Synthesis of α,β-Unsaturated Caprolactams Starting from Heterocyclic Imines

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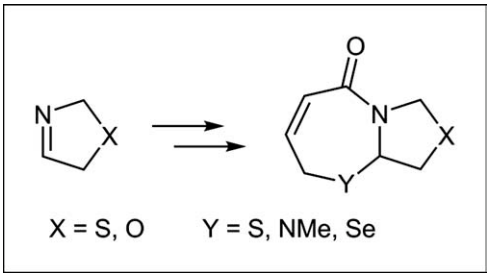

New classes of α,β-unsaturated caprolactams containing variable heteroatoms in δ-position were synthesized from heterocyclic imines as a starting material. The synthetic route is based on an acid chloride addition followed by a ring-closing metathesis using a ruthenium catalyst.

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INTRODUCTION

α,β-Unsaturated lactams are categorized as interesting structures because of their high bioactivity depending on their functionalities as lactams and Michael acceptors. Derivatives of α,β-unsaturated caprolactams, for example, show central nervous system activity by causing convulsions and loss of muscle control [1]. Furthermore, anticancer activity was reported [2]. Saturated caprolactam derivatives, for example, were effective as anti-inflammatory agent [3] or growth-inhibiting activity on plants [4].

In the recent past, we were able to report the first synthesis of α,β-unsaturated δ-oxacaprolactams. This new substance class was synthesized by using heterocyclic imines as precursors [5]. The reaction of imines with unsaturated acid chlorides followed by treatment with allyl alcohol led to acryl amides, which were used as a starting material in ring-closing metathesis (RCM).

This synthetic route shows potential for further investigations (Fig. 1). Our aim to expand the application range of this technology was realized by inserting different heteroatoms in the lactam structure. In addition to sulfur and nitrogen, the insertion of selenium was shown in one example. Thus, the design of two new substance classes was achieved in case of nitrogen and selenium containing seven-membered lactam structures shown in Figure 1. A few derivatives of α,β-unsaturated δ-thiacaprolactams were yet known, but synthesized in a photochemical reaction [6].

RESULTS AND DISCUSSION

We focused our attention on different heterocyclic imines serving as a starting material in the intended synthetic route. The monocyclic five-membered 2,5-dihydrothiazole **1a** [7] and 2,5-dihydrooxazole **1b** [8] were synthesized by a modified Asinger protocol [9] starting from the α-halogen aldehyde 2-chloro-2-methylpropanal.

In the first step of the synthesis, the heterocyclic imines 2,5-dihydrothiazole **1a** and 2,5-dihydrooxazole **1b** were used as precursors in the addition of unsaturated acid chloride. This type of reaction is based on Leuchs', Wulkow's, and Gerland's work [10], which described the addition of different acid chlorides to 3*H*-indole derivatives followed by addition of the nucleophiles, water, methanol, and ammonia. The insertion of thiols was published by Schwarze *et al*. [11]. Thus, the chosen acryloyl chloride and 2-methylacryloyl chloride were added to the heterocyclic imines **1** (Scheme 1). Without isolation of the α-chloro amides, allyl mercaptan or *N*-allylmethylamine was added in the presence of triethylamine to obtain the acryl amides **2** in yields up to 63% (Table 1).

The introduction of selenium into acryl amides is a demanding task because of the synthesis of allyl selenol. Because of exotic reagents used in known synthesis [12] of allyl selenol, we considered other procedures. The reaction of alkyl halogenides and sodium hydrogen selenide, formed in aqueous or ethanolic solution, leads to aliphatic selenols [13]. To prepare aromatic selenols,

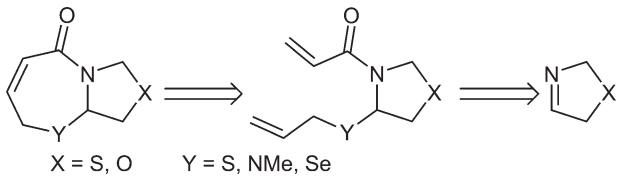
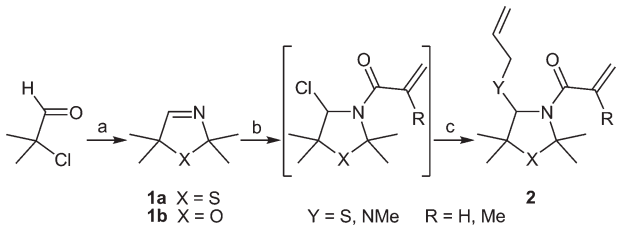


Figure 1. Retrosynthetical consideration of the target structure.

Scheme 1. Synthesis of acryl amides **2** starting from imines **1**. Reagents and conditions: (a) $(CH_3)_2CO$, NH_3, NaSH or H_2O, CH_2Cl_2, 0–5°C, (ii) r.t., 18 h; (b) (i) $H_2C{=}CRCOCl$, CH_2Cl_2, 0–5°C, (ii) r.t., 3 h; (c) (i) $H_2C{=}CHCH_2YH$, Et_3N, CH_2Cl_2, 0–5°C, (ii) **2d–f**: reflux, 5 h, 7–63%.



elementary selenium reacts with aryl magnesium halogenides (Grignard reagent) by inserting between magnesium and aryl moiety [14]. The first called option was not considered because water, respectively, ethanol in excess would act as nucleophile rather than the selenol. So, a selenium-Grignard reagent was formed and directly added to an α-chloro amide synthesized simultaneously of imine **1a** (Scheme 2). The acryl amide **2g** was obtained in small yield of only 6%.

Finally, the desired α,β-unsaturated caprolactams **3** were prepared from acryl amides **2** *via* RCM (Scheme 3). In the literature, only a few examples of RCM starting from acryl amides are described [5,15].

The optimized reaction conditions tested in the synthesis of α,β-unsaturated δ-oxacaprolactams [5] were transferred to the present reactions. The used ruthenium

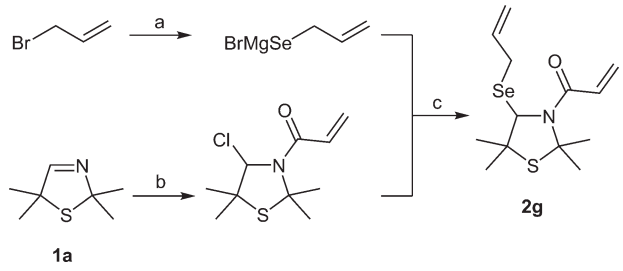
Table 1

Acryl amides **2**.

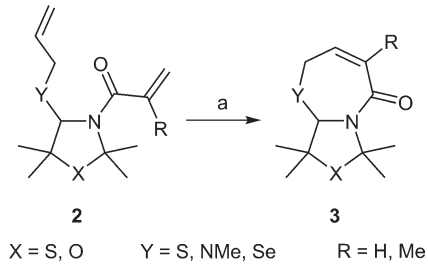
Imine	Acryl amide	X	Y	R	Yield (%)
1a	**2a**	S	S	H	44
1b	**2b**	O	S	H	15
1b	**2c**	O	S	Me	18
1a	**2d**	S	NMe	H	63
1b	**2e**	O	NMe	H	14
1b	**2f**	O	NMe	Me	7[a]

[a] The product was not obtained pure.

Scheme 2. Preparation of selenium containing acryl amide **2g**. Reagents and conditions: (a) (i) Mg, Et_2O, (ii) Se, reflux, 1 h; (b) (i) $H_2C{=}CHCOCl$, Et_2O, 0–5°C, (ii) r.t., 3 h; (c) r.t., 18 h, 6%.



Scheme 3. Ring-closing metathesis to form lactams **3**. Reagents and conditions: (a) 5 mol% catalyst **I**, toluene, r.t. up to 70°C, 2–6 h, 36–90%.



catalyst **I** is comparable to a Grubbs catalyst of the second generation (Fig. 2). The RCM was performed in toluene, starting at room temperature and slowly increasing the temperature up to 70°C. The lactams **3** were obtained in good yields up to 90% (Table 2). Accordingly, the catalyst shows a high tolerance to several functional groups.

CONCLUSION

In conclusion, we synthesized new α,β-unsaturated caprolactams **3** containing sulfur, nitrogen, or selenium in δ-position. Starting from heterocyclic imines **1**, an addition of unsaturated acid chlorides followed by

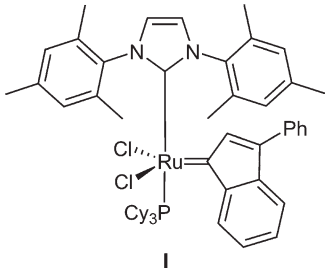


Figure 2. Used ruthenium catalyst **I**.

Table 2

α,β-Unsaturated caprolactams **3**.

Acryl amide	Lactam	X	Y	R	Yield (%)
2a	**3a**	S	S	H	74
2b	**3b**	O	S	H	45
2c	**3c**	O	S	Me	88
2d	**3d**	S	NMe	H	90
2e	**3e**	O	NMe	H	74
2f	**3f**	O	NMe	Me	50
2g	**3g**	S	Se	H	36

substituting the chloride with unsaturated nucleophiles and subsequent RCM led to lactams **3** offering opportunities for further functionalizations.

EXPERIMENTAL

Synthetic procedures were performed on a vacuum line using standard Schlenk techniques under argon. All reagents and solvents were commercial grade and purified before use when necessary. The ruthenium catalyst **I**, catMETium®IMesPCy [CAS 254972-49-1], is available at Strem Chemicals. Preparative column chromatography was carried out using Grace SiO_2 (0.040–0.063 mm, type KG 60). TLC was performed on Merck SiO_2 F254 plates on aluminum sheets. ^1H and ^{13}C NMR spectra were recorded with Bruker AMX R 500 and AM 300 spectrometers. NMR chemical shifts are reported in ppm using TMS as an internal standard. Assignments of the signals in the ^{13}C NMR spectrum were supported by measurements applying COSY and *J* modulated techniques. CI-MS and HRMS spectra were recorded on a Finnigan MAT 212 spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a GoldenGate diamond-ATR unit.

General procedure for the preparation of acryl amides 2 (GP A).. Under argon atmosphere, the respective imine **1** (1 equiv) dissolved in anhydrous dichloromethane (10 mL) was cooled down to 0–5°C before acid chloride (1.1 equiv) in anhydrous dichloromethane (15 mL) was added dropwise. After stirring for 3 h at room temperature, a mixture of allyl mercaptan or *N*-allylmethylamine (2 equiv) and anhydrous triethylamine (1.75 equiv) in anhydrous dichloromethane (10 mL) was added dropwise at 0–5 C. If *N*-allylmethylamine was used, the reaction mixture was refluxed for 5 h. After stirring overnight at room temperature, the solution was poured into ice-water (20 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (20 mL), water (2 × 20 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure and the product was purified as described later.

(*RS*)-1-(4-Allylsulfanyl-2,2,5,5-tetramethylthiazolidin-3-yl)-propenone (2a).. Following **GP A**, 2,5-dihydrothiazole **1a** (0.20 g, 1.4 mmol), acryloyl chloride (0.14 g, 1.5 mmol), allyl mercaptan (70%) (0.30 g, 2.8 mmol), and triethylamine (0.25 g, 2.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 0.17 g (0.6 mmol, 44%); colorless solid; mp 33°C; R_f = 0.53 (*n*-hexane–EtOAc, 7:3); IR: 3078, 2982, 2960, 2933, 1650, 1631, 1607, 1464, 1404, 1376, 1346, 957, 918 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.51 [s, 3 H, $SC(CH_3)_2CH$], 1.60 [s, 3 H, $SC(CH_3)_2CH$], 1.88 [s, 3 H, $SC(CH_3)_2N$], 1.96 [s, 3 H, $SC(CH_3)_2N$], 3.24 (dd, ^2J = 13.4 Hz, ^3J = 7.5 Hz, 1 H, SCH_2CHCH_2), 3.32 (dd, ^2J = 13.4 Hz, ^3J = 6.8 Hz, 1 H, SCH_2CHCH_2), 5.08 (br s, 1 H, NCH), 5.16–5.19 (m, 2 H, SCH_2CHCH_2), 5.69 (d, ^3J = 10.4 Hz, 1 H, $COCHCH_2$), 5.80–5.89 (m, 1 H, SCH_2CHCH_2), 6.32 (d, ^3J = 16.6 Hz, 1 H, $COCHCH_2$), 6.55 (dd, ^3J = 10.4 Hz, ^3J = 16.6 Hz, 1 H, $COCHCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.2 [$SC(CH_3)_2CH$], 31.7 [$SC(CH_3)_2N$], 35.9 (SCH_2CHCH_2), 53.7 [$SC(CH_3)_2CH$], 72.3 [$SC(CH_3)_2N$], 78.0 (NCH), 117.9 (SCH_2CHCH_2), 127.9 ($COCHCH_2$), 130.6 ($COCHCH_2$), 133.8 (SCH_2CHCH_2), 165.0 (CO); MS (CI, isobutane): *m*/*z* (%): 272.1 (28) $[M + H]^+$, 198.1 (100) $[MH - CH_3SH]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{13}H_{22}NOS_2]^+$: 272.1143; found: 272.1143.

(*RS*)-1-(4-Allylsulfanyl-2,2,5,5-tetramethyloxazolidin-3-yl)-propenone (2b).. Following **GP A**, 2,5-dihydrooxazole **1b** (0.64 g, 5.0 mmol), acryloyl chloride (0.50 g, 5.5 mmol), allyl mercaptan (70%) (1.06 g, 10.0 mmol), and triethylamine (0.89 g, 8.75 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 0.19 g (0.7 mmol, 15%); yellow oil; R_f = 0.58 (*n*-hexane–EtOAc, 7:3); IR: 2980, 2937, 1655, 1614, 1411, 1356 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 [s, 3 H, $OC(CH_3)_2CH$], 1.50 [s, 3 H, $OC(CH_3)_2CH$], 1.60 [s, 3 H, $OC(CH_3)_2N$], 1.70 [s, 3 H, $OC(CH_3)_2N$], 3.15–3.27 (m, 2 H, SCH_2CHCH_2), 4.70 (br s, 1 H, NCH), 5.09–5.22 (m, 2 H, SCH_2CHCH_2), 5.72 (dd, ^2J = 1.8 Hz, ^3J = 10.3 Hz, 1 H, $COCHCH_2$), 5.82–5.91 (m, 1 H, SCH_2CHCH_2), 6.39 (dd, ^2J = 1.8 Hz, ^3J = 16.6 Hz, 1 H, $COCHCH_2$), 6.56 (dd, ^3J = 10.3 Hz, ^3J = 16.6 Hz, 1 H, $COCHCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.2 [$OC(CH_3)_2CH$], 27.6 [$OC(CH_3)_2N$], 27.8 [$OC(CH_3)_2N$], 28.7 [$OC(CH_3)_2CH$], 35.6 (SCH_2CHCH_2), 69.7 (NCH), 82.0 [$OC(CH_3)_2CH$], 95.3 [$OC(CH_3)_2N$], 118.0 (SCH_2CHCH_2), 128.0 ($COCHCH_2$), 129.5 ($COCHCH_2$), 133.1 (SCH_2CHCH_2), 163.3 (CO); MS (CI, isobutane): *m*/*z* (%): 256.1 (100) $[M + H]^+$, 182.2 (55) $[M - SCH_2CHCH_2]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{13}H_{22}NO_2S]^+$: 256.1371; found: 256.1369.

(*RS*)-1-(4-Allylsulfanyl-2,2,5,5-tetramethyloxazolidin-3-yl)-2-methylpropenone (2c).. Following **GP A**, 2,5-dihydrooxazole **1b** (0.32 g, 2.5 mmol), 2-methylacryloyl chloride (0.29 g, 2.75 mmol), allyl mercaptan (70%) (0.53 g, 5.0 mmol), and triethylamine (0.45 g, 4.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 0.12 g (0.4 mmol, 18%); light yellow solid; mp 54–56 C; R_f = 0.60 (*n*-hexane–EtOAc, 7:3); IR: 2979, 2936, 1652, 1630, 1410, 1391, 1368 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 [s, 3 H, $OC(CH_3)_2CH$], 1.45 [s, 3 H, $OC(CH_3)_2CH$], 1.60 [s, 3 H, $OC(CH_3)_2N$], 1.65 [s, 3 H, $OC(CH_3)_2N$], 2.04–2.05 [m, 3 H, $COC(CH_3)CH_2$], 3.15 (dd, ^2J = 13.5 Hz, ^3J = 7.5 Hz, 1 H, SCH_2CHCH_2), 3.20 (dd, ^2J = 13.5 Hz, ^3J = 7.1 Hz, 1 H, SCH_2CHCH_2), 4.96 (br s, 1 H, NCH), 5.05–5.11 (m, 2 H, SCH_2CHCH_2), 5.14–5.15 [m, 1 H, $COC(CH_3)CH_2$], 5.24–5.25 [m, 1 H, $COC(CH_3)CH_2$], 5.72–5.80 (m, 1 H, SCH_2CHCH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3 [$COC(CH_3)CH_2$], 25.5 [$OC(CH_3)_2CH$], 27.6 [$OC(CH_3)_2N$], 28.0 [$OC(CH_3)_2N$], 28.6 [$OC(CH_3)_2CH$], 36.3

(SCH_2CHCH_2), 72.0 (NCH), 81.5 [$OC(CH_3)_2CH$], 94.8 [$OC(CH_3)_2N$], 115.4 ($COC(CH_3)CH_2$), 117.4 (SCH_2CHCH_2), 133.7 (SCH_2CHCH_2), 142.2 ($COC(CH_3)CH_2$), 170.5 (CO); MS (CI, isobutane): *m/z* (%): 270.1 (100) $[M + H]^+$, 196.1 (72) $[M - SCH_2CHCH_2]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{14}H_{24}NO_2S]^+$: 270.1528; found: 270.1529.

(*RS*)-1-[4-(Allylmethylamino)-2,2,5,5-tetramethylthiazolidin-3-yl]-propenone (2d).. Following **GP A**, 2,5-dihydrothiazole **1a** (0.20 g, 1.4 mmol), acryloyl chloride (0.14 g, 1.5 mmol), *N*-allylmethylamine (0.20 g, 2.8 mmol), and triethylamine (0.25 g, 2.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 0.24 g (0.9 mmol, 63%); colorless oil; $R_f = 0.67$ (*n*-hexane–EtOAc, 7:3); IR: 3077, 2982, 2932, 1652, 1612, 1468, 1406, 1338, 972, 918 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 [s, 3 H, $SC(CH_3)_2CH$], 1.54 [s, 3 H, $SC(CH_3)_2CH$], 1.93 [s, 3 H, $SC(CH_3)_2N$], 1.94 [s, 3 H, $SC(CH_3)_2N$], 2.57 (s, 3 H, NCH_3), 3.42 (dd, ^2J = 14.8 Hz, ^3J = 6.0 Hz, 1 H, NCH_2CHCH_2), 3.73 (d, ^2J = 14.8 Hz, 1 H, NCH_2CHCH_2), 4.68 (br s, 1 H, NCH), 5.06 (dd, ^2J = 1.5 Hz, ^3J = 10.0 Hz, 1 H, NCH_2CHCH_2), 5.13 (dd, ^2J = 1.5 Hz, ^3J = 17.1 Hz, 1 H, NCH_2CHCH_2), 5.62 (dd, ^2J = 1.6 Hz, ^3J = 10.4 Hz, 1 H, $COCHCH_2$), 5.64–5.71 (m, 1 H, NCH_2CHCH_2), 6.32 (dd, ^2J = 1.6 Hz, ^3J = 16.3 Hz, 1 H, $COCHCH_2$), 6.50 (dd, ^3J = 10.4 Hz, ^3J = 16.3 Hz, 1 H, $COCHCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6 [$SC(CH_3)_2CH$], 33.8 [$SC(CH_3)_2CH$], 28.9 [$SC(CH_3)_2N$], 32.1 [$SC(CH_3)_2N$], 37.2 (NCH_3), 53.1 [$SC(CH_3)_2CH$], 55.5 (NCH_2CHCH_2), 71.7 [$SC(CH_3)_2N$], 91.0 (NCH), 116.3 (NCH_2CHCH_2), 126.9 ($COCHCH_2$), 131.3 ($COCHCH_2$), 136.3 (NCH_2CHCH_2), 166.2 (CO); MS (CI, isobutane): *m/z* (%): 269.2 (100) $[M + H]^+$, 198.1 (50) $[MH - C_4H_9N]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{14}H_{25}N_2OS]^+$: 269.1688; found: 269.1688.

(*RS*)-1-[4-(Allylmethylamino)-2,2,5,5-tetramethyloxazolidin-3-yl]-propenone (2e).. Following **GP A**, 2,5-dihydrooxazole **1b** (0.32 g, 2.5 mmol), acryloyl chloride (0.25 g, 2.75 mmol), *N*-allylmethylamine (0.36 g, 5.0 mmol), and triethylamine (0.45 g, 4.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 0.09 g (0.4 mmol, 14%); light yellow oil; $R_f = 0.83$ (*n*-hexane–EtOAc, 1:1); IR: 2980, 2941, 1651, 1613, 1414, 1353 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 [s, 3 H, $OC(CH_3)_2CH$], 1.34 [s, 3 H, $OC(CH_3)_2CH$], 1.67 [s, 3 H, $OC(CH_3)_2N$], 1.72 [s, 3 H, $OC(CH_3)_2N$], 2.44 (s, 3 H, NCH_3), 3.31 (dd, ^2J = 14.6 Hz, ^3J = 6.0 Hz, 1 H, NCH_2CHCH_2), 3.43 (dd, ^2J = 14.6 Hz, ^3J = 5.8 Hz, 1 H, NCH_2CHCH_2), 4.50 (s, 1 H, NCH), 5.08 (dd, ^2J = 1.0 Hz, ^3J = 10.2 Hz, 1 H, NCH_2CHCH_2), 5.15 (dd, ^2J = 1.0 Hz, ^3J = 17.1 Hz, 1 H, NCH_2CHCH_2), 5.65 (dd, ^2J = 1.7 Hz, ^3J = 10.2 Hz, 1 H, $COCHCH_2$), 5.67–5.73 (m, 1 H, NCH_2CHCH_2), 6.38 (dd, ^2J = 1.7 Hz, ^3J = 16.7 Hz, 1 H, $COCHCH_2$), 6.53 (dd, ^3J = 10.2 Hz, ^3J = 16.7 Hz, 1 H, $COCHCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.3 [$OC(CH_3)_2CH$], 27.2 [$OC(CH_3)_2N$], 28.1 [$OC(CH_3)_2N$], 30.0 [$OC(CH_3)_2CH$], 36.8 (NCH_3), 56.0 (NCH_2CHCH_2), 82.5 [$OC(CH_3)_2CH$], 83.9 (NCH), 94.5 [$OC(CH_3)_2N$], 116.6 (NCH_2CHCH_2), 127.3 ($COCHCH_2$), 130.2 ($COCHCH_2$), 136.2 (NCH_2CHCH_2), 164.6 (CO); MS (CI, isobutane): *m/z* (%): 253.2 (20) $[M + H]^+$, 182.1 (52) $[M - N(CH_3)CH_2CHCH_2]^+$, 142.1 (100) $[C_7H_{14}N_2O]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{14}H_{25}N_2O_2]^+$: 253.1916; found: 253.1916.

(*RS*)-1-[4-(Allylmethylamino)-2,2,5,5-tetramethyloxazolidin-3-yl]-2-methylpropenone (2f).. Following **GP A**, 2,5-dihydrooxazole **1b** (0.32 g, 2.5 mmol), 2-methylacryloyl chloride (0.29 g, 2.75 mmol), *N*-allylmethylamine (0.36 g, 5.0 mmol), and triethylamine (0.45 g, 4.4 mmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 0.05 g (0.2 mmol, 7%); yellow oil; R_f = 0.83 (*n*-hexane–EtOAc, 1:1). The product was not obtained pure, but its structure was verified by MS, HRMS and further reaction to analytically pure (*RS*)-1,4,7,7,9,9-hexamethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]diazepin-5-one **3f**; MS (CI, isobutane): *m/z* (%): 267.4 (12) $[M + H]^+$, 196.3 (60) $[M - N(CH_3)CH_2CHCH_2]^+$, 142.1 (100) $[C_7H_{14}N_2O]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{15}H_{27}N_2O_2]^+$: 267.2073; found: 267.2068.

(*RS*)-1-(4-Allylselanyl-2,2,5,5-tetramethylthiazolidin-3-yl)-propenone (2g).. Under argon atmosphere, 2,5-dihydrothiazole **1a** (0.30 g, 2.1 mmol) was dissolved in anhydrous diethyl ether (5 mL) and cooled to 0–5°C before acryloyl chloride (0.19 g, 2.1 mmol) dissolved in anhydrous diethyl ether (1 mL) was added dropwise. The solution was stirred for 3 h at room temperature. Simultaneously, in another flask magnesium turnings (0.08 g, 3.1 mmol) were covered with anhydrous diethyl ether (5 mL) under argon atmosphere. Under continuous boiling, allyl bromide (0.38 g, 3.1 mmol) was added dropwise. After finishing addition, selenium (0.25 g, 3.1 mmol) was added and the reaction mixture was refluxed for 1 h. At room temperature, the first prepared solution of α-chloro amide was added to selenium-Grignard reagent dropwise. After stirring overnight, water (10 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 43 mg (0.14 mmol, 6%); light yellow oil; $R_f = 0.53$ (*n*-hexane–EtOAc, 7:3); the product was not obtained pure, but its structure was verified by further reaction to analytically pure (*RS*)-7,7,9,9-tetramethyl-9,9a-dihydro-2*H*-thiazolo[4,3-*b*][1,3]selenazepin-5-one **3g**; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.53 [s, 3 H, $SC(CH_3)_2CH$], 1.65 [s, 3 H, $SC(CH_3)_2CH$], 1.87 [s, 3 H, $SC(CH_3)_2N$], 1.99 [s, 3 H, $SC(CH_3)_2N$], 3.32–3.43 (m, 2 H, $SeCH_2CHCH_2$), 5.09–5.12 (m, 2 H, $SeCH_2CHCH_2$), 5.30 (s, 1 H, NCH), 5.70 (dd, ^2J = 1.6 Hz, ^3J = 10.4 Hz, 1 H, $COCHCH_2$), 5.96 (dddd, ^3J = 7.8 Hz, ^3J = 7.8 Hz, ^3J = 9.6 Hz, ^3J = 17.3 Hz, 1 H, $SeCH_2CHCH_2$), 6.33 (dd, ^2J = 1.6 Hz, ^3J = 16.6 Hz, 1 H, $COCHCH_2$), 6.57 (dd, ^3J = 10.4 Hz, ^3J = 16.6 Hz, 1 H, $COCHCH_2$); MS (CI, isobutane): *m/z* (%): 320.1 (18) $[M + H]^+$, 198.1 (100) $[MH - C_3H_6Se]^+$; HRMS (CI, isobutane): *m/z* calcd for $[C_{13}H_{22}NOSSe]^+$: 320.0587; found: 320.0587.

General procedure for the preparation of lactams 3 (GP B).. Acryl amide **2** (1 equiv) and the ruthenium catalyst **I** (0.05 equiv) were dissolved in toluene (8 mL) and heated to 30°C. Following the solution was slowly heated to at most 70°C over a period of 2-6 h (heating rate: about 10°C /h) until the reaction was complete as continuously controlled by TLC. The solvent was removed under reduced pressure and the product was purified as described later.

(*RS*)-7,7,9,9-Tetramethyl-9,9a-dihydro-2*H*-thiazolo[4,3-*b*][1,3]thiazepin-5-one (3a).. Following **GP B**, the acryl amide **2a** (41 mg, 0.15 mmol) and ruthenium catalyst **I** (7.2 mg, 8

μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 27 mg (0.11 mmol, 74%); colorless solid; mp 120°C; $R_f = 0.47$ (*n*-hexane–EtOAc, 1:1); IR: 2964, 2932, 1643, 1609, 1467, 1437, 1375, 1338, 808 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.46 [s, 3 H, $SC(CH_3)_2CH$], 1.67 [s, 3 H, $SC(CH_3)_2CH$], 1.95 [s, 3 H, $SC(CH_3)_2N$], 2.09 [s, 3 H, $SC(CH_3)_2N$], 3.14 (ddd, ^2J = 13.3 Hz, ^3J = 7.4 Hz, ^4J = 1.8 Hz, 1 H, CH_2), 3.40 (ddd, ^2J = 13.3 Hz, ^3J = 6.4 Hz, ^4J = 0.9 Hz, 1 H, CH_2), 5.10 (s, 1 H, NCH), 6.04–6.12 (m, 2 H, COCHCH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.0 [$SC(CH_3)_2CH$], 30.2 [$SC(CH_3)_2CH$], 25.6 (CH_2), 32.6 [$SC(CH_3)_2N$], 32.9 [$SC(CH_3)_2N$], 51.7 [$SC(CH_3)_2CH$], 73.4 [$SC(CH_3)_2N$], 78.1 (NCH), 126.9 (CO*C*HCH), 129.7 (COCH*C*H), 166.3 (CO); MS (CI, isobutane): *m*/*z* (%): 244.1 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{11}H_{18}NOS_2]^+$: 244.0830; found: 244.0832.

(*RS*)-7,7,9,9-Tetramethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]thiazepin-5-one (3b).. Following **GP B**, the acryl amide **2b** (40 mg, 0.16 mmol) and ruthenium catalyst **I** (7.4 mg, 8 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 16 mg (0.07 mmol, 45%); colorless solid; mp 79–80°C; $R_f = 0.23$ (*n*-hexane–EtOAc, 7:3); IR: 2984, 2935, 1656, 1605, 1393, 1370, 1195 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 [s, 3 H, $OC(CH_3)_2CH$], 1.45 [s, 3 H, $OC(CH_3)_2CH$], 1.73 [s, 3 H, $OC(CH_3)_2N$], 1.79 [s, 3 H, $OC(CH_3)_2N$], 3.16 (dd, ^2J = 13.9 Hz, ^3J = 7.6 Hz, 1 H, CH_2), 3.35 (ddd, ^2J = 13.9 Hz, ^3J = 6.8 Hz, ^4J = 1.0 Hz, 1 H, CH_2), 4.88 (s, 1 H, NCH), 6.08 (dd, ^3J = 10.9 Hz, ^4J = 1.0 Hz, 1 H, COC*H*CH), 6.20 (ddd, ^3J = 6.8 Hz, ^3J = 7.6 Hz, ^3J = 10.9 Hz, 1 H, COCHC*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.2 [$OC(CH_3)_2CH$], 26.2 (CH_2), 28.0 [$OC(CH_3)_2N$], 28.4 [$OC(CH_3)_2N$], 29.4 [$OC(CH_3)_2CH$], 69.7 (NCH), 80.6 [$OC(CH_3)_2CH$], 95.9 [$OC(CH_3)_2N$], 129.2 (CO*C*HCH), 129.6 (COCH*C*H), 164.5 (CO); MS (ESI): *m*/*z* (%): 250.0 (100) $[M + Na]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{11}H_{18}NO_2S]^+$: 228.1058; found: 228.1058.

(*RS*)-4,7,7,9,9-Pentamethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]thiazepin-5-one (3c).. Following **GP B**, the acryl amide **2c** (40 mg, 0.15 mmol) and ruthenium catalyst **I** (7.0 mg, 7 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 31 mg (0.13 mmol, 88%); light yellow solid; mp 75–78°C; $R_f = 0.51$ (*n*-hexane–EtOAc, 7:3); IR: 2991, 2929, 1650, 1627, 1402, 1374, 1203 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40 [s, 3 H, $OC(CH_3)_2CH$], 1.43 [s, 3 H, $OC(CH_3)_2CH$], 1.73 [s, 3 H, $OC(CH_3)_2N$], 1.80 [s, 3 H, $OC(CH_3)_2N$], 1.96 [dd, ^4J = 1.6 Hz, ^5J = 1.0 Hz, 3 H, $COC(CH_3)CH$], 2.97 (dd, ^2J = 13.2 Hz, ^3J = 8.4 Hz, 1 H, CH_2), 3.28 (ddd, ^2J = 13.2 Hz, ^3J = 7.7 Hz, ^5J = 1.0 Hz, 1 H, CH_2), 4.81 (s, 1 H, NCH), 5.83 [ddq, ^3J = 7.7 Hz, ^3J = 8.4 Hz, ^4J = 1.6 Hz, 1 H, $COC(CH_3)CH$]; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1 [$COC(CH_3)CH$], 24.8 [$OC(CH_3)_2CH$], 25.3 (CH_2), 28.2 [$OC(CH_3)_2N$], 28.4 [$OC(CH_3)_2N$], 29.3 [$OC(CH_3)_2CH$], 69.5 (NCH), 80.5 [$OC(CH_3)_2CH$], 95.7 [$OC(CH_3)_2N$], 122.3 [$COC(CH_3)CH$], 137.9 [$COC(CH_3)CH$], 167.2 (CO); MS (CI, isobutane): *m*/*z*(%): 242.2 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{12}H_{20}NO_2S]^+$: 242.1215; found: 242.1213.

(*RS*)-1,7,7,9,9-Pentamethyl-9,9a-dihydro-2*H*-thiazolo[4,3-*b*][1,3]diazepin-5-one (3d).. Following **GP B**, the acryl amide **2d** (36 mg, 0.15 mmol) and ruthenium catalyst **I** (7.0 mg, 7 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 32 mg (0.13 mmol, 90%); colorless solid; mp 67°C; $R_f = 0.40$ (*n*-hexane–EtOAc, 1:1); IR: 2986, 2953, 2859, 1655, 1604, 1469, 1440, 1416, 1398, 1365, 1344, 815 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 [s, 3 H, $SC(CH_3)_2CH$], 1.57 [s, 3 H, $SC(CH_3)_2CH$], 1.89 [s, 3 H, $SC(CH_3)_2N$], 1.94 [s, 3 H, $SC(CH_3)_2N$], 2.54 (s, 3 H, NCH_3), 3.19–3.23 (m, 1 H, CH_2), 3.85 (ddd, ^2J = 20.7 Hz, ^3J = 2.8 Hz, ^4J = 2.6 Hz, 1 H, CH_2), 4.72 (s, 1 H, NCH), 5.91 (ddd, ^3J = 12.9 Hz, ^4J = 2.6 Hz, ^4J = 1.7 Hz, 1 H, COC*H*CH), 6.02 (ddd, ^3J = 2.8 Hz, ^3J = 2.9 Hz, ^3J = 12.9 Hz, 1 H, COCHC*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.3 [$SC(CH_3)_2CH$], 34.7 [$SC(CH_3)_2CH$], 38.0 [$SC(CH_3)_2N$], 31.6 [$SC(CH_3)_2N$], 36.5 (NCH_3), 50.0 [$SC(CH_3)_2CH$], 59.2 (CH_2), 70.8 [$SC(CH_3)_2N$], 88.8 (NCH), 128.0 (CO*C*HCH), 140.4 (COCH*C*H), 165.6 (CO); MS (CI, isobutane): *m*/*z* (%): 241.2 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{12}H_{21}N_2OS]^+$: 241.1375; found: 241.1376.

(*RS*)-1,7,7,9,9-Pentamethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]diazepin-5-one (3e).. Following **GP B**, the acryl amide **2e** (37 mg, 0.15 mmol) and ruthenium catalyst **I** (6.9 mg, 7 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 24 mg (0.11 mmol, 74%); colorless solid; mp 83–86°C, $R_f = 0.09$ (*n*-hexane–EtOAc, 7:3); IR: 2956, 2936, 2871, 1651, 1604, 1428, 1405, 1369, 1198 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 [s, 3 H, $OC(CH_3)_2CH$], 1.38 [s, 3 H, $OC(CH_3)_2CH$], 1.67 [s, 3 H, $OC(CH_3)_2N$], 1.69 [s, 3 H, $OC(CH_3)_2N$], 2.37 (s, 3 H, NCH_3), 3.25 (ddd, ^2J = 20.4 Hz, ^3J = 3.3 Hz, ^4J = 1.6 Hz, 1 H, CH_2), 3.83 (ddd, ^2J = 20.4 Hz, ^3J = 2.6 Hz, ^4J = 2.6 Hz, 1 H, CH_2), 4.53 (s, 1 H, NCH), 5.92 (ddd, ^3J = 13.1 Hz, ^4J = 1.6 Hz, ^4J = 2.6 Hz, 1 H, COC*H*CH), 6.05 (ddd, ^3J = 2.6 Hz, ^3J = 3.3 Hz, ^3J = 13.1 Hz, 1 H, COCHC*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2 [$OC(CH_3)_2CH$], 26.6 [$OC(CH_3)_2N$], 27.7 [$OC(CH_3)_2N$], 30.9 [$OC(CH_3)_2CH$], 36.5 (NCH_3), 58.8 (CH_2), 80.6 [$OC(CH_3)_2CH$], 82.2 (NCH), 93.9 [$OC(CH_3)_2N$], 127.5 (CO*C*HCH), 140.3 (COCH*C*H), 164.4 (CO); MS (CI, isobutane): *m*/*z* (%): 225.2 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{12}H_{21}N_2O_2]^+$: 225.1603; found: 225.1602.

(*RS*)-1,4,7,7,9,9-Hexamethyl-9,9a-dihydro-2*H*-oxazolo[4,3-*b*][1,3]diazepin-5-one (3f).. Following **GP B**, the acryl amide **2f** (47 mg, 0.18 mmol) and ruthenium catalyst **I** (8.4 mg, 9 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 7:3); yield: 21 mg (0.09 mmol, 50%); colorless solid; mp 39–43°C; $R_f = 0.26$ (*n*-hexane–EtOAc, 7:3); IR: 2987, 2936, 1649, 1592, 1423, 1367, 1198 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.34 [s, 3 H, $OC(CH_3)_2CH$], 1.37 [s, 3 H, $OC(CH_3)_2CH$], 1.68 [s, 3 H, $OC(CH_3)_2N$], 1.71 [s, 3 H, $OC(CH_3)_2N$], 1.97–1.98 [m, 3 H, $COC(CH_3)CH$], 2.31 (s, 3 H, NCH_3), 3.29 (dd, ^2J = 18.9 Hz, ^3J = 2.2 Hz, 1 H, CH_2), 3.63 (d, ^2J = 18.9 Hz, 1 H, CH_2), 4.24 (s, 1 H, NCH), 6.00–6.02 [m, 1 H, $COC(CH_3)CH$]; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7 [$COC(CH_3)CH$], 24.3 [$OC(CH_3)_2CH$], 27.0 [$OC(CH_3)_2N$], 28.0 [$OC(CH_3)_2N$], 30.5 [$OC(CH_3)_2N$], 37.7 (NCH_3), 56.7 (CH_2), 81.0 [$OC(CH_3)_2CH$], 82.1 (NCH), 94.5 [$OC(CH_3)_2N$], 133.6 [$COC(CH_3)CH$], 133.7 [$COC(CH_3)CH$], 166.2 (CO); MS (CI, isobutane): *m*/*z* (%): 239.2 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{13}H_{23}N_2O_2]^+$: 239.1760; found: 239.1760.

(*RS*)-7,7,9,9-Tetramethyl-9,9a-dihydro-2*H*-thiazolo[4,3-*b*][1,3]selenazepin-5-one (3g).. Following **GP B**, the acryl amide **2g** (15 mg, 0.05 mmol) and ruthenium catalyst **I** (2.4 mg, 3 μmol) were used. The product was purified by column chromatography (silica gel; *n*-hexane–EtOAc, 1:1); yield: 5 mg (0.02 mmol, 36%); colorless solid; R_f = 0.50 (*n*-hexane–EtOAc, 1:1); IR: 2964, 2925, 2855, 1655, 1612, 1465, 1377, 795 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.50 [s, 3 H, $SC(CH_3)_2CH$], 1.69 [s, 3 H, $SC(CH_3)_2CH$], 2.01 [s, 3 H, $SC(CH_3)_2N$], 2.10 [s, 3 H, $SC(CH_3)_2N$], 3.12 (ddd, ^2J = 11.8 Hz, ^3J = 7.6 Hz, ^4J = 1.9 Hz, 1 H, CH_2), 3.47 (dd, ^2J = 11.8 Hz, ^3J = 7.1 Hz, 1 H, CH_2), 5.31 (s, 1 H, NCH), 5.99–6.07 (m, 2 H, COCHCH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.4 $[SC(CH_3)_2CH]$, 39.9 $[SC(CH_3)_2CH]$, 29.7 (CH_2), 32.2 $[SC(CH_3)_2N]$, 33.2 $[SC(CH_3)_2N]$, 52.5 $[SC(CH_3)_2CH]$, 73.7 $[SC(CH_3)_2N]$, 75.0 (NCH), 127.1 (COCHCH), 128.0 (COCHCH), 166.1 (CO); MS (CI, isobutane): *m*/*z* (%): 292.0 (100) $[M + H]^+$; HRMS (CI, isobutane): *m*/*z* calcd for $[C_{11}H_{18}NOSSe]^+$: 292.0274; found: 292.0276.

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