6.2 Hz, CH_2), 3.66 (3H, s, Me), 3.67 (minor 3H, s, Me), 4.49 (minor 1H, s, CH), 4.50 (1H, s, CH), 7.25–7.42 (5H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 20.8, 22.4, 30.4, 44.1, 60.0, 69.7, 95.4, 127.8, 128.3, 128.4, 135.4, 163.9; minor: δ 20.8, 22.6, 29.3, 44.2, 59.9, 67.7, 96.2, 127.8, 128.3, 128.4, 135.4, 164.2; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 305.7; minor: δ 341.6; MS (EI): m/z = 343 $[M]^+$; HRMS (EI): Calcd for $C_{14}H_{17}NO_2SSe$: 343.0145, Found: 343.0126.

1-Cyclohexyl-3-methoxy-5-selena-9-thia-1-azaspiro[3.5]-nonan-2-one (8h). Colorless solid; mp: 73.5–75 °C; IR (KBr): 1760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14–1.32 (m), 1.58–1.66 (m), 1.76–2.10 (m), 2.80–3.12 (m), 3.18–3.28 (m), 3.64 (3H, s, Me), 3.67 (minor 3H, s, Me), 4.40 (1H, s, CH), 4.71 (minor 1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 21.4, 22.2, 24.9, 25.35, 25.49, 30.9, 31.1, 31.3, 54.2, 59.7, 70.7, 95.5, 162.8; minor: δ 22.6, 23.1, 24.9, 25.35, 25.49, 30.1, 31.3, 31.6, 54.3, 59.6, 67.8, 96.3, 163.4; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 291.8; minor: δ 356.0; MS (EI): m/z = 336 $[M]^+$; HRMS (EI): Calcd for $C_{13}H_{21}NO_2SSe$: 335.0458, Found: 335.0433.

3-(4-Chlorophenoxy)-1-phenyl-5-selena-9-thia-1-azaspiro[3.5]-nonan-2-one (8i). Colorless oil; IR (KBr): 1235, 1365, 1489, 1769 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94–2.13 (2H, m, CH_2), 2.80–3.10 (4H, m, CH_2), 5.38 (1H, s, CH), 5.62 (minor 1H, s, CH), 7.15 (2H, d, J = 9.2 Hz, Ar), 7.20–7.27 (1H, m, Ar), 7.32 (2H, d, J = 9.2 Hz, Ar), 7.36–7.45 (2H, m, Ar), 7.80 (2H, d, J = 8.7 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): major: δ 22.4, 22.1, 31.4, 68.7, 91.7, 117.6, 120.8, 126.3, 127.8, 129.1, 129.6, 135.2, 155.8, 160.6; minor: δ 22.3, 23.6, 30.4, 66.3, 92.7, 117.4, 120.3, 126.1, 127.8, 129.1, 129.6, 135.3, 155.9, 160.9; ^{77}Se NMR (75 MHz, $CDCl_3$): major: δ 319.6; minor: δ 380.1; MS (EI): m/z = 425 $[M]^+$; HRMS (EI): Calcd for $C_{18}H_{16}ClNO_2SSe$: 424.9755, Found: 424.9772.

2-Methoxy-*N*-phenyl-2-(1,3-thiaselenan-2-ylidene)acetamide (9a). Major isomer: colorless solid; mp: 115–116 °C; IR (KBr): 1003, 1235, 1438, 1509, 1537, 1592, 1649 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (2H, tt, J = 6.8 Hz, CH_2), 2.88 (2H, t, J = 6.8 Hz, $^2J(^{77}Se–^1H)$ = 32.5 Hz, CH_2), 2.99 (2H, t, J = 6.8 Hz, CH_2), 3.73 (3H, s, Me), 7.10 (1H, t, J = 7.4 Hz, Ar), 7.32 (2H, t, J = 7.8 Hz, Ar), 7.60 (2H, d, J = 8.2 Hz, Ar), 8.14 (1H, brs, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 22.8, 31.4, 119.6, 124.1, 128.9, 137.1, 137.6, 141.1, 160.7; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 315.0; MS (EI): m/z = 329 $[M]^+$; HRMS (EI): Calcd for $C_{13}H_{15}NO_2SSe$: 328.9989, Found: 328.9977; minor isomer: colorless solid; mp: 119–120 °C; IR (KBr): 1024, 1256, 1316, 1440, 1536, 1593, 1635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (2H, tt, J = 6.9 Hz, CH_2), 2.92 (2H, t, J = 6.7 Hz, $^2J(^{77}Se–^1H)$ = 27.5 Hz, CH_2), 3.04 (2H, t, J = 7.1 Hz, CH_2), 3.71 (3H, s, Me), 7.10 (1H, t, J = 7.6 Hz, Ar), 7.32 (2H, t, J = 7.8 Hz, Ar), 7.60 (2H, d, J = 7.8 Hz, Ar), 8.04 (1H, brs, NH), ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 22.7, 32.1, 59.2, 119.5, 124.1, 128.9, 137.7, 141.2, 159.5, ^{77}Se NMR (75 MHz, $CDCl_3$): δ 259.2, MS (EI): m/z = 329 $[M]^+$, HRMS (FAB): Calcd for $C_{13}H_{15}NO_2SSe$: 328.9989, Found: 328.9977 $[M]^+$.

2-Phenoxy-*N*-phenyl-2-(1,3-thiaselenan-2-ylidene)acetamide (9b). Major isomer: colorless solid; mp: 142–143 °C; IR (KBr): 1213, 1435, 1503, 1595, 1632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (2H, tt, J = 6.9Hz, CH_2), 2.94–3.00 (4H, m, CH_2), 7.06 (4H, d, J = 8.2 Hz, Ar), 7.26 (4H, t, J = 8.0 Hz, Ar), 7.33 (2H, t, J = 7.8 Hz, Ar), 7.47 (2H, d, J = 7.8 Hz, Ar), 7.72 (1H, brs, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 23.2, 32.3, 114.9, 119.8, 123.1, 124.2, 128.8, 130.3, 135.2, 137.4, 142.1, 155.9, 159.3; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 276.6; MS (EI): m/z = 391 $[M]^+$; HRMS (FAB): Calcd for $C_{18}H_{17}NO_2SSe$: 391.0145, Found: 391.0100 $[M]^+$; minor isomer: colorless solid; mp: 134–136 °C; IR (KBr): 1436, 1489, 1594, 1642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (2H, tt, J = 6.9 Hz, CH_2), 2–86–2.96 (4H, m, CH_2), 6.97–7.10 (4H, m, Ar), 7.26 (2H, t, J = 7.7 Hz, Ar), 7.33 (2H, t, J = 8.0 Hz, Ar), 7.47 (2H, d, J = 8.3 Hz, Ar), 7.81 (1H, brs, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 31.5, 114.8, 119.8, 122.9, 124.2, 128.8, 130.0, 134.8, 137.3, 140.8, 156.1, 160.4; ^{77}Se NMR (75 MHz, $CDCl_3$): δ 328.4; MS (EI): m/z = 391 $[M]^+$; HRMS (FAB): Calcd for $C_{18}H_{17}NO_2SSe$: 391.0145, Found: 391.0165 $[M]^+$.

Single crystal X-ray structure analysis

Crsytals of **6c**, **8b**, and **9a** were obtained by slow evaporation of hexane–EtOAc solution. X-ray diffraction measurements were carried out on a Rigaku AFC-7R Mercury CCD diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å). The structures were solved by direct methods SIR97 and refined with Shelxl97 using interface program Yadokari2009. The final least-squares cycle included non-hydrogen atoms with anisotropic thermal parameters. H atoms on C and N atoms were placed in idealized positions and treated as

riding atoms with C–H distances in the range 0.93–0.99 Å and N–H distances of 0.86 Å.

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Notes and references

1 H. Staudinger, *Justus Liebigs Ann. Chem.*, 1907, **356**, 51.
2 For recent reviews of the Staudinger reaction, see: (*a*) F. P. Cossio, A. Arrieta and M. A. Sierra, *Acc. Chem. Res.*, 2008, **41**, 925; (*b*) A. Brandi, S. Cicchi and F. M. Cordero, *Chem. Rev.*, 2008, **108**, 3988; (*c*) N. Y. Fu and T. T. Tidwell, *Tetrahedron*, 2008, **64**, 10465.
3 For reviews of spiro-β-lactams, see: (*a*) S. S. Bari and A. Bhalla, *Top. Heterocycl. Chem.*, 2010, **22**, 49; (*b*) G. S. Singh, M. D'hooghe and M. De Kimpe, *Tetrahedron*, 2011, **67**, 1989 and references there in.
4 (*a*) L. Chevolot, A. M. Chevolot, M. Gajhede, C. Larsen, U. Anthoni and C. Christophersen, *J. Am. Chem. Soc.*, 1985, **107**, 4542; (*b*) U. Anthoni, L. Chevolot, C. Larsen, P. H. Nielsen and C. Christophersen, *J. Org. Chem.*, 1987, **52**, 4709; (*c*) P. S. Baran and R. A. Shenvi, *J. Am. Chem. Soc.*, 2006, **128**, 14028.
5 (*a*) E. Alonso, F. Lopez-Ortiz, C. del-Pozo, E. Peralta, A. Macia and J. Gonzalez, *J. Org. Chem.*, 2001, **66**, 6333; (*b*) J. D. Tyndall, B. Pfeiffer, G. Abbenante and D. P. Fairlie, *Chem. Rev.*, 2005, **105**, 793; (*c*) H. Bittermann and P. Gmeiner, *J. Org. Chem.*, 2006, **71**, 97; (*d*) G. Ruiz-Gomez, J. D. A. Tyndall, B. Pfeiffer, G. Abbenante and D. P. Fairlie, *Chem. Rev.*, 2010, **110**, 1.
6 (*a*) M. Perelman and S. A. Mizsak, *J. Am. Chem. Soc.*, 1962, **84**, 4988; (*b*) A. K. Bose, J. C. Kapur, S. G. Amin and M. S. Manhas, *Tetrahedron Lett.*, 1974, **15**, 1917; (*c*) M. Cardellini, F. Claudi and F. M. Moracci, *Synthesis*, 1984, 1070; (*d*) I. Antonini, M. Cardellini, F. Claudi and F. M. Moracci, *Synthesis*, 1986, 379; (*e*) K. Thiagarajan, V. G. Puranik, A. R. A. S. Deshmukh and B. M. Bhawal, *Tetrahedron*, 2000, **56**, 7811.
7 S. D. Sharma, U. Mehra, J. P. S. Khurana and S. B. Pandhi, *Synthesis*, 1987, 990.
8 (*a*) C. W. Nogueira, G. Zeni and J. B. T. Rocha, *Chem. Rev.*, 2004, **104**, 6255; (*b*) M. Ninomiya, D. R. Garud and M. Koketsu, *Heterocycles*, 2010, **81**, 2027; (*c*) M. Ninomiya, D. R. Garud and M. Koketsu, *Coord. Chem. Rev.*, 2011, **255**, 2968.
9 (*a*) G. L. Sommen, A. Linden and H. Heimgartner, *Eur. J. Org. Chem.*, 2005, 3128; (*b*) G. L. Sommen, A. Linden and H. Heimgartner, *Tetrahedron Lett.*, 2005, **46**, 6723; (*c*) Y. Toyoda, D. R. Garud and M. Koketsu, *Heterocycles*, 2009, **78**, 449.
10 D. R. Garud, Y. Toyoda and M. Koketsu, *Tetrahedron Lett.*, 2009, **50**, 3035.
11 For the *Z*/*E* isomerism of selenium-containing exocyclic imines, see: Y. Toyoda and M. Koketsu, *Tetrahedron*, 2012, **68**, 10496.
12 For reviews of isoselenocyanate, see: (*a*) D. R. Garud, M. Koketsu and H. Ishihara, *Molecules*, 2007, **12**, 504; (*b*) H. Heimgartner, Y. Zhou, P. K. Atanassov and G. L. Sommen, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2008, **183**, 840.
13 (*a*) D. R. Garud, H. Ando, Y. Kawai, H. Ishihara and M. Koketsu, *Org. Lett.*, 2007, **9**, 4455; (*b*) D. R. Garud and M. Koketsu, *Org. Lett.*, 2008, **10**, 3319; (*c*) D. R. Garud, D. D. Garud and M. Koketsu, *Org. Biomol. Chem.*, 2009, **7**, 2591; (*d*) D. B. Banker and M. Koketsu, *Eur. J. Org. Chem.*, 2010, 2742; (*e*) D. R. Garud, M. Makimura and M. Koketsu, *New J. Chem.*, 2011, **35**, 581.
14 (*a*) Y. Nagao, T. Kumagai, S. Takao, T. Abe, M. Ochiai, Y. Inoue, T. Taga and E. Fujita, *J. Org. Chem.*, 1986, **51**, 4737; (*b*) T. Inayama, K. Izawa, K. Soda, H. Tanaka and H. Nagao, 1988, JP 63,83,091; *Chem. Abstr.*, 1999, **109**, 149216; (*c*) G. A. Brown, K. M. Anderson, M. Murray, T. Gallagher and N. J. Hales, *Tetrahedron*, 2000, **56**, 5579; (*d*) K. Tsuchii, Y. Tsuboi, S. Kawaguchi, J. Takahashi, N. Sonoda, A. Nomoto and A. Ogawa, *J. Org. Chem.*, 2007, **72**, 415.
15 2-Imino-1,3-oxaselenane **12** was obtained as a *Z*/*E* mixture (86 : 14) by the reaction of phenylisoselenocyanate **1a** with 3-bromo-1-propanol. This compound was reported in: G. L. Sommen and H. Heimgartner, *Pol. J. Chem.*, 2007, **81**, 1413.
16 A single crystal for the X-ray analysis was obtained by recrystallization of the major isomer of the target compounds, which was stored at 4 °C after isomer separation with column chromatography. During this storage period, the isomeric equilibrium reaction proceeded.
17 A single crystal for the X-ray analysis was obtained from the separated major isomer. As well as **9a**, isomerization would occur over long storage periods.
18 L. Jiao, Y. Liang and J. Xu, *J. Am. Chem. Soc.*, 2006, **128**, 6060.
19 J. G. Fernández-Bolaños, Ó. López, V. Ulgar, I. Maya and J. Fuentes, *Tetrahedron Lett.*, 2004, **45**, 4081.

