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First Examples of Reactions of 3-Trimethylsilyl-2-Propynamides and Organic Diselenides: Synthesis of Novel Derivatives of Propynamides

Mikhail V. Andreev, Vladimir A. Potapov *, Maxim V. Musalov and Lyudmila I. Larina

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Division of The Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russia; miand@irioch.irk.ru (M.V.A.); musalov_maxim@irioch.irk.ru (M.V.M.); larina@irioch.irk.ru (L.I.L.)

* Correspondence: v.a.potapov@mail.ru

Abstract: First examples of the reactions of 3-trimethylsilyl-2-propynamides with organic diselenides yielding 3-alkylselanyl-2-propenamides and 3-organylselanyl-2-propynamides were realized. The latter compounds were obtained by the Cu-catalyzed reaction of organic diselenides with 4-propioloylmorpholine. The reaction of 3-trimethylsilyl-2-propynamides with dialkyl diselenides in the system $NaBH_4/H_2O/K_2CO_3$/THF proceeded in a regio- and stereoselective fashion, affording 3-alkylselanyl-2-propenamides in 90–94% yields. An unsymmetrical divinyl selenide with the cyclic amide groups and a product, containing two selanyl-2-propenamide moieties and three cyclic amide groups, were synthesized. The Cu-catalyzed allylation reaction of 3-trimethylsilyl-2-propynamides was accompanied with desilylation to yield 3-allyl-2-propynamides.

Keywords: acetylenes; divinyl selenides; 3-trimethylsilyl-2-propynamides; organic diselenides; propynamides; vinyl selenides

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1. Introduction

Selenium is an essential trace element for humans. A number of selenium-containing enzymes (e.g., glutathione peroxidase) have been discovered [1–5]. Glutathione peroxidase plays an important role in the human body, protecting the body from oxidative damage and supporting the antioxidant-antiradical defense system [1–5].

Organoselenium compounds exhibit a variety of biological activities [6–22] including antitumor [10–13], antibacterial [13,14], antiviral [15,16] and glutathione peroxidase mimetic properties [17–19].

The most studied in terms of biological activity is 2-phenyl-1,2-benzoselenazol-3(2*H*)-one (ebselen). This well-known selenium-containing heterocyclic drug exhibits anti-inflammatory, neuroprotective and glutathione peroxidase mimetic properties [22–26]. Interestingly, ebselen also inhibits the SARS-CoV-2 viral replication [25,26]. This compound has been investigated in clinical trials as a therapeutic agent for the treatment of a number of diseases including COVID-19, hearing loss and bipolar disorder [22,23].

An important structural feature of ebselen is the presence of an amide group in its molecule. Some functional derivatives of ebselen are superior to this drug in glutathione peroxidase mimetic activity [22,23]. Along with ebselen and its functional derivatives, a number of biologically relevant organoselenium compounds contain the amide group in their structure (Figure 1). The presence of the amide group in organoselenium compounds is considered as a favorable circumstance for the possible manifestation of biological activity [21,22].

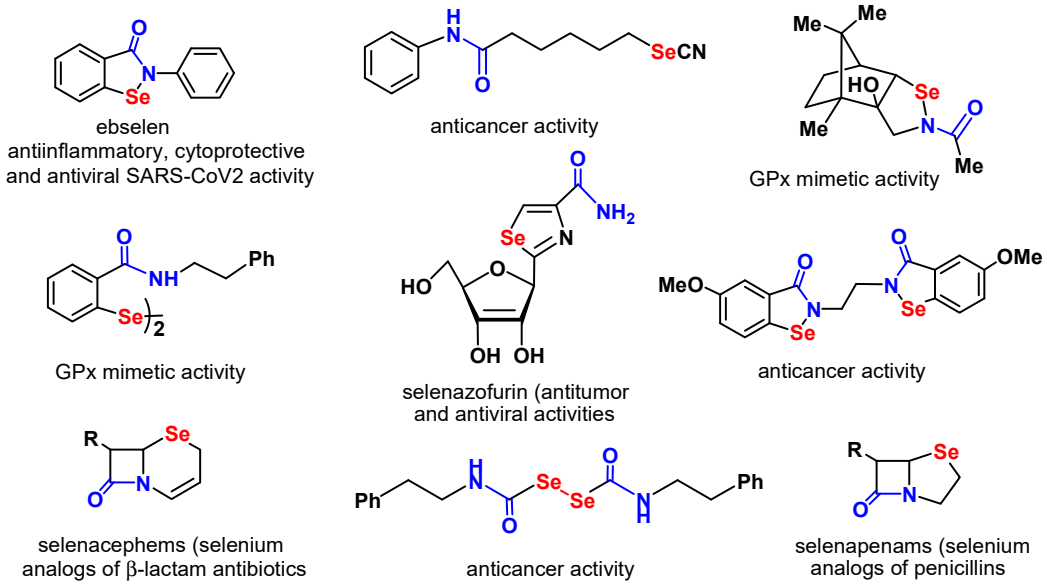


Figure 1. Examples of biologically relevant organoselenium compounds containing the amide group.

An important achievement in the synthetic organoselenium chemistry is the development of effective methods for the preparation of selenium analogs of β-lactam antibiotics—selenacephems and selenium analogs of penicillins—selenapenams (Figure 1) [21,22].

The synthesis of various functionalized organoselenium compounds with the amide group and studying their properties is a promising area of research. In this work, we developed the synthesis of vinylic and acetylenic selenides with the amide group based on 3-trimethylsilyl-2-propynamides and organic diselenides. The first examples of reactions of organic diselenides with 3-trimethylsilyl-2-propynamides were realized. The reactions of 3-trimethylsilyl-2-propynamides were accompanied by the desilylation process. The copper-catalyzed allylation reaction of propynamides afforded 3-allyl-2-propynamides. The starting 3-trimethylsilyl-2-propynamides were prepared from 3-trimethylsilylpropiolic acid and amines according to methods previously developed at this institute [27].

It is worth noting that vinylic selenides are versatile intermediates for organic synthesis. Recently, vinyl and divinyl selenides have been served as useful starting materials in various reactions [28–38]. A variety of valuable products including resveratrol and some its analogs have been synthesized based on vinyl and divinyl selenides [28–38].

The synthesis of various vinylic selenides is within the scope of our scientific interests, and a number of effective methods for the preparation of functionalized vinyl and divinyl selenides, including unsubstituted divinyl selenide, have been previously developed [39–46].

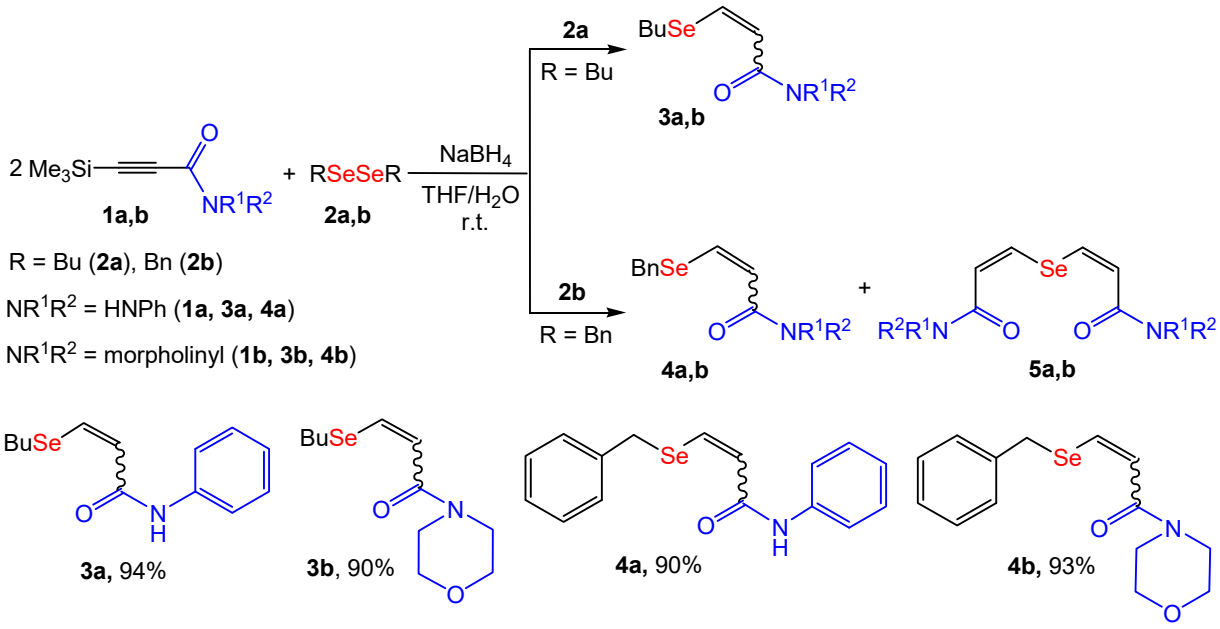
2. Results and Discussion

Most of the catalytic reactions of 3-trimethylsilyl-2-propynamides and 2-propynamides have not yet been investigated, and we continue to study the chemical properties of these compounds.

The goal of this work is to implement the first examples of the reactions of 3-trimethylsilyl-2-propynamides and organic diselenides and to develop an effective and selective synthesis of the first representatives of 3-alkylselanyl-2-propenamides and 3-organylselanyl-2-propynamides (4-organylselanylprop-2-ynoylmorpholines), as well as allylacetylenes, containing the amide group at the triple bond.

The addition of alkylselenolate anions to 2-propynamides has not yet been reported. We have studied the nucleophilic addition reaction of alkylselenolates to 2-propynamides. Sodium benzyl- and butyl selenolates were generated from dibenzyl and dibutyl diselenides under the action of sodium borohydride. The reaction was carried out by portionwise

addition of sodium borohydride to a solution of 3-trimethylsilyl-2-propynamides **1a** or **1b** and dibenzyl or dibutyl diselenides in THF containing some water to dissolve sodium borohydride. Experimental studies of this reaction showed that these conditions are favorable for the formation of the target products. The synthesis of compounds **3a** and **3b** was developed from dibutyl diselenide **2a** and 3-trimethylsilyl-2-propynamides **1a** and **1b** in 94% and 90% yields, respectively (Scheme 1).



Scheme 1. The reaction of 3-trimethylsilyl-2-propynamides **1a,b** with diselenides **2a,b**.

In the case of the reaction of 3-trimethylsilyl-2-propynamides **1a**,**b** with dibenzyl diselenide **2b** and sodium borohydride, along with the target products **4a**,**b**, formed in high yields (90–93%), the formation of divinyl selenides **5a**,**b** in 7–10% yields was observed (Scheme 1).

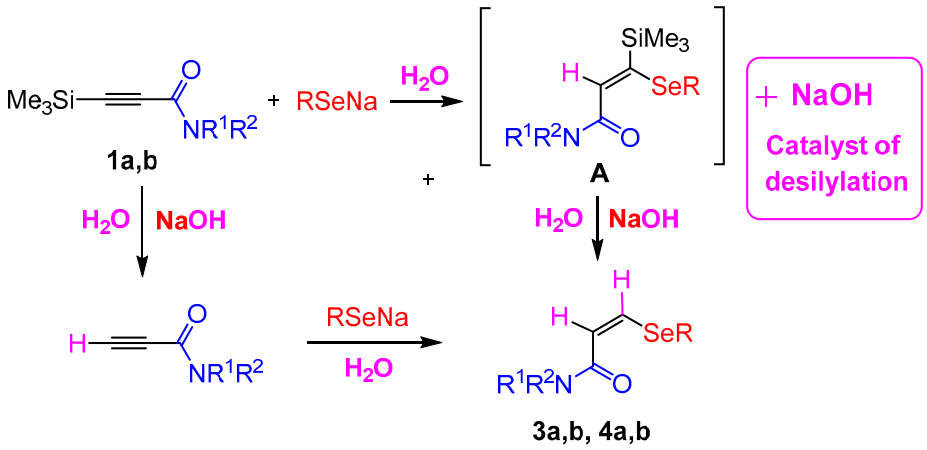
It was assumed that the formation of divinyl selenides **5a**,**b** resulted from the reaction of sodium benzylselenolate with excess sodium borohydride, leading to the formation of some sodium selenide (Na_2Se). We previously obtained selenides **5a**,**b** in high yields through the nucleophilic addition of sodium selenide (generated from elemental selenium and $NaBH_4$) to 3-trimethylsilyl-2-propynamides in a THF/water mixture at room temperature [40].

The reaction proceeded in a regio- and stereoselective fashion as anti-addition with the formation of the target product predominantly with (*Z*)-configuration. The content of (*E*)-isomers was less than 8% (Table 1). Table 1 shows the *Z*/*E* ratios of the products **3a**,**b** and **4a**,**b** formed in the reaction of propynamide **1a**,**b** with diselenides **2a**,**b**, as well as the *Z*/*E* ratio of these products in the fractions isolated by column chromatography on silica gel. The pure (*Z*)-isomers were isolated by column chromatography in the case of morpholine derivatives **3b** and **4b** (entries 2 and 4). The content of (*E*)-isomers in the samples of compounds **3a** and **4a** (entries 1 and 3) was less than 2% (practically pure (*Z*)-isomers). The (*E*)-isomer of product **4b** was also isolated, containing less than 4% of the (*Z*)-isomer.

Table 1. A *Z*/*E* ratio of the products **3a**,**b** and **4a**,**b** in the reaction of propynamides **1a**,**b** with diselenides **2a**,**b**.

Entries	Amides 1a,b, R^1NR^2	Diselenides 2a,b	Product, Yield	Ratio (*Z*/*E*)	The Fractions Isolated by Column Chromatography
entry 1	**1a** HNPh	BuSeSeBu (**2a**)	**3a**, 94%	100/7	(*Z*/*E*) = 100/2
entry 2	**1b** Morpholinyl	BuSeSeBu (**2a**)	**3b**, 90%	100/7	(*Z*)
entry 3	**1a** HNPh	BnSeSeBn (**2b**)	**4a**, 90%	100/4	(*Z*/*E*) = 100/2
entry 4	**1b** Morpholinyl	BnSeSeBn (**2b**)	**4b**, 93%	100/8	47% (*Z*); 25% (*Z*/*E*) = 100/33; 2% (*Z*/*E*) = 4/100

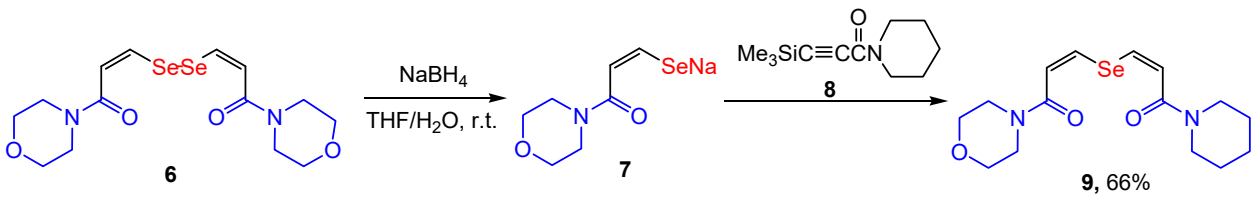
The process was accompanied by the desilylation of the trimethylsilyl group. This desilylation reaction proceeded under the action of water and was catalyzed by a base, sodium hydroxide, formed by the nucleophilic addition of sodium selenolates to the triple bond (Scheme 2).



Scheme 2. The reaction path of the formation of the products **3a**,**b** and **4a**,**b**.

The desilylation reaction of the trimethylsilyl group can occur in the starting 3-trimethylsilyl-2-propynamides **1a**,**b**, as well as in the intermediate **A**, formed by the nucleophilic addition of sodium selenolates to the triple bond (Scheme 2).

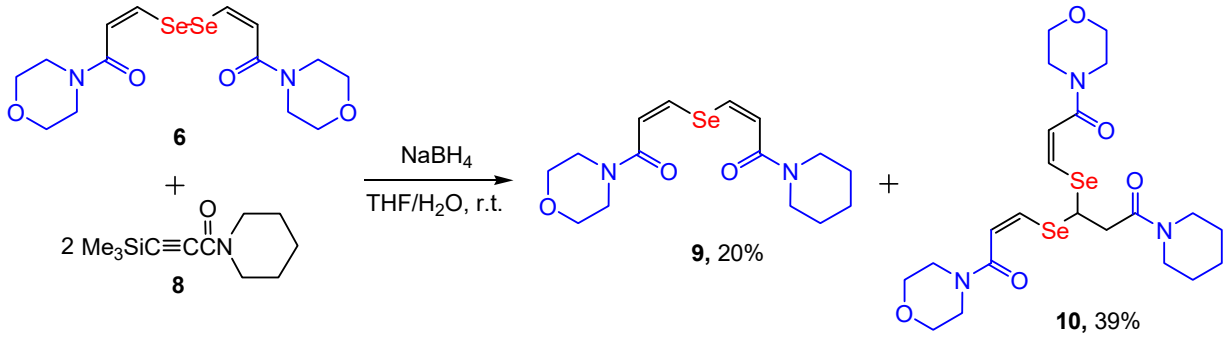
Unsymmetrical divinyl selenides with the amide function at the double bond have not yet been described in the literature. We obtained unsymmetrical bis(3-amino-3-oxo-1-propenyl) selenide **9** in 66% yield from divinyl diselenide **6** and 3-trimethylsilyl-2-propynamide **8**, containing a piperidine heterocycle in the amide function (Scheme 3).



Scheme 3. The addition reaction of sodium selenolate **7** to acetylene **8**.

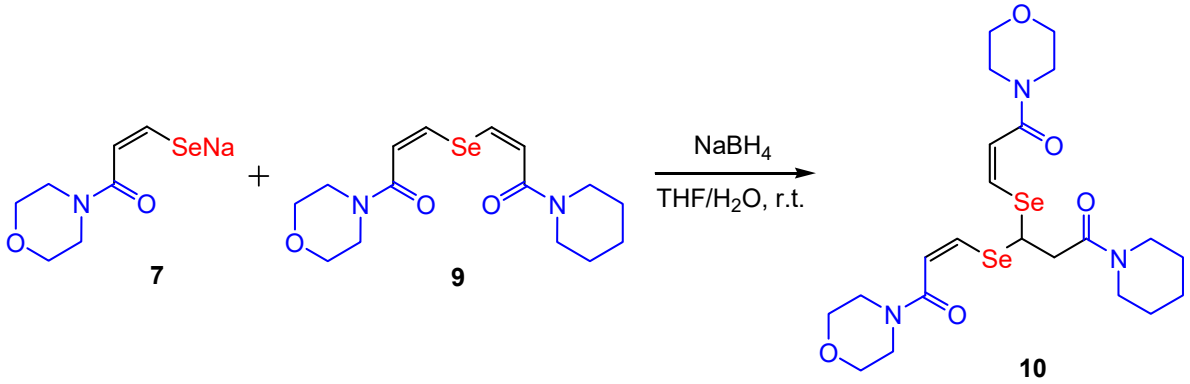
The reaction was carried out through the generation of sodium selenolate **7** from divinyl diselenide **6** under the action of sodium borohydride in a THF/water mixture, followed by the addition of 3-trimethylsilyl-2-propynamide **8** to the reaction mixture at room temperature (Scheme 3). We previously obtained diselenide **6** in a high yield through the nucleophilic addition of sodium diselenide to 3-trimethylsilyl-2-propynamides [39].

Conducting another experiment, we changed the sequence of adding reagents to the reaction mixture. Sodium borohydride was added portionwise to the solution of divinyl diselenide **6** and 3-trimethylsilyl-2-propynamide **8** in a THF/water mixture. In this case, along with unsymmetrical divinyl selenide **9**, a very interesting compound **10** was obtained, containing two selanyl-2-propenamide moieties and three cyclic amide groups (Scheme 4).



Scheme 4. The reaction of divinyl diselenide **6** with acetylene **8**.

The yields of compound **10** and unsymmetrical divinyl selenide **9** after purification by column chromatography were 39% and 20%, respectively (Scheme 5). It is assumed that the route of the formation of polyfunctional compound **10** involves the nucleophilic addition of sodium selenolate **7** (formed from divinyl diselenide **6**) to unsymmetrical divinyl selenide **9** (Scheme 5). This assumption about the formation route of compound **10** was confirmed by an additional experiment.

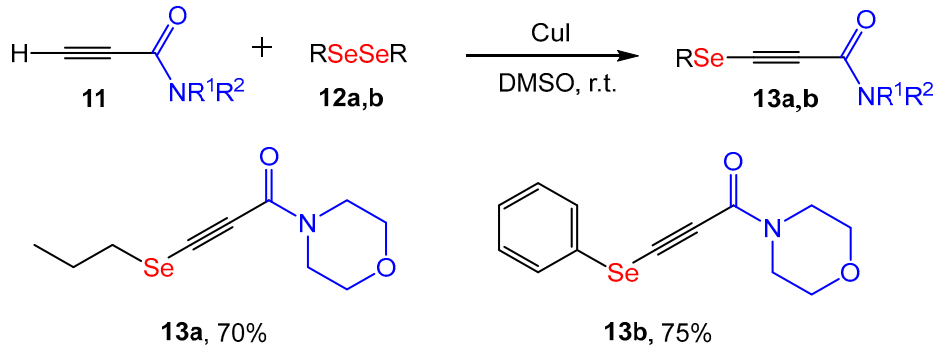


Scheme 5. The path of the formation of compound **10**.

The reaction of organic diselenides with 2-propynamides with the formation of selanyl-propynamide has not been previously reported. We studied the copper-catalyzed reaction of organic diselenides with 2-propynamide **11**, containing a morpholine heterocycle in the amide group. The CuI-catalyzed reaction of dipropyl and diphenyl diselenides **12a**,**b** with 4-propioloylmorpholine **11** was carried out in DMSO at room temperature, producing acetylenic selenides **13a**,**b** in 70% and 75% yields, respectively (Scheme 6).

Recently, we developed the synthesis of 2,6-bis(1,2,3-triazol-1-yl)-9-selenabicyclo[3.3.1] nonanes through the copper-catalyzed azide-alkynes 1,3-dipolar cycloaddition reaction [47,48]. The $Cu(OAc)_2$/sodium ascorbate catalytic system was used to carry out the cycloaddition reaction. This system has proven to be very effective in the reactions of selenium-containing organic azides with terminal acetylenes [49,50]. The active Cu(I) catalyst was generated in situ from copper acetate by its reduction with sodium ascorbate. It is known that the mechanism of the copper-catalyzed azide-alkynes 1,3-dipolar cycloaddition reactions involves the formation of copper acetylide intermediates [51]. Assuming that the Cu-catalyzed reaction of organic diselenides with 2-propynamide may also involve the

formation of copper acetylide intermediates, we attempted to use the $Cu(OAc)_2$/sodium ascorbate catalytic system in the reaction of diselenides **12a**,**b** with 4-propioloylmorpholine **11** (Scheme 6). The target products **13a**,**b** were also obtained in this case, but in lower yield (about 50%), and the reaction proceeded less selectively.

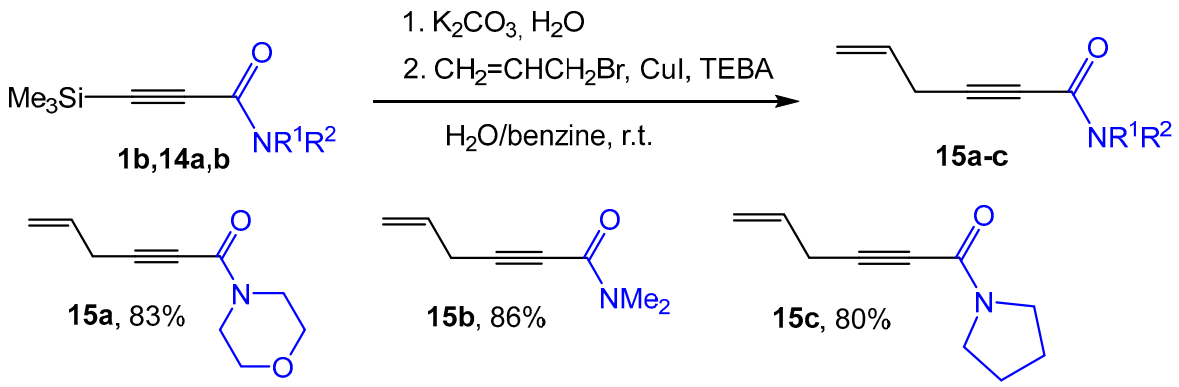


Scheme 6. The Cu-catalyzed reaction of diselenides **12a**,**b** with 4-propioloylmorpholine **11**.

4-Propioloylmorpholine **11** with the terminal triple bond was obtained by desilylation of the corresponding 3-trimethylsilyl-2-propynamide **1b**.

The allylation reaction of propynamides has not yet been reported. We performed the copper-catalyzed allylation reaction of propynamides starting from 3-trimethylsilyl-2-propynamide **1b**,**14a**,**b** and obtained new unsaturated compounds containing both triple and double bonds. The reaction used copper(I) iodide, which has been proven to be an excellent catalyst for the allylation of acetylenes [52,53].

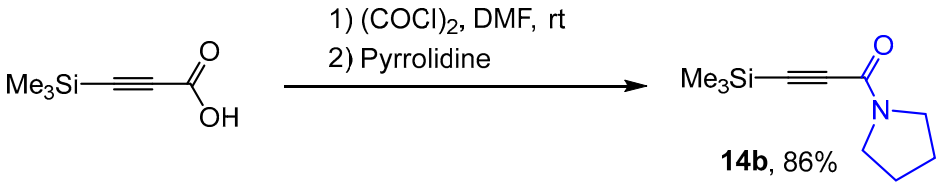
The CuI-catalyzed reaction of 3-trimethylsilyl-2-propynamide **1b**,**14a**,**b** with allyl bromide was carried out at room temperature under phase transfer catalysis conditions (phase transfer catalyst: triethylbenzylammonium chloride) in the two-phase system K_2CO_3/water/benzene affording 5-hexen-2-ynamides **15a–c** in 83%, 86% and 80% yields, respectively (Scheme 7).



Scheme 7. The synthesis of 5-hexen-2-ynamides **15a**–**c**.

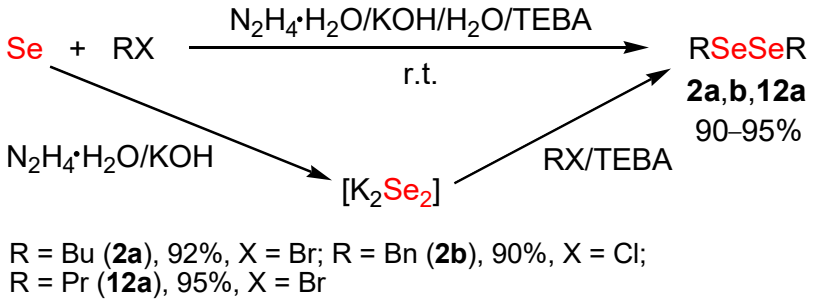
The first stage of this process was the desilylation, followed by the allylation reaction of 2-propynamides with terminal triple bond.

The compound **15c** was obtained from 1-[3-(trimethylsilyl)prop-2-ynoyl]pyrrolidine (**14b**). The synthesis of the latter silylpropynamide has not previously been reported. We obtained the compound **14b** in 86% yield through the reaction of trimethylsilylpropiolic acid with oxalyl chloride followed by amidation (Scheme 8).



Scheme 8. The synthesis of compound **14b**.

Dialkyl diselenides **2a**, **12a** and dibenzyl diselenide **2b** were synthesized in high yields (90–95%) from elemental selenium and corresponding alkyl halides in the two-phase catalytic system: hydrazine hydrate/potassium hydroxide/water/triethylbenzylammonium chloride/alkyl halide (Scheme 9). Alkyl halides also played a role of the organic phase in this reaction, and no organic solvent was added during the synthesis.



Scheme 9. The synthesis of dialkyl diselenides **2a**, **12a** and dibenzyl diselenide **2b**.

Elemental selenium under the action of an aqueous solution of hydrazine hydrate and potassium hydroxide was reduced to potassium diselenide, which underwent the nucleophilic substitution reaction with alkyl halides (butyl bromide, benzyl chloride and propyl bromide) under phase-transfer catalysis conditions at room temperature (Scheme 9).

It is worth noting that hydrazine hydrate selectively reduces elemental selenium to diselenide anion in the presence of potassium hydroxide. The selectivity of the reduction may be determined by the selenium-catalyzed generation of the highly reactive reducing agent diimide from hydrazine [54].

It may be assumed that the target products can be obtained by the reactions of acetylenes containing terminal triple bond. However, 2-propynamides with terminal triple bond are difficult to obtain and even the simplest representatives of these reagents are absent in the catalogs of the most leading suppliers of chemicals. The efficient synthesis of a number of 3-trimethylsilyl-2-propynamides by the reaction of 3-trimethylsilylpropiolic acid with oxalyl chloride, followed by amidation of 3-trimethylsilylprop-2-ynoyl chloride with amines, was previously developed in this institute [27].

Thus, first examples of reactions of 3-trimethylsilyl-2-propynamides and organic diselenides were realized. Efficient and selective methods for the preparation of 3-alkylselanyl-2-propenamides, 3-organylselanyl-2-propynamides and 3-allyl-2-propynamide derivatives were developed based on 3-trimethylsilyl-2-propynamides and organic diselenides.

The structural assignment of the obtained compounds was carried out based on the multinuclear NMR investigations and confirmed by the data from mass spectra, IR data and elemental analysis. Some of the obtained compounds may contain amide rotamers [55]. Figure S1 can be found in Supplementary Materials.

3. Materials and Methods

3.1. General Information

The ^{1}H (400.1 MHz), ^{13}C (100.6 MHz), ^{77}Se (76.3 MHz) and ^{15}N (40.6 MHz) NMR spectra (the spectra can be found in Supplementary Materials) were recorded on a Bruker

DPX-400 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) in $CDCl_3$ or DMSO-d_6 solutions and referred to the residual solvent peaks ($CDCl_3$, δ = 7.27 and 77.1 ppm; DMSO-d_6, δ = 2.50 and 39.6 ppm for ^{1}H- and ^{13}C-NMR, respectively), nitromethane (^{15}N) and dimethyl selenide (^{77}Se).

IR spectra were taken on a Bruker Vertex-70 spectrometer (Bruker, Karlsruhe, Germany). Melting points were determined on a Kofler Hot-Stage Microscope PolyTherm A apparatus (Wagner & Munz GmbH, München, Germany). Elemental analysis was performed on a Thermo Scientific Flash 2000 Elemental Analyzer (Thermo Fisher Scientific Inc., Milan, Italy). The distilled organic solvents and degassed water were used in syntheses. Diphenyl diselenide was purchased from Sigma-Aldrich (St. Louis, MO, USA).

3.2. Synthesis of Vinyl Selenides **3a**,**b** *and* **4a**,**b** *from 3-Trimethylsilyl-2-Propynamides and Organic Diselenides*

General Procedure. Sodium borohydride (30 mg, 0.79 mmol) was added portionwise to a solution of 3-trimethylsilyl-2-propynamide (0.48 mmol) and organic diselenide (0.24 mmol) in THF (2 mL), which contained water (0.5 mL). The mixture was stirred at room temperature for 4 h and water (0.5 mL) and chloroform (2 mL) were added. The mixture was extracted with chloroform (4 × 2 mL) and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was dissolved in chloroform, and precipitated by cold hexane. The target products were isolated by column chromatography on silica gel.

(Z)-N-Phenyl-3-(butylselanyl)-2-propenamide (**3a**). Yield: 94% (*Z*/*E* = 100:7). The product was purified by column chromatography (eluent: chloroform; R(f) = 0.33). Yield: 69 mg (51%), *Z*/*E* = 100:2, white solid; mp 126–128 °C.

^{1}H NMR (400 MHz, d_6-DMSO): δ 0.89 (t, CH_3, ^3J = 7.4, 3H), 1.37 (m, 2H, $CH_3C\underline{H}_2$), 1.64 (m, 2H, $C\underline{H}_2CH_2Se$), 2.65 (t, ^3J = 7.3 Hz, 2H, CH_2Se, *Z*-), 2.91 (t, ^3J = 7.3 Hz, 2H, CH_2Se, E-), 6.37 (d, ^3J = 15.4 Hz, 1H, =CHCO, *E*-), 6.58 (d, ^3J = 9.4 Hz, 1H, =CHCO, *Z*-), 7.03 (t, ^3J = 7.5 Hz, 1H, H^p), 7.29 (dd, ^3J = 7.5 Hz, ^3J = 8.3 Hz 2H, H^m), 7.62 (d, ^3J = 8.3 Hz, 2H, H^o), 7.67 (d, ^3J = 9.4 Hz, 1H, SeC=, *Z*-), 7.94 (d, ^3J = 15.4 Hz, 1H, SeC=, *E*-), 9.90 (br s, 1H, NH, *E*-), 10.05 (br s, 1H, NH, *Z*-).

^{13}C NMR (100 MHz, d_6-DMSO): δ 13.5 (CH_3), 22.3 ($CH_3\underline{C}$), 27.5 ($SeCH_2$, $^1J_{Se–C}$ = 55.1 Hz), 32.7 ($\underline{C}CH_2Se$), 118.8 (C^o), 119.6 (=$\underline{C}$CO), 123.1 (C^p), 128.8 (C^m), 139.3 (C^i), 144.3 (SeC=, $^1J_{Se–C}$ = 134.3 Hz), 164.8 (C=O).

^{77}Se NMR (76 MHz, d_6-DMSO): δ 365.2. ^{15}N NMR (40 MHz, d_6-DMSO): δ −244.1 ($^1J_{N–H}$ = 90.7 Hz); The 2D ^{15}N NMR HMBC {^{1}H–^{15}N} spectrum contain cross-peaks of the nitrogen atom with protons of H^o and NH.

IR (KBr): 3320, 3203, 3134, 3066, 3024, 2954, 2923, 2859, 1643 (C=O), 1599 (C=C, Ph), 1549 (C=C, Ph), 1535 (C=C, Ph), 1494, 1435, 1363, 1306, 1243, 1188, 1168, 974, 898, 839, 791, 752, 719, 694, 613, 508 cm^{-1}.

Anal. calcd for $C_{13}H_{17}NOSe$ (282.24): C 55.32, H 6.07, N 4.96, Se 27.98; found: C 55.56, H 6.20, N 4.46, Se 28.06.

(Z)-N-Morpholino-3-(butylselanyl)-2-propenamide (**3b**): Yield: 90%, *Z*/*E* = 100:7. Pure *Z*-isomer was isolated by column chromatography (eluent: chloroform:ethyl acetate = 1:1; R_f = 0.93). Yield: 72 mg (54%); viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, CH_3, ^3J = 7.3 Hz, 3H), 1.40 (m, 2H, $CH_3C\underline{H}_2$), 1.68 (m, 2H, $C\underline{H}_2CH_2Se$), 2.62 (t, ^3J =7.5 Hz, 2H, CH_2Se), 3.49 (br m, 2H, $H^{3,5}$), 3.65 (br m, 6H, $H^{2,6}$, $H^{3,5}$), 6.63 (d, ^3J = 9.4 Hz, 1H, =CHCO), 7.56 (d, ^3J = 9.4 Hz, 1H, SeCH=).

^{13}C NMR (100 MHz, $CDCl_3$): 13.6 (CH_3), 22.7 (CH_3CH_2), 28.5 (CH_2Se, $^1J_{Se–C}$ = 56.2 Hz), 32.9 ($\underline{C}H_2CH_2$), 41.9, 45.8 ($C^{2,6}$), 66.6, 66.8 ($C^{3,5}$), 114.0 (=CCO), 147.3 (SeC=, $^1J_{Se–C}$ = 136.2 Hz), 166.1 (C=O).

^{77}Se NMR (76 MHz, d_6-DMSO): δ 373.1. ^{15}N NMR (40 MHz, d_6-DMSO): δ −268.2; The 2D ^{15}N NMR HMBC {^{1}H–^{15}N} spectrum contain cross-peaks of the nitrogen atom with protons of $H^{3,5}$ and the =CHCO group.

IR (KBr): 3165, 2958, 2922, 2856, 1620 (C=O), 1552 (C=C, Ph), 1433, 1348, 1298, 1264, 1236, 1202, 1116, 1043, 968, 914, 838, 783, 740, 627, 574, 534 cm^{-1}.

Anal. calcd for $C_{11}H_{19}NO_2Se$ (276.23): C 47.83, H 6.93, N 5.07, Se 28.58; found: C 47.48, H 6.84, N 4.82, Se 28.49.

(Z)-N-Phenyl-3-(benzylselanyl)-2-propenamide (**4a**). Yield: 90%, *Z*/*E* = 100:8. The product was purified by column chromatography (eluent: chloroform, R_f = 0.96); Yield: 106 mg (70%); *Z*/*E* = 100:2, white solid; mp 163–164 °C.

^{1}H NMR (400 MHz, d_6-DMSO, Figure 2): δ 3.94 (s, 2H, CH_2Se, *Z*-), 4.20 (s, 2H, CH_2Se, *E*-), 6.44 (d, ^3J = 15.9 Hz, 1H, =CHCO, *E*-), 6.56 (d, ^3J = 9.4 Hz, 1H, =CHCO, *Z*-), 7.02 (t, ^3J = 7.3 Hz, 1H, H^p), 7.20 (t, ^3J = 7.3 Hz, 1H, $H^{p'}$), 7.26–7.33 (m, 4H, H^m, $H^{m'}$), 7.36 (d, ^{3}J = 7.0 Hz, 2H, $H^{o'}$), 7.59 (d, ^3J = 7.8 Hz, 2H, H^o), 7.75 (d, ^3J = 9.4 Hz, 1H, SeCH=, *Z*-), 7.97 (d, ^3J = 15.9 Hz, 1H, SeCH=, *E*-), 9.93 (br s, 1H, NH, *E*-), 10.08 (br s, 1H, NH, *Z*-).

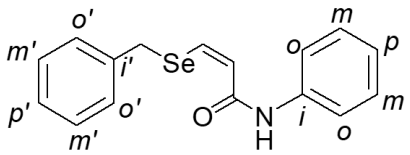


Figure 2. The structure of the compound **4a**.

^{13}C NMR (100 MHz, d_6-DMSO, Figure 2): δ 30.9 ($SeCH_2$, $^1J_{Se-C}$ = 53.2 Hz), 119.0 (C^o), 120.0 (=C̲CO), 123.3 (C^p), 126.6 ($C^{p'}$), 128.7 ($C^{m'}$), 128.8 (C^m), 128.9 ($C^{o,o'}$), 139.3 ($C^{i'}$), 140.3 (C^i), 143.9 (SeC=, $^1J_{Se-C}$ = 137.3 Hz), 164.9 (C=O).

^{77}Se NMR (76 MHz, d_6-DMSO): δ 447.1. ^{15}N NMR (40 MHz, d_6-DMSO): δ −245.8 ($^1J_{N-H}$ = 90.0 Hz); The 2D ^{15}N NMR HMBC {^{1}H–^{15}N} spectrum contain cross-peaks of N-atom with protons of H^o and NH.

IR (KBr): 3443, 3247, 3117, 3036, 1633 (C=O), 1593, 1564, 1531, 1494, 1441, 1359, 1297, 1254, 1180, 1164, 1068, 1027, 983, 909, 839, 791, 746, 692, 613, 502 cm^{-1}.

Anal. calcd for $C_{16}H_{15}NOSe$ (316.26): C 60.76, H 4.78, N 4.43, Se 24.97; found: C 60.75, H 4.65, N 4.32, Se 25.13.

1-Morpholino-3-(benzylselanyl)-2-propen-1-one (**4b**). Yield: 93%, *Z*/*E* = 100:8). Pure *Z*-isomer (67 mg), a mixture of *Z*,*E*-isomers (36 mg, *Z*/*E* = 100:33) and almost pure *E*-isomer (3 mg, *Z*/*E* = 4:100) were isolated by column chromatography (eluent: chloroform:ethyl acetate = 1:1; R_f = 0.88). *Z*-isomer, yield: 74%; white solid; mp 124–126 °C.

(*Z*)-4b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40–3.52 (m, 2H, $H^{3,5}$), 3.53–3.75 (m, 6H, $H^{2,6}$, $H^{3,5}$), 3.87 (s, 2H, CH_2Se), 6.61 (d, ^3J = 9.4 Hz, 1H, =CHCO), 7.18–7.25 (m, 2H, H^m), 7.29–7.35 (m, 3H, Ph), 7.56 (d, ^3J = 9.4 Hz, 1H, SeCH=).

^{13}C NMR (100 MHz, $CDCl_3$): δ 31.5 ($SeCH_2$, $^1J_{Se-C}$ = 55.1 Hz), 41.9 ($C^{3,5}$), 45.8 ($C^{3,5}$), 66.6, 66.8 ($C^{2,6}$), 114.1 (=C̲CO), 126.7 (C^p), 128.6 ($C^{o,m}$), 128.9 ($C^{o,m}$), 139.0 (C^i), 145.9 (SeC=, $^1J_{Se-C}$ = 137.7 Hz), 165.9 (C=O).

^{77}Se NMR (76 MHz, $CDCl_3$): δ 442.4. ^{15}N NMR (40 MHz, $CDCl_3$): δ–266.2; The 2D ^{15}N NMR HMBC {^{1}H–^{15}N} spectrum contain cross-peaks of the nitrogen atom with the proton of the =CHCO group.

IR (KBr): 3499, 3443, 3045, 2958, 2905, 2849, 1611 (C=O), 1546, 1451, 1349, 1304, 1266, 1229, 1190, 1107, 1063, 1036, 965, 916, 834, 774, 751, 695, 664, 618, 577, 533, 453 cm^{-1}.

Anal. calcd for $C_{14}H_{17}NO_2Se$ (296.22): C 54.20, H 5.52, N 4.51, Se 25.45; found: C 54.23, H 5.36, N 4.27, Se 25.26.

(*E*)-4b.^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42–3.55 (m, 2H, $H^{3,5}$), 3.55–3.75 (m, 6H, $H^{2,6}$, $H^{3,5}$), 4.08 (s, 2H, CH_2Se), 6.45 (d, ^3J = 15.0 Hz, 1H, =CHCO), 7.18–7.25 (m, 2H, H^m), 7.29–7.35 (m, 3H, Ph), 8.02 (d, ^3J = 15.0 Hz, 1H, SeCH=).

^{13}C NMR (100 MHz, $CDCl_3$): δ 30.2 ($SeCH_2$), 42.4 ($C^{3,5}$), 46.0 ($C^{3,5}$), 66.9 ($C^{2,6}$), 118.6 (=C̲CO), 127.5 (C^p), 128.9 ($C^{o,m}$), 137.4 (C^i), 141.0 (SeC=), 163.9 (C=O).

^{77}Se NMR (76 MHz, $CDCl_3$): δ 357.2.

3.3. Synthesis of Compounds **9** *and* **10**

(Z)-3-[(Z)-3-oxo-3-piperidino-1-propenyl]selanyl-1-morpholino-2-propen-1-one (**9**). To a stirred mixture of diselenide **6** (39 mg, 0.09 mmol), THF (3 mL) and water (1 mL), $NaBH_4$ (20 mg) portions were added at room temperature. Then, 3-trimethylsilyl-2-propynamide **8** (0.18 mmol) in THF (2 mL) was added. The solution was stirred at room temperature for 2 h and $CHCl_3$ (2.0 mL) were added. An aqueous layer was extracted with $CHCl_3$ (4 × 2 mL) and extract was dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$, precipitated by cold hexane that afforded the compound **9** (42 mg, 66%); white solid; mp 204–205 °C.

^{1}H NMR (400 MHz, $CDCl_3$, Figure 3): δ 1.56, 1.62 (br m, 6H, $H^{3',5'}$, $H^{4'}$), 3.46, 3.58, 3.66 (br m, 12H, $H^{2',6'}$, $H^{3,5}$, $H^{2,6}$), 6.69 (d, ^3J = 9.8 Hz, 1H, =CHCO), 6.76 (d, ^3J = 9.7 Hz, 1H, =CH′CO), 7.48 (d, ^3J = 9.7 Hz, 1H, SeCH′=), 7.58 (d, ^3J = 9.8 Hz, 1H, SeCH=).

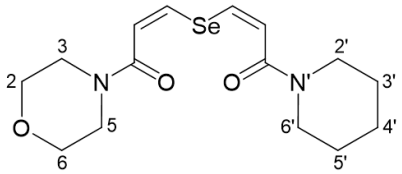


Figure 3. The structure of the compound **9**.

^{13}C NMR (100 MHz, $CDCl_3$, Figure 3): δ 24.5 ($C^{4'}$), 25.5, 26.6 ($C^{3',5'}$), 42.0 ($C^{3,5}$), 49.9 ($C^{2',6'}$), 46.0 ($C^{3,5}$), 46.8 ($C^{2',6'}$), 66.8 ($C^{2,6}$), 115.8 (=CCO, $^1J_{C–H}$ = 159.4 Hz), 117.0 (=C′CO, $^1J_{C–H}$ = 161.1 Hz), 146.9 (SeC′=, $^1J_{C–H}$ = 169.7 Hz, $^2J_{C–H}$ = 5.1 Hz), 148.9 (SeC=, $^1J_{C–H}$ = 169.5 Hz, $^2J_{C–H}$ = 5.9 Hz), 165.3 (C′=O), 165.7 (C=O).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ 518.5. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ −266.2 (N), −256.8 (N′); The 2D ^{15}N NMR HMBC {^{1}H–^{15}N} spectrum contain cross-peaks of N-atom with protons of $H^{2,6}$, =CHCO and N′-atom with protons of $H^{3',5'}$, =CH′CO.

IR (KBr): 2930, 2855, 1613 (C=O), 1564 (C=C), 1441, 1344, 1233, 1114, 1036, 1019, 962, 856, 831, 783, 644, 601, 573 cm^{-1}.

MS (EI), m/z (%): 358 (6) $[M + 1]^+$, 356 (4) $[M - 1]^+$, 277 (11), 220 (9), 218 (16), 216 (8), 187 (7), 161 (17), 159 (10), 140 (23), 138 (59), 114 (14), 112 (24), 86 (32), 85 (13), 84 (100), 82 (8), 70 (26), 69 (27), 57 (8), 56 (31), 55 (26), 44 (8), 42 (20), 41 (27).

Anal. calcd for $C_{15}H_{22}N_2O_3Se$ (357.31): C 50.42, H 6.21, N 7.84, Se 22.10; found: C 50.27, H 6.05, N 7.93, Se 22.01.

(Z)-3-[(1-[(Z)-3-morpholino-3-oxo-1-propenyl]selanyl-3-oxo-3-piperidinopropyl)selanyl]-1-morpholino-2-propen-1-one (**10**).

$NaBH_4$ (30 mg) was added portionwise to a stirred mixture solution of diselenide **6** (63 mg, 0.14 mmol) and 3-trimethylsilyl-2-propynamide **8** (59 mg, 0.28 mmol) in THF (2.5 mL) and water (0.5 mL). The solution was stirred at room temperature for 2 h, and water (0.5 mL) and $CHCl_3$ (2.0 mL) were added. The aqueous layer was extracted with $CHCl_3$ (4 × 2 mL), and the extract was dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was dissolved in chloroform, precipitated by cold hexane and subjected to column chromatography (SiO_2, eluent: ethyl acetate/methanol = 30/1), resulting in the compounds **9** (20%, R_f = 0.76) and **10** (32 mg, 39%, R_f = 0.47); white solid; mp 60–62 °C.

^{1}H NMR (400 MHz, $CDCl_3$, Figure 4): δ 1.56, 1.64 (br m, 6H, $H^{3',5'}$, H^4), 3.10 (d, ^3J = 7.1 Hz, 2H, CH_2CO), 3.39–3.76 (m, 20H, $H^{2,6}$, $H^{3,5}$, $H^{2',6'}$), 4.57 (t, ^3J = 7.1 Hz, 1H, Se_2CH), 6.70, 6.76 (d, ^3J = 9.2 Hz, 2H, =CHCO), 7.76, 7.89 (d, ^3J = 9.2 Hz, 2H, SeCH=).

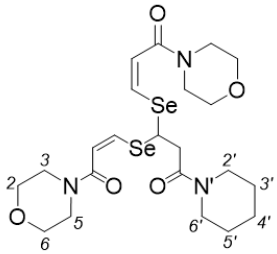


Figure 4. The structure of the compound **10**.

^{13}C NMR (100 MHz, $CDCl_3$, Figure 4): δ 24.6, 25.6, 26.7 ($C^{3',5'}$, $C^{4'}$), 34.7 (Se_2CH), 40.9 ($\underline{C}H_2CO$), 42.2, 43.1, 46.0, 46.8 ($C^{3,5}$), 43.4, 46.3 ($C^{2',6'}$), 66.6, 66.8 ($C^{2,6}$).

^{77}Se NMR (76.3 MHz, $CDCl_3$): δ 477.0, 482.2. ^{15}N NMR (40.6 MHz, $CDCl_3$): δ −262.7 (N), −256.4 (N′); The 2D ^{15}N NMR HMBC {^{1}H–^{15}N} spectrum contains cross-peaks of nitrogen atoms with $H^{3',5'}$ and $H^{2,6}$ protons.

MS, m/z: 577 (9) [M], 279 (10), 277 (8), 220 (20), 218 (28), 161 (18), 159 (11), 140 (42), 138 (44), 135 (15), 133 (12), 114 (40), 112 (19), 86 (69), 84 (100), 70 (56), 69 (24), 57 (30), 56 (66), 55 (36), 44 (13), 42 (38), 41 (34).

Anal. calcd for $C_{22}H_{33}N_3O_5Se_2$ (577.43): C 45.78, H 5.76, N 7.28, Se 27.35; found: C 46.07, H 5.95, N 6.97, Se 27.05.

3.4. Synthesis of Acetylenic Selenides **13a**,**b**

The solution of propynamide (0.36 mmol), CuI (34 mg, 0.18 mmol) and diorganyl diselenide (0.18 mmol) in DMSO (1 mL) was stirred at room temperature for 20 h. Water (3.0 mL) was added and the mixture was extracted with Et_2O (5 × 5.0 mL), and the organic lay was washed with water (4 × 10 mL). Washing water was again extracted with Et_2O (2 × 15 mL). The organic phase was dried over Na_2SO_4. After removal of the solvent on a rotary evaporator, the residue was dried in vacuum while yielding the product, which did not require additional purification.

4-[3-(propylselanyl)prop-2-ynoyl]morpholine (**13a**). *Yield: 66 mg (70%); viscous oil.*

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, ^3J =7.2 Hz, 3H, CH_3), 1.85 (q, ^3J = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 2.87 (t, ^3J = 7.2 Hz, 2H, CH_2Se), 3.59–3.66 (m, 4H, $H^{3,5}$), 6.66–3.70 (br m, 4H, $H^{2,6}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (CH_3), 23.3 (CH_2), 31.8 (Se–CH_2), 41.4, 46.8 ($C^{3,5}$) 66.1, 66.5 ($C^{2,6}$), 79.1 (SeC≡, $^1J_{Se\text{-}C}$ = 204.1 Hz), 93.2 (≡$\underline{C}$CO, $^2J_{Se\text{-}C}$ = 37.7 Hz), 152.0 (C=O).

^{77}Se NMR (76 MHz, $CDCl_3$): δ 163.5. ^{15}N NMR (40 MHz, $CDCl_3$): δ −261.3.

$C_{10}H_{15}NO_2Se$ (260.19): calcd. C 46.16, H 5.81, N 5.38, Se 30.35; found: C 45.89, H 5.68, N 5.22, Se 30.61.

4-[3-(Phenylselanyl)prop-2-ynoyl]morpholine (**13b**). *Yield: 80 mg (75%); viscous oil*

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63–3.69 (m, 4H, $H^{3,5}$), 3.69–3.76 (m, 4H, $H^{2,6}$), 7.32–7.41 (m, 3H, $H^{3',4',5'}$), 7.55–7.62 (m, 2H, $H^{2',6'}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 40.7, 47.0 ($C^{3,5}$), 66.3, 66.7 ($C^{2,6}$), 77.9 (SeC≡, $^1J_{Se–C}$ = 197.4 Hz), 96.0 (≡CCO, $^2J_{Se–C}$ = 35.8 Hz), 126.5 ($C^{1'}$), 128.1 ($C^{4'}$), 129.8 ($C^{3'}$), 130.2 ($C^{2'}$), 152.0 (C=O).

^{77}Se NMR (76 MHz, $CDCl_3$): δ 279.3 Hz. ^{15}N NMR (40 MHz, $CDCl_3$): δ −262.6 (NH, $^1J_{N–H}$ = 90.4 Hz).

$C_{13}H_{13}NO_2Se$ (294.21): calcd. C 53.07, H 4.45, N 4.76, Se 26.84; found: C 52.95, H 4.47, N 4.64, Se 27.00.

3.5. Synthesis of Compound **14b**

1-[3-(Trimethylsilyl)prop-2-ynoyl]piperidine (**14b**). Compound was prepared by the method [27]. Yield: 86%; beige powder; mp 37–38 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.23 (s, 9H, Me_3Si), 1.86–1.98, 1.99–2.03* (m, 4H, $H^{3,4}$), 3.31*, 3.46, 3.63 (t, ^3J = 6.5 Hz, 4H, $H^{2,5}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ −1.0 (Si–C), 24.3, 25.0 ($C^{3,4}$), 44.9, 47.8 ($C^{2,5}$), 95.0 (Si–C≡), 96.9 (≡CCO), 151.7 (C=O).

^{15}N NMR (40 MHz, $CDCl_3$): δ −245.9. ^{29}Si NMR (79 MHz, $CDCl_3$):δ −15.4. IR (KBr): 2965, 2885, 1636 (C=O), 1472, 1423, 1340, 1251, 1227, 1196, 1176, 1117, 1046, 1006, 967, 912, 847, 761, 732, 705, 630, 604, 572.

$C_{10}H_{17}NOSi$ (195.33): calcd. C 61.49, H 8.77, N 7.17, Si 14.38; found: C 61.55, H 8.64, N 7.26, Si 14.48. *Content of other rotamer 10%.

3.6. Synthesis of 5-Hexen-2-Ynamides **15a–c**

Potassium carbonate (K_2CO_3, 14 mg, 0.10 mmol) was added to a solution of 3-trimethylsilyl-2-propynamide (0.50 mmol) in water (1.5 mL) and the mixture was stirred for 1 h. Another portion of potassium carbonate (86 mg. 0.62 mmol) and CuI (95 mg, 0.50 mmol) were added followed by the addition of a solution of allyl bromide (73 mg, 0.60 mmol) in benzene (1 mL) and TEBA (2 mg). The reaction mixture was stirred for 96 h at room temperature and extracted with methylene chloride (6 × 5 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed on a rotary evaporator. The residue was dried in vacuum, yielding the target product as colorless viscous liquids.

1-Morpholino-5-hexen-2-yn-1-one (**15a**). Yield: 83%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12–3.20 (m, 2H, CH_2C≡), 3.62–3.68 (m, 4H, $H^{3,5}$), 3.68–3.80 (m, 4H, $H^{2,6}$), 5.18, 5.32 (d, ^3J = 10.0 Hz, 16.6 Hz, 2H, =CH_2), 5.75–5.86 (m, 1H, =CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 ($\underline{C}H_2C$≡), 41.8, 47.2 ($C^{3,5}$), 66.4, 66.9 ($C^{2,6}$) 75.2 (≡$\underline{C}$CO), 90.4 ($CH_2\underline{C}$≡), 117.5 (=CH_2), 130.3 (CH=), 153.1 (C=O).

Anal. Calcd for $C_{10}H_{13}NO_2$ (179.22): C 67.02; H 7.31; N 7.82%. Found: C 66.79; H 7.13; N 8.02%.

N,N-dimethyl-5-hexen-2-ynamide (**15b**). Yield: 86%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (s, 3H, CH_3), 3.09–3.15 (m, 2H, CH_2C≡), 3.19 (s, 3H, CH_3), 5.15, 5.32 (d, ^3J = 9.9 Hz, 16.9 Hz, 2H, =CH_2), 5.72–5.85 (m, 1H, =CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 ($\underline{C}H_2C$≡), 34.0, 38.3 (CH_3), 76.0 (≡$\underline{C}$CO), 89.3 ($CH_2\underline{C}$≡), 117.3 (=CH_2), 130.6 (CH=), 154.6 (C=O).

Anal. Calcd for $C_8H_{11}NO$ (137.18): C 70.04; H 8.08; N 10.21%. Found: C 69.86; H 7.89; N 9.94%.

1-(1-Pyrrolidinyl)-5-hexen-2-yn-1-one (**15c**). Yield: 80%.

^{1}H NMR (400 MHz, $CDCl_3$): 1.85–2.04 (m, 4H, $H^{3,4}$), 3.11–3.18 (m, 2H, CH_2C≡), 3.47, 3.64 (t, ^3J = 6.8 Hz, 6.4 Hz, 4H, $H^{2,5}$), 5.17, 5.34 (d, ^3J = 9.9 Hz, 17.0 Hz, 2H, =CH_2), 5.75–5.87 (m, 1H, =CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 ($\underline{C}H_2C$≡), 24.8, 25.4 ($C^{3,4}$), 45.2, 48.2 ($C^{2,5}$) 76.9 (≡$\underline{C}$CO), 87.7 ($CH_2\underline{C}$≡), 117.2 (=CH_2), 130.7 (CH=), 152.7 (C=O).

Anal. Calcd for $C_{10}H_{13}NO$ (163.22): C 73.59; H 8.03; N 8.58%. Found: C 73.85; H 7.86; N 8.75%.

3.7. Synthesis of Organic Diselenides **2a**,**b**,**12a**

A mixture of powdered selenium (7.9 g, 0.1 mol), hydrazine hydrate (6 mL), KOH (8 g) and water (40 mL) was stirred at room temperature for 4 h. Alkyl halide (0.12 mol) and TEBA (0.2 g) were added, and the mixture was vigorously stirred for 4 h. The mixture was extracted with hexane (3 × 20 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed by a rotary evaporator to give organic diselenides **2a**,**b**,**12a** in 90–95% yields (Scheme 9).

4. Conclusions

Efficient and selective methods for the preparation of 3-alkylselanyl-2-propenamides, 3-organylselanyl-2-propynamides and 3-allyl-2-propynamide derivatives were developed based on 3-trimethylsilyl-2-propynamides and organic diselenides. The copper-catalyzed reaction of organic diselenides with 4-propioloylmorpholine was conducted in DMSO

at room temperature to yield corresponding acetylenic selenides. The reaction of 3-trimethylsilyl-2-propynamides with dialkyl diselenides was carried out in the system $NaBH_4/H_2O/K_2CO_3/THF$ and was accompanied by the generation of sodium alkylselenolates and desilylation. The nucleophilic addition of sodium alkylselenolates to propynamides occurred in a regio- and stereoselective fashion, producing corresponding (*Z*)-vinyl selenides in 90–94% yields. Unsymmetrical divinyl selenide with the amide groups was synthesized from (*Z*,*Z*)-bis(3-morpholino-3-oxo-1-propenyl) diselenide and 1-[3-(trimethylsilyl) prop-2-ynoyl]piperidine. Using the same starting compounds, a very unusual product: (*Z*)-3-[(1-[(*Z*)-3-morpholino-3-oxo-1-propenyl]selanyl-3-oxo-3-piperidinopropyl)selanyl]-1-morpholino-2-propen-1-one was obtained in 39% yield. The copper-catalyzed allylation reaction of propynamides was carried out. 3-Trimethylsilyl-2-propynamides were used as starting material in this reaction, which was accompanied by desilylation to form 3-allyl-2-propynamides in 80–86% yields.

The obtained products are promising intermediates for organic synthesis. The synthesized organoselenium compounds with the amide group can exhibit glutathione peroxidase-like activity.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal13101326/s1, Figure S1: Examples of ^{1}H and ^{13}C NMR spectra of the products.

Author Contributions: Conceptualization, V.A.P. and M.V.A.; methodology, V.A.P. and M.V.A.; formal analysis, M.V.A. and M.V.M.; investigation, M.V.A. and L.I.L.; data curation, V.A.P. and M.V.M.; supervission, V.A.P.; Writing—original draft preparation, M.V.A.; Writing—review and editing, V.A.P. and M.V.M. All authors have read and agreed to the published version of the manuscript.

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