Introduction

Sulfur containing compounds are very interesting molecules for their use in many chemical and biochemical processes. In addition, organosilicon derivatives have many applications in organic chemistry, for example as protecting groups, derivatizing agents and intermediates in organic synthesis. They found a wide application as nucleophilic reagents in various organic transformations.[1] The utility of such reagents is mainly due to their behaviour as "non-basic organometallics", thus they are compatible with groups unstable under strong basic conditions. The interest in the chemistry of organosilanes is related to the well known "proton-silicon correlation". For example, a considerable number of organic derivatives of silicon undergo reactions analogue to those of the corresponding protonated systems, and the use of organosilanes led to synthesize molecules scarcely accessible with the classical organic procedures.

In this context, organosulfur derivatives of silicon have been extensively studied over the years and different methods and examples have been developed for their synthesis and application.[2] In fact, silyl sulfides can be formally considered similar to thiols, but possess a peculiar reactive behaviour, and the unique and complementary properties of sulfur and silicon outline silyl sulfides as a versatile class of compounds in the delivery of sulfur functionalities under mild conditions. Their application in the search for alternative strategies and for the development of novel molecular structures has been constantly growing. For example, thiosilanes are used for selective protection of carbonyl compounds[2,3] as well as in reactions of alkyl halides[4] or alkyl acetates[5] for the preparation of symmetrical and unsymmetrical sulfides. Also epoxides were efficiently reacted with thiosilanes to synthesize β-functionalized sulfides or thiols. [6]

On the other hand, organic derivatives of selenium have attracted considerable attention in very recent years for their importance both from the synthetic and biological point of view. [7]

Selenium was discovered in 1818 by the Swedish chemist J. J. Berzelius, who studied this element and its compounds in detail.[8] The first organoselenium

derivative, ethyl selenol, was published in 1847 by Wöhler and Siemens and selenium dioxide was described as an oxidant in a 1929 patent.

Organoselenium compounds represent relevant intermediates and reagents in organic synthesis, being able to react under mild conditions as electrophiles, nucleophiles or radicals, usually in a chemo-, regio- and stereoselective way.[9] They behave as useful building blocks for the synthesis of a large number of organic structures[10] and they are able to participate as catalysts and ligands in a variety of reactions.[11]

Moreover, the introduction of selenium in a molecule allows its further manipulation and the conversion in different functional groups. This allowed the synthesis of a wide range of organic selenium compounds, which found application in different fields such as physical and organic chemistry, as well as in biological chemistry and material science. [9]

Selenium and sulfur resemble each other in some properties, nonetheless selenium derivatives are often more active than sulfur analogues. As a matter of fact, selenium compounds usually exhibit higher chemical and biological activity in comparison with the sulfurated ones, due also to their higher nucleophilicity and their enhanced redox reactivity. As an example, selenocysteine (Sec) is more active than cysteine and the use of Sec residue in the catalytic site of proteins often enhances their properties. [7a]

Actually, organoselenium derivatives are involved in different organic transformations to obtain various biologically active compounds, such as selenated proteins (containing selenocysteine and selenomethionine) and selenated heterocycles. More than 20 enzymes with a Se atom in the active site have been described. [12]

It is reported that the formation of selenium-containing compounds, and not the element itself, is critical for biological activities.[13] Thus, organic derivatives of selenium have continued to attract considerable attention for their peculiar features, such as, for instance, antioxidant, antiinflammatory and neuroprotective properties.[14]

In this context, several methods are reported for the synthesis of organosulfur and organoseleno compounds, but little is known about methodologies based on the reactivity of thiosilanes and selenosilanes.

Thus, in the course of this PhD thesis the research was mainly focused on the study of the reactivity of sulfurated and selenated derivatives with different substrates, aimed to develop mild and general approaches to obtain useful acyclic and cyclic compounds containing sulfur and/or selenium moieties, together with other heteroatoms (N, O).

In this context, synthetic strategies based on the functionalization of bidentate compounds and on the reactivity of various silanes were studies.

Particular attention was also paied to the determination of the antioxidant activity of selected, novel and simple molecules obtained during this work, as well as in the evaluation of their behaviour as synthetic mimics of glutathione peroxidase (GPx).

In this connection was also studied the functionalization of natural substrates, such as eugenol, limonene, resveratrol and ascorbic acid, to introduce these chalchogens at selected positions of the natural molecular skeleton, in order to evaluate whether a synergistic effect could be obtained to increase their activity.

During the period spent at the University of Bristol the research was focused on the chemistry of boronic esters as versatile intermediates in the asymmetric synthesis of a variety of organic compounds, with the aim to apply these findings also to the stereoselective synthesis of suitable enantioenriched precursors of more complex sulfurated and selenated derivatives.

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Chapter 1

Synthesis of β-functionalised diselenides and selenides

1.1 Introduction

Among the variety of organic derivatives, the chemistry of diselenides and selenides is of great interest both from the synthetic and biologic point of view, and much effort has been directed toward their synthesis. Diselenides can be considered as analogues of organic peroxides, but more stable and easy to handle. Nonetheless, they are reactive enough to participate in electrophilic, nucleophilic and radical processes, and can be transformed to other electrophilic species, as selenenyl halides or seleninic anhydrides, or to nucleophilic reagents, as selenols or selenolates.

Particular attention has been devoted over the past years to chiral selenium based methods as useful tools in organic synthesis,[1] and chiral diselenides appeared very interesting reagents,[2] due to their higher stability with respect to parent selenols. They are used in stereoselective processes, as ring opening of epoxides[3] and electrophilic selenenylation of alkynes.[4] Chiral diselenides find application in asymmetric reactions, such as addition of Et_2Zn to aldehydes,[5] conjugated addition of Grignard reagents to enones[6] and asymmetric hydrosilylation.[7]

Diorganyl selenides as well represent an important class of compounds employed as reagents in organic synthesis.[8] For instance, they are used for the preparation of alkenes,[9] epoxides,[10] aldehydes and ketones,[11] and as intermediates for the synthesis of organoselenium compounds.[8,12]

Different methods for the synthesis of diselenides and selenides have been reported, most of them including multistep procedures. A common access is the reaction of metal diselenides (Se_2^{2-}) or selenides (Se^{2-}) with organic halides or pseudohalides.[13]

Unsymmetrical organoselenides can be accessed from selenazole derivatives[14] or benzeneselenol in the presence of cesium bases and alkyl halides.[15] Oxidation of selenols,[16] alkylation of selenolates[17] to diselenides or selenides and dimerization with selenocyanates are commonly used procedures. Cross-coupling of selenium and

aryl halides catalyzed by CuO nanoparticles led to a variety of symmetrical diselenides via one-pot coupling-reduction procedure.[18] Elemental selenium can be reduced by carbon monoxide under aqueous basic conditions in the presence of organic halides to afford selenides or diselenides,[19] while enantiomerically pure diselenides containing *p*-menthane system were formed through reaction of Na_2Se_2 with alkyl tosylates and chlorides.[2b]

Chiral aziridines have also been used as suitable substrates to obtain chiral aliphatic β-amino diselenides and non-natural selenated amino acid derivatives through reaction with Li_2Se_2,[5a] tetraselenotungstate[20] and $(PhSe)_2/NaBH_4$.[21]

Thus, there is still a growing interest in the synthesis of such compounds and in developing new selenating reagents, which can afford regio- and stereocontrolled selenium transfer in a single step.

As described, although a number of synthetic processes based on selenium chemistry have been reported, little is known about methodologies based on the reactivity of selenosilanes. Reaction of arylselenotrimethylsilanes with acetates and epoxides in the presence of different catalysts (ZnI_2, alkyl halides/SmI_2, salen(chromium) complexes)[22] provides alternative methods for the introduction of an arylseleno group on organic molecules, leading to alkyl aryl selenides.

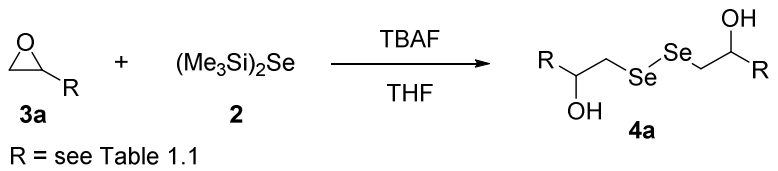
The long dated interest of our group in the development of organosilicon chemistry led to disclose a protocol based on bis(trimethylsilyl)sulfide (HMDST) **1** as efficient reagent in the delivery of sulfur functionalities, such as the generation of thiocarbonyl compounds.[23] More recently we described the reaction of epoxides with HMDST, that afforded a direct access to β-marcaptoalcohols in a regio- and stereoselective way.[24]

On the other hand, the chemistry of the corresponding selenium derivative, bis(trimethylsilyl)selenide (TMS-Se-TMS, HMDSS)[25] **2** has received less attention. It may be regarded as the synthetic equivalent of H_2Se, but it is much easier to handle and to measure, and can be stored under inert atmosphere for months at low temperature, without appreciable decomposition. Preliminary findings on the reactivity of HMDSS with three-membered heterocycles, showed the possibility to synthesise β-functionalized diselenides.[26]

In order to extend our studies on HMDSS reactivity and to obtain small libraries of selenated compounds with various and defined substituents, we deeply investigated the chemistry of this selenosilane with ring strained heterocycles. A smooth, direct and selective access to β-hydroxy-, β-mercapto- and β-amino-diselenides and -selenides through the use of suitable conditions and stoichiometric ratios of the reagents was disclosed.[27]

1.2 Results and Discussion

For the synthesis of β-hydroxy diselenides we explored differently substituted epoxides. The initial reaction involved the treatment under inert atmosphere of isopropyl glycidyl ether **3a** (1 mmol) in THF with HMDSS **2** (1.6 equiv) at room temperature, in the presence of TBAF as catalyst. Under these conditions we observed the formation of β-hydroxy-β-substitued diselenide **4a** as mixture of diastereoisomers (Scheme 1.1). This compound is obtained from a regioselective attack of the seleno nucleophile on the less hindered side of the epoxide, no trace of the other regioisomer was evidenced, followed by oxidation of the selenosilane (or selenol) intermediate.



Scheme 1.1. Synthesis of β-hydroxy-diselenides. Reagents and conditions: epoxide (1 equiv.), $(Me_3Si)_2Se$ (1.6 equiv.), TBAF (0.64 equiv), THF, r.t., 4h

Attempts to isolate the β-hydroxy silylselenide (or selenol) intermediate were performed. To avoid oxidation, all the manipulations (work-up, filtration on anhydrous Na_2SO_2 and evaporation of solvents) were carried out under inert atmosphere, but, at this stage, all attempts were unsuccessful, and the corresponding diselenide **4a** was always isolated.

Such behaviour discloses a potentially useful and straightforward access to β-disubstituted diselenides. To the best of our knowledge, only very few examples

have been described for the synthesis of β-hydroxy diselenides,[25b,28] with a limited diversity of functional groups of starting epoxides.

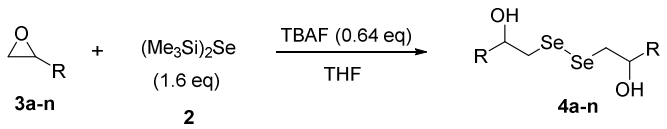
In order to evaluate the generality of such methodology, a series of substituted oxiranes was reacted under the same conditions. Results of this investigation are listed in Table 1.1.

As can be seen in the Table, the reactivity proved general, leading to the regioselective formation of β-hydroxy diselenides with different alkyl groups, containing moieties that can be further functionalized. This reaction appears operationally simple and represents a direct access to this class of compounds under very mild conditions, in the presence of TBAF (40%). It was observed that, when a catalytic amount (ca. 10-20%) of the ammonium salt was used, the reaction was efficient as well, either the alcohol and the silyl ether were isolated. To obtain the formation of β-hydroxy derivatives as the major compounds, a larger amount of TBAF was used, to avoid further treatment of the silyl ether to undergo deprotection.

All the reactions occur with good yields of monosubstituted epoxides, while in the case of disubstituted ones, as limonene oxide **3l** (Table 1.1, entry 12) and cyclooctene oxide **3m** (Table 1.1, entry 13) the yields tend slightly to decrease.

The mildness of this methodology allowed to obtain diselenides from more labile compounds, such as glycidol derivatives (Table 1.1., entries 1-4) and epichlorohydrin (Table 1.1, entries 6 and 7), that can behave as useful intermediates in different synthetic transformations. In the case of the halogenated epoxide **3e** the reaction was performed at 0°C, at room temperature a complex mixture of products was formed. Worth noting that under these reaction conditions protective moieties in glycidol derivatives **3a-c** and the halogen in **3e** were preserved on the side chain. When 1,3-butadiene diepoxide **3n** was reacted with HMDSS (3.4 equiv) and TBAF a convenient access to the cyclic diselenide as bis-trimethylsilyloxy derivative was obtained. Further treatment with TBAF led to the formation of the hydroxy derivative **4n** (Table 1.1, entry 14).

Table 1.1. Synthesis of β-hydroxy dialkyl diselenides



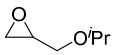
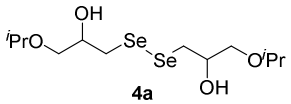
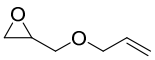
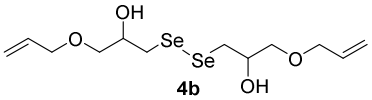
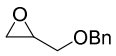
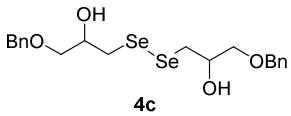
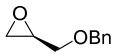
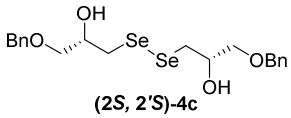
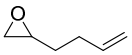
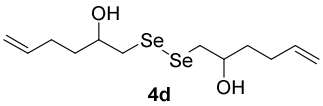
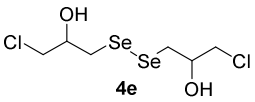
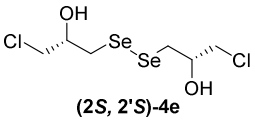
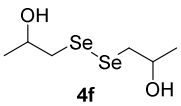
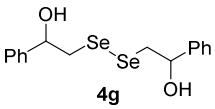
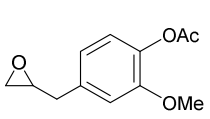
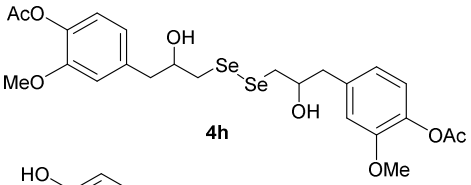
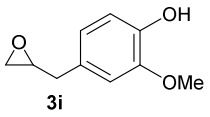
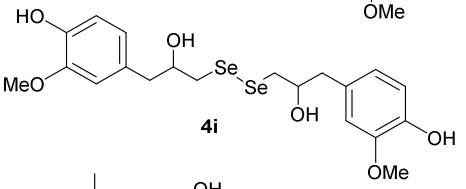
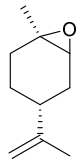
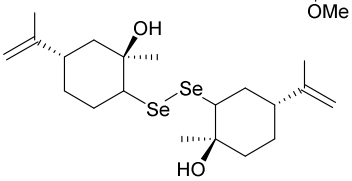
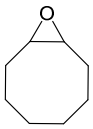
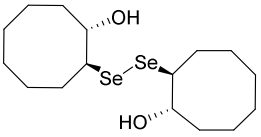
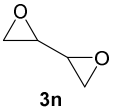
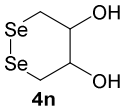
Entry	Reagent	Product	Yield (%)[a]
1	 **3a**	 **4a**	76[b]
2	 **3b**	 **4b**	61[b]
3	 **3c**	 **4c**	89[b]
4	 ***(R)*-3c**	 **(2*S*, 2'*S*)-4c**	87
5	 **3d**	 **4d**	65[b]
6	 **3e**	 **4e**	41[b]
7	 ***(R)*-3e**	 **(2*S*, 2'*S*)-4e**	39
8	 **3f**	 **4f**	62[b]
9	 **3g**	 **4g**	73[b,c]

Table 1.1 | Continued

Entry	Reagent	Product	Yield (%)[a]
10	 **3h**	 **4h**	67[b]
11	 **3i**	 **4i**	62[b,d]
12	 **3l**	 **4l**	51[b]
13	 **3m**	 **4m**	56[e]
14	 **3n**	 **4n**	64[b,f]

[a] Isolated yield is given. [b] Mixture of diastereoisomers. [c] The minor regioisomer $[CH_2(OH)CHPhSe]_2$ was formed (ca. 20%). [d] Refers to crude product. [e] Racemic. [f] Ref. [27b]

The corresponding *trans*-1,2-diselenane-4,5-diol (DST^{ox}) has been reported as a useful new water-soluble selenium reagent for the redox control of protein structures.[28b]

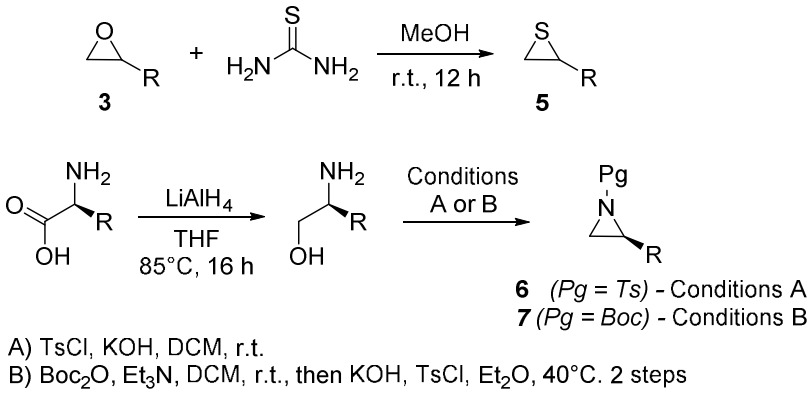
This procedure may be applied also to chiral epoxides, leading to the formation of optically active β-hydroxy diselenides (*2S,2'S*)-**4c** and (*2S,2'S*)-**4e** (Table 1.1, entries 4 and 7). When racemic compounds were used, diselenides were obtained as almost equimolar mixtures of diastereoisomers. No diastereoselectivity could be obtained.

Of particular interest are diselenides **4h-l** (Table 1.1, entries 10-12), arising from epoxides obtained from natural products, as eugenol and limonene. In particular,

diselenides **4h** and **4i** contain the eugenol skeleton, whose antioxidant activity will be investigated.

It is interesting to underline that the procedure is highly regioselective. Only in the case of styrene oxide **3g**, the corresponding regioisomer $[CH_2(OH)CHPhSe]_2$ was formed (ca. 20%) (Table 1.1, entry 9), as indeed already observed in the reaction of the analogue HMDST.[24]

With the aim to evaluate the limits and the potential of this methodology, we extended this reactivity to different ring strained compounds, such as thiiranes **5** and aziridines **6** and **7**, obtained from natural aminoacids. These three-membered heterocycles can be easily synthesised following leterature procedures (Scheme 1.2).[29a-d]

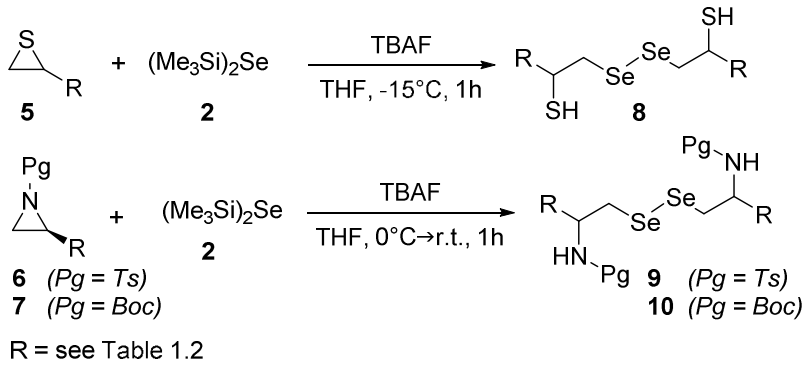


Scheme 1.2. Synthesis of thiiranes and *N*-protected aziridines

This investigation led to the disclosure of an easy and simple access to a variety of β-mercapto diselenides **8a-c** (Scheme 1.3) and chiral *N*-tosyl- or *N*-Boc-protected β-amino diselenides **9a-d** and **10a,b** (Scheme 1.3) in a single regioisomer, following the S_N2 pathway exclusively.

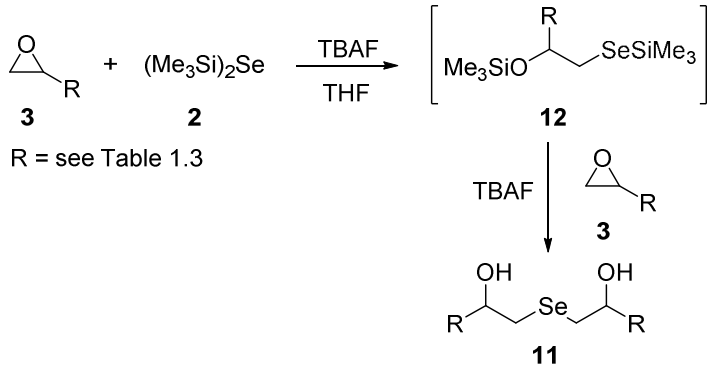
Examples of this reactivity are summarized in Table 1.2 (entries 1-3 and 4-9). As mentioned above, chiral amino diselenides represent a very interesting class of compounds as catalysts in asymmetric synthesis[5] and as suitable substrates for obtaining non-natural selenium containing amino acids.[30] To the best of our knowledge, while several methods are reported for the synthesis of β-

aminoderivatives, no example is described to obtain β-mercapto diselenides, that could represent a new class of polyfunctionalized organic molecules.



Scheme 1.3. Synthesis of β-mercapto- and β-amino- diselenides

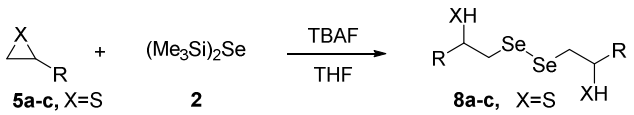
Even more interesting appeared the reactivity of HMDSS with an excess of electrophiles. As a further step, bis(trimethylsilyl)selenide was reacted at room temperature with an excess of epoxides and a catalytic amount of TBAF, leading this time to the formation of β-hydroxy selenides **11a-f** in good yields (Scheme 1.4), arising from the attack of the selenosilane intermediate **12** onto a second molecule of the epoxide.



Scheme 1.4. Synthesis of β-hydroxy selenides. Reagents and conditions: epoxide (1 equiv), $(Me_3Si)_2Se$ (0.6 equiv), TBAF (0.24 equiv), THF, r.t., 4h.

The possible formation of such intermediate could be explained by a mechanism which involves the generation of hypervalent silicon compounds, on the basis of considerations and hypotheses reported by several authors on the activation of C-Si

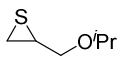
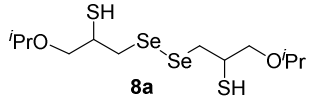
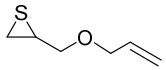
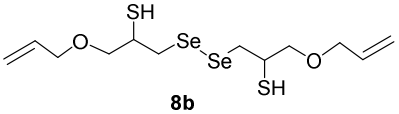
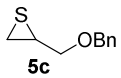
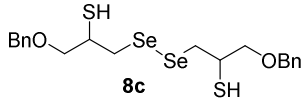
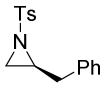
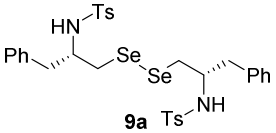
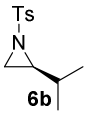
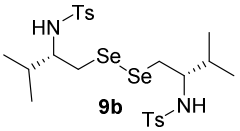
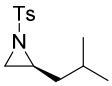
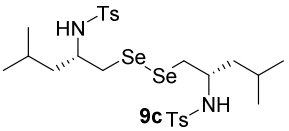
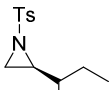
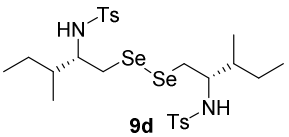
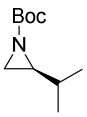
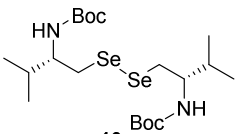
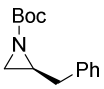
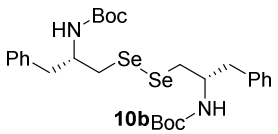
Table 1.2. Synthesis of β-mercapto and β-amino dialkyl diselenides



5a-c, X=S
6a-d, X=N-Ts
7a,b, X=N-Boc

2

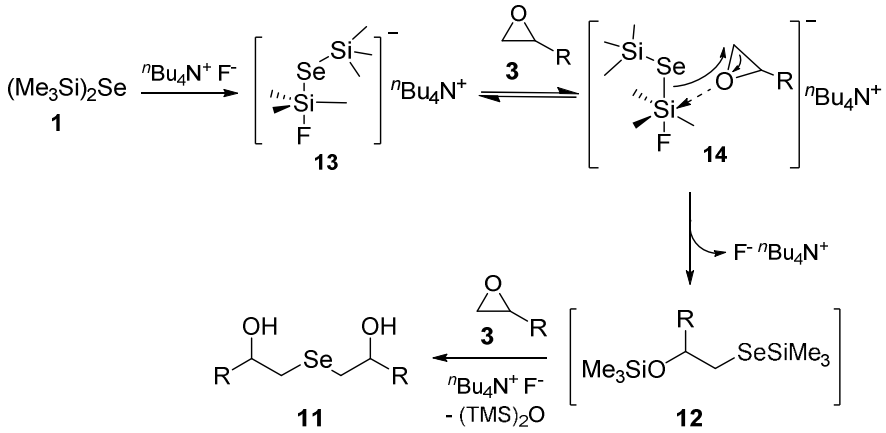
8a-c, X=S
9a-d, X=N-Ts
10a,b, X=N-Boc

Entry	Reagent	Product	Yield (%)[a]
1	 **5a**	 **8a**	37[b,c]
2	 **5b**	 **8b**	57[b,c]
3	 **5c**	 **8c**	36[b,c,d]
4	 **6a**	 **9a**	73[e]
5	 **6b**	 **9b**	59[d,e]
6	 **6c**	 **9c**	62[e]
7	 **6d**	 **9d**	58[d,e]
8	 **7a**	 **10a**	74[f]
9	 **7b**	 **10b**	65[f]

[a] Isolated yield is given. [b] Mixture of diastereoisomers. [c] Refers to crude product. [d] Minor amount (5-10%) of the corresponing selenide was observed. [e] Ref. [20]. [f] Ref. [5a]

and heteroatom-Si bonds mediated by fluoride ion[30] (Scheme 1.5), even if the real mechanism of the action of TBAF is still not completely clear.

In the first step the coordination of the fluoride ion to the Si atom leads to a pentacoordinate species **(13)**, which interacts with the epoxide to give a hexacoordinate silicon intermediate **(14)**, making possible the attack of the seleno-nucleophile. Ring-opening of the oxirane and releasing of TBAF allows the formation of intermediate **12**, which in turn can react with another molecule of epoxide (in excess).



Scheme 1.5. Proposed mechanism for TBAF-mediated reaction of HMDSS with epoxides

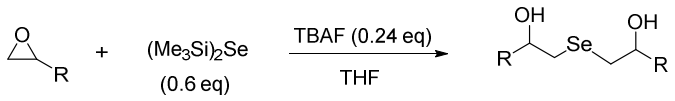
An alternative mechanism could not be excluded, with the formation in our case of a tetrabutylammonium selenate, but usually this hypothesis is mainly considered when allylsilanes are reacted.[31]

This methodology was extended to various substrates, thus showing its generality. Results are reported in Table 1.3.

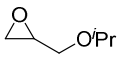
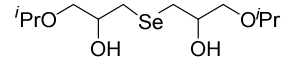
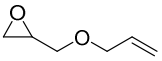
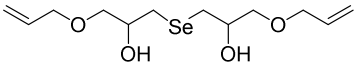
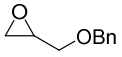
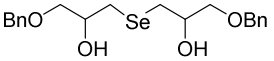
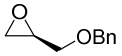
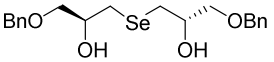
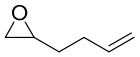
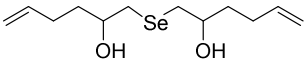
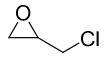
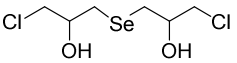
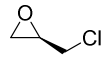
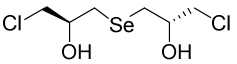
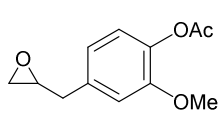
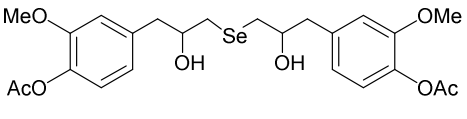
A regioselective addition on the less hindered side of the oxirane ring was always observed to afford compounds **11**. 2-Hydroxy dialkyl selenides can be prepared in a one-flask operation in good to high yields, and this procedure may be regarded as a mild and efficient approach, alternative to those reported to obtain these useful organoseleno compounds.[13a,22a,b,32]

Interestingly, no appreciable contamination was found between diselenides and selenides, this procedure generally affording a selective entry to each class of compounds.

Table 1.3. Synthesis of β-hydroxy dialkyl selenides



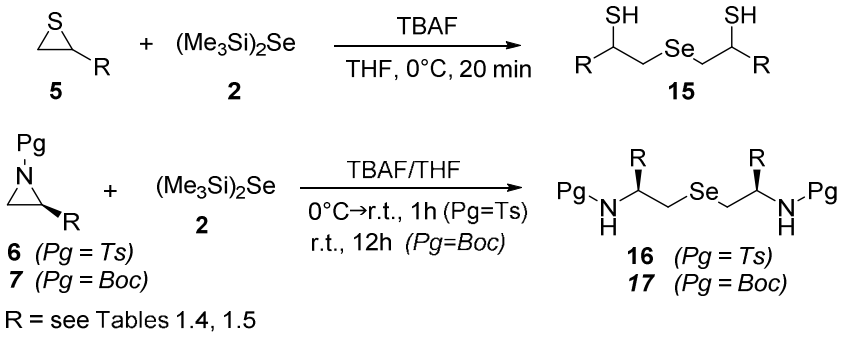
3 **1** **11**

Entry	Reagent	Product	Yield (%)[a]
1	 **3a**	 **11a**	72[b]
2	 **3b**	 **11b**	76[b]
3	 **3c**	 **11c**	96[b]
4	 ***(R)*-3c**	 **(2*S*, 2'*S*)-11c**	87
5	 **3d**	 **11d**	78[b]
6	 **3e**	 **11e**	66[b]
7	 ***(R)*-3e**	 **(2*S*, 2'*S*)-11e**	65
8	 **3h**	 **11f**	84[b,c]

[a] Isolated yield is given. [b] Mixture of diastereoisomers. [c] Refers to crude product.

To expand the scope of this methodology, our attention was focused to the reactivity of other three-membered heterocycles. The reaction appeared even more versatile in the case of episulfides **5a-f**. When in fact HMDSS was reacted with

these substrates, a more general and milder access to β-mercapto derivatives **15a-f** was obtained with respect to the corresponding diselenides (Scheme 1.6).



Scheme 1.6. General scheme for the synthesis of β-mercapto and β-amino selenides

This could be ascribed to the higher reactivity of thiiranes with the intermediate thio-selenosilane, thus reducing undesired oxidation reactions. This higher reactivity can be also confirmed by the reaction conditions: episulfides in fact were reacted at lower temperature (0°C instead of r.t. as for epoxides) and for a shorter reaction time (less than 1 h). Treatment with citric acid during work-up procedure allowed to isolate the β-mercapto selenides in very good yields.

Results of this investigation are listed in Table 1.4. This procedure can therefore be proposed as a novel, mild access to new functionalized chalchogen derivatives.

The synthetic approach was also efficient in obtaining β-amino selenides. When 2 equiv of *N*-Tosyl- or *N*-Boc-aziridines **6a,b,d** and **7a,b** respectively (obtained from phenylalanine, valine, leucine, isoleucine) were treated with 1.2 equiv of HMDSS in the presence of TBAF, a representative series of chiral amino selenides **16a-c** and **17a,b** was isolated. Results of this reactivity are reported in Table 1.5.

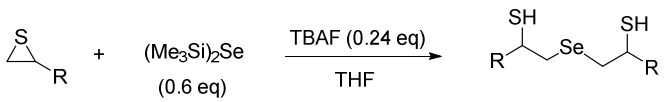
While the less activated *N*-Boc aziridines were reacted at room temperature for 12 h, reactions of *N*-Ts-aziridines were carried out at 0°C as for episulfides, and showed shorter reaction time with respect to epoxides (ca. 1 h).

Syntheses of chiral amino selenides have been reported through reaction of aziridines and diselenides in the presence of different reducing agents, usually leading to the formation of phenylseleno substituted β-amino selenides.[21,30a,33] Functionalized organoseleno derivatives of this type find application as key

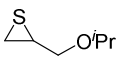
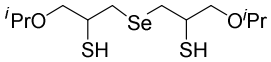
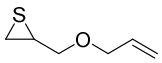
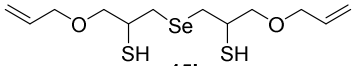
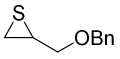
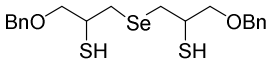
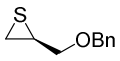
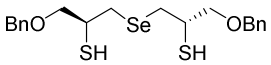
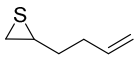
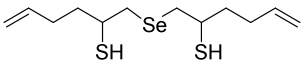
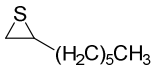
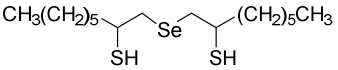
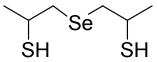
intermediates for the synthesis of non-natural selenated amino acid derivatives and peptides, and as ligands in asymmetric catalysis.

In this context, the described procedure provides a simple, mild and straightforward access to a variety of 2-substituted 2-amino selenides in a higly regio- and stereocontrolled way.

Table 1.4. Synthesis of β-mercapto dialkyl selenides



5a-f **2** **15a-f**

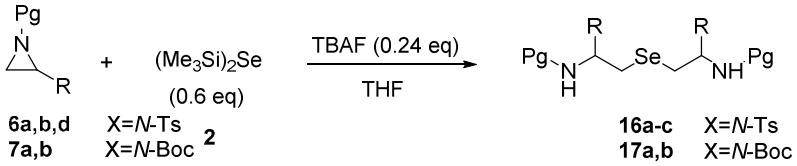
Entry	Reagent	Product	Yield (%)[a]
1	 **5a**	 **15a**	89[b,c]
2	 **5b**	 **15b**	86[b,c]
3	 **5c**	 **15c**	88[b]
4	 ***(S)*-5c**	 **(2*S*, 2'*S*)-15c**	86[c]
5	 **5d**	 **15d**	84[b,c]
6	 **5e**	 **15e**	79[b,c]
7	 **5f**	 **15f**	73[b,c]

[a] Isolated yield is given. [b] Mixture of diastereoisomers. [c] Refers to crude product.

It is also interesting to underline that in most cases the products were obtained in a very pure form, thus avoiding their purification. This is particularly useful when labile groups as thiols are present, for their easy oxidation during manipulation procedures.

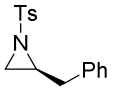
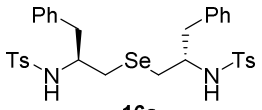
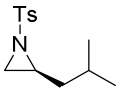
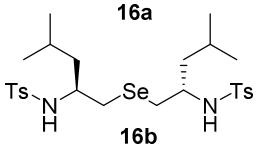
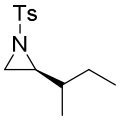
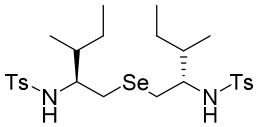
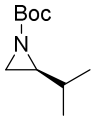
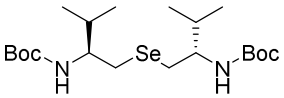
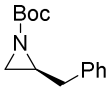
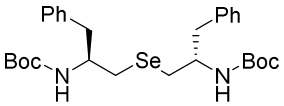
β-Mercapto and β-amino selenides and diselenides were selectively formed under the reported conditions. In a limited number of examples the presence of minor amount of the other selenated derivative was observed (see notes in Tables).

Table 1.5. Synthesis of β-amino dialkyl selenides



6a,b,d X=*N*-Ts
7a,b X=*N*-Boc **2**

16a-c X=*N*-Ts
17a,b X=*N*-Boc

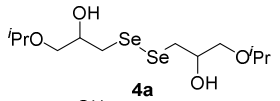
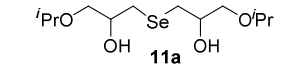
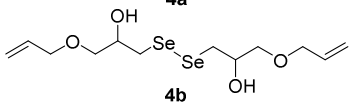
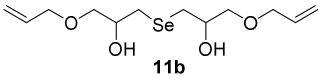
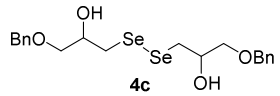
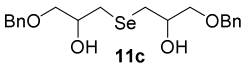
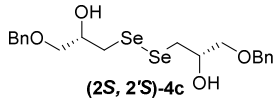
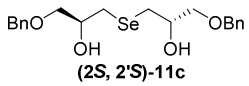
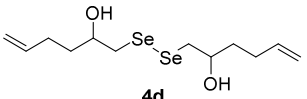
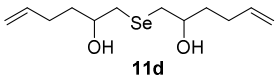
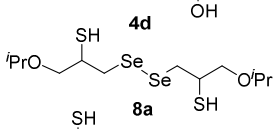
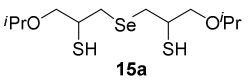
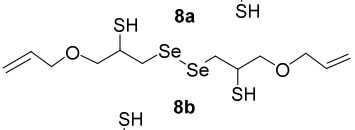
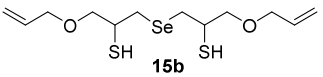
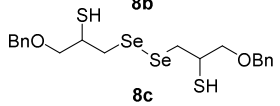
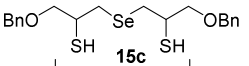
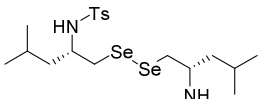
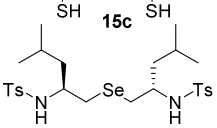
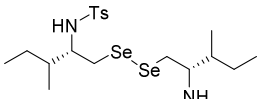
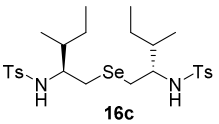
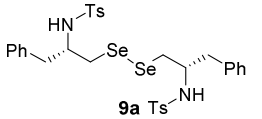
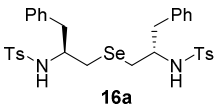
Entry	Reagent	Product	Yield (%)[a]
1	 **6a**	 **16a**	67
2	 **6b**	 **16b**	68
3	 **6d**	 **16c**	68[b]
4	 **7a**	 **17a**	56[b]
5	 **7b**	 **17b**	92

[a] Isolated yield is given. [b] Traces of the corresponding diselenide were observed (ca. 5-10%).

On the basis of our previous results on the catalytic activity of tetrabutylammonium phenoxide in reactions of silyl chalchogenides with epoxides,[26a] we evaluated its efficiency also in this kind of reactions. We found that the formation of β-substituted diselenides and selenides catalyzed by PhO*n*-Bu_4 occurred under similar conditions, leading to the regioselective formation of

diselenides and selenides in good yields, comparable to those obtained with fluoride ion.

Table 1.6. Representative ^{77}Se NMR of selected diselenides and selenides

Diselenides	^{77}Se-NMR (δ)[a]	Selenides	^{77}Se-NMR (δ)[a]
 **4a**	279.8, 280.4[b]	 **11a**	67.9, 70.3[b]
 **4b**	279.4	 **11b**	68.3, 71.0[b]
 **4c**	277.5, 280.3[b]	 **11c**	69.1, 71.4[b]
 **(2*S*, 2'*S*)-4c**	277.5	 **(2*S*, 2'*S*)-11c**	69.1
 **4d**	267.6, 268.6[b]	 **11d**	50.9, 59.5[b]
 **8a**	308.6, 310.5[b]	 **15a**	123.8
 **8b**	310.6, 311.9[b]	 **15b**	124.5, 125.4[b]
 **8c**	310.8, 311.6[b]	 **15c**	124.8, 126.7[b]
 **9c**	282.3	 **16b**	38.2
 **9d**	288.6	 **16c**	48.0
 **9a**	283.2	 **16a**	59.8

[a] Relative to Ph_2Se_2 (461 ppm). [b] Chemical shift of each diastereoisomer.

For all the diselenides and selenides herein described, their characterization, as well as the unique formation of diselenides and selenides, cannot be unequivocally obtained either from ^{1}H or ^{13}C NMR spectra, the signals being very similar, but

could nonetheless be easily obtained through their ^{77}Se NMR spectra. Actually it is known the high sensitivity of ^{77}Se chemical shifts to chemical environment, that suggests how NMR of selenium represents a useful and powerful technique to determine selenated compounds.[34]

^{77}Se NMR chemical shifts of selected diselenides and selenides are collected in Table 1.6.

As can be seen from Table, they show very different and typical range of absorption for the two classes of compounds, depending on the substituents and the groups (hydroxyl, mercapto, amino) present in β-position. ^{77}Se resonance is shielded by ~200 ppm on going from R_2Se_2 to R_2Se, and was found to be in the range ~267-310 ppm (relative to Ph_2Se_2) for diselenides and ~38-124 ppm for selenides, thus showing a clear evidence for the presence of each class of organoseleno derivatives.

1.3 Conclusions

In summary, we have developed a direct, selective and novel access to a wide range of diorganyl diselenides and selenides, bearing different substituents on β-position, together with hydroxyl, mercapto and amino groups. Bis(trimethylsilyl)selenide behave as efficient transfer agent of selenium moiety through a regio- and stereoselective reaction with differently substituted epoxides, episulfides and *N*-Ts- or *N*-Boc-protected aziridines promoted by TBAF. Several of these molecules offer interesting possibilities for further synthetic applications as well as for the evaluation of their antioxidant properties.

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Chapter 2

Synthesis of 3,6-disubstituted 1,2,5-trithiepanes and dithiaselenepanes

2.1 Introduction

Sulfur containing compounds are very interesting molecules for their applications in synthetic organic chemistry and for their properties as biologically active compounds. A large number of sulfurated systems have been shown to be odor-active and odor-relevant molecules in different kind of plants[1].

Several examples refer to aliphatic derivatives, and in recent years the interest towards thiaheterocyclic compounds has increased, owing to their utilization in different fields of organic chemistry, biochemistry and food chemistry. Polysulfurated heterocycles represent as well an interesting class of compounds for their physical and chemical properties, and for their synthetic utility.[2] Several cyclic polysulfides of different ring size have been isolated from marine bacteria, and a profile of the pharmaceutical and agrochemical properties was investigated.[3]

In this context, seven-membered rings appear interesting structures, and synthetic processes to obtain cyclic trisulfides, such as trithiepane derivatives, have been reported. Generally these compounds have been obtained in moderate yields and in complex mixture of products.[2c,3b,4]

In addition, the last decades have witnessed a growth interest in the chemistry of organoselenium compounds, mainly due to their antioxidant, antitumoral and antimicrobial activities.[5] Among these compounds, selenides, diselenides and selenium containing heterocycles have attracted considerable attention, for their useful reactivity in organic synthesis and for their potential biological applications.[6]

Our group, from long time interested in the chemical behaviour of bis(trimethylsilyl)sulfide (HMDST),[7] previously reported the efficiency of this thiosilane as a useful reagent in the synthesis of β-mercaptoalcohols and 1,2-dithiols through the ring opening of epoxides and thiiranes.[8] More recently, we described an efficient and selective synthesis of β-hydroxy-, β-mercapto-, β-amino- selenides and

diselenides exploiting the reactivity of bis(trimethylsilyl)selenide (HMDSS) with three-membered heterocycles.[9]

During the course of an investigation on the synthesis of different heterocyclic systems through the reactivity of thiosilanes and selenosilanes, we turned our attention to seven-membered thiaheterocycles of type **18** and **19**, namely 1,2,5-trithiepanes and 1,2,5-dithiaselenepane (Figure 2.1).

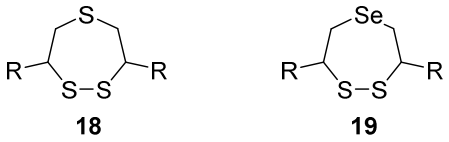


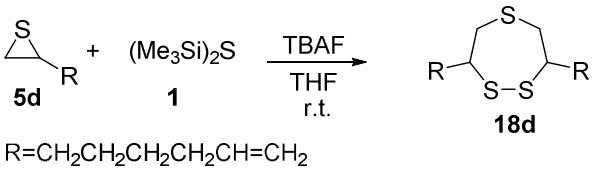
Fig. 2.1. Trithiepane and dithiaselenepane core

To the best of our knowledge, only few examples are reported in the literature for the synthesis of the sulfurated derivative, while no example is present for the selenated analogue.

In this context, we thought that thiosilanes and selenosilanes could provide a convenient access to these molecules through reaction with episulfides, followed by intramolecular oxidative ring closure.[10]

2.2 Results and discussion

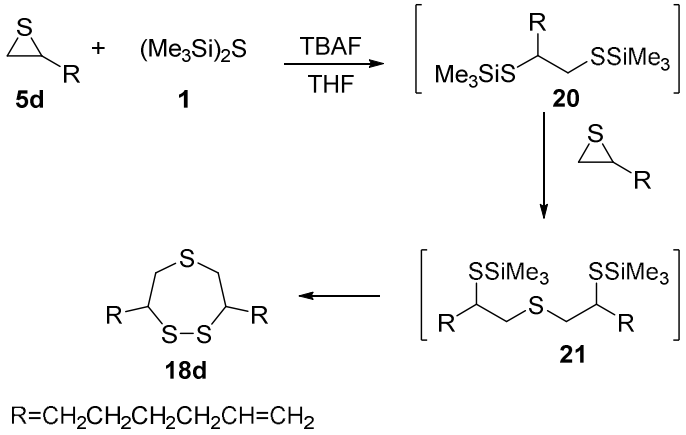
With this concept in mind, we reacted two equivalents of 2-(5-hexenyl)thiirane **5d** with HMDST under the catalysis of TBAF. The reaction proved quite efficient, leading to the formation of 3,7-di(5-hexenyl)-1,2,5-trithiepane **18a-h** as ca. 1:1 mixture of *cis*/*trans* diastereoisomers (Scheme 2.1 and Table 2.1).



Scheme 2.1. Synthesis of trithiepane from thiirane

A reasonable mechanism for the formation of compound **18d** is proposed in Scheme 2.2. On the basis of our previous results in the fluoride ion induced ring

opening of episulfides with HMDST, the formation of the substituted β-dithiosilane intermediate **20** can be expected. This in turn should react with another equivalent of thiirane, leading, after oxidation of two sulfur units of intermediate **21,** to the target trithiepane **18d**.



Scheme 2.2. Proposed mechanism

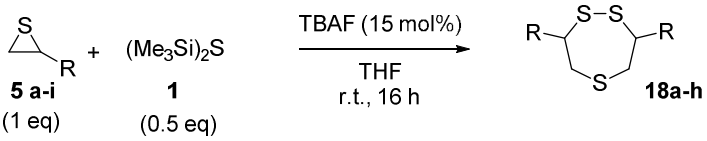
Taking into account that the ring opening of episulfides by thiosilanes proceeds in a regioselective way with the attack on the less substituted position, the formation of the isomeric 3,6-disubstituted-1,2,5-trithiepane can be excluded.

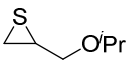
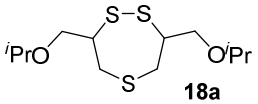
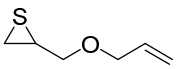
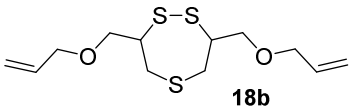
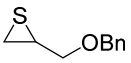
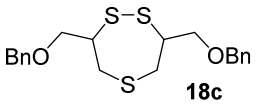
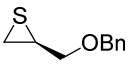
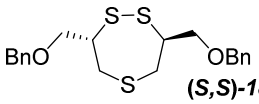
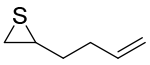
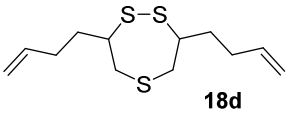
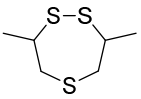
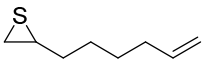
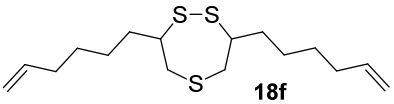
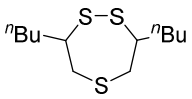
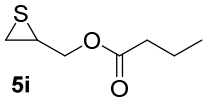
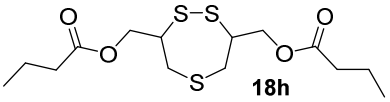
The structure of **18d** was assigned by NMR and MS investigation, and by comparison with literature data reported on analogue derivatives.[3b, 4b] GC/MS analysis revealed the presence of two peaks with very close retention times (15.43 and 15.52 min) and very similar mass spectra. Mass spectrometric fragmentation contains a characteristic ion at *m/z* 206 $[M^{+\cdot}\text{-}C_8H_{14}]$, that suggests the formation of a 4-substituted-1,2,3-trithiolane substructure. Other characteristic ions are at *m/z* 141 $[C_8H_{13}S]^+$ and 109 $[C_8H_{13}]^+$. Proton NMR spectra appear to be second-order spectra, due to chemical nonequivalence of the methylene protons, while ^{13}C NMR shows signals in agreement with the proposed symmetric structure, while in the unsymmetrical 3,6-disubstituted trithiepane all carbon atoms are differentiated, due to the missing simmetry plane. As already described in literature,[3b] the complexity of proton spectra can be also due to rapid ring interconversion of the thiepane-ring, thus showing broad signals.

In order to evaluate the generality of such methodology, a series of substituted episulfides was reacted under the same conditions. Results are summarized in Table 2.1. The reactivity proved general, leading in good yields to the synthesis of trithiepanes **18a-h**, bearing different moieties, that could be further elaborated. The reaction is operationally simple and represents a direct, smooth access to cyclic polysulfides. Purification on silica gel allowed the isolation of products as mixture of diastereoisomers, which were difficult to separate. Due to the mildness of experimental conditions, this procedure can be applied also to very useful, but more labile compounds, such as thioglycidol derivatives, which can represent versatile structures to be further functionalized. In fact protected thioglycidols **5a-c,5i** reacted in good yields, and the protective groups were not removed under these conditions (Table 2.1, entries 1-4,9). When enantiopure thiirane **(*S*)-5c** is reacted, trithiepane **(*S,S*)-18c** is formed as single diastereoisomer, due to enantioselective ring opening of the episulfide.

Taking into account the interest in the evaluation of the biological activity of small sulfurated cyclic structures, it is noteworthy to underline that the so obtained compounds, with different substituents and different polarity, could represent intersting substrates to be tested for applications in pharmaceutical or agrochemical field. Once established the efficiency of HMDST/TBAF in the formation of trithiepanes, we turned our attention to the reactivity of the corresponding selenium derivative bis(trimethylsilyl)selenide (TMS-Se-TMS, HMDSS). This compound has received less attention with respect to the analogue HMDST, despite the relevance that organoselenium compounds have actually gained. On the other hand we described our results in HMDSS induced regioselective ring opening of epoxides and episulfides in the synthesis of β-functionalized diselenides or selenides. [9] Thus, on the basis of these results we decided to evaluate the efficiency of HMDSS in the synthesis of unreported 1,2,5-dithiaselenepane derivatives. In a test reaction thiirane **5d** was reacted under TBAF catalysis at 0°C with HMDSS (Scheme 2.3).

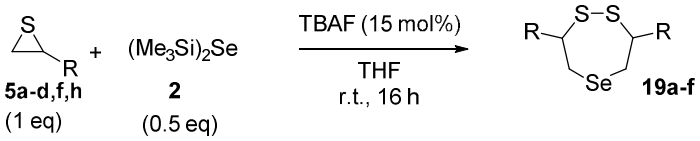
Table 2.1. Synthesis of 1,2,5-trithiepanes

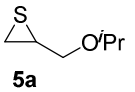
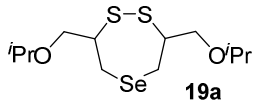
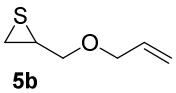
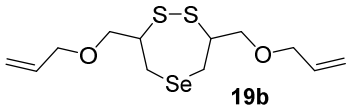
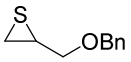
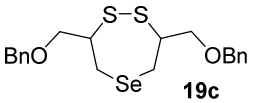
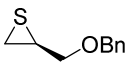
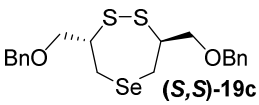
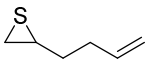
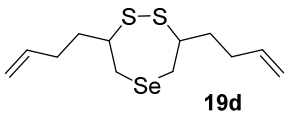
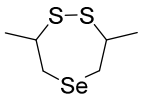
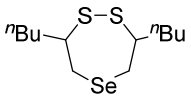


Entry	Thiirane	Product	Yield (%)[a]
1	 **5a**	 **18a**	72[b]
2	 **5b**	 **18b**	65
3	 **5c**	 **18c**	64
4	 ***(S)-5c***	 ***(S,S)-18c***	65[d]
5	 **5d**	 **18d**	86[b]
6	 **5f**	 **18e**	85[c]
7	 **5g**	 **18f**	83[b]
8	 **5h**	 **18g**	75
9	 **5i**	 **18h**	68

[a] Yields referred to chromatographically pure material. Isolated as a mixture of diastereoisomers
[b] Referred to crude product
[c] Ref 4a-c
[d] Single diastereoisomer

Table 2.2. Synthesis of 1,2,5-dithiaselenepanes

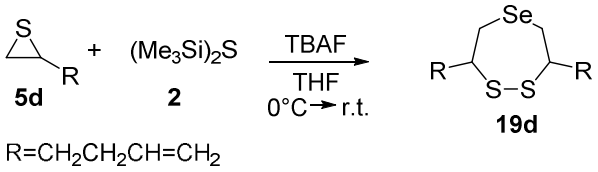


Entry	Thiirane	Product	Yield (%)[a]
1	 **5a**	 **19a**	85[b]
2	 **5b**	 **19b**	73
3	 **5c**	 **19c**	73
4	 **(*S*)-5c**	 **(*S,S*)-19c**	71[c]
5	 **5d**	 **19d**	68
6	 **5f**	 **19e**	67
7	 **5h**	 **19f**	87[b]

[a] After purification. Isolated as mixture of diastereoisomers
[b] Yield refers to crude product
[c] Single diastereoisomer

The reaction proved quite efficient, affording as a predominant product 3,7-di(but-3-en-1-yl)-1,2,5-dithiaselenepane **19d** in good yield, together with minor amount (ca. 10%) of the corresponding eight-membered 3,8-disubstituted-1,2,5,6-dithiadiselenocane, arising from oxidation of both sulfur and selenium units of the

selenium-intermediate (analogue of **20** described in Scheme 2.2). A mechanism similar to that proposed in Scheme 2.2 can in fact be responsible for the formation of **19d**.



Scheme 2.3. Synthesis of dithiaselenepane from thiirane

This result was interesting, showing that under these mild conditions the silyl selenide intermediate (analogue of **20** in Scheme 2.2) was stable enough to attack another molecule of thiirane, minimizing the well known high tendency of selenol-derivatives to be oxidized.

Similarly to what described for the sulfur analogue, the structure of dithiaselenepane **19d** was determined also on the basis of MS and NMR data, that indicate the formation of a symmetric structure, arising from the expected regioselective ring opening of thiirane through attack on the less hindered position.

Then, with the aim to evaluate the limits and the potential of this reaction, thiiranes with different substituents were reacted. The studied examples are listed in Table 2.2. They show the versatility of this synthetic approach to a novel class of mixed thia-seleno heterocycles.

2.3 Conclusions

We have devised a general and convenient access to differently 3,7-disubstituted-1,2,5-trithiepanes and -1,2,5-dithiaselenepanes through reaction of thiiranes with HMDST and HMDSS, followed by an intramolecular oxidative cyclization.

The reactions occur in a regioselective way and stereoselective formation of seven-membered heterocycles is observed when an enantiopure thiirane is used as a substrate.

2.4 References

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Chapter 3

Synthesis of 1,2 mercaptoamines

3.1 Introduction

β-aminothiols have found various applications in many areas, including synthetic and medicinal chemistry, catalysis and materials chemistry. Their versatility is mainly due to the nucleophilicity of the two heteroatoms (potential to act as *N*- or *S*-nucleophiles or as *N*,*S*-binucleophiles), as well as their ability to chelate metals. Some β-amino thiols (i.e., cysteine, cysteamine, penicillamine) are naturally occurring compounds and are involved in important biological processes. They are constituents of complex molecules of biological interest, natural (e.g. glutathione, coenzyme A) or unnatural. The commonest applications of β-amino thiols include their use as enzyme inhibitors,[1] radioprotective agents,[2] intermediates for the synthesis of biologically active compounds (especially in peptide synthesis),[3] and as precursors for various *N*,*S*-heterocycles (e.g. thiazolines,[4] thiazolidines,[5] thiomorpholines,[6] thiazepines[7]). More recently, 2-amino thiols and their thioether derivatives have been used as ligands in organometallic catalysis.[8]

Syntheses starting either from α-amino acids or from β-amino alcohols through the introduction of sulfur nucleophiles, from five-membered *N*,*S*-heterocycles, or based on opening of an aziridine or thiirane ring with a sulfur or a nitrogen nucleophile, respectively, have been described, as well as recent methodologies using new convenient sulfur reagents. Nonetheless, a mild, easy and direct synthetic route to 1,2 mercaptoamines is still in demand. On the basis of these considerations, we investigated the reactivity of bis(trimethylsilyl)sulfide (HMDSS) with aziridines aimed to straightforwardly access title compounds through a process that did not require *S*-protecting groups.

Aziridines due to their high propensity for acting as carbon electrophiles, are versatile intermediates for the synthesis of biologically and chemically important compounds. A number of ring opening reactions of activated and unactivated aziridines have been reported, including reactions with a wide range of heteroatom

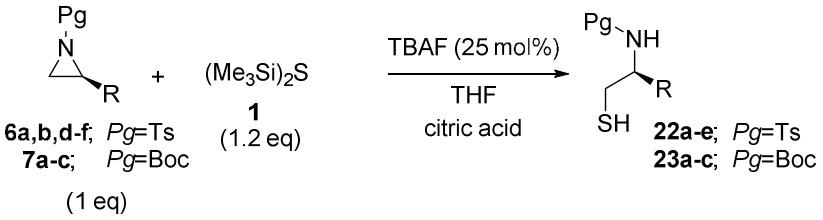
and carbon nucleophiles.[9] The orientation of the attack generally occurs at the less sterically hindered position to provide ring opened products, but in some examples, the formation of mixtures of regioisomers is reported. Ring opening with sulfurated nucleophiles is an interesting procedure for accessing β-amino sulfides, which are compounds of undoubted synthetic utility in organic chemistry.[10] While the nitrogen of non-activated aziridines behaves as a base to form the nucleophilic thiolate anion, activated aziridines often require a strong acid (such as CF_3SO_3H)[11]

or a Lewis acid (i.e. BF_3,[12] $ZnCl_2$[13] or $MgBr_2$,[14]). Examples of the cleavage of *N*-tosyl aziridines have been reported in water in the presence of β-cyclodextrin or PBu_3.[15] Ring opening reactions with nucleophiles can also be achieved under basic conditions (Et_3N),[16] and TBAF has been used when silylated nucleophiles have been reacted.[17] Recently, TMS–CN, TMS–N_3, TMS–Br and TMS–I were demonstrated to attack aziridines under Lewis base catalysis with a high regioselectivity. Thiosilanes and selenosilanes,[18] TMS–CN[19] and TMS–N_3[20] have been reported in desymmetrization of *meso*-aziridines.

3.2 Results and discussion

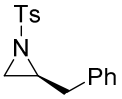
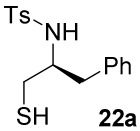
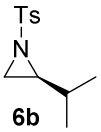
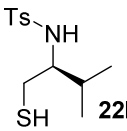
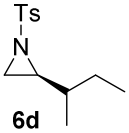
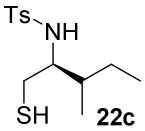
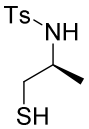
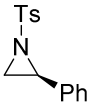
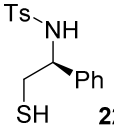
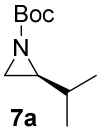
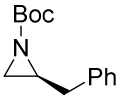
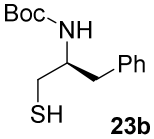
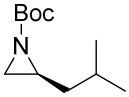
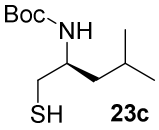
Since long time our group is interested in the study of the reactivity of $(Me_3Si)_2S$. We previously reported that treatment of oxiranes and thiiranes with this thiosilane in the presence of a catalytic amount of TBAF led to the regioselective formation of 1,2-mercaptoalcohols and 1,2-dithiols.[21] Thus, we wonder whether this reactivity could be extended to the related *N*-containing three membered heterocycles. Preliminary results showed that $(Me_3Si)_2S$ gave nucleophilic addiction on aziridines but the disulfide was the largely predominant reaction product. On the basis of these findings we turned our attention on the optimization of the reaction conditions, aimed to minimize the disulfide formation. Temperature and reaction time were found to be the most important parameters to control the output of the transformation.

Table 3.1. Synthesis of β-amino thiols

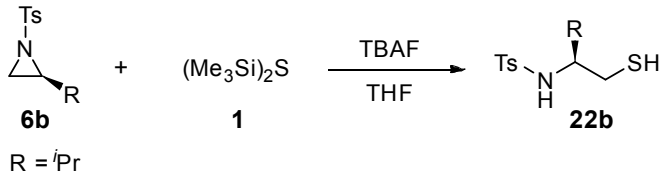


6a,b,d-f; *Pg*=Ts
7a-c; *Pg*=Boc
(1 eq)

22a-e; *Pg*=Ts
23a-c; *Pg*=Boc

Entry	Aziridine	Product	Yield (%)
1	 **6a**	 **22a**	98
2	 **6b**	 **22b**	93
3	 **6d**	 **22c**	92
4	 **6e**	 **22d**	86
5	 **6f**	 **22e**	98
6	 **7a**	 **23a**	91
7	 **7b**	 **23b**	92
8	 **7c**	 **23c**	89

attack on the less hindered side of the aziridine, was achieved in excellent yield (Scheme 3.1).



Scheme 3.1. Synthesis of 1,2-mercaproamines. Reagents and conditions: aziridine (1 equiv.), $(Me_3Si)_2S$ (1.2 equiv.), TBAF (0.25 mol%), THF, 0°C, 15 min

Thus, when (*S*)-2-isopropyl-1-tosylaziridine **6b** was treated with $(Me_3Si)_2S$ in presence of TBAF at 0°C for 15 min, the corresponding (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide **22b**, arisen from a regioselective

The procedure proved to be general and variously substituted chiral aziridines, derived from natural aminoacids, led smoothly and simply to enantiopure 2-substituted 1,2 mercaptoamines (Table 3.1, entries 1-4).

All the reactions occur with very good yields and the process is highly regioselective, only one isomer being observed in the crude. Only in the case of the styrene derivative was the corresponding regioisomer detected (Table 3.1, entry 5). The reported reactivity may be conveniently extended to *N*-Boc protected aziridines. Taking into account the less activation of these heterocycles, the reaction conditions were slightly modified. Therefore, ring opening of *N*-Boc aziridines was performed at r.t., for 1 hour in the presence of 1 equivalent of TBAF. Once again the reaction afforded the wanted optically active *N*-Boc-1,2-mercaptoamines in very good yield and in a complete regioselective way (table 3.1, entries 6-8).

3.3 Conclusions

In conclusion, we have devised a general and efficient ring-opening of differently *N*-protected aziridines by HMDST, which behaves as an effective synthetic equivalent of H_2S, leading directly to non racemic β-mercaptoamines, very interesting starting materials of more complex molecules.

The reactions occur with high regio- and stereoselectivity and are operationally simple with short reaction times. The mildness of this procedure should be useful in the synthesis of sensitive substrates, which preclude the use of strong reaction conditions.

Moreover, the present trasformation may represent a valuable and useful alterntive to the classical access route to aminothiols, such as Mitsunobu reaction, usually based on multi-step procedures, including the final cleavage of the protected thiol.

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Chapter 4

β-Functionalised selenols: synthesis, characterization and reactivity

4.1 Introduction

Formation of selenium-carbon or selenium-heteroatom bonds is widely applied in the synthesis of complex molecules with important biological properties such as antioxidant and antiviral activities. On the other hand, selenols are much more unstable with respect to their sulfurated analogues thus prompting organic chemists to go through routes that involve synthetic equivalents of SeH group whose functionalzation often requires harsh reaction conditions and is not compatible with labile functional groups. In this context, even though selenols may represent interesting and useful compounds, only a few examples are described for their synthesis. These compounds have been generally obtained through reduction of corresponding diselenides followed by treatment with acid.

Grignard reagents have been converted in the corresponding selenols by treatment with selenium followed by an acidic quench.[1] Selenols have been obtained through the reaction of alkyl halides with Se^{2-} (generated from Se(0) and Na in liquid NH_3[2] or reducting selenium with $NaBH_4$[3]). Zinc under acid conditions has been applied to the reduction of diselenides to the corresponding selenols which can be isolated or reacted with electrophiles.[4] Guillemin and co-workers reported the synthesis of allylic selenols by reductive cleavage of tetraglyme diluted diselenides with $^{n}Bu_3SnH$ or by a two-step reaction sequence involving the addition of the corresponding selenocyanate to $LiAlH_4$ and subsequent treatment with an acid. [5] Other papers dealing with the synthesis of selenocyanates and their conversion to the corresponding selenols have been published.[5b,c,6]

Ring-opening of epoxides with various nucleophiles is an important and useful synthetic transformation providing an easy access to a large number of functionalized intermediates, useful in the synthesis of more complex organic structures.[7]

Stereoselective ring-opening of chiral epoxides with thiols is often achieved and catalytic asymmetric oxirane ring-openings are usually obtained through the use of chiral metal complexes, leading to desymmetrization of meso-epoxides and introduction of two contiguous stereogenic centers.[8]

Thiosilanes have also been used as nucleophiles in reactions with oxiranes in place of thiols.[9-14]Reactions of arylselenotrimethylsilanes with epoxides in the presence of different catalysts[15] have been reported as alternative methods for the synthesis of alkyl aryl selenides. Examples of desymmetrization of *meso*-epoxides[16] and *meso*-aziridines[17] using selenols and selenosilanes have been reported.We recently reported a convenient route to access β-functionalised selenides and diselenide through the reaction of $(Me_3Si)_2Se$ with three-membered heterocycles.[18]

Nonetheless, among the reactions of selenium nucleophiles with epoxides, to the best of our knowledge there are only very few methods which allow an access to β-hydroxyselenols, which could represent very interesting intermediates in the synthesis of various biologically important compounds. These procedures are mainly based on the reduction of β-hydroxydiselenides, obtained through a nucleophilic replacement on β-haloalcohols[19] or ring opening of epoxides.[20]

Only one example of epoxides ring opening with H_2Se is described, allowing a direct access to β-hydroxyselenols in moderate yield (12-15%) together with large amount of the corresponding diselenide.[21] Limitations of such methodology consist in the toxicity of H_2Se, low yields and missing of generality of the reaction.

To the best of our knowledge, β-mercapto selenols represent unreported compounds and no example of thiiranes ring opening with selenium nucleophiles is described,

Only one example of aziridine ring opening has been described for the H_2Se promoted synthesis of unsubstituted 1,2-hydroselenoamine.[22]

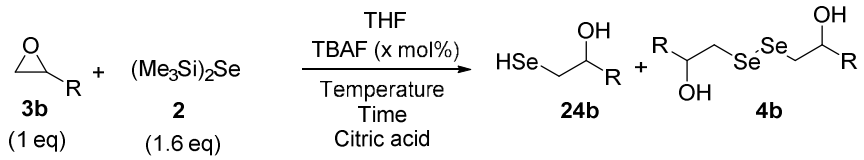
On the basis of these considerations, a direct access to selenols under mild conditions may be an interesting advance in organoselenium chemistry.

4.2 Results and discussion

During the course of our research on the evaluation of the reactivity of bis(trimethylsilyl)selenide in the addition to strained heterocycles we wondered whether strictly controlled reaction conditions could allow to isolate the selenol.

Thus, reaction of 2-((allyloxy)methyl)oxirane **3b** with HMDSS was carried out in different conditions as is reported in table 4.1 Treatment with citric acid during the work up was performed.

Table 4.1. Synthesis of β-hydroxy selenols. Optimization of the reaction conditions



3b (1 eq) + $(Me_3Si)_2Se$ **2** (1.6 eq) → **24b** + **4b**

R = $CH_2OCH_2CH=CH_2$

Entry	Temperature (°C)	Time (min)	TBAF (x mol%)	Product (**24b:4b**)	Conversion (%)[a]
1	r.t.	60	20	0:100	>95
2	r.t.	20	20	0:100	>95
3	r.t.	5	10	<10:90	>95
4	0	30	10	60:40	>95
5	0	10	20	>90:10	>95[b]
6	-15	10	20	90:10	70
7	-15	10	30	80:20	80
8	-15	20	20	60:40	>95
9	-30	40	20	20:80	25

[a] Consumption of SM **3b** determined by ^1H NMR of the crude. [b] 88% yield as isolated product

We found that the reaction time and the temperature were the main control parameters to avoid the oxidation of **24b** to the corresponding diselenide **4b** While **4b** is the exclusive product observed when the reaction is performed at r.t. (Table 4.1, entries 1-3), independently of the time and the loading of the catalyst. The wanted selenol **24b** can be obtained reacting **3b** with HMDSS under milder conditions, at 0°C for 10 min, in the presence of 10% TBAF (Table 4.1, entry 5).

Lower temperatures, requiring longer times to reach acceptable conversion levels, lead to the formation of **4b** as a main product, thus giving interesting insights in the kinetic of oxidation which seems faster than the HMDSS induced ring opening of the epoxide.

These findings disclose a potentially useful and straightforward access to 2-hydroxyselenols. In order to evaluate the generality of such methodology, a series of substituted epoxides was reacted under the same conditions (Table 4.1).

The reactivity proved general, leading to the synthesis of substituted 2-hydroxyselenols bearing different moieties in rather good yield. This reaction appears quite interesting, in so far as it is operationally simple and represents a direct access to this novel class of organoselenium compounds under very mild conditions with a catalytic amount of TBAF. It is interesting to underline that the process is highly regioselective, only one isomer being observed in the crude.

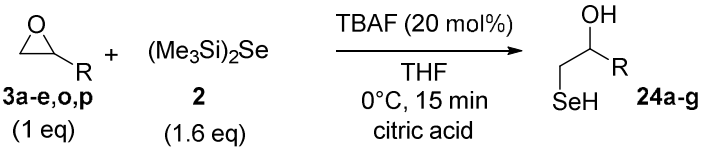
Due to the mildness of the experimental conditions, this methodology can be applied also to very useful, but labile compounds such as glycidol derivatives, which represent important structures in different fields. Protected glycidols **3a-c** were opened in good yields and the protective moieties were not removed under the reaction conditions (Table 4.2, entries 1-4).

Moreover, epichlorohydrin (**3e**) reacts smoothly with HMDSS (Table 4.2, entry 6). The oxirane is again regioselectively opened at the less hindered carbon, and nucleophilic attack occurs exclusively on the epoxide, the halide being preserved on the side chain.

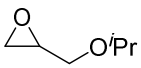
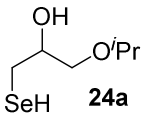
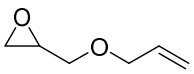
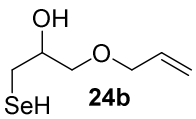
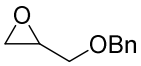
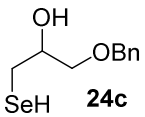
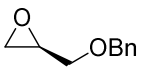
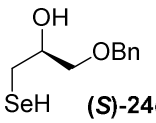
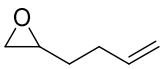
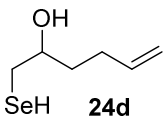
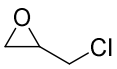
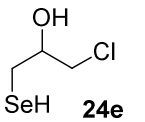
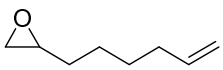
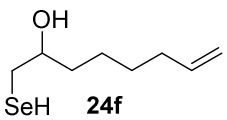
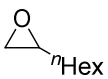
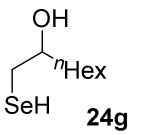
This mild and selective procedure may be usefully applied also to chiral molecules. When an enantiopure epoxide **(*R*)-3c** was reacted under the same conditions, optically active β-hydroxy selenols were regioselectively formed (Table 4.2, entry 4).

With the aim to evaluate the limits and the potential of this methodology, we extended this reactivity to different ring strained compounds, such as thiiranes. Thus, 2-(benzyloxymethyl)thiirane **5c** was treated with $(Me_3Si)_2Se$ in presence of a catalytic amount of TBAF under conditions listed in Table 4.3.

Table 4.2. Synthesis of β-hydroxy selenols

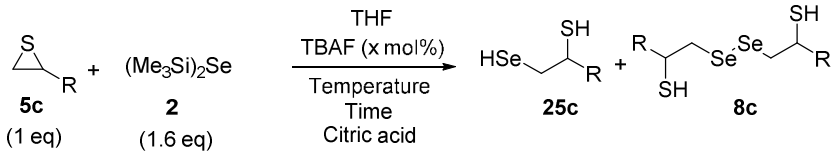


3a-e,o,p (1 eq) **2** (1.6 eq) **24a-g**

Entry	Epoxide	Product	Yield (%)
1	 **3a**	 **24a**	62
2	 **3b**	 **24b**	88
3	 **3c**	 **24c**	86
4	 **(*R*)-3c**	 **(*S*)-24c**	84
5	 **3d**	 **24d**	71
6	 **3e**	 **24e**	58
7	 **3o**	 **24f**	44[a]
8	 **3p**	 **24g**	62[b]

[a] Product obtained together with 30% of the corresponding diselenide.
[b] Product obtained together with 20% of the corresponding diselenide.

Table 4.3. Synthesis of β-mercapto selenols. Optimization of the reaction conditions



5c (1 eq) **2** (1.6 eq) **25c** **8c**

R = CH_2OBn

Entry	Temperature (°C)	Time (min)	TBAF (x mol%)	Product (**25c**:**8c**)	Conversion (%)[a]
1	0	10	10	50:50	>95
2	-15	10	20	70:30	>95
3	-15	5	10	>90:10	>95[b]
4	-30	30	20	30:70	40[c]

[a] Consumption of SM **5c** determined by ^1H NMR of the crude. [b] 93% yield as isolated product
[c] 30% of selenide **15c** was detected.

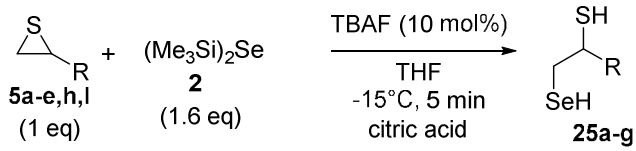
Once again, the reaction time and the temperature proved to be very important parameters to selectively achieve the formation of the selenol. The best results were obtained performing the reaction at -15°C for 5 min. It is interesting to evidence that the compound **25c** bears both the thiol and the selenol function, well known as highly oxidable moieties. The survival of these groups can be gained by the mildness of the used conditions.

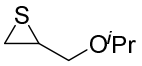
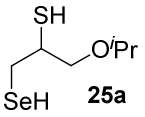
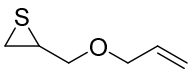
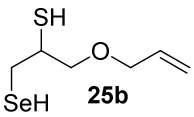
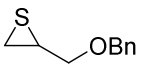
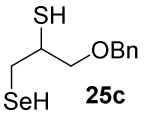
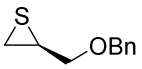
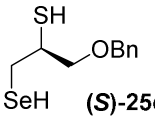
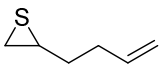
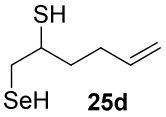
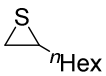
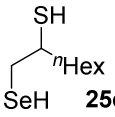
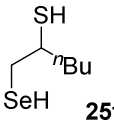
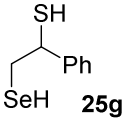
Seeking for the generality of such methodology, variously substituted thiiranes were reacted under the same conditions (Table 4.4), leading simply and smoothly to β-mercapto selenols arising from a clean regioselective attack of the selenated nucleophile on the less hindered side of the thiirane, disclosing a potentially useful and straightforward route to 1,2-hydroselenothiols.

The reactivity proved general and β-mercapto selenols, substituted with aromatic or aliphatic groups, and containing moieties that can be further functionalized, were obtained. Interestingly, as already observed in the case of oxiranes, the reactivity can be efficiently extended to chiral substrates leading to the synthesis of optically active 1,2-hydroselenothiols (Table 4.4, entry 4).

We have previously described a simple route for the synthesis of β-amino selenide and β-amino diselenides from aziridines and $(Me_3Si)_2Se$.

Table 4.4. Synthesis of β-mercapto selenols



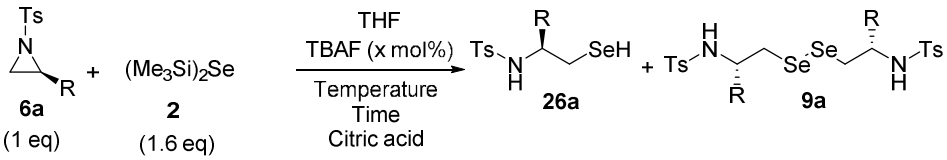
Entry	Thiirane	Product	Yield (%)
1	 **5a**	 **25a**	86
2	 **5b**	 **25b**	71
3	 **5c**	 **25c**	93
4	 **(*S*)-5c**	 **(*S*)-25c**	90
5	 **5d**	 **25d**	67
6	 **5e**	 **25e**	43[a]
7	 **5h**	 **25f**	42[b]
8	 **5l**	 **25g**	53[c]

[a] Product obtained together with 33% of the corresponding diselenide.
[b] Product obtained together with 25% of the corresponding diselenide.
[c] The minor regioisomer [CH_2(OH)CHPhSeH] was formed (ca. 40%)

The direct access to stable β-hydroxy- and β-mercapto- selenols through the reactivity of HMDSS with oxiranes and thiiranes, respectively, prompted us to investigate whether was possible to synthesize β-amino selenols from aziridines.

Thus, a set of ring opening reactions of (*S*)-2-benzyl-1-tosylaziridine **6a** with $(Me_3Si)_2Se$ was performed. The outcome is reported in Table 4.5.

Table 4.5. Synthesis of β-amino selenols. Optimization of the reaction conditions



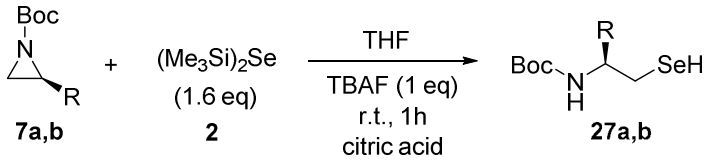
Entry	Temperature (°C)	Time (min)	TBAF (x mol%)	Product (**26a:9a**)	Conversion (%)[a]
1	r.t.	2	10	0:100	>95
2	0	10	20	20:80	>95
3	0	3	20	>95:5	>95[b]
4	-15	10	20	60:40	>95
5	-15	5	50	<10:90	>95
6	-15	20	5	20:80	25

[a] Consumption of SM **6a** determined by ^{1}H NMR of the crude. [b] 82% yield as isolated product

When **6a** is treated with HMDSS in presence of 20% mol of TBAF at 0°C for 3 min, a smooth reaction occurs, leading to the formation of (*S*)-*N*-(1-hydroseleno-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide **26a** in good yield. The reported reactivity may be conveniently extended to other *N*-Ts protected chiral aziridines, synthesized from natural aminoacids. Thus, aziridines **6a-e** were reacted with $(Me_3Si)_2Se$ under the described conditions and a straightforward, regioselective and stereoconservative transformation led to the synthesis of chiral 1,2-hydroselenoamines in good yield (Table 4.6, entries 1-5).

The less activated *N*-Boc aziridines required longer reaction time, higher temperature and a major amount of catalyst to promote the desired transformation (Scheme 4.1). Thence **7a** and **7b** were treated with HMDSS in the presence of 1

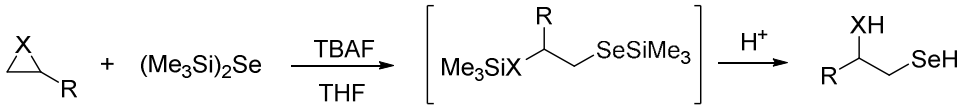
equivalent of TBAF at r.t. for 1 hour and the corresponding *N*-Boc β-amino selenols were obtained in good yield (Table 4.6, entries 6,7). All the 1,2-hydroselenoamines synthesized (Table 4.6) arose from a clean attack on the less hindered side of the aziridine and the optical purity was preserved.



R = see Table 4.6

Scheme 4.1. General scheme for the synthesis of *N*-Boc-β-amino selenides

Besides citric acid other proton sources, such as NH_4Cl and HCl, were tested in the synthesis of selenols proving to be efficient in this transformation (Scheme 4.2), without the diselenide formation. However, in our hands citric acid allowed to gain better results in terms of diselenide/selenol ratio minimization.



X = O, S, *N*-Pg

Scheme 4.2. Synthesis of β-functionalized selenols

The formation of the selenol can be univocally determined by ^{1}H and ^{77}Se NMR spectroscopies.

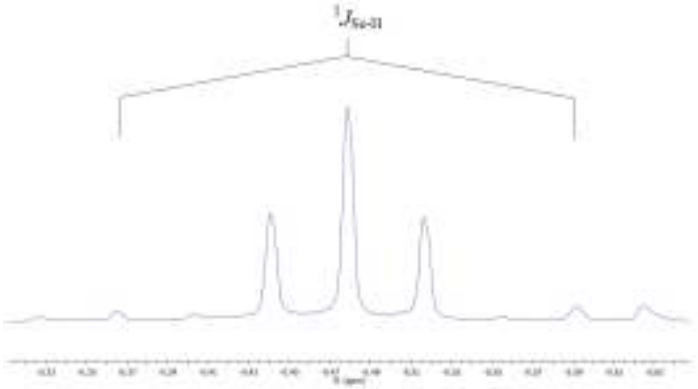
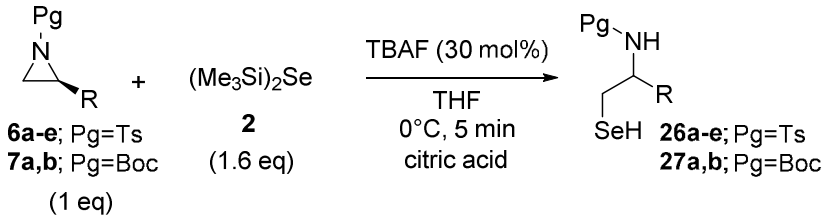


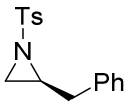
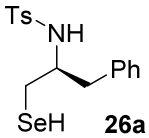
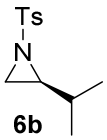
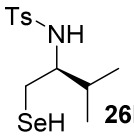
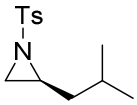
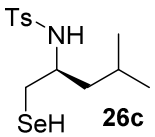
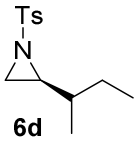
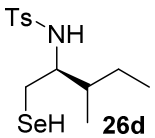
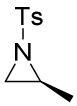
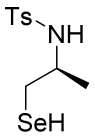
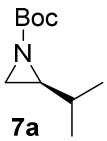
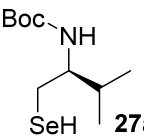
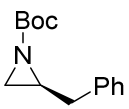
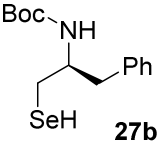
Fig. 4.1. Typical ^{1}H NMR chemical shift of selenol

Table 4.6. Synthesis of β-amino selenols



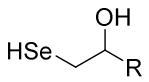
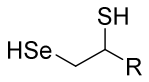
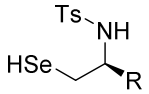
6a-e; Pg=Ts
7a,b; Pg=Boc
(1 eq)

26a-e; Pg=Ts
27a,b; Pg=Boc

Entry	Aziridine	Product	Yield (%)
1	 **6a**	 **26a**	82
2	 **6b**	 **26b**	84
3	 **6c**	 **26c**	77
4	 **6d**	 **26d**	78
5	 **6e**	 **26e**	80
6	 **7a**	 **27a**	93
7	 **7b**	 **27b**	88

The proton bound to the selenium atom (Se**H**) is strongly shielded and has a typical resonance frequency between -0.4 and -0.9 ppm (Fig. 4.1 and Table 4.7). Similarly, ^{77}Se resonance is shifted upfield to -40/-90 ppm. The $^{1}J_{Se\text{-}H}$ - direct coupling constant Se-H - measured on the coupled proton spectrum (natural abundance of ^{77}Se: 7.63%), is approximately 45 Hz (Table 4.7).

Table 4.7. Typical NMR values of β-functionalized selenols

Entry	Selenol[a]	^{1}H NMR (δ)[b]	^{77}Se NMR (δ)[c]	$^{1}J_{Se\text{-}H}$ (Hz)[d]
1		-0.55/-0.70	-78.0/-90.5	45.0/46.0
2		-0.39/-0.49	-42.0/-55.0	43.8/46.0
3		-0.72/-0.92	-90.0/-96.0	40.0/45.6

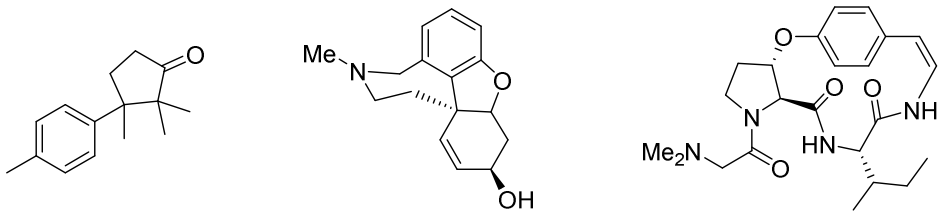
[a] Specific values for each R are described in experimental part. [b] ref. $CDCl_3$ 7.26 ppm. [c] Relative to Ph_2Se_2 (461 ppm). [d] Calculated from coupled ^{1}H NMR signals.

4.3 Reactivity of selenols as nucleophiles

As we stated before, formation of selenium-carbon bonds is often required in the synthesis of new antioxidant or biologically active compounds. Organoseleno derivatives find also application as ligands and catalysts in asymmetric transformations. Moreover, chemistry of organoselenium compounds has been applied in total synthesis of complexe molecules such as α-Cuparenone[25], (-)-Galanthamine,[23] (-)-Nummularine[24] (Fig. 4.2). In this context a general, mild and reliable methodology for the formation of new C-Se bonds can attract the interest or organic chemists.

Various nucleophilic selenium species have been widely applied in organic synthesis. Several methods to generate selenolates have been reported. The introduction of a selenium atom into a metal-carbon bond and reductive cleavage of the Se-Se bond represent the most frequently applied.[26,27] Reducing agents such as

Na, NaH, $NaBH_4$, $LiBEt_3H$, $^{i}Bu_2AlH$, SmI_2 and, more recently, Zn/HCl[4], $Zn/ZrCl_4$[28], $Zn/AlCl_3$[29,30] or $Zn/RuCl_3$[31] have been used in generating selenolates. InI, InBr[32,33] and $Sm/CeCl_3$[34] were also used to reduce diaryl diselenides. Other procedures include the use of $^{n}Bu_3SnH$.[35] Selenolates of many other elements such as Si, Ge, Ti, Pr, U, Nb, W, Hf, have been also obtained.[36]



α-Cuparenone (-)-Galanthamine (-)-Nummularine

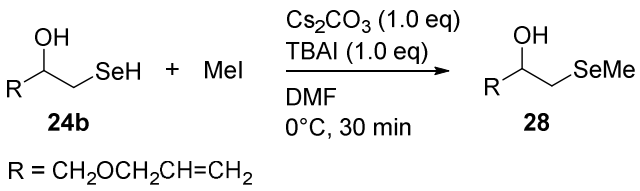
Fig. 4.2

β-Functionalized selenols can be considered extremely versatile building blocks and precursors of cyclic and open chain selenated derivatives. To evaluate this versatility we investigated the behaviour of such molecules as organic nucleophilic selenium reagents. Taking into account that selenols are stronger acid with respect to the corresponding thiols (PhSeH and PhSH, pK_a values 5.9 and 6.62 respectively), a selenolate ion could be formed under very mild conditions.

It is described that S-alkylation can be achieved treating thiols with alkyl halides at r.t. for few hours in presence of Cs_2CO_3 and TBAI. Thus, on the basis of these finding 1-(allyloxy)-3-hydroselenopropan-2-ol **24b** was stirred at 0°C in presence of Cs_2CO_3 and TBAI, as a phase transfer catalyst, and then treated with methyl iodide (Scheme 4.3).

Taking into account the major acidity and the higher instability of the selenolic proton, the procedure reported for the alkylation of thiols has been slightly modified. Thereby, the reaction was performed at lower temperature and for shorter time. Under these conditions, the reaction proved efficient leading to the isolation of the Se-methylated product.

Seeking for the generality of this procedure in the formation of C-Se bonds, different electrophiles were reacted with selenols under the same conditions.



Scheme 4.3. Alkylation of β-functionalized selenols

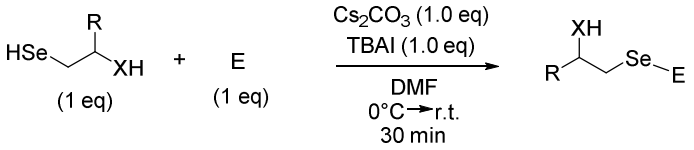
The results are listed in Table 4.8. Both alkyl bromides and iodides can be used efficiently in this transformation (Table 4.8, entries 4-8). In the case of the reaction of α-bromo esters, the nucleophilic displacement occurs only on the brominated chain, preserving untouched the carboxyl derivative. Intriguingly, when β-mercapto selenols are reacted, selectivity in Se-alkylation (*vs* S-alkylation) can be achieved (Table 4.8, entry 5). Strained heterocycles such as aziridines behave as well as good electophiles and, when 1-chloro-3-hydroselenopropan-2-ol **24e** was involved in this transformation the nucleophilic attack occurs exclusively on the aziridine, the halide being preserved on the side chain and not being formed the self-alkylation product due to the halide replacement (Table 4.8, entry 3). The three-membered heterocycle is regioselectively opened at the less hindered carbon.

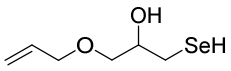
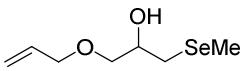
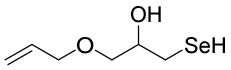
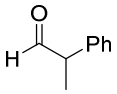
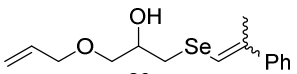
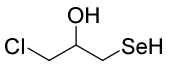
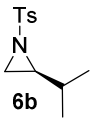
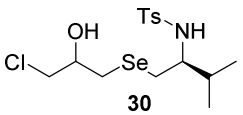
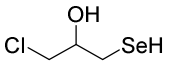
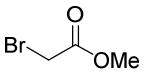
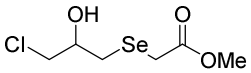
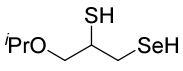
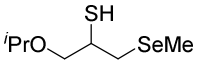
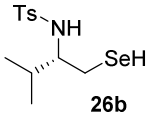
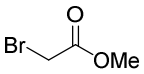
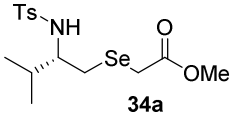
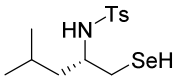
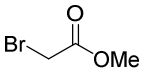
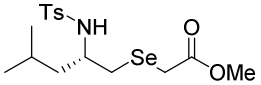
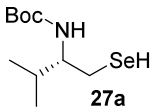
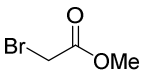
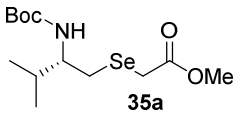
When aldehydes were used as electrophiles, we observed that addition on aldehydes is possible if spontaneous water elimination occurs and leads to an extended conjugated system, with the formation of a β-phenyl vinyl selenide (Table 4.8, entry 2). This particular reactivity could be exploited to synthesize novel selenated antioxidants. Aldehydes bearing phenolic groups could be precursors of structures where the electronic delocalization can stabilize the extraction of a hydrogen radical from the hydroxyl moiety, decreasing the BDE (bond-dissociation enthalpy).

Differently *N*-protected β-amino selenols **26-27** worked well too, giving the Se-alkylated amino derivatives **34-35** in a stereoconservative way and in good yield (Table 4.8, entries 6-8).

Exclusive chemoselective Se-alkylation using unprotected mercaptoselenols and aminoselenols is a particularly noteworthy feature of this approach.

Table 4.8. β-functionalyzed selenols as versatile nucleophiles

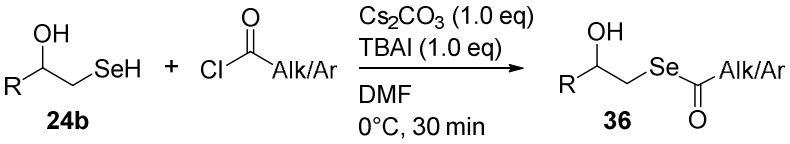


Entry	Selenol	Electrophile (E)	Product	Yield (%)
1	 **24b**	MeI	 **28**	76
2	 **24b**		 **29**	47[a]
3	 **24e**	 **6b**	 **30**	87
4	 **24e**	 **31**	 **32**	78
5	 **25a**	MeI	 **33**	64[b]
6	 **26b**	 **31**	 **34a**	84
7	 **26c**	 **31**	 **34b**	81
8	 **27a**	 **31**	 **35a**	69

[a] 1:1 mixture of *cis* and *trans* isomers was formed.[b] Reaction time 5 min. Good Se/S selectivity in methylation has been achieved.

This procedure can be proposed as a novel, mild way to access differently functionalised non-symmetric selenides, which can be further elaborated.

β-Functionalized selenols can be efficiently reacted also with acyl chloride leading to a clear and straightforward access to selenol esters **36** under mild conditions (Scheme 4.4).



R = $CH_2OCH_2CH{=}CH_2$
Alk = $(CH_2)_7CH{=}CH(CH_2)_7CH_3$ (64%)
Ar = Ph (36%)

Scheme 4.4. Synthesis of selenol esters

4.4 Conclusions

In conclusion, we developed an easy, mild and general procedure to synthesize selenols bearing at the C-2 the hydroxy, mercapto and amino functionalities. This novel class of organoselenium compounds can be efficiently reacted with suitable electrophiles to access a wide range of selenated derivatives. Interestingly, due to the mildness of the experimental conditions, labile moieties can be successfully used in this process that represents a robust and valuable alternative in the formation of C-Se bond strategies.

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Chapter 5

Synthesis of sulfur and selenium containing six-membered heterocycles

5.1 Introduction

Heterocyclic compounds include many of the biochemical material essential to life. Many naturally occurring derivatives, like for instance pigments, vitamins, and antibiotics, as well synthetic derivatives, like drugs, pesticides, dyes, and plastics contain a heterocyclic skeleton. In this context are included also six-membered heterocycles, which represent relevant organic structures for their different applications, and can behave as useful intermediates in organic chemistry.

Nitrogen containing compounds represent the most common and important derivatives which are found in various natural products, biologically active structures, and medicinally relevant compounds.

Also systems with different heteroatoms, such S, O, N and Se can find interesting applications.

Substituted 1,4-oxathianes are important precursors for the synthesis of biologically interesting derivatives, which are used as fungides and pesticides.[1] In addition, functionalized 1,4-oxathianes show activity against cancer and antibacterial, antimalarial and analgesic properties.

Several preparative methods are available for their synthesis, [2] but a very limited number is suitable to place various substituents at selected position of the basic heterocycle.

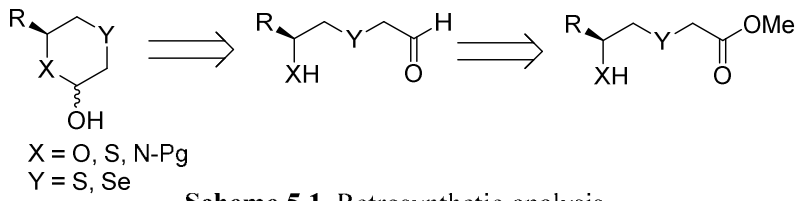
S,N-containing systems, such as 1,4-thiazines, are obtained through multi-step procedures. Depending on the substituents on the ring, they can be considered, for example, as vinyl chloride metabolites.[3]

On the other hand, selenated analogues, namely 1,4-oxaselenanes and -selenazines, represent as well interesting structures.[4] For example, 1,3-selenazines show significant anti-bacterial activity against both Gram-negative and Gram-positive bacteria and potential anti-tumor effects against several kinds of human

cancer cell lines.[5] Despite their potentialities, few reports are present in literature, with a limited diversity of substituents.[6]

5.2 Results and discussion

We considered that a retrosynthetic approach to this class of heterocyclic compounds could be the intramolecular cyclization of a α-thio- or α-seleno-aldehyde, obtainable through reduction of a methyl ester, bearing on δ-position a suitable nucleophilic moiety, i.e. OH, SH and *N*HPg.

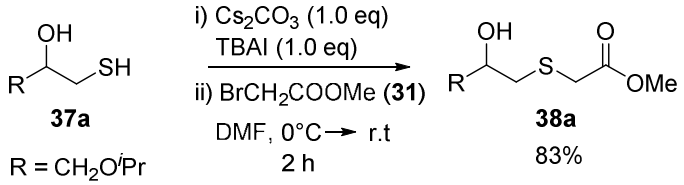


Scheme 5.1. Retrosynthetic analysis

The latter can be achieved exploiting the reactivity of β-functionalized thiols and selenols with a suitable electrophile, such as the methyl 2-bromoacetate **31**, that we already used for the Cs_2CO_3 promoted Se-alkylation of selenols.

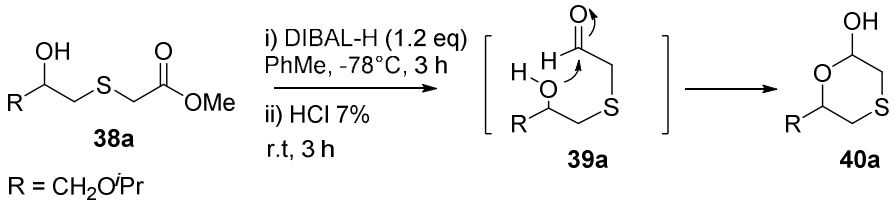
On the other hand, S-alkylation of thiols can be performed following several reported procedures, using different bases. The Cs_2CO_3/TBAI system could be one of the mildest conditions, then we wonder whether 1,2-mercaptoalcohols and 1,2-mercaptoamines could behave as convenient nucleophiles in the reaction with **31**, which represent the first step toward the synthesis of the wanted heterocycles.

Thus, 1-isopropoxy-3-mercaptopropan-2-ol **37a** was stirred under nitrogen atmosphere at 0°C for 10 min in the presence of Cs_2CO_3 (1 mmol), TBAI (1 mmol) and DMF. Subsequently methyl 2-bromoacetate XX (1.1 mmol) was added, and the reaction mixture was allowed to slowly warm to room temperature (Scheme 5.2).



Scheme 5.2. Alkylation of β-functionalized thiols

The so obtained α-mercapto-ester **38a** was then reduced with DIBAL-H with the aim to synthesize the corresponding δ-hydroxy-aldehyde **39a** but, intriguingly, a spontaneous intramolecular cyclization led smoothly to the desired 6-(isopropoxymethyl)-1,4-oxathian-2-ol **40a** as a equimolar mixture of diastereoisomers (Scheme 5.3).



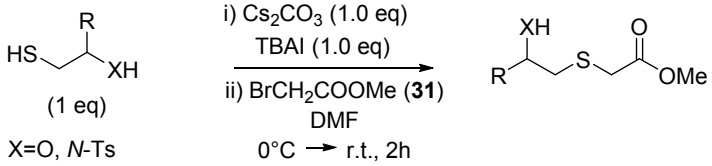
Scheme 5.3. Reduction and cyclization of α-mercapto esters

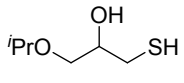
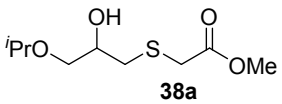
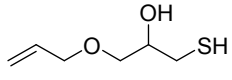
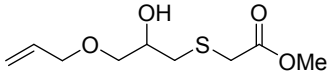
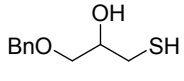
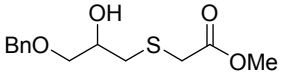
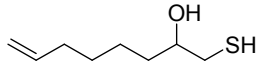
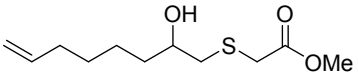
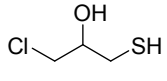
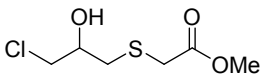
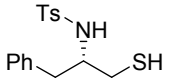
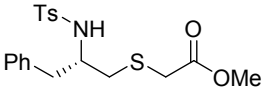
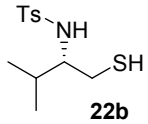
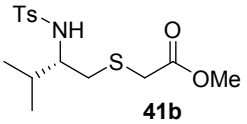
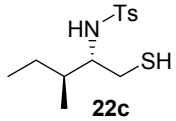
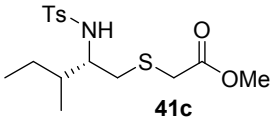
Next, to evaluate the generality of the methodology, variously substituted β-hydroxy- and β-amino- thiols were reacted with **31** under the described conditions and the corresponding α-thio esters were achieved. All the reactions occur with high yield and complete chemoselectivity.

Treatment of **38a-e** with DIBAL-H led again straightforwardly to the 2,6-disubstituted 1,4-oxathianes **40a-e** (Table 5.2), thus demonstrating the efficiency and the generality of this procedure.

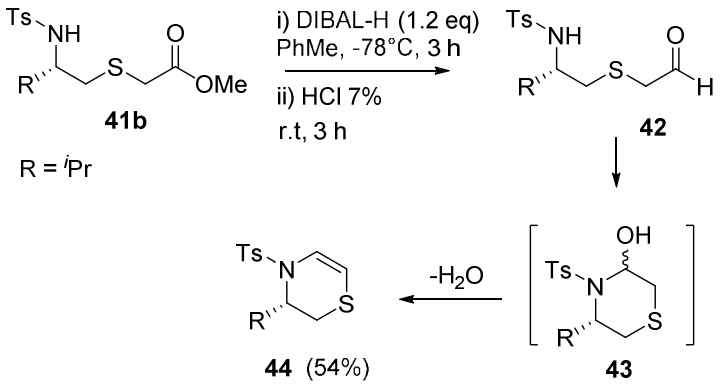
Interestingly, in the case of reduction of (*S*)-methyl 2-(3-methyl-2-(4-methylphenylsulfonamido)butylthio)acetate **41b**, only the formation of the unsaturated 3,4-dihydro-2*H*-1,4-thiazine **44**, was detected (Scheme 5.4) and no trace of the hydroxy thiazine **43** was evidenced.

Table 5.1. S-alkylation of β-functionalyzed thiols



Entry	Thiol	Sulfide	Yield (%)[a]
1	 **37a**	 **38a**	83
2	 **37b**	 **38b**	88
3	 **37c**	 **38c**	68
4	 **37d**	 **38d**	91
5	 **37e**	 **38e**	89
6	 **22a**	 **41a**	78
7	 **22b**	 **41b**	86
8	 **22c**	 **41c**	81

[a] Yield referred to isolated products



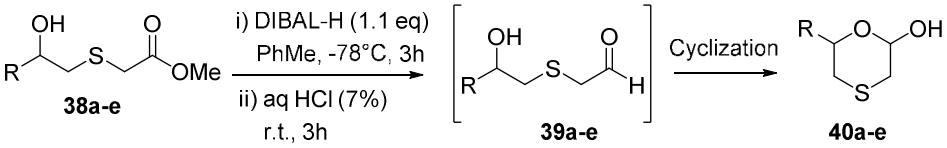
Scheme 5.4. Synthesis of 3,4-dihydro-2*H*-1,4-thiazines.

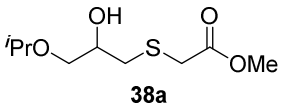
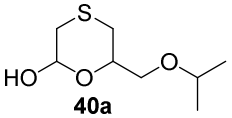
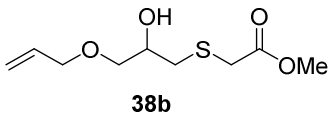
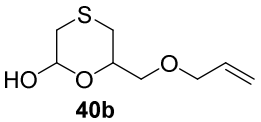
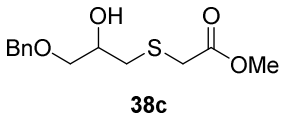
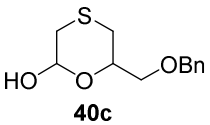
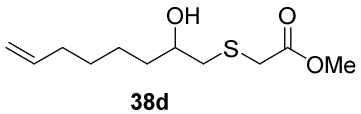
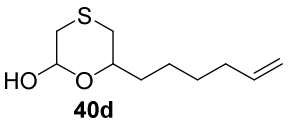
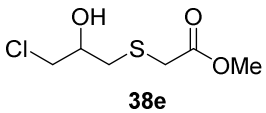
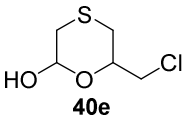
Thus, under these conditions the aldehyde **42**, obtained through reduction of ester **41b**, undergoes to intramolecolar cyclization yielding the intermediate **43** that, upon elimination of H_2O, gives the ciclic sulfurated enamine **44**.

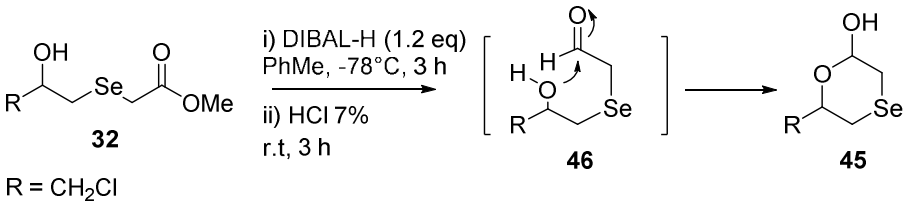
Having developed an effective sulfur-containing heterocycles synthesis protocol, we sought to target selenium containing structures. As previously described, the access to β-functionalized selenols disclosed a novel smooth route for the synthesis of unsymmetrical selenides. Thus, methyl 2-(3-chloro-2-hydroxypropylselanyl)acetate **32**, conveniently obtained - as described before, Table 4.8, entry 5 - from 1-chloro-3-hydroselenopropan-2-ol **24e** and methyl 2-bromoacetate **31**, was reduced under DIBAL-H conditions, leading directly to the isolation of the 1,4-oxaselenane **45** (Scheme 5.5). The reaction proceeds through the formation of the aldehydic intermediate **46**, following a similar pathway we considered for the sulfur containing derivatives.

The behaviour of δ-amino-α-seleno esters was then evaluated. Reduction of **34a** and **34b** led to the formation of the aldehydes **47a** and **47b** that were interestingly stable enough to be characterized by ^{1}H NMR and ^{13}C NMR. The ring closure of the compound **47a** was followed by NMR, acquiring at intervals the proton spectra.

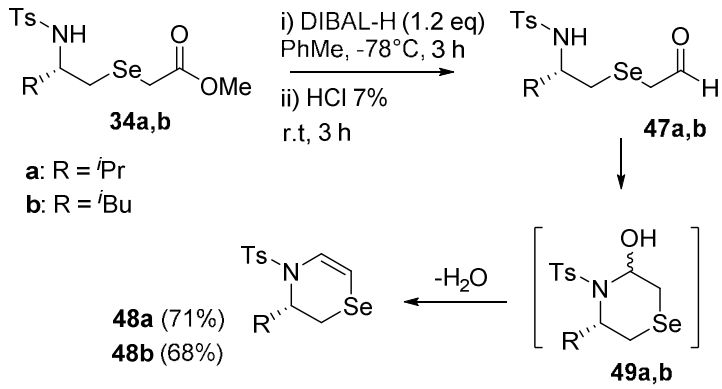
Table 5.2 Reduction/cyclization of δ-hydroxy-α-thio esters



Entry	Reagent (Ester)	Heterocycle	Yield (%)
1	 **38a**	 **40a**	72
2	 **38b**	 **40b**	63
3	 **38c**	 **40c**	56
4	 **38d**	 **40d**	58
5	 **38e**	 **40e**	82



Scheme 5.5. Reduction and cyclization of α-seleno esters



Scheme 5.6. Synthesis of 3,4-dihydro-2*H*-1,4-selenazines. Both the aldehydes **47a** and **47b** were stable enough to allow a ^{1}H NMR and ^{13}C NMR characterization.

Intriguingly, studying the ring closure of **47a** *via* NMR spectroscopy, the intermediate **49a** was not detected, revealing that the dehydration to the corresponding enamine **48a** is faster than the NMR time-scale, whereas the addition to the carbonyl group of **47a** is the rate determining step.

5.3 Conclusions

In conclusion, we have developed a novel synthetic strategy for the synthesis of variously substituted six-membered heterocycles. Different heteroatoms (N, O, S, Se) can be introduced in the heterocycle at predetermined positions, representing a particularly noteworthy feature of this general approach. Functionalities, such as double bonds, hydroxyl groups and halides may offer the possibilities to further elaborate the structure toward more complex molecules different for the ring size and for the nature of the heteroatoms.

5.4 References

[1] (a) A. Samzadeh-Kermani *Synlett,* **2014**, 1839 and references cited therein. (b) W. T. Murray, J. W. Kelly, S. A. Evans, Jr. *J. Org. Chem.*, **1987**, *52*, 525.

[2] (a) V. Y. Vshivtsev, E. P. Levanova, V. A. Grabel'nykh, L. V. Klyba, E. R. Zhanchipova, E. N. Sukhomazova, A. A. Tatarinova, A. I. Albanov, N. V. Russavskaya, and N. A. Korchevin *Russ. J. Org. Chem,* **2008**, *44*, 43. (b) V. Nevalainen, E. Pohjala, P. Malkonen, H. Hukkanene *Acta Chem. Scand.,* **1990**, 591.

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[4] a) V. Potapov, M. Musalov, E. Abramova, M. Musalova, Y. Rusakov, S Amosova *Chem, Heterocycl. Compd.,* **2014**, *49*, 1821.

[5] M. Koketsu and H Ishihara *Curr. Org. Chem*., **2015**, *7,* 175 and references cited therein.

[6] *Oxathiolanes*: (a) T. Shimizu, N. Kamigata *Science of Synthesis*, **2007**, *39*, 1053 and references cited therein. (b) J. Bergman, T. Laitalainen, S. Kaltia, M. Klinga, R. Kivekas, *Acta Chem. Scand., Ser. B,* **1986**, *B40,* 715. *Selenazolidines*: (c) C. Viglianisi L. Simone, S. Menichetti *Adv. Synth. Catal.,* **2012,** *354*, 77. (d) Z.Casar, D. Lorcy, P. Benard-Rocherulle, A. Majcen-Le Marechal *Chem. Commun*., **2001**, 1336. (e) D. E. Ames, A. G. Singh, W. F. Smyth *Tetrahedron*, **1983**, *39*, 831. (f) F. Asinger, M. K. Schmitz, *Monatsh. Chem.,* **1982**, *113*, 1191

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Chapter 6

Synthesis and functionalization of silyl selenium containing heterocycles

6.1 Introduction

Umpolung reactivity is a valuable synthetic strategy in organic synthesis, providing unconventional access to molecules through the formation of bonds *via* the inversion of normal reactivity.[1]

In this context, the development of synthetic equivalents to acyl anions has recently attracted a great deal of interest for the synthetic potential that such reactions may disclose. In relation to this, suitably protected carbonyl derivatives represent a very interesting class of compounds that are able to act as equivalents of acyl anions, and there are now a wide range of molecules that can behave in this way.

Several acyclic derivatives have been shown to react as masked formyl and acyl anion synthons. Some selected examples are α-silyl sulfides ($PhSCH_2TMS$[2] and MeO(PhS)CHTMS[3]), α-lithiated derivatives such as tris(phenylthio)methyllithium[4] and methoxy(phenyldimethylsilyl)methyllithium,[5] and α-metalated enol carbamates.[6] Formaldehyde hydrazones have been used as neutral formyl anion equivalents in Michael additions to conjugated enones,[7] while protected hydroxymalonitriles were reported for the preparation of activated esters in the synthesis of dipeptides.[8] Thioacetals are probably one of the most versatile classes of acyl anion equivalents, and among them, heterocyclic examples offer a variety of methods for the development of such reactivity. For a long time, two of the most commonly used classes of cyclic S,S-acetals have been 1,3-dithianes and 1,3-dithiolanes, which are useful carbonyl protecting groups and can react as masked acyl carbanions.[9] These compounds are easier to obtain with respect to their oxygen analogues and more stable to hydrolytic cleavage due to their stability towards acidic and basic conditions. Many methods for their unmasking are reported, but several require harsh conditions, frequently use heavy and toxic metal

ions, have long reaction times, suffer for the occurrence of side reactions and often lack generality.[10]

1,3-Dithianes can be easily metalated with BuLi and reacted with a wide range of electrophiles, thus demonstrating their behaviour as useful synthons and umpoled reagents.[9,11] On the other hand, deprotonation of related 1,3-dithiolanes invariably leads to unstable anions and cleavage of the heterocyclic ring is always reported, thus limiting their use in functionalization under strong basic conditions.[12]

Despite the large scale application of these cyclic S,S-acetals, the use of chiral 1,3-dithianes did not afford any success in stereoselective synthesis, and thus different heterocycles have been considered, such as 1,3-oxathianes,[13] 1,3-dioxanes[14] and 1,4-oxazines as representative examples.[15]

Besides six-membered heterocycles, five-membered ring heterocyclic derivatives are valuable intermediates in organic synthesis. Compounds containing either one heteroatom, as in furans and pyrrolidines, or derivatives bearing two or more heteroatoms have played an important role in different synthetic strategies. Among these latter structures, 1,3-dioxolanes,[14b,16] 1,3-oxathiolanes,[17] 1,3-thiazolidines, 1,3-oxazolidines, imidazolines and benzotriazole derivatives[18] have found large scale application as building blocks for the construction of more complex molecules.[15]

In recent years, chiral acyl anion equivalents have seen increased use in asymmetric synthesis. There are many examples of chiral masked acyl carbanions, and several reports deal with five-membered heterocyclic systems.

Lithiated chiral oxazolidinones, including compounds derived from camphor,[19] have been reported to react with aldehydes, ketones and imines, leading to enantioselective formylation of the carbonyl compounds.[20] Oxazolidines have also found applications as chiral formyl anion equivalents, either for direct metalation in the presence of (-)-sparteine[21] or through the transmetalation of tributylstannyl derivatives with BuLi and condensation with benzaldehyde.[22] Thiazolidines, upon treatment with BuLi and aldehydes or ketones in the presence of (-)-sparteine, also afforded products with high *ee* but moderate diastereoselectivity.[23] Isopropyl *N*-Boc-thiazolidines have been used as chiral organolithium compounds in the addition

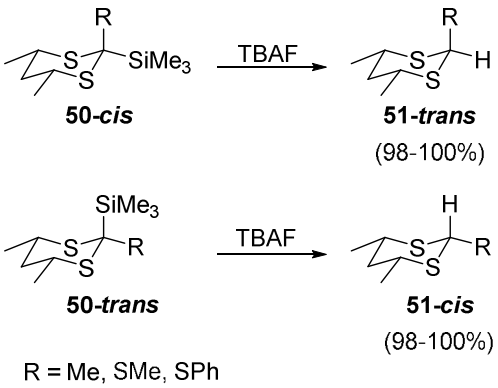
to aldehydes, leading to products in good stereoselectivity.[24] Thiazolidines are also metalated with BuLi *via* their respective formamidines, but 40–50% fragmentation of the heterocyclic ring has been observed.[25] Chiral dioxolanes.[22a] and dioxolanones[16] have also found applications as acyl anion equivalents. In recent years, the chemistry of organosilicon compounds has witnessed an unbelievable growth as a consequence of the critical role it plays in many chemical and biochemical transformations. Extensive investigations have been carried out over the years, outlining these compound's tolerance of other functional groups and their versatility as intermediates in organic synthesis. Thus, reagents and methods based on organosilicon chemistry are an area of increasing interest in organic synthesis. The application of heterocyclic silanes to organic synthesis offers the opportunity for new synthetic strategies, since these compounds can behave as effective precursors to heterocyclic carbanions and as masked functional group equivalents. In this field the reactivity of 2-(trimethylsilyl)oxazoles and oxazolines, their stannylated analogues[26] as powerful building blocks and their synthetic utility with respect the corresponding 2-lithio derivatives have been reported, providing molecules which are unaccessible by classical metallation. Moreover, 2-(trimethylsilyl)thiazole has been shown to be a versatile reagent, leading to carbodesilylation reactions with various electrophiles. When chiral aldehydes were used, a good diastereoselectivity was achieved in the final adducts.[27]

6.1.1. 1,3-Dithianes. 1,3-Dithianes have been widely used as acyl anion equivalents, and some examples of silyl dithiane functionalization have been reported.[9d] On the other hand, it is firmly established that metalation of 1,3-dithianes[11,28] and 1,3-diselenanes[29] occurs regioselectively at C-2 at the equatorial hydrogen rather than at the axial hydrogen, and that their metallo derivatives lead invariably, upon reaction with electrophiles, to products bearing the incoming group at the equatorial position, whatever the other substituent eventually present at C-2 is. Krief and co-workers have extensively investigated the related 4,6-disubstituted sixmembered rings, 1,3-dithianes and diselenanes, and found that their treatment, even at very low temperatures (down to -130 °C), still affords invariably the equatorially-

functionalized products, irrespective of the configuration of the 2-substituted starting compound.[30]

Axial functionalization has nevertheless been obtained in the diselenane series upon reacting 4,6-dimethyl-2-methylseleno-1,3-diselenane through a Se/Li exchange. On the other hand, when the same protocol was applied to the dithiane series, again, the equatorial isomer was the sole product obtained, providing evidence in this case of an unexpectedly lower configurational stability.

Furthermore, some examples of the functionalization of a C–Si bond to a new C–C bond with retention of configuration has been reported. In fact, with the exception of allylsilanes,[31] there are only a few cases of stereoselective synthetic transformations of sp^3 C–Si bonds to C–C bonds. Such examples include conversions of the C–Si bonds of epoxysilanes to C–C bonds upon reaction with aldehydes,[32] stereoselective insertion into strained bonds,[33] palladium-catalyzed conversions of chiral trifluoro benzyl silanes to chiral diaryl silanes,[34] the diastereoselective intramolecular reaction of a benzyl silane,[35] retention of configuration in the desilylative hydroxymethylation of α-silyl sulfides[36] and, more recently, the reactivity of chiral benzyl silanes[37] and silylated aziridines[38] with aldehydes.

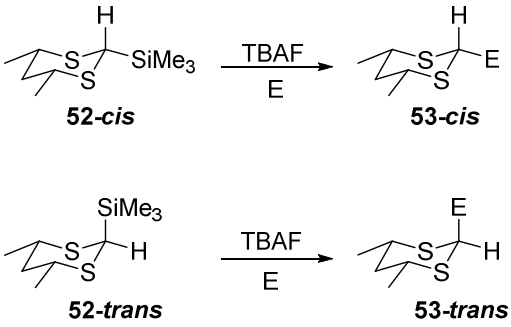


Scheme 6.1. Stereoconservative protodesilylation of 2-silyl dithianes

Thus, for instance, both *cis*- (**50**) and *trans*- (**50**) 2-silyl-2,4,6-trimethyl dithiane, when subjected to fluoride-induced desilylation with TBAF at rt for 4 h, reacted

smoothly to afford the corresponding 1,3,5-trimethyl dithianes **51**-*trans* and **51**-*cis* , respectively, in good yields with clean retention of configuration (Scheme 6.1).

The possible effect of carbanion-stabilizing species on C-2 in the stereochemistry of the desilylation was also considered, and it was shown that even in the presence of a further sulfurated moiety or a sulfoxide group, no trace of epimerization could be detected, thus showing an interesting generality of this behaviour. 2,2-Bis-trimethylsilyl-1,3-dithiane was also investigated in order to ascertain whether there could be a possible discrimination between the two identical silyl groups, and it was found that the trimethylsilyl moiety in the equatorial position is the more reactive.



E = CH_3I, PhCHO, $C_6H_{11}CHO$, 2-Furyl-CHO, (*p*-CH_3O-)-C_6H_4-CHO

Scheme 6.2. Stereoconservative carbodesilylation of 2-silyl dithianes

When 2-phenyl substituted 2-silyl-dithiane was taken into consideration, the result of the desilylation reaction was less straightforward, appearing to be a function of temperature and the equivalents of TBAF. These results therefore most likely indicate that all the reported reactions proceed through a pentacoordinated silicon intermediate rather than through a free carbanion, which should be expected to epimerize easily. In this context, even more interesting are the findings related to the synthetically useful carbodesilylation reaction. Various stereochemically defined silyl dithianes, **52**, were reacted with electrophiles and showed interesting stereoconservative functionalization (Scheme 6.2).

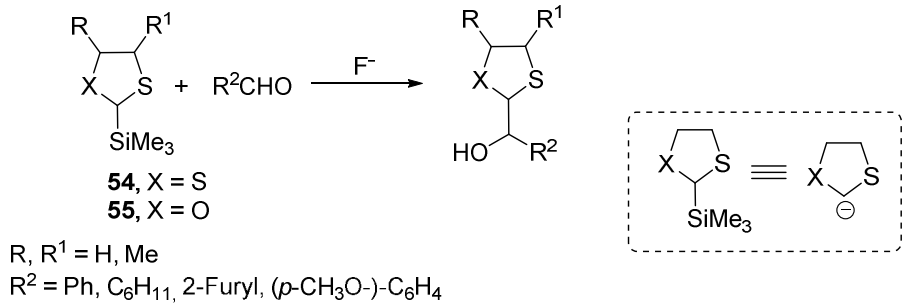
All the reactions yielded the corresponding adducts in good yield. While the reactions of **52**-*cis* appear quite obvious, and disclose an alternative and milder methodology for functionalizing such molecules, the reactions of the *trans*

diastereoisomer yielded products **53**-*trans*, in which the electrophile is unequivocally in the axial position. Such results outlined for the first time a successful, selective functionalization of the axial position of such molecules, suggesting interesting applications in stereoselective synthesis (Scheme 6.2).

The stereoconservative behaviour observed in the protodesilylation was thereby successfully extended to the formation of new C–C bonds.

6.1.2. 1,3-Dithiolanes and 1,3-oxathiolanes. As mentioned above and as is well known, 1,3-dithiane anions have been extensively used in the last decades as masked acyl carbanions in umpolung reactivity being useful intermediates in a number of organic processes.[9] Nonetheless, although several methods for their unmasking have been reported,[10] they still suffer from the generally harsh conditions required for their unprotecting. On the other hand, dioxolanes, oxathiolanes, dithiolanes and even thiazolidines have been reported to be unmasked under milder conditions, thus possibly giving a broader spectrum of applications to such molecules in the generation of formyl and acyl anion equivalents. Unfortunately, such heterocycles generally suffer difficulties in their functionalization under strongly basic conditions. 1,3-dithiolane anions, for instance, upon treatment with bases, have been reported to undergo either deprotonation at C-2, with subsequent cycloelimination to dithiocarboxylate anions and ethylene derivatives,[12c] or C-4, to afford products derived from thiocarbonyl derivatives and vinyl thiolate anion.[12a,b] A similar behaviour was observed in unsubstituted dioxolanes, whose anions undergo fragmentation. Only two examples of dithiolanes bearing an electron withdrawing group undergoing functionalization in basic conditions are reported in the literature. Thiazolidines are also reported to be metalated, but only in the presence of specific nitrogen protecting groups. These considerations highlighted the remaining need for a general protocol for the functionalization of such labile heterocycles.[40,41] A solution to this problem was found by our group that, taking advantage of the previously outlined results for the reactivity of dithianes, which seem to occur *via* pentacoordinated silicon species and not a free carbanion, envisaged in the

functionalization of the C–Si bond the key to develop a novel and general functionalization methodology for the heterocycles in question (Scheme 6.3).



Scheme 6.3. Carbodesilylation of 2-silyl oxathiolanes and dithiolanes

Treatment of silyl dithiolanes and oxathiolanes with electrophiles, such as aldehydes, in the presence of different sources of fluoride ion (TBAF, TBAT, TASF), afforded to a smooth reaction that leads to the corresponding functionalized α-hydroxy derivatives (together with desilylated product, ca. 20%), revealing the effective transfer of a "dithiolane anion" and "oxathiolane" onto electrophiles under mild conditions.[42] Complete retention of configuration at C-2 was maintained in both reactions, showing that the stereoconservative behaviour observed in the dithiane series also holds also for the dithiolane and oxathiolane series. These results showed that, under the described conditions, **54** and **55** could behave as a masked dithiolane and oxathiolane anion.

6.2 Results and discussion

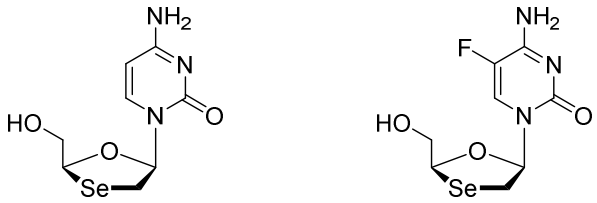
6.2.1. General. Beside the underlined aspects related to their reactivity and their use as a novel class of acyl anion synthons, the present heterocyclic rings are contained in several pharmacologically active molecules. In fact, suitably substituted 1,3-oxathiolanes behave as muscarinic agents, antiviral agents and also show biological activity.

In this context, taking into account the growing interest towards organoselenium compounds as useful tools in organic synthesis, the biological relevance covered by

these molecules and the recent advances achieved by our group in the field of the selenium chemistry, we moved to evaluate the synthesis and the reactivity of the related selenated silyl heterocycles, named 1,3-oxaselenolanes and 1,3-thiaselenolanes.

Selenium is an important nutritional trace element involved in different physiological functions and its deficiency plays a crucial role in the development of many diseases. It is reported that the formation of selenium-containing compounds, and not the element itself, is critical for biological activities. In this context, organoselenium compounds have continued to attract considerable attention for their essential role in many biological processes, showing for istance antioxidant, antiinflammatory and neuroprotective properties. Selenoderivatives are also involved in different organic reactions to obtain various biologically active compounds,[43] such as selenated aminoacids and proteins, and selenium containing heterocycles. Additionally, they are used as useful building blocks for the synthesis of a large number of organic structures.

A meaningful example of biologically relevant structures bearing the oxaselenolane core is given by (±)-β-Se-ddC and (±)-β-Se-FTC, active as antiviral against HIV and HIB virus (Fig. 6.1).[43a]

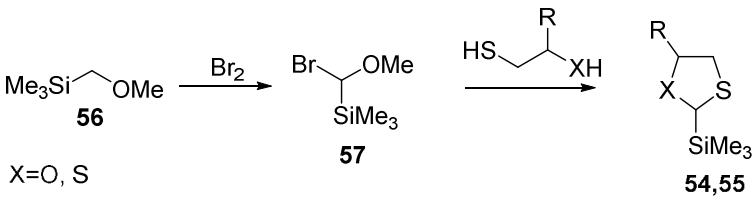


(±)-β-Se-ddC (±)-β-Se-FTC

Fig. 6.1. Biologically active oxaselenolanes

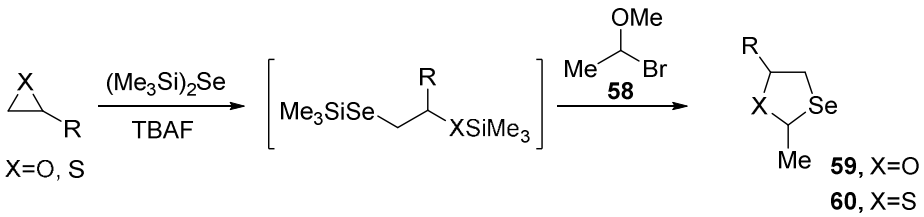
Thus, we thought to evaluate the possibility to have an access to these selenium containing heterocyclic compounds exploiting the results previously obtained on the synthesis of the above described sulfurated molecules.

6.2.2. Synthesis of 2-silyl oxa- and thia- selenolanes. A general route for the synthesis of five membered ring silylated heterocycles was found through the reaction of bifunctional molecules, such as dithiols, amino alcohols and mercapto alcohols with bromo(methoxy)methyl trimethylsilane. The choice of this reagent as a synthetic equivalent of formyl trimethylsilane is due to the fact that the latter is a labile molecule, difficult to generate and to handle. Bromo(methoxy)methyl trimethylsilane can be obtained in a quantitative yield by treatment of commercially available methoxymethyl trimethylsilane **56** with bromine. A subsequent one-pot treatment with the required mercaptan leads to the desired silylated heterocycle.



Scheme 6.4. Synthesis of silyl heterocycles

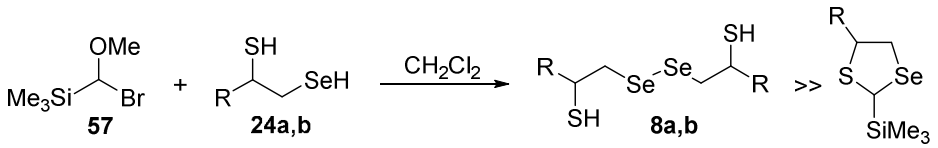
On the other hand, selenated five membered ring such as oxaselenolanes and thiaselenolanes can be synthesized in poor yield by trapping *in situ* the bis-silyl intermediate, whose formation has been previously described, with the species **58**.



Scheme 6.5. Synthesis of selenium containing heterocycles

This route proved to be ineffective when the silane **57** was used. As already mentioned silylated oxaselenolanes and thiaselenolanes may represent an important class of compounds, useful both from the chemical and biological point of view. Therefore, with the aim to obtain this kind of molecules and having in our hands a good and versatile procedure for the synthesis of stable β-hydroxy and β-mercapto selenols, we envisaged to achieve the desired heterocycles by the simple reaction of these bidentate compounds with **57**. On the basis of these considerations the silane

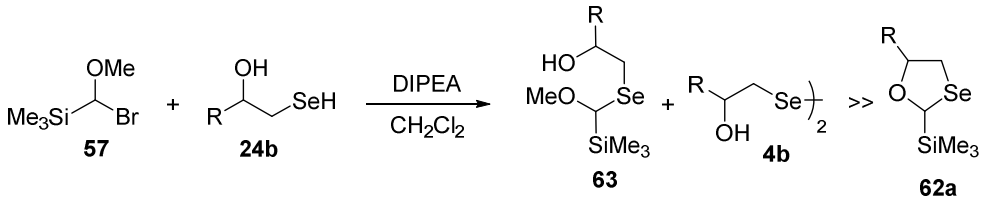
57 was reacted with suitable β-mercapto selenols and the wanted silyl-1,3-thiaselenolanes **61** were obtained, despite in moderate yield (Scheme 6.6).



a, R = CH_2O^iPr
b, R = $CH_2OCH_2CH{=}CH_2$

Scheme 6.6. Synthesis of 2-silyl-1,3-thiaselenolanes

Then, seeking for the generality of this procedure, we decided to test whether β-hydroxy-selenols could be valuable precursors in the synthesis of another interesting class of heterocycles such as 2-silyl-1,3-oxaselenolanes. Thus the freshly prepared bromo(methoxy)methyl trimethylsilane was reacted *in situ* with 1-(allyloxy)-3-hydroselenopropan-2-ol **24b** in the presence of DIPEA (diisopropylethylamine) and stirred overnight, but this time the desired oxaselenolane **62** was formed only in poor yield and the main products obtained were a mixture of the diselenide **4b** and the intermediate compound **63** (Scheme 6.7).



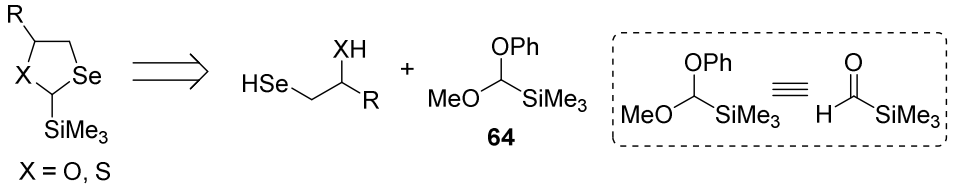
R = $CH_2OCH_2CH{=}CH_2$

Scheme 6.7. Synthesis of 2-silyl-1,3-oxaselenolanes

The formation of the sulfurated analogues of **63** has been previously observed also when β-mercapto-alcohols were reacted with the silane **57** under the same conditions but, in that case, the problem was overcame by treating the mixture with HCl conc.to achieve the silyl heterocycle. Because of the instability of the selenium containing molecules, the same synthetic approach proved to be inadequate in the

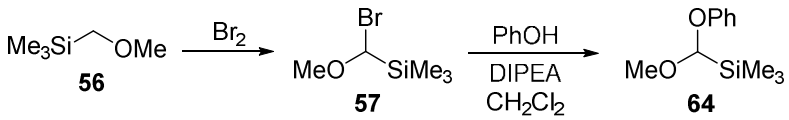
synthesis of oxaselenolanes and the treatment with HCl led to a complex mixture of products, likely arising from the fragmentation of the species **62** and **63**.

The failure in the synthesis of silyl-oxaselenolanes and the low yield observed in the synthesis of silyl-thiaselenolanes prompted us to seek for the possibility to use a different synthetic equivalent of formyl trimethylsilane capable to react with β-functionalized selenols under Lewis acid activation, as described in the retrosynthetic analysis (Scheme 6.8).



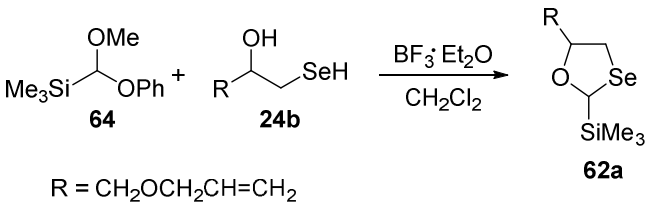
Scheme 6.8. Retrosynthetic analysis to selenium containing silyl heterocycles

We envisaged in (methoxy(phenoxy)methyl)trimethylsilane **64** the desired features, therefore the silane **57** was reacted with phenol in presence of DIPEA to give the acetal **64** in nearly quantitative yield (Scheme 6.9).[42]



Scheme 6.9. Synthesis of (methoxy(phenoxy)methyl)trimethylsilane

Thus the silyl acetal **64** was reacted with 1-(allyloxy)-3-hydroselenopropan-2-ol **24b** in the presence of boron trifluoride diethyl etherate as a catalyst and stirred at -18°C overnight.



Scheme 6.10. Synthesis of 2-silyl-1,3-oxaselenolanes

Thereby, the formation of (5-((allyloxy)methyl)-1,3-oxaselenolan-2-yl)trimethylsilane **62a** as a largely predominant product was indeed clearly evident by the ^{1}H NMR signals of the crude mixture (Scheme 6.10), evidencing the ability of **64** to act, under these conditions, as a real synthetic equivalent of formyl silane.

Nonetheless, attempts of purification on silica gel were unsuccessful and fragmentation of the oxaselenolanic ring was always observed, most likely promoted by the action of SiO_2 as Lewis acid. On the basis of this result we sought for a different stationary phase finding that neutral Al_2O_3 was compatible with the silylated heterocycle. Thus, the desired (5-((allyloxy)methyl)-1,3-oxaselenolan-2-yl)trimethylsilane **62a** was purified under these conditions and isolated in rather good yield (58%) as a mixture of diastereoisomers (6:1).

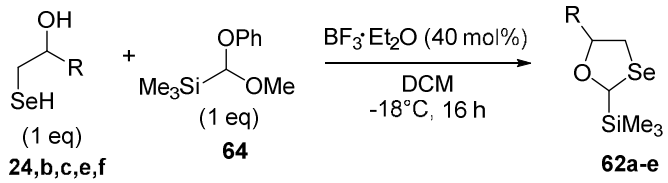
To explore the scope of this route we reacted different substituted β-hydroxy-selenols with **64** under the described conditions and a representative series of 2-silyl-oxaselenolanes was obtained, showing the generality of the procedure (Table 6.1). Due to the mildness of the experimental conditions, this methodology can also be applied to very useful but labile compounds such as glycidol and epichloridrin derivatives (Table 6.1, entries 1-3, 5) which may represent important structures in different application fields.

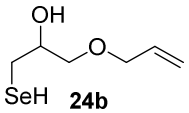
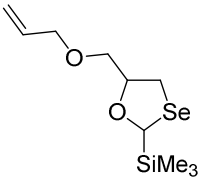
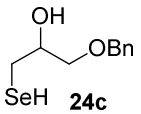
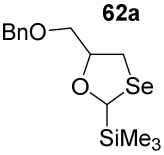
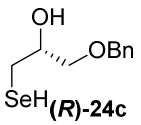
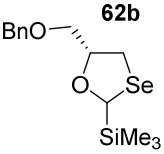
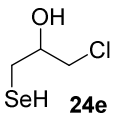
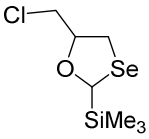
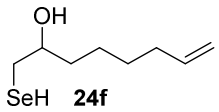
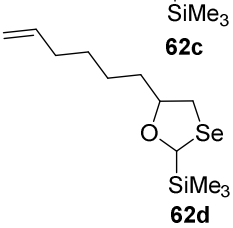
These 5-substituted oxaselenolanes were isolated as a mixture of diastereoisomers that could be chromatographically separated. Interestingly the dr was usually greater than 6:1 and when enantiopure 1,2-selenolalcohols were reacted (Table 6.1, entry 3), chiral oxaselenolanes were obtained as *cis*- and *trans*-isomers, the *cis*-derivative being the major diastereoisomer.

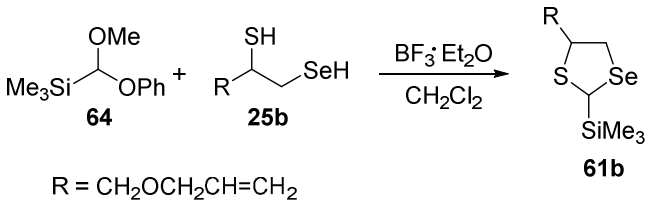
The advantages, achieved exploiting the reactivity of silyl acetal **64** in the synthesis of oxaselenolanes, prompted us to extend this procedure to the synthesis of 2-silyl-thiaselenolanes **61**, with the aim to improve the yields previously obtained.

In this context, 1-(allyloxy)-3-hydroselenopropane-2-thiol **25b** was reacted with (methoxy(phenoxy)methyl)trimethylsilane **64** under the same condition and the corresponding 2-silyl heterocycle **61b** was obtained, after purification on neutral Al_2O_3, in rather good yield (Scheme 6.11 and Table 6.2, entry 2).

Table 6.1. Synthesis of 2-silyl-1,3-oxaselenolanes



Entry	β-Hydroxy-selenol	2-Silyl-1,3-oxaselenolane	dr	Yield (%)
1	 **24b**	 **62a**	6:1	58
2	 **24c**	 **62b**	6:1	60
3	 **(*R*)-24c**	 **(*R*)-62b**	6:1	58
4	 **24e**	 **62c**	3:1	47
5	 **24f**	 **62d**	8:1	63

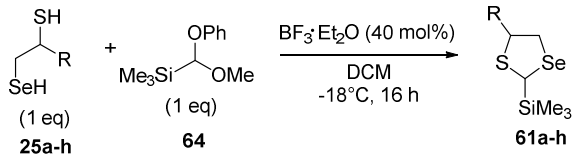


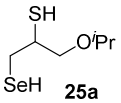
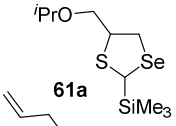
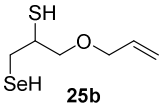
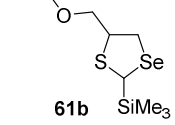
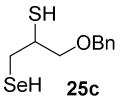
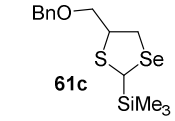
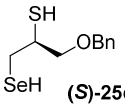
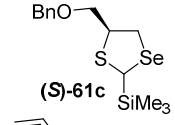
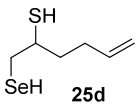
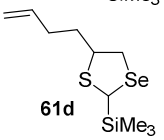
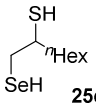
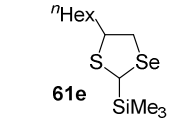
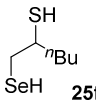
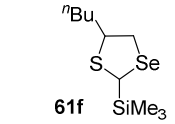
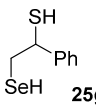
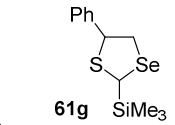
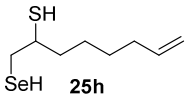
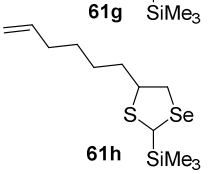
Scheme 6.11. Synthesis of 2-silyl-1,3-thiaselenolanes

To explore the scope of this reaction, a representative number of β-mercapto-selenols bearing different functionalities was reacted with the silane **64**. The reactivity proved general, leading smoothly to the synthesis of 2-silyl-1,3-thiaselenolanes with a widely variable nature of the substituent at C-5 of the ring, including aliphatic chains of different length (Table 6.2, entries 6, 7), unsaturated or aromatic moieties (Table 6.2, entries 5, 9 and 8 respectively) and differently protected hydroxyl group (Table 6.2, entries 1-4). The present thiaselenolanes were isolated as a mixture of diastereoisomers that could be chromatographically separated and chiral derivatives can be achieved reacting enantiopure β-mercapto-selenols (Table 6.2, entry 4). Interestingly, the dr was lower than that observed in the synthesis of oxaselenolanes described above. As example of separation, the 2-silyl-thiaselenolan **61a** was purified on basic Al_2O_3 allowing to separate the *cis* and *trans* diastereoisomers (*cis*-**61a**.and *trans*-**61a**). An intriguing observation in this study was that *trans*-**61a** riequilibrated into a *cis*/*trans* mixture when left for a long time (months) in $CDCl_3$, due to an epimerization occurring at the C-2 of the ring (Scheme 6.12). The same behaviour was observed for the *cis* diastereoisomer.

6.2.3. Functionalization of silyl thiaselenolanes with electrophiles. Similar to their sulfurated analogues, oxa- and thia- selenolanes when deprotonated at the position-2 suffer from cycloreversion to the corresponding alkene and thio- and seleno- carbonyl compounds. Thus, their metalation is not a feasible route for the

Table 6.2. Synthesis of 2-silyl-1,3-thiaselenolanes

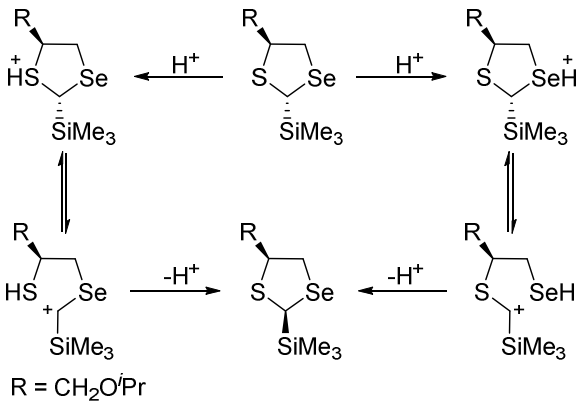


Entry	β-Mercapto-selenol	2-Silyl-1,3-thiaselenolane	dr	Yield (%)[a]
1	 **25a**	 **61a**	2:1	67
2	 **25b**	 **61b**	5:1	63
3	 **25c**	 **61c**	3:2	61
4	 **(*S*)-25c**	 **(*S*)-61c**	2:1	59
5	 **25d**	 **61d**	2.1	73
6	 **25e**	 **61e**	3:2	63
7	 **25f**	 **61f**	7:5	68
8	 **25g**	 **61g**	1:1	61[b]
9	 **25h**	 **61h**	7:5	67

[a] Yields referred to the purified products

[b] The 4-substituted isomer, arising from [CH_2(OH)CHPhSeH], is also formed (ca. 40%) as a equimolar mixture of diatercoisomers

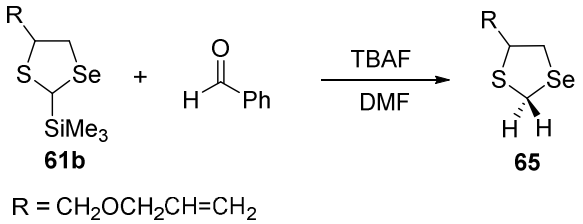
reaction with electrophiles. A solution to this problem can be found through the functionalization of the C-Si bond.[44]



Scheme 6.12. *cis*/*trans* riequilibrium of 2-silyl-thiaselenolanes

Having found conditions to obtain 2-silyl- oxaselenolanes and thiaselenolanes in rather good yields, we examined the reactivity of such compounds with electrophiles.

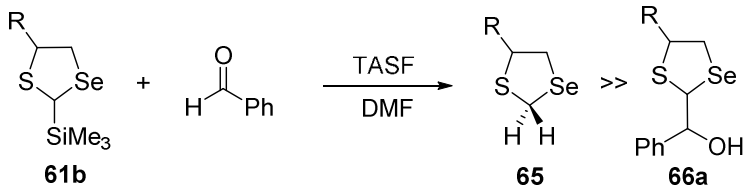
Thus, (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane **61b** was treated with benzaldehyde in presence of a catalytic amount of TBAF but no traces of the desired adduct were observed. In fact, the isolated products were the thiaselenolane **65**, arose from protodesilylation reaction, and unreacted benzaldehyde (Scheme 6.13).



Scheme 6.13

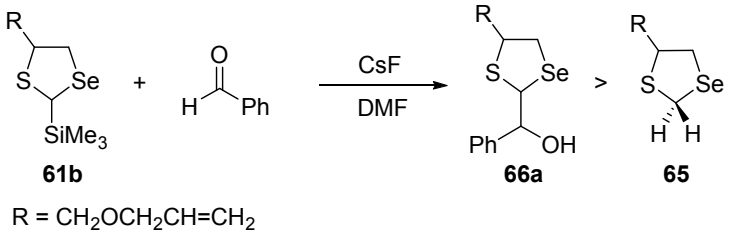
It is well know that carbodesilylation reactions are sensitive to the different sources of fluoride ion, therefore, besides TBAF, TBAT and TASF were tested in promoting this transformation. Complete protodesilylation was again observed with

TBAT, whereas the adduct **66a** was formed in traces upon catalysis of TASF (Scheme 6.14).



Scheme 6.14

On the other hand, when the reaction was performed using CsF (dried at 250°C for 3 hours prior to use) the expected carbodesilylation product was obtained in moderate yield as a mixture of the four possible diastereoisomers (Scheme 6.15).



Scheme 6.15. Reaction of 2-silyl-thiaselenolanes with aldehydes

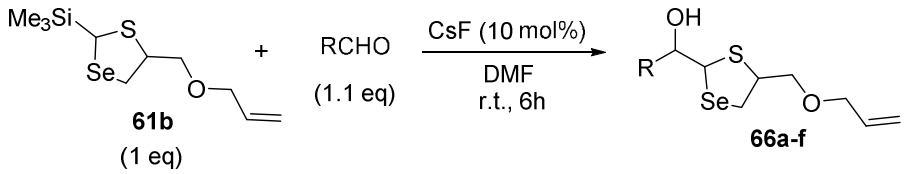
On the base of this result we went through the exploration of the scope and limitation of this reaction, thus **61b** was treated with several aromatic aldehydes bearing EDG or EWG at different positions. In this way a smooth access to α-hydroxy thiaselenolanes was achieved (Table 6.3).

2-silyl thiaselenolanes variously substituted at position-5 (including differently protected glycidol derivatives) were reacted under the described conditions to test the generality of this reaction. The formation of the corresponding adduct was always observed in moderate to good yield, thus proving that the reaction is independent from the nature of the substituent at C-5 (Table 6.4, 6.5, 6.6).

The limitations of such reaction were found in the reactivity with aliphatic and α,β–unsaturated aldehydes, the expected α–hydroxy thiaselenolanes being formed only in traces. Reaction with different electrophiles is now under investigation.

Once established the possibility of an easy functionalization of silyl-thiaselenolanes, the stereochemical fate of the reaction was considered.

Table 6.3. Synthesis of α-hydroxy-5-((allyloxy)methyl)-1,3-thiaselenolanes



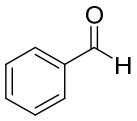
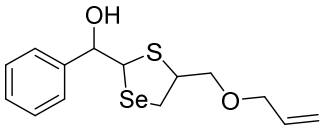
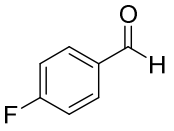
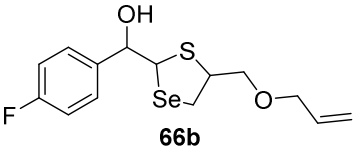
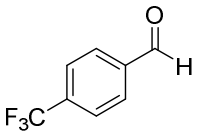
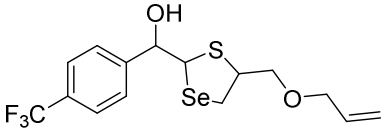
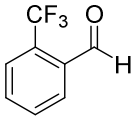
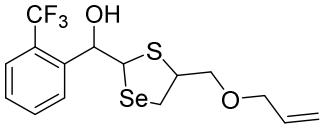
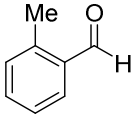
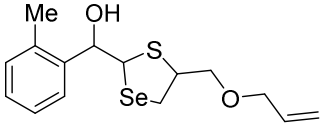
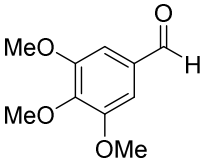
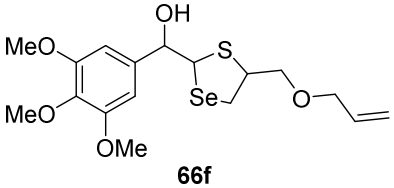
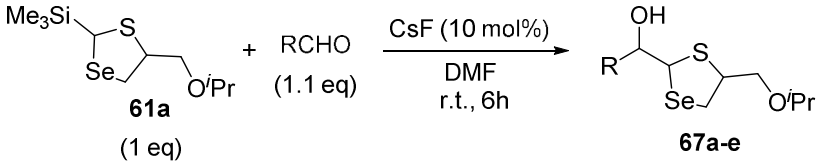
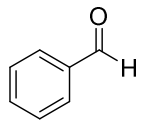
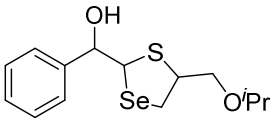
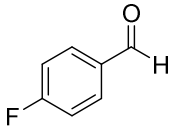
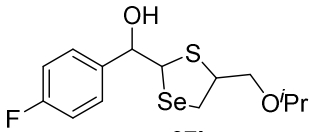
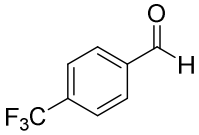
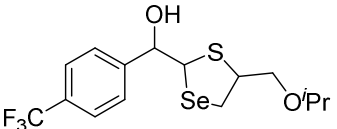
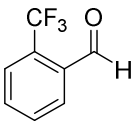
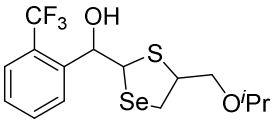
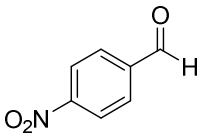
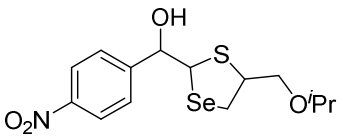
Entry	Aldehyde	1,3-Thiaselenolanes	Yield (%)
1		 **66a**	42
2		 **66b**	54
3		 **66c**	38
4		 **66d**	30
5		 **66e**	46
5		 **66f**	26

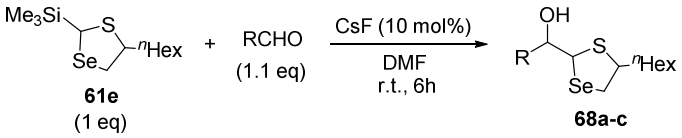
Table 6.4. Synthesis of 5-(isopropoxymethyl)-1,3-thiaselenolanes



Entry	Aldehyde	1,3-Thiaselenolanes	Yield (%)
1		 **67a**	38
2		 **67b**	54
3		 **67c**	60
4		 **67d**	38
5		 **67e**	43

Thus, both *cis*- and *trans*-(5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)trimethylsilane **61a** were separated by TLC and subsequently reacted with 4-(trifluoromethyl)benzaldehyde and the stereochemical outcome was analysed.

Table 6.5. Synthesis of 5-hexyl-1,3-thiaselenolanes



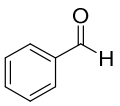
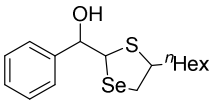
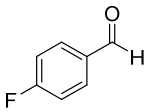
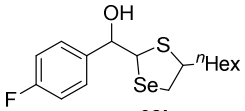
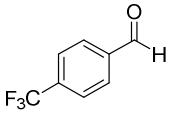
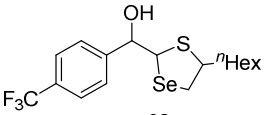
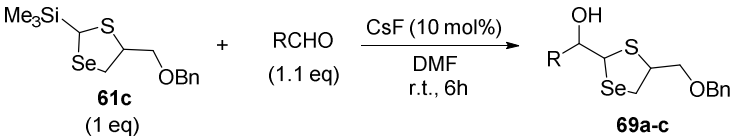
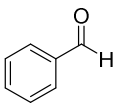
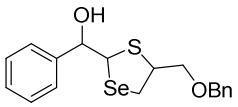
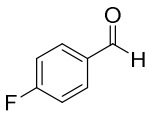
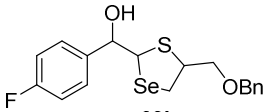
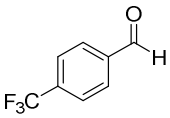
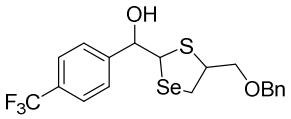
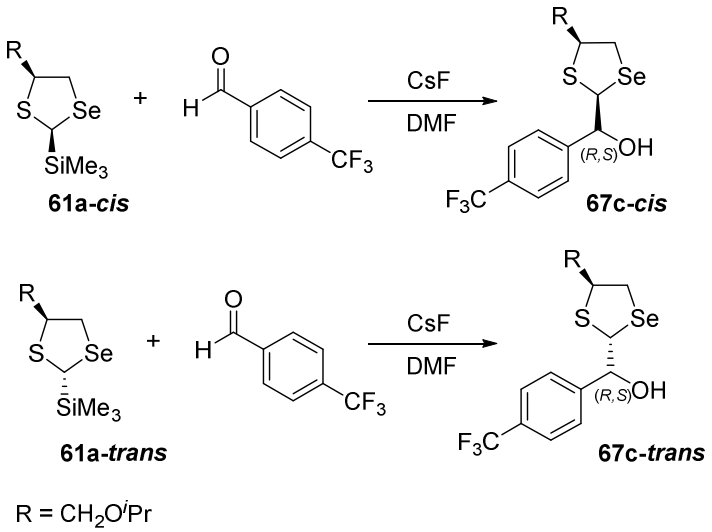
Entry	Aldehyde	1,3-Thiaselenolanes	Yield (%)
1		 **68a**	38
2		 **68b**	61
3		 **68c**	40

Table 6.6. Synthesis of 5-((benzyloxy)methyl)-1,3-thiaselenolanes



Entry	Aldehyde	1,3-Thiaselenolanes	Yield (%)
1		 **69a**	41
2		 **69b**	32
3		 **69c**	35

The reaction led to the selective formation of the corresponding adducts **67c**-*cis* and **67c**-*trans*, as mixtures of diatereoisomer at the neoformed stereocenter, showing that complete retention of configuration at C-2 was maintained in both reactions. This shows that the stereoconservative behaviour observed in dithiane and dithiolane series also holds for the thiaselenolanes series (Scheme 6.16).



Scheme 6.16. Stereoconservative functionalization of 2-silyl-thiaselenolanes

6.3 Conclusions

In conclusion, we developed a novel method to synthesise selenium containing silyl heterocycles. This class of compounds may be attractive for possible applications as building blocks in the synthesis of bioactive molecules. Stereoselective functionalization of the C-Si bond of thiaselenolanes with aldehydes allowed to access interesting systems challenging to achieve with classic procedures.

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Chapter 7

Stereoselective synthesis of 1,3-thiazolidines and 1,3-selenazolidines

7.1 Introduction

The thiazolidine ring system derives special importance from the fact that it is an integral part of medicinally important compounds like penicillins[1] and some antiradiation drugs.[2] Substituted thiazolidine derivatives represent important key intermediates for the synthesis of pharmacologically active drugs.[3] Recently, a number of thiazolidines have been claimed to be retroviral protease inhibitors[4,5] and have also been investigated as possible substitutes for the carbohydrate moiety in the synthesis of new antiviral nucleosides.[6] More recently, they have also been shown to be antitussive-active molecules.[7] Thiazolidines are also relevant in food chemistry as they are incorporated into flavor enhancing additives.[8] Their synthetic utility has been demonstrated by their use as blocking groups[9] and intermediates in the synthesis of aldehydes[10] and aminoethane thiols.[11]

Thiazolidines are recognised to have a number of biological properties, thence their synthesis is applied to obtain molecules finding application in medicinal chemistry (Fig. 7.1).

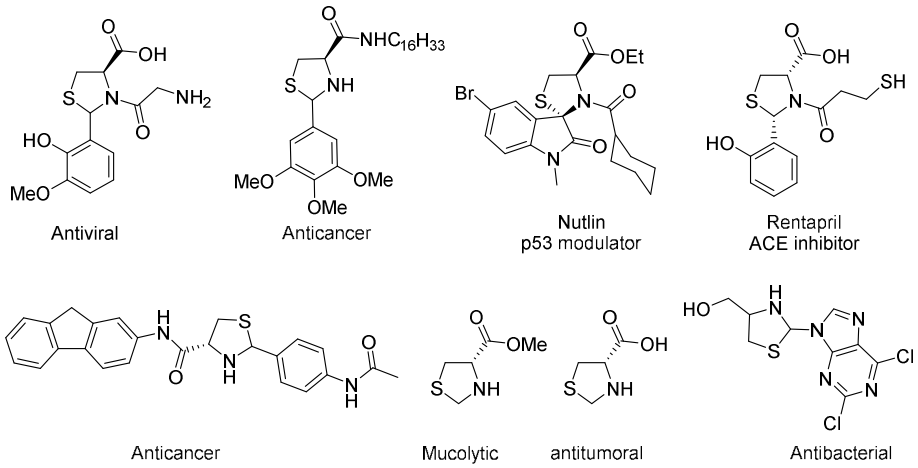


Fig. 7.1. Biologically active thiazolidines

In this context easy and stereocontrolled processes to access these compounds are highly desirable.

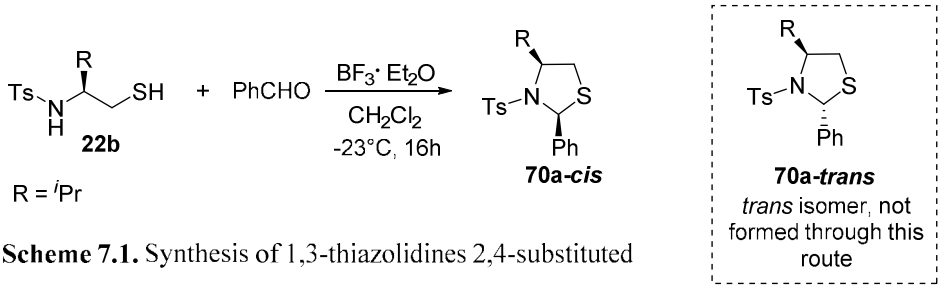
A common route to 2-substituted thiazolidines-4-carboxilic acids is obtained through the reaction of L-cysteine with aldehydes.[12]

A general access to 2-substituted-1,3-thiazolidines with different substituents on positions 4 and/or 5 is usually obtained through a multi-step approach from natural *N*-protected amino acids, after reduction of the carboxilic group. Oxygen to sulfur exchange is achieved *via* a thioacetate by the Mitsunobu reaction,[13] followed by hydrolysis of the thioester to obtain the amino thiol. Reaction with aldehydes allows the synthesis of differently substituted 1,3-S,N-heterocycles.[14]

7.2 Stereoselective synthesis of 2,4-disubstituded 1,3-thiazolidines

Having developed an effective procedure for the synthesis of differently *N*-protected enantioenriched 1,2-mercaptoamines and 1,2-hydroselenoamines we sought the synthesis of five-membered heterocycles through their reactivity with aldehydes. Hindered protecting groups were expected to have an effect on the stereochemical outcome.

On the basis of these considerations (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide **22b**, obtained from L-valine as described above, was treated with benzaldehyde in the presence of boron trifluoride diethyl etherate under conditions reported in Scheme 7.1. We were pleased to find that the corresponding (2*S*,4*S*)-4-isopropyl-2-phenyl-3-tosylthiazolidine **70a** was formed in good yield in a stereoselective way, being the *cis* isomer obtained as the exclusive product and the *trans* isomer not detected.

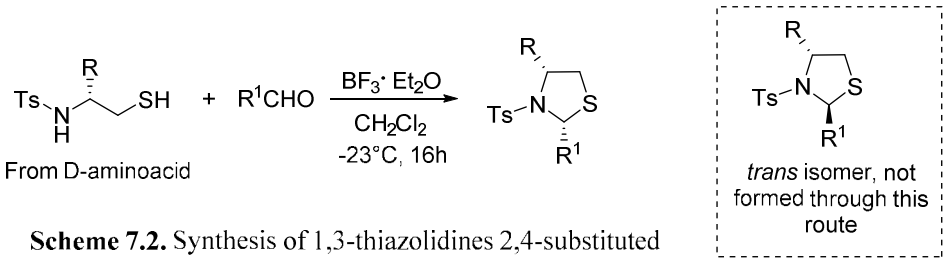


Scheme 7.1. Synthesis of 1,3-thiazolidines 2,4-substituted

The reaction was conveniently extended to different aldehydes (Table 7.1). The process proved to be efficient and highly stereoselective with aliphatic (Table 7.1, entries 5, 6, 7) and differently substituted aromatic aldehydes. 1,3-Thiazolidines bearing both electron-deficient (Table 7.1, entry 2) and electron-rich (Table 7.1, entries 3, 4) aromatics were isolated in good yield and high d.r.

To evaluate the generality of this procedure, enantioenriched β-aminothiols synthesised from L-alanine, L-isoleucine and L-phenylalanine were treated with aldehydes under the described conditions to afford stereodefined 2,4-disubstituted 1,3-thiazolidines in good yield (Table 7.2). The absolute stereochemistry was assigned in accordance with literature reported data.

The (2*R*,4*R*) enantiomers of *cis* thiazolidines **70-73** can be easily synthesised through reaction of β-aminothiols prepared from D-aminoacids with aldehydes (Scheme 7.2).



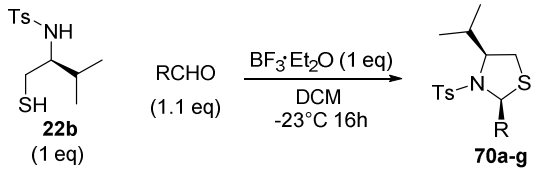
Scheme 7.2. Synthesis of 1,3-thiazolidines 2,4-substituted

A variability of moieties can be introduced on the thiazolidine core, therefore the route can be easily modulated as a function of synthetic ends.

Product **70d** (Table 7.1, entry 4), for instance, bears at C-2 the BHT residue potentially related to antioxidant properties. **70c** is structurally similar to antiviral compounds for the presence of the 2-OH,3MeO- groups on the aromatic ring at C-2 (see Table 7.1, entry 3 and Fig. 7.1).

To ascertain whether the nitrogen protecting group was involved in determining such stereoselectivity, *N*-Boc protected β-amino thiols were reacted with aldehydes under the described conditions (Scheme 7.3). In this case 1,3-thiazolidines were achieved in rather good yields (65-80%) as a mixture of *cis* and *trans* diastereoisomers, being the stereochemistry at C-2 not controlled. Minor amount of unprotected thiazolidine **75** was also detected.

Table 7.1. Synthesis of diastereoenriched 4-isopropyl-1,3-thiazolidines



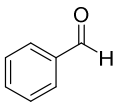
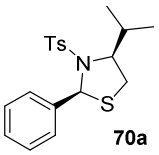
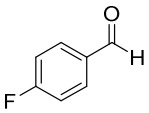
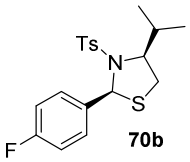
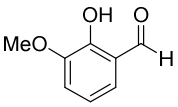
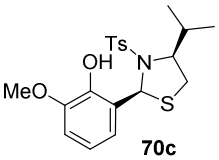
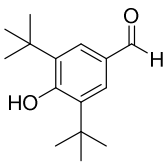
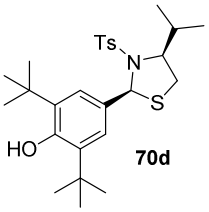
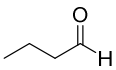
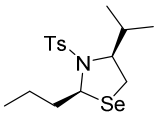
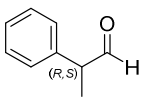
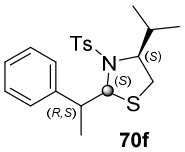
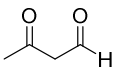
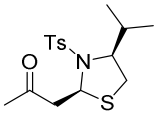
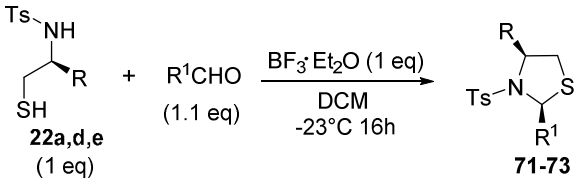
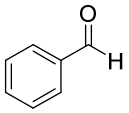
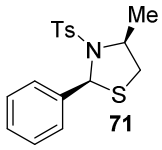
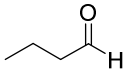
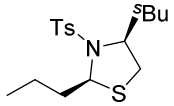
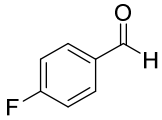
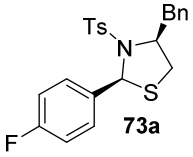
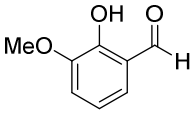
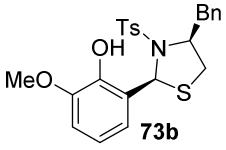
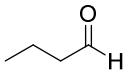
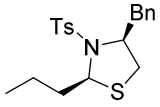
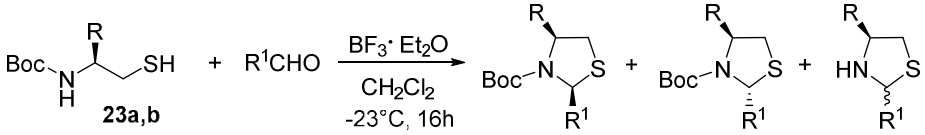
Entry	Aldehyde	1,3-Thiazolidine	d.r.	Yield (%)
1		 **70a**	>96:4	88
2		 **70b**	>96:4	78
3		 **70c**	>96:4	72
4		 **70d**	>96:4	67
5		 **70e**	>96:4	77
6		 **70f**	1:1	58
7		 **70g**	>96:4	87

Table 7.2. Synthesis of diastereoenriched 1,3-thiazolidines



Entry	R	Aldehyde	1,3-Thiazolidine	d.r.	Yield (%)
1	Me		 **71**	>96:4	83
2	^{s}Bu		 **72**	>96:4	76
3	Bn		 **73a**	>96:4	81
4	Bn		 **73b**	>96:4	78
5	Bn		 **73c**	>96:4	84

This result clearly shows that the nature of the group on the nitrogen is strongly involved in leading the stereochemistry of such process.



R = ^{i}Pr, Bn

R^1 = Ph, *p*F-C_6H_4, *p*NO_2-C_6H_4

Scheme 7.3. Synthesis of 1,3-thiazolidines 2,4-substituted

7.3 Stereoselective synthesis of 2,4-disubstituded 1,3-selenazolidines

As stated above, in the recent years interest in the chemistry of selenium-containing compounds has increased remarkably due to their chemical properties, biological activity, and pharmaceutical potential.[15]

In this context, selenium-containing heterocycles represent a very interesting class of compounds, being involved in different processes in pharmacological and biological fields.[16]

In particular, 1,3-selenazolidines are valuable derivatives for cancer chemoprevention and other clinical uses.[17] They found also application as prodrugs of selenocysteine[17a,b] and then represent novel, efficient organoselenium delivery agents.[18] The selenazolidine-system is also contained in various bicyclic systems, including β-lactam skeletons (selenapenams), selenacephems and selenazepines.[19]

The chemical rationale for the selenazolidines mainly relies on the corresponding chemistry of thiazolidines. Most of the reported examples for these two classes of compounds are derived from cysteine and selenocysteine. It is well known that L-selenocysteine (Sec) is very unstable in its monomeric form (as selenol) and prone to rapid auto-oxidation.

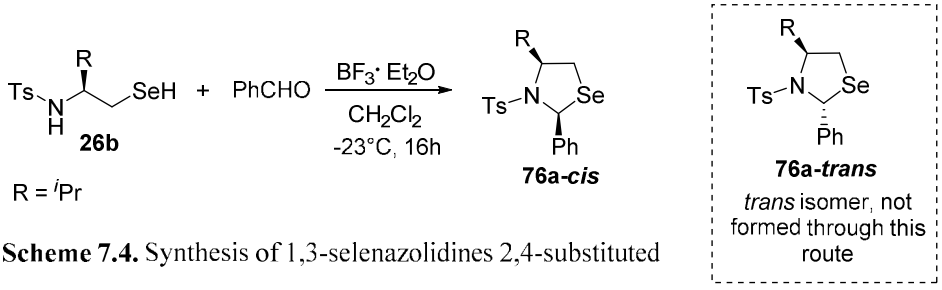
Thus, being prevented the use of Sec itself, the corresponding diselenide L-selenocystine is used. Its *in situ* reduction by $NaBH_4$ allows to generate the selenide-anion, which can be reacted with the appropriate carbonyl compound to obtain 2-substituted selenazolidine-4(*R*)-carboxilic acids.[17a,19,20]

It must be considered that physicochemical, biochemical and nutritional properties can be modified depending on the nature of moieties on the heterocyclic ring, and new methods for their preparation are therefore important targets.

Thus, with the aim to introduce different substituents at positions 2 and 4 and to verify whether these new selenated heterocycles can find application in different fields (i.e. pharmacological or nutritional), we focused our attention to the synthesis of 2,4-disubstituted-1,3-selenazolidines.

Having studied this easy route to 1,3-thiazolidines, the unexplored reactivity of β-amino selenols with aldehydes was then considered.

With the aim to synthesise 1,3-selenazolidines, (*S*)-*N*-(1-hydroseleno-3-methylbutan-2-yl)-4-methylbenzenesulfonamide **26b** was treated with benzaldehyde in the presence of BF_3 as previously described. The wanted (2*S*,4*S*)-4-isopropyl-2-phenyl-3-tosyl-1,3-selenazolidine *cis*-**76a** was obtained as the only product, showing the high stereoselectivity of such process. The *trans* isomer **76a** was not formed through this route.



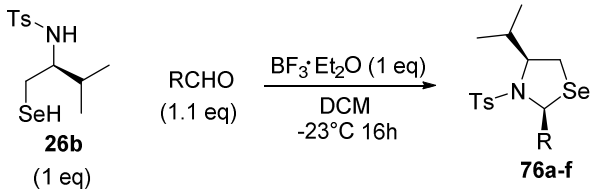
Scheme 7.4. Synthesis of 1,3-selenazolidines 2,4-substituted

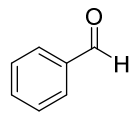
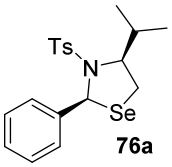
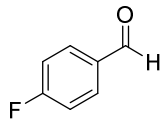
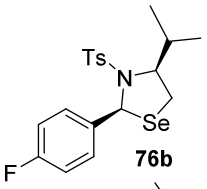
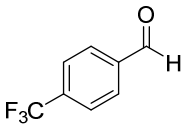
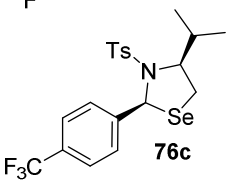
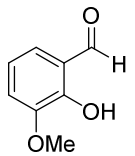
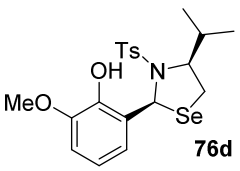
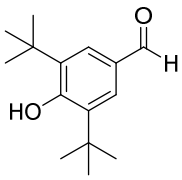
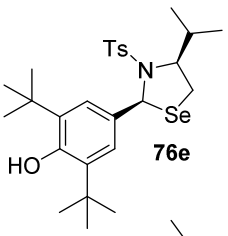
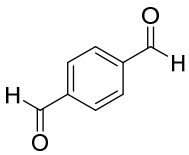
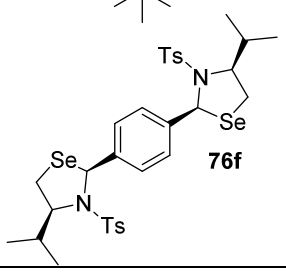
Seeking for the generality of this easy synthetic approach a number of 2,4-disubstituted 1,3-selenazolidines were yielded treating β-aminoselenols (obtained from L-aminoacids) with aliphatic or aromatic aldehydes. The results are listed in Tables 7.3-7.7.

The reaction proved general and highly stereoselective, being 2,4-disubstituted 1,3-selenazolidines obtained as a single enantioenriched *cis* diastereoisomer. Selenazolidines bearing different groups at C-2 and C-4 were achieved. Aliphatic, electron-rich and electron-deficient aromatics moieties could be successfully introduced on the selenzolidine core, as reported in Tables 7.3-7.7. The products were isolated in good yield and with a d.r. higher than 96:4. Only in the reaction of NO_2-substituted benzaldehydes a *cis*/*trans* mixture was formed (Table 7.4, entry 7, Table 7.5, entry 5, Table 7.6, entries 5 and 6).

When terephthalaldehyde was treated with two equivalents of β-aminoselenol the bis selenazolidine **76f** having four defined stereocenters was achieved (Table 7.3, entry 6). Such versatile procedure allows the introduction of a large variability of substituents. Among them there is some value in taking into consideration groups potentially related to biological activities or antioxidant properties.

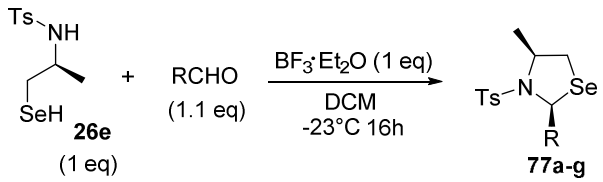
Table 7.3. Synthesis of diastereoenriched 4-isopropyl-1,3-selenazolidines



Entry	Aldehyde	1,3-Selenazolidine	d.r.	Yield (%)
1		 **76a**	>96:4	71
2		 **76b**	>96:4	73
3		 **76c**	>96:4	62
4		 **76d**	>96:4	72
5		 **76e**	>96:4	77
6		 **76f**	>96:4	52[a]

[a] 0.45 eq of terephthalaldehyde were used

Table 7.4. Synthesis of diastereoenriched 4-methyl-1,3-selenazolidines



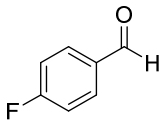
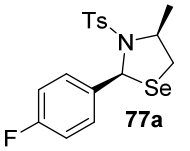
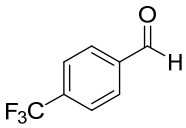
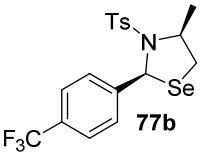
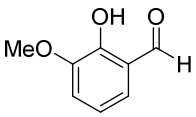
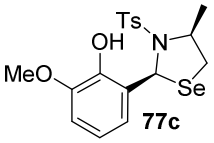
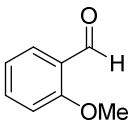
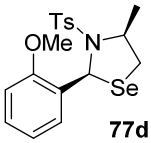
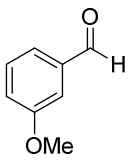
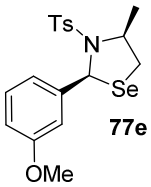
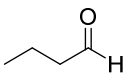
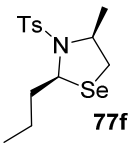
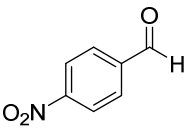
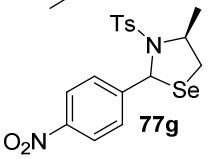
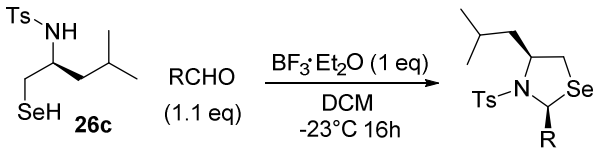
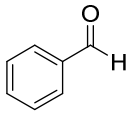
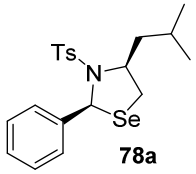
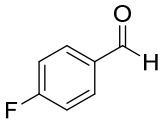
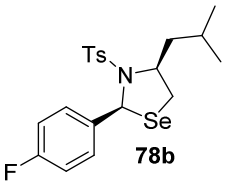
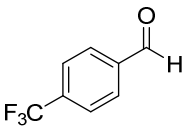
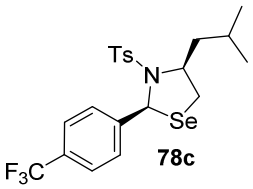
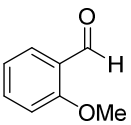
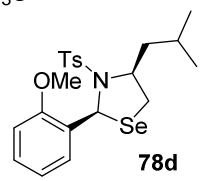
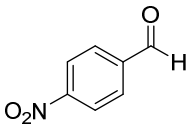
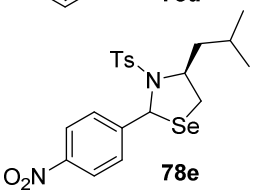
Entry	Aldehyde	1,3-Selenazolidine	d.r	Yield (%)
1		 **77a**	>96:4	81
2		 **77b**	>96:4	76
3		 **77c**	>96:4	71
4		 **77d**	>96:4	91
5		 **77e**	>96:4	86
6		 **77f**	>96:4	86
7		 **77g**	1:1	81

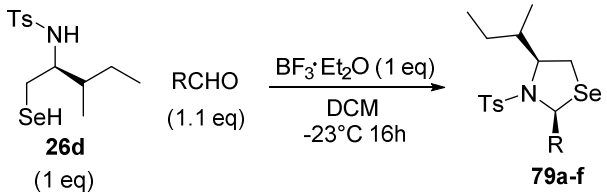
Table 7.5. Synthesis of diastereoenriched 4-isobutyl-1,3-selenazolidines

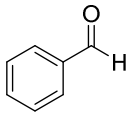
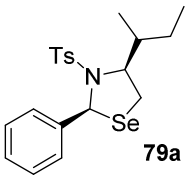
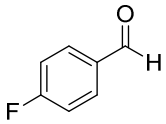
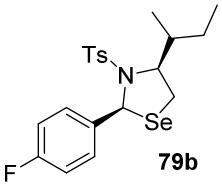
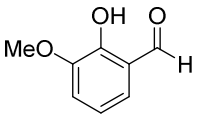
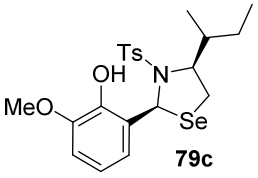
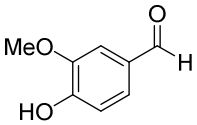
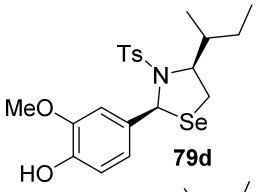
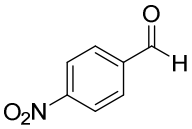
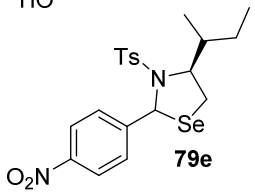
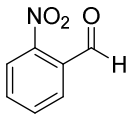
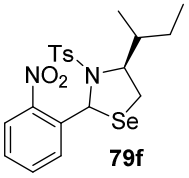


Entry	Aldehyde	1,3-Selenazolidine	d.r.	Yield (%)
1		 **78a**	>96:4	87
2		 **78b**	>96:4	63
3		 **78c**	>96:4	74
4		 **78d**	>96:4	68
5		 **78e**	2:1	47

In medicinal chemistry, the incorporation of fluorine into an organic compound can result in improved metabolic stability and bioavailability and enhances the binding efficacy when compared to the non- fluorinated analogue.[21] Consequently, ~20−25% of all pharmaceuticals on the market contain fluorine.[22]

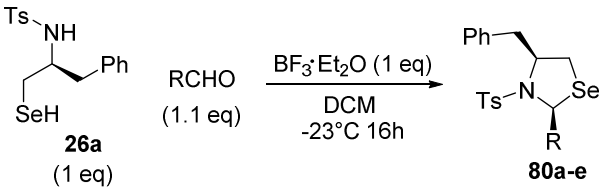
Table 7.6. Synthesis of diastereoenriched 4-sec-butyl-1,3-selenazolidines

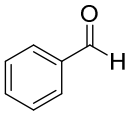
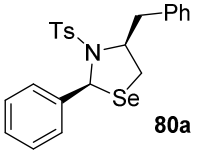
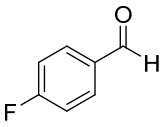
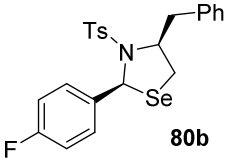
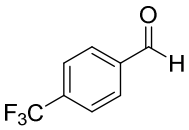
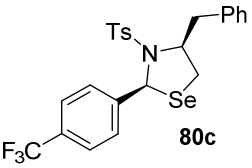
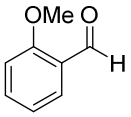
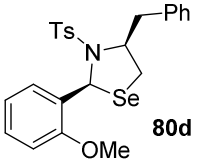
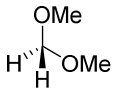
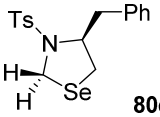


Entry	Aldehyde	1,3-Selenazolidine	d.r.	Yield (%)
1		 **79a**	>96:4	75
2		 **79b**	>96:4	79
3		 **79c**	>96:4	81
4		 **79d**	>96:4	73
5		 **79e**	1:1	62[a]
6		 **79f**	2:1	51[a]

[a] mixture of *cis* and *trans* diastereoisomers was achieved

Table 7.7. Synthesis of diastereoenriched 4-benzyl-1,3-selenazolidines



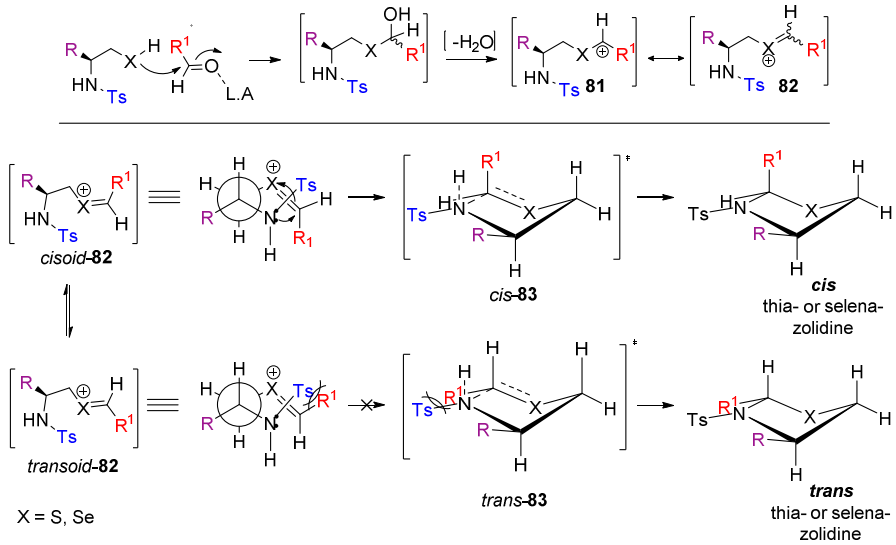
Entry	Aldehyde/acetal	1,3-Selenazolidine	d.r.	Yield (%)
1		 **80a**	>96:4	84
2		 **80b**	>96:4	91
3		 **80c**	>96:4	77
4		 **80d**	>96:4	83
5		 **80e**	--	46

Fluorinated moieties can be easily incorporate in selenazolidines by reacting suitable aldehydes (i.e. see Table 7.4, entries 1 and 2, Tables 7.3, 7.5, 7.7, entries 2 and 3). Phenolic groups (see i.e. Table 7.3, entry 5), synergically with Se, could result in a increased free radical neutralization action. A number of selenium isosteric substitution analogues of sulfurated molecules have shown increased pharmaceutical properties. The S/Se substitution of selenazolidines **76d, 77c** and

79c, structurally related to sulfurated antiviral systems, might improve such biological activity. Synthesis of *N*-Boc-selenazolidines from the corresponding hydroselenoamines afforded a mixture of *cis*/*trans* diastereoisomers, showing less stereoselectivity as already observed for the sulfurated analogues.

7.4 Hypothesis of mechanism

In order to explain the stereoselectivity of the described route we reasoned the following mechanism. We hypothesised a first attack of the thiol or selenol moiety of, more nucleophile than the sulphonamide nitrogen, on the carbonyl group, activated by the Lewis acid. The resulting thio- or seleno- hemiacetal leads, after water elimination, to the formation of the carbocationic species **81** in resonance with the sulfonium or selenonium ion **82** (Scheme 7.5, top). The *cisoid* and *transoid* form of **82** are in equilibrium through the carbocation. The five member ring arises from a 5-*endo*-*trig* cyclization (exception to Baldwin's rules) that, as can be seen in the Scheme 7.5, is more favoured in the *cisoid* **82** than in the more sterically congested *transoid* form.



Scheme 7.5. Proposed mechanism

Thence, the formation of the transition state *cis*-**83** is faster than *trans*-**83** and *cis* heterocycle is selectively obtained. Preliminary calculations showed that *cis* product is also the thermodynamically favoured isomer.

In the synthesis of *N*-Boc protected thiazolidines and seleazolidines cyclization occurs on both the *cisoid* and *transoid* form of sulfonium or selenonium ion - probably due to the lower steric effect of this protecting group with respect to the tosyl - leading to the formation of a *cis*/*trans* mixture of diastereoisomers.

7.5 Synthesis of 2-silyl 1,3-thiazolidines

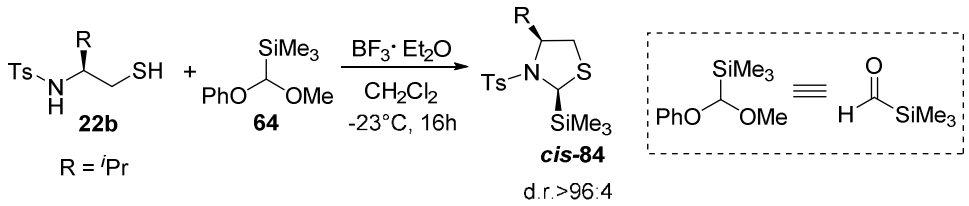
Despite the utility of the thiazolidine moiety, very few methodologies for the functionalization of position-2 of the heterocyclic ring exist. This is due to their high instability under strong basic conditions, thus preventing their functionalisation through metalation procedures.

To the best of our knowledge, only very few reports deal with such functionalization, and their efficiency seems to be related to the presence of specific *N*-protecting groups. Meyers *et al*. reported the efficient metallation of the thiazolidine ring when a *tert*-butylformamidine group was present on the nitrogen atom,[23] while Gawley *et al*. have reported a nice functionalization of thiazolidines bearing an *N*-Boc system,[24] showing their possible use as chiral acyl anion synthons. Toru *et al*. have recently reported a functionalization of *N*-Boc protected thiazolidines in the presence of (-)-sparteine,[25] which afforded the corresponding adducts with low de values but with very interesting ee (up to 93%). In this context, 4-Substituted 2-silyl thiazolidines might represent a useful class of functionalizable systems.

Having elucidated this simple route to thiazolidines and selenazolidines, the synthesis of analogue 2-silyl heterocycles was investigated. As described above (Chapter 6) we found that **57** and **64** behave as convenient synthetic equivalents of formyl silane under suitable conditions.

Thus, *N*-Tosyl 1,2-mercaptoamine **22b** was treated with silyl acetal **64** in the presence of boron trifluoride diethyl etherate to yield (2*R*,4*S*)-4-isopropyl-3-tosyl-2-

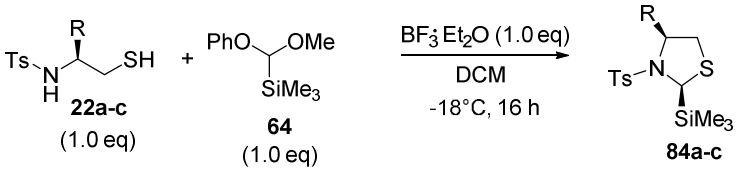
(trimethylsilyl)-1,3-selenazolidine *cis*-**84** with high stereoselectivity, being the *trans* isomer at C-2 not detected.

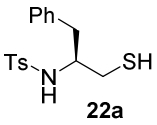
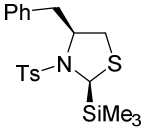
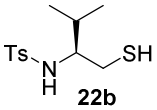
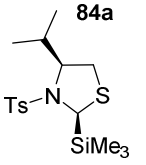
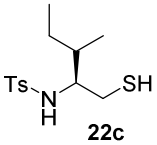
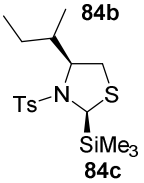


Scheme 7.6. Synthesis of 2-silyl 1,3-thiazolidines

The procedure proved to be general and enantioenriched differently 4-substituted 2-silyl thiazolidines were achieved, despite the moderate yields, by treating 1,2-mercaptoamines under the reported conditions (Table 7.8).

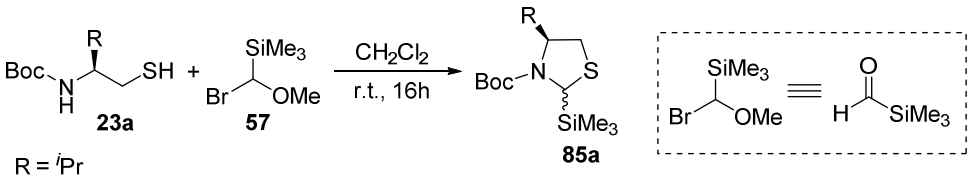
Table 7.8. Synthesis of 2-silyl thiazolidines



Entry	Thiol	Product	d.r.	Yield (%)
1	 **22a**	 **84a**	>96:4	59
2	 **22b**	 **84b**	>96:4	43
3	 **22c**	 **84c**	10:1	39

N-Boc β-aminothiols demonstrated to be poorly reactive whit **64**. Thus, the more reactive (bromo(methoxy)methyl)trimethylsilane **57** was used as an alternative

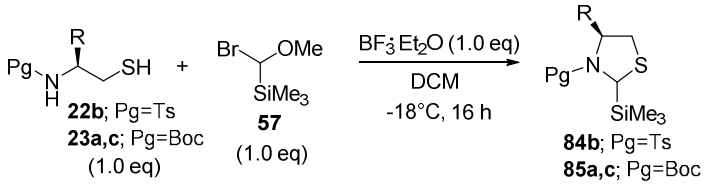
synthetic equivalent of formyl silane and, after optimization of reaction conditions, the thiazolidine **85** could be achieved from the corresponding aminothiol as a mixture of distereoisomers.

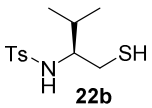
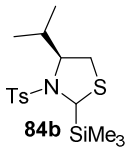
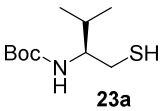
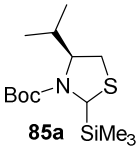
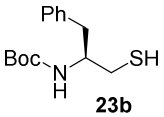
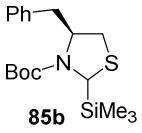
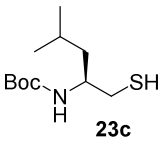
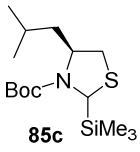


Scheme 7.7. Synthesis of 2-silyl 1,3-thiazolidines

This approach was extended to differently substituted *N*-Ts and *N*-Boc β-aminothiols, yielding the related 2-silyl 1,3-thiazolidines in moderate yields as a mixture of *cis*/*trans* diastereoisomers, which can be separated.

Table 7.9. Synthesis of 2-silyl thiazolidines

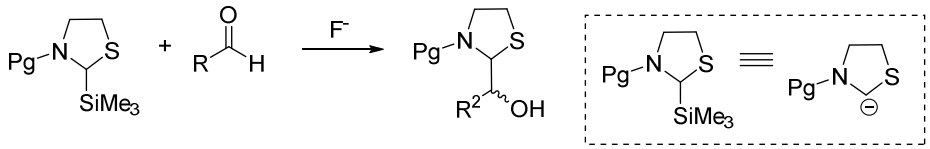


Entry	Thiol	Product	d.r.	Yield (%)
1	 **22b**	 **84b**	2:1	41
2	 **23a**	 **85a**	2:1	40
3	 **23b**	 **85b**	1:1	43
4	 **23c**	 **85c**	1:1	40

7.6 Functionalization of 4-substituted 2-silyl-1,3-thiazolidines

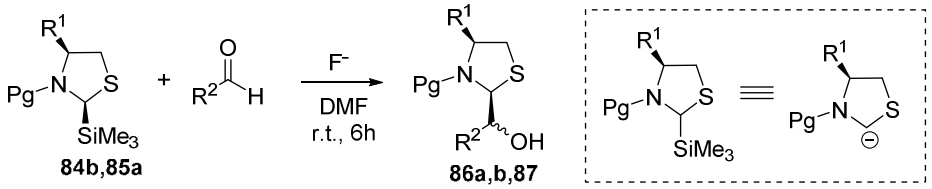
Variations in reaction conditions, such as the use of DIPEA as a base or different temperatures, did not afford appreciable yield improvement.

Our group previously described an efficient methodology for functionalization of unsubstituted 2-silyl-1,3-thiazolidines through their reaction with aldehydes under fluoride catalysis (Scheme 7.8).



Scheme 7.8: Functionalization of 2-silyl 1,3-thiazolidines with aldehydes

This approach has been now conveniently extended to 4-substituted substrates (Scheme 7.9).



84b,85a

86a: Pg = Ts, R^1 = ^{i}Pr, R^2 = Ph
86b: Pg = Ts, R^1 = ^{i}Pr, R^2 = *p*F-C_6H_4
87: Pg = Boc, R^1 = ^{i}Pr, R^2 = Ph

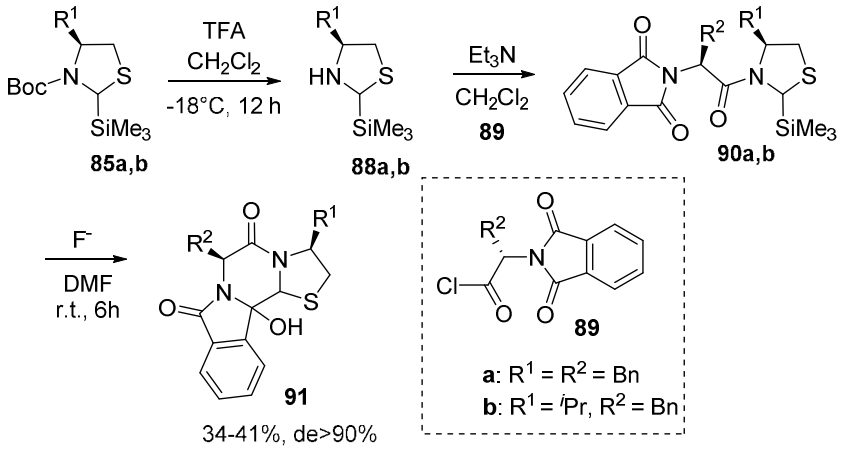
86a,b,87
37-45%

Scheme 7.9. Functionalization of 4-substituted 2-silyl 1,3-thiazolidines with aldehydes

These heterocyclic compounds are versatile building blocks toward the synthesis of more complex structures.

Cleavage of Boc group can be efficiently performed on the silylated thiazolidine under TFA conditions. As previously reported for the unsubstituted derivatives,[26] the endocyclic nitrogen can be functionalized with suitable groups further involved in a intramolecular cyclization exploiting the incipient carbanion formed upon fluoride ion activation. Following this route interesting polycyclic structures with possible biological activity can be achieved. For example, when the protecting group

is a phthalimido or succinimido derivative of a natural amino acid, silyl thiazolidines can be obtained as mixtures of enantiopure diastereoisomers **90**, which can be separated and reacted under fluoride ion conditions to afford direct access to polycyclic derivatives **91** (Scheme 7.10). Interestingly, only one diastereoisomer seems to be reactive in the present conditions, affording the polycyclic derivatives **91** with a good de (>90%).



Scheme 7.10. Intramolecular funzionalization of 2-silyl 1,3-thiazolidines

Attempts to synthesise 2-silyl selenazolidines through the reaction of β-aminoselenols with synthetic equivalents of formyl silane failed. Despite different conditions were tested, a complex mixture of open chain products was always formed, demonstrating once again that selenium chemistry cannot be merely deduced from the selenium one.

7.7 Conclusions

In conclusion, we developed an easy, high yielding and stereoselective process for the synthesis of 2,4-disubstituted 1,3- thiazolidines and selenazolidines. The procedure is versatile and, allowing the introduction of a groups variability on the heterocyclic core, gives the possibility of modulating the synthetic output in response to the needs arising from different applicative fields.

We reported also a convenient route to substituted 2-silyl thiazolidines and their functionalization. The use of suitable *N*-protected thiazolidines allowed to achieve

interesting polycyclic structures with potential biological activities. The possibility to synthesise compounds bearing different moieties might offer access to more complex systems. Optimization of the yield of described reactions as well as the synthesis of silyl selenazolidines is currently under investigation.

It is critically important that organic synthesis is performed in "green and sustainable" manners. Professor Ei-ichi Negishi stated that to this end, organic synthesis must be performed i) in high yields (Y), ii) efficiently (E), iii) selectively (S), iv) economically (E), and v) safely (S), namely in **Y(ES)^2** manner. The features of the discussed transformation fulfil the factors of Y(ES)^2 manner. The operative simplicity and the versatility are important added values that makes this process more attractive.

7.8. References

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Chapter 8

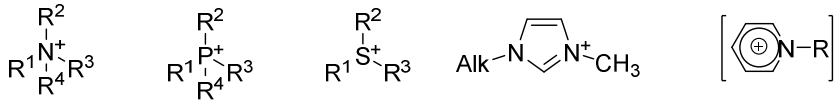
Synthesis of organosulfur and organoselenium compounds in ionic liquids

8.1 Ionic liquids - Introduction

The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons, that are widely used in organic synthesis have posed a serious threat to the environment. Consequently methods that successfully minimize their use are the focus of much attention.

In this respect, ionic liquids are attracting growing interest as alternative reaction media for various chemical and biotransformations.[1] Ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability, immiscibility with a number of organic solvents, negligible vapor pressure, and recyclability. Their high polarity and ability to solubilize both inorganic and organic compounds can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents

Ionic liquids are liquids that are composed entirely of ions. Molten sodium chloride, for example, is an ionic liquid but a solution of sodium chloride in water is an ionic solution. The term *molten salts*, which was previously used to describe such materials, evokes an image of high-temperature, viscous and highly corrosive media. The term *ionic liquid*, in contrast, implies a material that is fluid at (or close to) ambient temperature, is colourless, has a low viscosity and is easily handled, i.e. a material with attractive properties for a solvent.

cations: 

anions: BF_4^- , PF_6^- , SbF_6^- , $CF_3SO_3^-$, $(CF_3SO_3)_2N^-$, $CF_3CO_2^-$, $^-N(CN)_2$, $(C_2F_5)_3PF_3^-$

Room temperature ionic liquids are generally salts of organic cations, e.g. tetraalkylammonium, tetraalkylphosphonium, *N*-alkylpyridinium, 1,3-dialkylimidazolium and trialkylsulfonium cations.

In order to be liquid at room temperature, the cation should preferably be unsymmetrical, e.g. R^1 and R^2 should be different alkyl groups in the dialkylimidazolium cation. The melting point is also influenced by the nature of the anion.

Room temperature ionic liquids are not new. Ethylammonium nitrate, which is liquid at room temperature (but usually contains 200–600 ppm water) was first described in 1914.

In the late 1940s, *N*-alkylpyridinium chloroaluminates were studied as electrolytes for electroplating aluminium.

The first examples of ionic liquids based on dialkylimidazolium cations were reported in the early 1980s by Wilkes and coworkers.

The first example of the new ionic liquids, that currently are receiving so much attention as novel media for homogeneous catalysis, ethylmethylimidazolium tetrafluoroborate (emimBF_4) was reported by Wilkes et al. in 1992.[2] The synthesis of the corresponding hexafluorophosphate followed shortly thereafter.[3] In contrast to the chloroaluminate salts the fluoroborates and hexafluorophosphates are stable towards hydrolysis.

Subsequently, 1,3-dialkylimidazolium salts containing a wide variety of anions, e.g. $CF_3SO_3^-$, $[CF_3SO_2]_2N^-$, $CF_3CO_2^-$, $CH_3CO_2^-$, $PhSO_3^-$ and many more have been prepared.[4] Ionic liquids can be prepared by direct quaternisation of the appropriate amine or phosphine. Different anions can subsequently be introduced by anion exchange.

Room temperature ionic liquids exhibit many properties which make them potentially attractive media for homogeneous catalysis:

- They have essentially no vapour pressure, i.e. they do not evaporate and are easy to contain. - They generally have reasonable thermal stability. While tetraalkylammonium salts have limited thermal stability, owing to decomposition via the Hoffmann elimination, emimBF_4^- is reportedly stable up to 300 °C and emim-$(CF_3SO_2)_2N^-$ up to 400 °C.[4a] In other words many ionic liquids have liquid ranges of more than 300 °C, compared to the 100 °C liquid range of water.

- They are able to dissolve a wide range of organic, inorganic and organometallic compounds.

- The solubility of gases, e.g. H_2, CO and O_2, is generally good which makes them attractive solvents for catalytic hydrogenations, carbonylations, hydroformylations, and aerobic oxidations.

- They are immiscible with some organic solvents, e.g. alkanes, and, hence, can be used in two-phase systems. Similarly, lipophilic ionic liquids can be used in aqueous biphasic systems.

- Polarity and hydrophilicity/lipophilicity can be readily adjusted by a suitable choice of cation/anion and ionic liquids have been referred to as "designer solvents".

- They are often composed of weakly coordinating anions, e.g. BF_4^- and PF_6^- and, hence, have the potential to be highly polar yet non-coordinating solvents. They can be expected, therefore, to have a strong rate-enhancing effect on reactions involving cationic intermediates.

Room temperature ionic liquids, especially those based on the 1-*n*-alkyl-3-methylimidazolium cation, have shown great promise as an attractive alternative to conventional solvents. One of several advantages of ionic liquids is that they are environmentally benign since they have no detectable vapor pressure. As a result of their green credentials and potential to enhance rates and selectivities, ionic liquids are finding increasing applications in organic synthesis.[5,6]

8.2 Synthesis of thiocarbonyl compounds in ILs

Thiocarbonyl compounds play an important role in different fields. They represent very reactive and efficient intermediates in many chemical processes for the synthesis, for instance, of pharmaceutically active compounds.[7] Very recently, phenyl propyl thioketone has been isolated from seagrasses and identified as a novel antibacterial compound.[8] They participate also in obtaining molecules used in food chemistry as additives and aromas.[9] In fact it is well known that chemicals which

contain sulfur atoms often have a peculiar odour, depending on the nature of the sulfurated functional groups, i.e. sulfide, di- or higher sulfides, thiol, heterocyclic systems or thiocarbonyl derivatives.

In addition, it has been well established that the hetero Diels-Alder reaction is a very useful method for the preparation of six-membered heterocycles containing different heteroatoms, including sulfur and selenium. In fact carbon-chalcogen double bonds have been recognized as reactive groups, and in particular thiocarbonyl derivatives represent very valuable compounds to react as efficient heterodienophiles in cycloaddition reactions, including 1,3-dipolar cycloadditions.[10] Our group previously reported an efficient and direct conversion of a carbonyl function into a thiocarbonyl group through the reactivity with bis(trimethylsilyl)sulfide, $(Me_3Si)_2S$ (HMDST).[11] Using this procedure, a wide series of thioaldehydes, thioketones and thioacylsilanes was obtained and their behaviour as heterodienophiles with acyclic and cyclic dienes was elucidated.

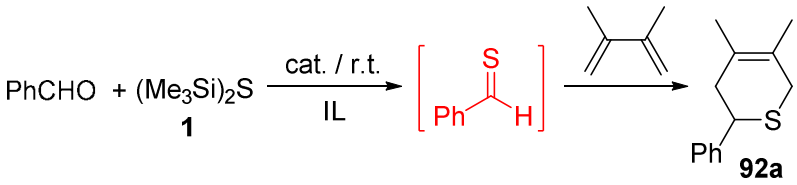
Although other efficient methods for the direct conversion of a C=O into a C=S group are described,[12] such as for instance the use of Lawesson's reagent or H_2S/HCl, the *n*-BuLi catalyzed reaction of a silyl sulfide, to date the conversion of a carbonyl group into a thiocarbonyl moiety in room temperature ionic liquids (RTILs) has not been yet reported. Thus, the development of new, alternative methodologies to access C=S containing systems under mild conditions, using non hazardous materials, is highly desirable.

Some papers dealing with the synthesis of organochalcogenides in ILs are also reported.[13] To the best of our knowledge no example is described for thionation reactions using ionic liquids as solvents.

In order to develop a clean thionation method, we investigated the use of ionic liquids as novel reaction media for the conversion of aldehydes into thioaldehydes, which reacted as heterodienophiles in Diels-Alder cycloadditions.[14]

As a model substrate to evaluate the best reaction conditions, we performed a set of experiments using benzaldehyde and bis(trimethylsilyl)sulfide **1** under $CoCl_2 \cdot 6H_2O$ or silyl triflate (TfOTMS) catalysis and 2,3-dimethyl-1,3-butadiene as

trapping agent (Scheme 8.1). We considered different ionic liquids, which are liquid at room temperature and stable under the used conditions.



cat.: **A** = $CoCl_2 \cdot 6H_2O$; **B** = TfOTMS

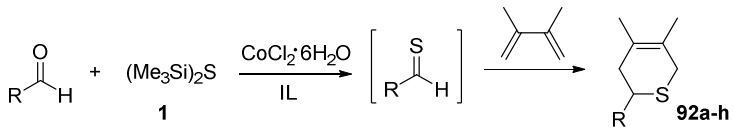
Entry	Ionic liquid	cat.	Yield (%)
1	[bmim][BF_4]	**A / B**	78 (A); 71 (B)
2	[bmim][PF_6]	**A / B**	72 (A); 73 (B)
3	[emim][TfO]	**A / B**	65 (A); 69 (B)
4	[emim][CH_3OSO_3]	**A / B**	75 (A); 67 (B)
5	[hmim][$N(Tf)_2$]	**A**	51
6	[bmpl][$N(Tf)_2$]	**A / B**	43 (A); 78 (B)
7	[bmpl][$N(CN)_2$]	**A / B**	--

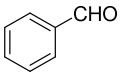
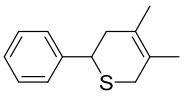
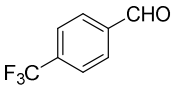
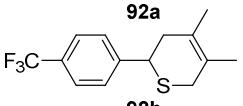
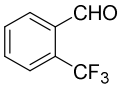
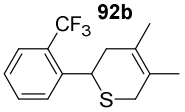
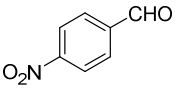
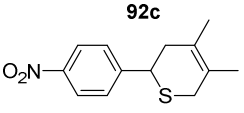
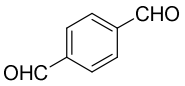
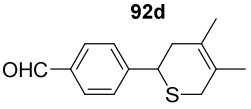
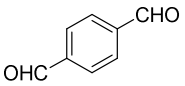
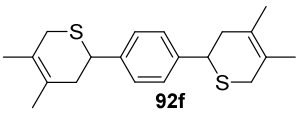
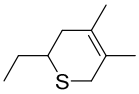
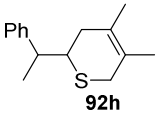
Scheme 8.1

All imidazolium derivatives, with different alkyl chains (butyl-methyl [bmim], ethyl-methyl [emim] and hexyl-methyl [hmim]) and various counter ions were efficient in promoting the thionation of PhCHO and the cycloaddition of the transient thioaldehyde with the diene (Scheme 8.1, entries 1-5), as demonstrated by the good yields of the corresponding dihydro-thiopyran derivative **92a**. When the reaction was performed in pyrrolidinium derivatives, only in [bmpl][$N(Tf)_2$] was observed the formation of the cycloadduct (Scheme 8.1, entry 6), while in [bmpl][$N(CN)_2$] any amount of the desired product was observed (Scheme 8.1, entry 7). This result can suggest the influence of the cation in such reactions. The ionic liquids used can be potentially recycled up to three times. The same thionation reaction was performed using as a medium the recovered IL/catalyst system just by adding more reagents, without the addition of more catalyst. Under these conditions the formation of the product **92a** was observed, even if in lower yield. These findings point out that the use of ionic liquids to promote this thionation is suitable, and that the conditions are mild enough to trap thiobenzaldehyde with the diene.

With the aim of evaluating the generality of this new protocol, differently substituted aromatic and aliphatic aldehydes were reacted under $CoCl_2 \cdot 6H_2O$ catalysis in selected ionic liquids. The results are summarized in Table 8.1.

Table 8.1. Synthesis of thioaldehydes in ionic liquids and their trapping by 2,3-dimethyl-1,3-butadiene



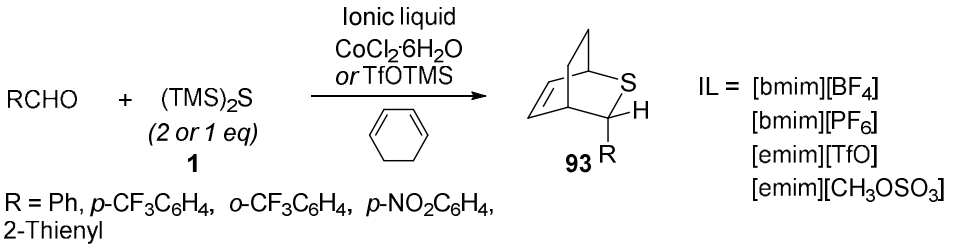
Entry	Ionic liquid	Aldehyde	Adduct[a]	Yield %[b]
1	[bmim][BF_4]		 **92a**	78
2	[bmim][BF_4]		 **92b**	63
3	[bmim][BF_4]		 **92c**	68
4	[bmim][BF_4]		 **92d**	57
5	[emim][TfO]		 **92e**	61
6	[emim][TfO]		 **92f**	70[c]
7	[bmim][BF_4]		 **92g**	--[d]
8	[bmim][BF_4]		 **92h**	--[d]

[a] Products **92a 92e**, **92f** have been previously reported in the literature.[11c]
[b] Isolated products.
[c] Bisadduct **92f** [1,4-bis(3,6-dihydro-4,5-dimethyl-2*H*-thiopyranyl)benzene] was obtained with a ratio aldehyde:HMDST:diene = 1:4:4.
[d] Trimers were formed as major products.

All aromatic aldehydes react smoothly, and the reaction appears to be general (Table 8.1, entries 2-6). The yields were generally good, comparable with those obtained in traditional solvents, and a rate enhancement was observed in ionic liquids. Also aliphatic thioaldehydes were formed under the present conditions, but they demonstrated unreactive towards the diene, leading to the formation of trimers and oligomeric material (Table 8.1, entries 7, 8), thus confirming their low reactivity in Diels-Alder reactions.

Even though it is reported that ionic liquids usually are effective in promoting cycloadditions of carbon or nitrogen containing dienophiles,[15] in our case alkanethials proved to be unreactive, as already observed in traditional solvents.[11c]

Then we turned our attention towards the reaction with 1,3-cyclohexadiene in order to evaluate the stereochemical outcome of the cycloaddition. The reaction with thiobenzaldehyde, generated under $CoCl_2 \cdot 6H_2O$ or TfOTMS catalysis with aldehyde:HMDST ratio of 1:2, occurs with a high preference for the formation of the *endo* adduct **93** (Scheme 8.2, R = Ph), as previously observed by us in acetonitrile.[11c]



Scheme 8.2

When PhCHO and HMDST were reacted in equimolar ratio in the presence of TfOTMS as catalyst, the *endo* adduct was again the major isomer isolated. This result was different from what was previously obtained in CH_3CN, where the *exo* adduct was predominant when aldehydes/HMDST were used in 1:1 molar ratio under TfOTMS catalysis.[11c] This behaviour was observed with a representative series of differently substituted aromatic and heteroaromatic aldehydes (Scheme 8.2).

Finally, in order to verify whether ionic liquids could behave also as catalysts, aldehydes were treated with HMDST and the diene in different ILs. Whilst it is reported that Diels-Alder cycloadditions can be performed under ionic liquids catalysis,[15] no example is described of thionation induced by ILs.

A series of imidazolium derivatives were then used to study the effect of changing the alkyl chain and the nature of the anion, but only [emim][TfO] was able to promote the conversion of PhCHO and *p*-$CF_3C_6H_4CHO$ into the corresponding thioaldehydes, isolated as cycloadducts with cyclohexadiene, even in a little bit lower yield with respect the catalyzed reaction.

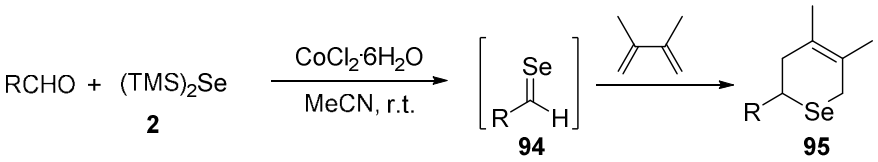
8.3 Synthesis of selenocarbonyl compounds in ILs

Selenium-containing heterocycles represent an interesting class of organic molecules both for their reactivity in organic synthesis and for their biological properties.[16] A convenient route to access these compounds can be envisioned in hetero Diels-Alder reactions[17] and, in this context, selenocarbonyl compounds are recognized as very reactive intermediates for the introduction of selenium into organic molecules, being able to act as a powerful 2π dienophiles in cycloaddition reactions.[18] Despite this interest, a limited number of synthetic methodologies for their preparation have been reported, mainly due to the instability of selenocarbonyl derivatives under the preparative conditions.[19]

Selenoaldehydes can be generated through base-catalyzed elimination reactions from α-silyl selenocyanates[20] or selenenyl derivatives,[21] by heating alkylidene phosphoranes with elemental selenium[22] or through reaction of ArLi with selenoformates.[23] The more convenient way to synthesize these compounds is probably the direct conversion of carbonyl compounds to selenocarbonyl. Methods based on the use of bis(diboryl)selenide,[24] bis(trimethylsilyl)selenide[25] **2** and bis(dimethylaluminium)selenide[26] under BuLi or Lewis acid treatment have been reported. Selenoaldehydes can be also generated by retro Diels-Alder reactions.[27]

Our group described a versatile procedure for the direct conversion of aldehydes into the corresponding selenocarbonyl derivatives exploiting the reactivity of HMDSS under suitable catalytic conditions. (Scheme 8.3).[25b] The *in situ* generated

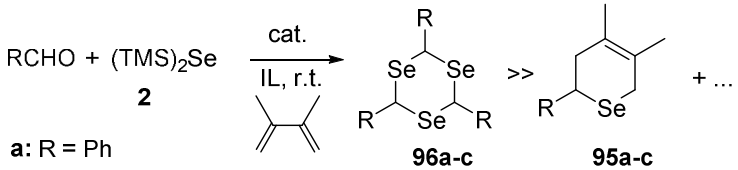
selenoaldehydes **94** were treated with dienes and the corresponding Diels-Alder adducts **95** were isolated.



Scheme 8.3

On the basis of these previous results and having demonstrated that ILs can behave as a suitable media to generate thioaldehydes and to their *in situ* trapping with dienes, we wondered whether the conversion of a carbonyl group in to the corresponding selenocarbonyl could be achieved in ILs.

Preliminary results showed that, when aldehydes were treated with HMDSS in presence of TfOTMS as catalyst and 2,3-dimethyl-1,3-butadiene as trapping agent in ILs, corresponding cycloadducts were isolated in rather low yield (18%). The same behaviour was observed reacting various aldehydes in different ILs ([bmim][BF_4], [bmim][PF_6], [emim][TfO]) under the same conditions (yields: 15-20%). When 1,3-cyclohexadiene was used the expected byciclic adduct was not formed. In all the cases 1,3,5-triselenane **96** - trimeric form of selenoaldehyde - was detected as the major reaction product, together with a variable amount of unknown by-products.



a: R = Ph

b: R = *p*CF_3-C_6H_4,

c: R = *o*CF_3-C_6H_4,

IL = [bmim][BF_4], [bmim][PF_6], [emim][TfO]

Scheme 8.4

significative yields improvements were not achieved neither by using $CoCl_2$ as the catalyst nor performing the reaction at different temperature.

8.4 Synthesis of other organoselenium compounds in ILs

With the aim deeply investigate the chemistry of HMDSS in ILs we evaluated its reactivity with three-membered heterocycles. As we discussed above (Chapter 1 and 4), treatment of epoxides, episulfides and aziridines with HMDSS under suitable conditions allowed a straightforward access to β-functionalised selenides, diselenides and selenols.

In a set of preliminary experiments, epoxides **3b**, **3c** and thiiranes **5b**, **5c** were treated with $(Me_3Si)_2Se$ in [bmim][BF_4] or [bmim][PF_6] in the presence of a catalytic amount of anhydrous TBAF. The wanted ring opening products were achieved (Chart 8.1).

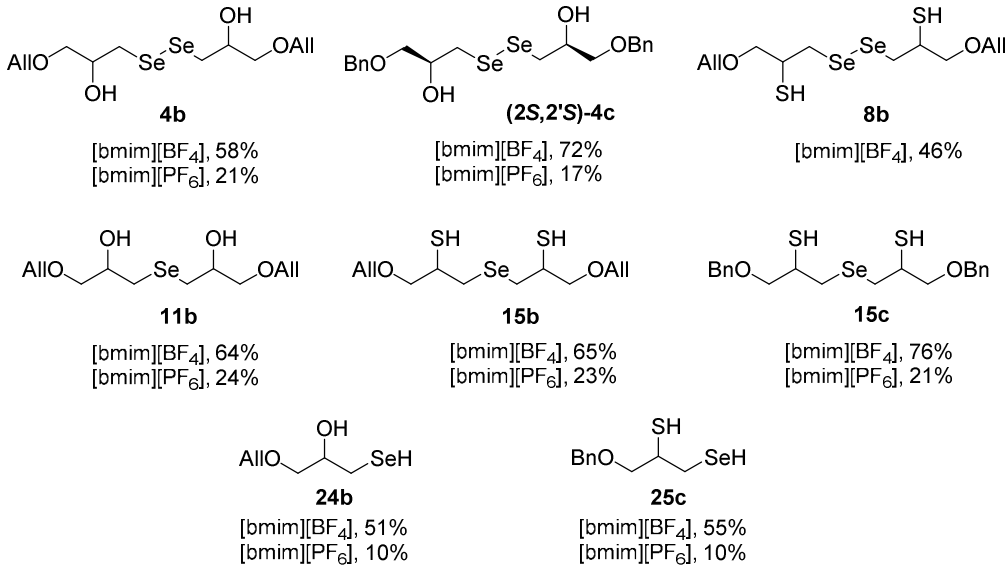


Chart 8.1. Synthesis of β-functionalised selenides, diselenides and selenols in ILs

Reactions were performed under the previously reported conditions (stoichiometry of reagents, temperature, time), using ILs instead of traditional organic solvents.

The ring opening reaction proved to be effective when [bmim][BF_4] was used as the reaction medium, being the wanted products obtained in rather good yield, despite lower than that observed carrying out the process in THF.

In order to begin a study on the IL effect on the chemistry of selenosilanes [bmim][BF_6] was tested as the medium for the described reactions. In this case all the products were formed in poor yields.

Preliminary results on the Lewis acid promoted reaction of **24b** and **25c** with aldehydes in [bmim][BF_4] showed that the synthesis of oxaselenolanes and thiaselenolanes is also possible in ILs.

8.5 Conclusions

In summary, we have shown that direct formation of thioaldehydes, and their trapping with dienes, are possible using ionic liquids as solvents under mild conditions, through reaction of silyl sulfide with aldehydes.

Theoretically, different interactions have to be considered for reactions in ILs, like for example the ability of the cation to act as hydrogen bond donor and the counter anion as hydrogen acceptor, solvent effects, as well as their basic or acid character.[28] Therefore various factors can affect the nucleophilic path, the fate of reaction intermediates (i.e. oxidation) and the behaviour of ILs as promoters of such processes. These effects are at present not fully understood, and further investigations will be necessary.

Preliminary results on the reactivity of $(Me_3Si)_2Se$ in ILs with different electrophiles have been also described.

Further studies to extend the described transformations to different substrates and to try to elucidate the interaction between the ionic liquids and the reagents are now under investigation

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Chapter 9

Synthesis of β-functionalised dialkyl tellurides and ditellurides

9.1 Introduction

The first organotellurium compound was reported more than 150 years ago with the synthesis of diethyl tellurides by Wöhler in 1840.[1] The area of organotellurium chemistry was slow to develop, but in the last 30 years, numerous books and reviews have appeared to cover the thousands of papers dealing with organotellurium compounds.[2] The organotellurium group can be introduced into organic substrates by either nucleophilic or electrophilic tellurium species. The nucleophilic organotellurium species can be produced from elemental tellurium by reaction with organolithium[3] or Grignard reagents.[4] Organotellurols can also be prepared by reduction of diorganoyl ditellurides.[5] Electrophilic organotellurium species can be prepared by reaction of an organic substrate with tellurium tetrachloride[6] or by halogenolysis of diorganoyl ditellurides.[7] The application of organotellurium compounds in organic synthesis has become attractive because of their chemio-, regio-, and stereoselectivity reactions.[8,9,10]

Recently a new application of vinylic tellurides utilizing palladium-catalyzed crosscoupling was reported.[11] In this case, they behave as aryl or vinyl carbocation equivalents. They react in a manner similar to vinylic halides or triflates in the Sonogashira,[12] Heck,[13] Suzuki,[14] and Stille[15] crosscoupling reactions with palladium as a catalyst.

Although the tellurium atom is generally regarded as a toxic metalloid, its role in biological systems has been reviewed.[16] Concerning organotellurium compounds little is known about their biological and pharmacological effects. Organotellurium compounds are readily oxidized from the divalent to the tetravalent state, consequently, tellurides can be studied as scavengers of reactive oxidizing agents such as hydrogen peroxide, hypochloride, and peroxyl radicals. In this context, several authors have described that substitution of selenium by tellurium in a series of diarylchalcogenides results in a pronounced increase in antioxidant activity.

Toxicity data on organotellurium compounds are still scarce in the literature. Although some authors have described that organotellurium compounds are less toxic than their selenium derivatives,[17] consistent data have indicated that organotellurium are more toxic than organoselenium compounds.[18-24]

Some organotellurium compounds have been described as inhibitors of thioredoxin reductase,[25,26] Glutathione peroxidase-like activity,[27,28,29] and chemopreventive activity[30,31,32] of a number of organotellurium compounds have been also reported.[33]

In the previous chapters we elucidated a versatile synthetic approach to β-functionalised thiols, selenides, diselenides and selenols through ring opening reactions of three-membered heterocycles with sulfur or selenium nucleophiles under controlled conditions. Among the 16th group elements, besides sulfur and selenium organic derivatives, also tellurium ones represent interesting systems for their synthetic applications and for their potential biological activities.

9.2 Results and discussion

On the basis of these considerations, and with the aim to compare the chemical behaviour of chalcogenides, we preliminary investigated the synthesis of tellurides and ditellurides through the reactivity of tellurium nucleophile species with three-membered heterocycles. To the best of our knowledge only a very few methods are described for the synthesis of β-amino tellurides and ditellurides.[34] Only two papers reported the synthesis of O-protected β-hydroxy ditellurides[35] and no example is available for OH free and SH derivatives.

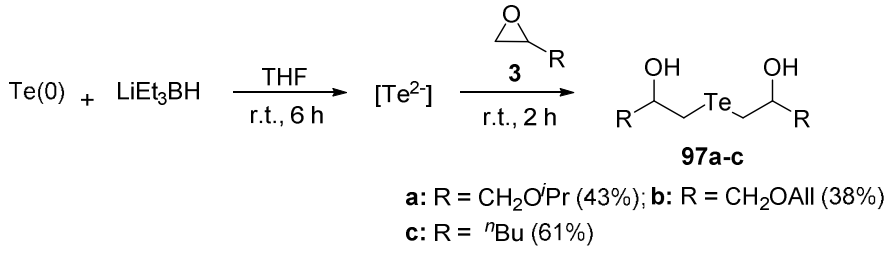
Elemental selenium is efficiently reduced by $NaBH_4$ to the corresponding dianion (Se^{2-}). Elemental tellurium does not react under these conditions. Nonetheless, Te^{2-} can be generated using lithium triethylborohydride ($LiEt_3BH$) as reducing agent.

Bis(trimethylsilyl)telluride, tellurated analogue of the deeply studied HMDST and HMDSS, can be synthesised treating *in situ* generated [Te^{2-}] with Me_3SiCl. Unfortunately, $(Me_3Si)_2Te$ is an unstable compound and - as reported by other -

rapidly decomposes on exposure to light, even if stored at low temperature and under inert atmosphere.[36]

The instability of this reagent and the difficulties encountered in handling it prompted us to directly react Te^{2-} with three-membered heterocycles.

We began our investigations with epoxides towards the synthesis of β-hydroxytellurides. Thus, elemental tellurium was treated with $LiEt_3BH$ to generate [Te^{2-}], *in situ* reacted with 2-(isopropoxymethyl)oxirane **3a**. The reaction regioselectively afforded the wanted 3,3'-tellurobis(1-isopropoxypropan-2-ol) **97** together with a complex mixture of byproducts. A partial decomposition was observed on silica gel, thence flash chromatography purification gave **97** in moderate yield (Scheme 9.1).



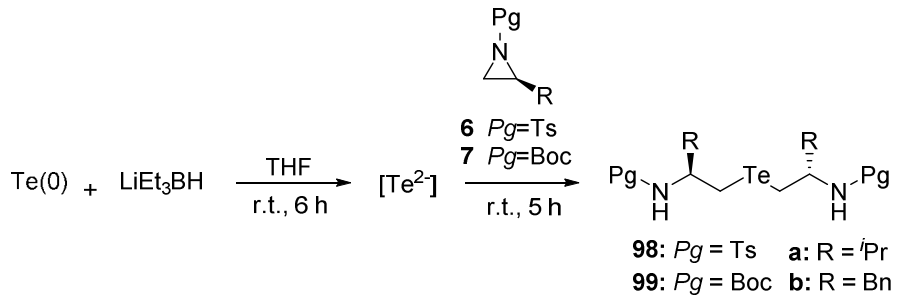
Scheme 9.1. Synthesis of β-hydroxy-tellurides. Reagent and conditions: elemental Te (1 eq.), $LiEt_3BH$ (2.1 eq.), epoxide (2 eq.).

Under the same conditions, differently substituted epoxides were reacted to yield the corresponding β-hydroxy telluride arising from a regioselective attack of the tellurated nucleophile on the less hindered side of the oxirane (Scheme 9.1).

Seeking for the generality of such synthetic approach to β-functionalised tellurides, we reacted *N*-protected aziridines under the above described conditions. A general access to substituted *N*-Boc and *N*-Tosyl β-amino tellurides (**98** and **99**, respectively) was found (Scheme 9.2).

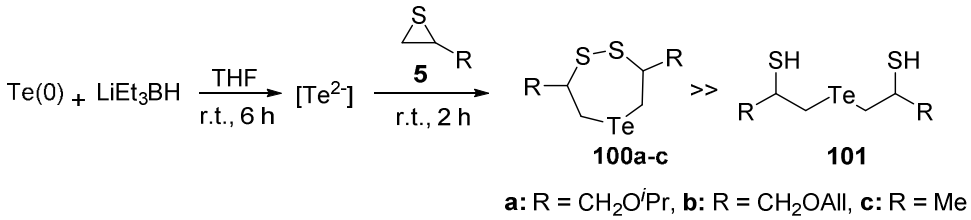
With the aim to extend this procedure to sulfur-containing derivatives, the behaviour of the more reactive thiiranes was studied. Thus, the *in situ* generated [Te^{2-}] was treated with 2-(isopropoxymethyl)thiirane **5a** under the conditions described in the Scheme 9.3. The reaction led to the regioselective formation of the 3,6-disubstituted 1,2,5-dithiatellurepane **100**, arisen from an oxidative

intramolecular disulfide bond formation, as the predominant product. The β-mercapto telluride **101** was obtained only in traces.



Scheme 9.2. Synthesis of β-amino-tellurides. Reagent and conditions: elemental Te (1 eq.), $LiEt_3BH$ (2.1 eq.), aziridine (2 eq.).

Despite the reaction was performed under different conditions (time, temperature, acid work-up), the seven-membered heterocycle was always isolated as major compound.



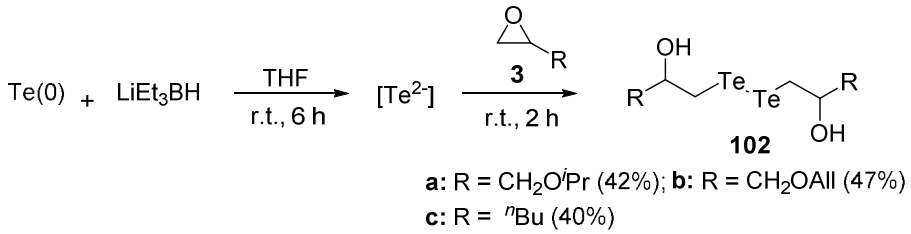
Scheme 9.3. Synthesis of disubstituted 1,2,5-dithiatellurepanes. Reagent and conditions: elemental Te (1 eq.), $LiEt_3BH$ (2.1 eq.), thiirane (2 eq.).

The procedure was extended to differently substituted episulfides and a general route to this novel class of telluro-heterocycles was disclosed.

Having demonstrated the possibility to obtain differently protected and functionlalised telluro-ethers through reaction of $[Te^{2-}]$ with three-membered heterocycles, we turned our attention on the synthesis of ditellurides. Elemental tellurium can be reduced to the ditelluride dianion $[Te_2^{2-}]$ by modifying the stoichiometry of the reaction with $LiEt_3BH$.

Once again, we began our studies with a screening reaction on 2-(isopropoxymethyl)oxirane **3a**. Elemental tellurium was treated with $LiEt_3BH$ under the conditions described in the Scheme 9.4 and the *in situ* generated $[Te_2^{2-}]$ was

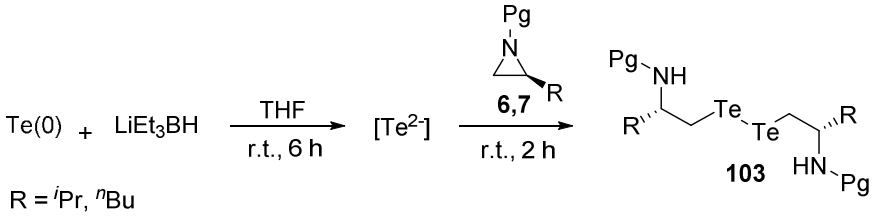
treated with **3a**. The corresponding β-hydroxy ditelluride **102a** was formed, together with a minor amount (< 10%) of the tellurides **97a**. Partial decomposition was observed on silica gel, thus isolation of pure **102** was achieved in moderate yield.



Scheme 9.4. Synthesis of β-hydroxy-ditellurides. Reagent and conditions: elemental Te (1 eq.), $LiEt_3BH$ (1 eq.), epoxide (1 eq.).

Differently substituted epoxides were reacted under the described conditions, affording the corresponding ditellurides (Scheme 9.4).

β-Amino ditellurides **103** could be achieved by reacting differently substituted *N*-protected aziridines under the same conditions (Scheme 9.5).



Scheme 9.5. Synthesis of β-amino-ditellurides. Reagent and conditions: elemental Te (1 eq.), $LiEt_3BH$ (1 eq.), aziridine (1 eq.).

Intriguingly, decomposition on silica was not observed for the β-amino tellurides and ditellurides.

9.3 Conclusions

In conclusion, we described our preliminary findings towards an easy and versatile procedure to incorporate tellurium atom into organic molecules through regioselective ring opening reactions of three-membered heterocycles. A fine tuning

of the reaction stoichiometry allowed a selective access to β-functionalised tellurides and ditellurides. This novel class of organotellurium compounds could find applications in organic synthesis and in biology. Very interesting preliminary results on the GPx-like activity of dithiatellurepanes were achieved.

Optimization of reaction conditions and of purification methods is under investigation. Studies on the possible catalytic role of chiral β-functionalised tellurides and ditellurides in asymmetric transformations are currently ongoing in our laboratories.

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Chapter 10

GPx-like activity of organoselenium and organotellurium compounds

10.1 Introduction

Interconversion reactions between thiols and disulfides are important chemical processes involved in many biological phenomena, such as antioxidant functions of cells against reactive oxygen species[1] and the oxidative folding of proteins having several disulfide (SS) bonds.[2] Modeling these processes by using small organic molecules is important for elucidation of the phenomena, which in reality are regulated by a complex system comprising a number of enzymes and substrates, at the atomic and molecular resolutions.[3]

Organic selenides and selenoxides can be easily inter-converted by using hydrogen peroxide and thiols as the oxidizing and reducing reagents, respectively (Figure 10.1, reactions A and B).

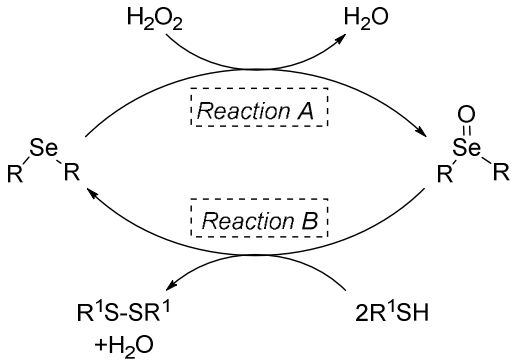


Fig. 10.1 Organoselenium catalysed oxidation of thiols

The redox reactions normally proceed rapidly and quantitatively, hence the selenide-selenoxide chemistry would be applied to regulation of the redox states in various biological as well as the mimic systems that include thiol and disulfide species.[4]

Organic selenides have frequently been applied as synthetic mimics of glutathione peroxidase (GPx), a selenium containing antioxidant enzyme catalyzing

the reduction of hydroperoxides at the expense of two molecules of glutathione (GSH).[4b,5]

GPx is the first selenoprotein discovered in mammals and one of the most studied because of its central role in the defense against the oxidative stress.

Oxidative stress is essentially due to i) an increased oxidant generation, ii) a decreased antioxidant protection and iii) a failure in repairing oxidative damage. Cell damage is induced by reactive oxygen species (ROS). The main source of ROS *in vivo* is aerobic respiration and the main damage to cells results in the alteration of some macromolecules such as polyunsaturated fat acids in membrane lipids, proteins and DNA. Besides ROS, also reactive sulfur species (RSS) and reactive nitrogen species (RNS) are known to be responsible of cells damage.

A number of human diseases such as cancer, neurodegenerative pathologies, inflammation, immune disorder, atherosclerosis, cystic fibrosis[6,7] have been correlated to the reduced ability of the radical scavenging systems on balancing the ROS production.

Thus, redox chemistry of organoselenium compounds has attracted increasing interest in relation to their biochemical applications and the synthesis of small organoselenium compounds able to reproduce the antioxidant activity of glutathione peroxidase is highly sought after.

For example, selenomethionine, a selenium analog of amino acid methionine, was demonstrated to have an antioxidative catalytic activity[8] and has been widely applied as an anticancer reagent or an antioxidant.[9] Bis(3-hydroxypropyl) selenide and the related selenide compounds were recently found to exhibit strong antioxidative catalytic activities as GPx mimics.[4,10] Redox reactions of many other selenides have also been investigated.[4,11] Iwaoka *et al.* recently synthesized and demonstrated the GPx mimic activity of trans-3,4-dihydroxyselenolane (DHSred), and of the corresponding selenoxide (DHSox). The latter proved to be a powerful oxidant for the rapid and quantitative transformation of cysteinyl thiol groups into the disulfide (SS) bond over a wide pH range.[12]

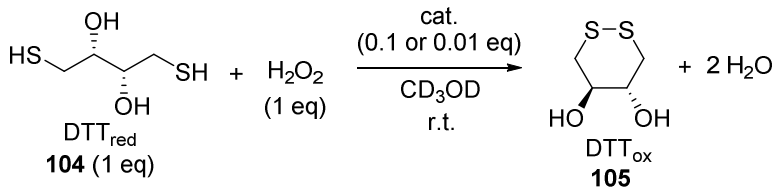
Ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)one) and Ebselen analogues have been widely studied and their GPx-like activity evaluated. Several ciclic and open

chain diselenides, selenides, selenolates, selenoxides were also reported as GPx mimics. [5b,13]

In literature, several methods for the evaluation of GPx-like activity have been reported. Procedures based on spectrophotometrical measurement of the concentration of cofactors or substrates involved in the redox process have been developed.[5b,13,14] Some NMR based assays have also been reported.[12,15] These methods are based on the determination of the time required to reduce a thiol concentration of 50% in the presence of a stoichiometric amount of H_2O_2 and a catalytic amount of an organoselenium compound. A number of thiols such as *N*-acetylcysteine, tert-butyl mercaptan and 1-octyl mercaptan were used in these assays and showed low oxidation rates. Iwaoka and co-workers reported a similar test with the dithiotreitol (DTT) and CD_3OD as the solvent. Santi *et al*. recently modified this procedure using D_2O in order to obtain experimental conditions closer to the physiological one.[15b]

10.2 Results and discussion

During the course of our studies in the selenium chemistry we disclosed synthetic routes to access several classes of novel interesting organoselenium derivatives. This might offer the possibility to design new GPx mimics. Catalytic activity of such compounds was investigated following the dithiothreitol (DTT_{red}) oxidation by the mean of ^1H NMR. Methanol (CD_3OD) was selected as a solvent in this assay because the reaction proceeded too fast in water and its monitoring by ^1H NMR spectroscopy resulted challenging.



Scheme 10.1: DTT oxidation

We began our investigations with compound **11b**. In the series of the ^1H NMR spectra (Figure 10.2), the absorptions at δ = 2.63, 3.67 ppm due to DTT_{red} decreased

with increasing reaction time, whereas those at δ = 2.87, 3.03, 3.49 ppm due to DTT_{ox} increased. Thus, **11b** behaves as a catalyst in promoting oxidation of DTT under these conditions. β-Hydroxy- dialkyl selenides and diselenides synthesised as described above were then tested in these preliminary studies. Compounds **4b**, **11b** and **11c** showed catalytic activity and complete oxidation of DTT was observed within 150-180 min. 0.5 value of DTT_{red}/DTT_{ox} is reached in 50-60 min. Data of these measurements are reported in Fig. **10.3**. As the control experiment DTT was treated with hydrogen peroxide in CD_3OD and almost 90% of unreacted DTT_{red} was detected after 250 min.

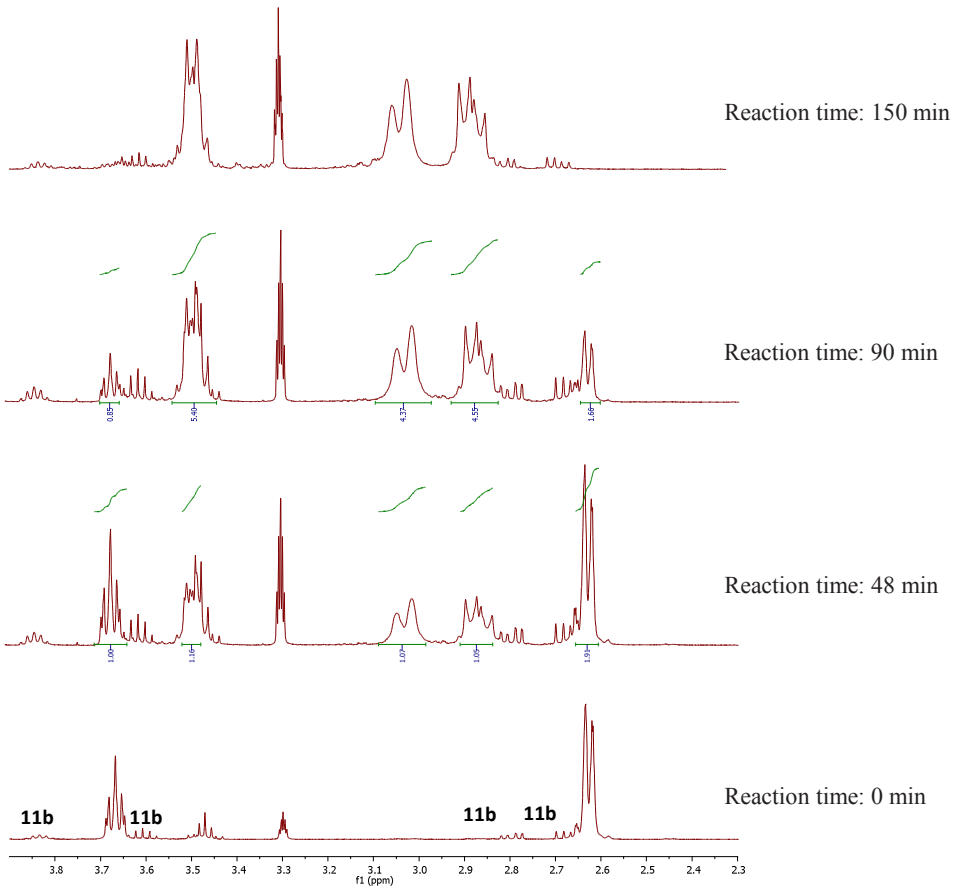


Fig. 10.2. A series of 400 MHz ^1H NMR spectra obtained in the oxidation of DTT_{red} (0.15 mmol) with H_2O_2 (0.15 mmol) in the presence of catalytic amount of **11b** (0.015 mmol) in CD_3OD at 25 °C.

N-Tosyl β-amino diselenides proved to be less active catalysts and after 180 min 40% of DTT_{red} was still remaining.

Dithiaselenepanes were also evaluated. When **19e** was used as a catalyst, complete oxidation of DTT was achieved in only 50 min. The more hindered **19c** showed a lower activity than **19e** but comparable with respect to the open chain selenides **11b** and **11c**.

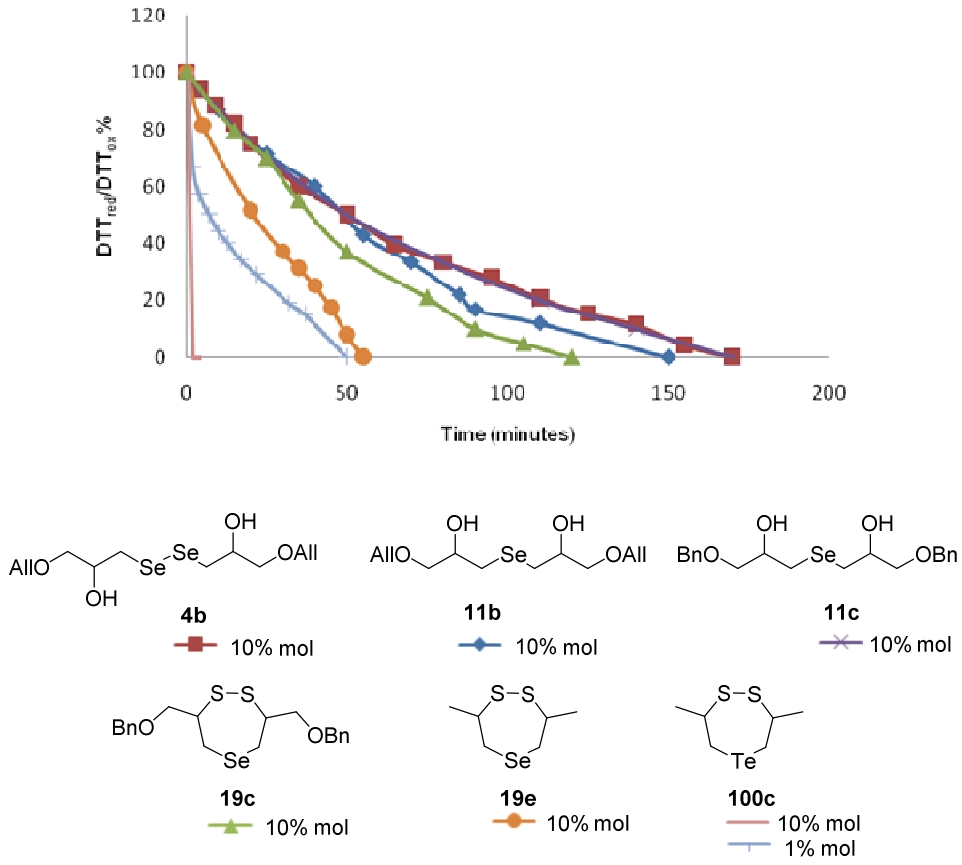


Fig. 10.3. Percentages of residual DTT_{red} as a function of the reaction time in the oxidation of DTT_{red} with H_2O_2 in the presence of selenium or tellurium containing catalysts in CD_3OD

GPx like activity of a number of organotellurium compounds have been also described.[16].Thus, we tested the dithiatellurepane **100c**, the tellurium containing analogue of **19e**, and instantaneous complete oxidation of DTT was observed when

10% mol of **100c** were used. On the basis of these results we performed the reaction using 1% mol of Te-catalyst **100c** and complete DTT_{red} conversion was obtained after 50 min, evidencing a strong activity of this thia-telluro heterocycle.

Interesting catalytic activities have been observed when substituted 3,4-dihydro-2*H*-selenopyranes were used (Fig. 10.4). Compounds **95b** and **95e** (10% mol) were tested under the above-described conditions and complete oxidation of DTT was detected within 25-30 min. The high oxidation rate of DTT observed using 10% mol of **95d** or **95f** as catalysts (almost instantaneous reactions) prompted us to decrease their amount. Thus, when the assays were carried out with 1% mol of **95d** or **95f** complete DTT_{red} conversion was obtained in 28-35 min, revealing that - according to this test - these systems behave as effective GPX mimics.

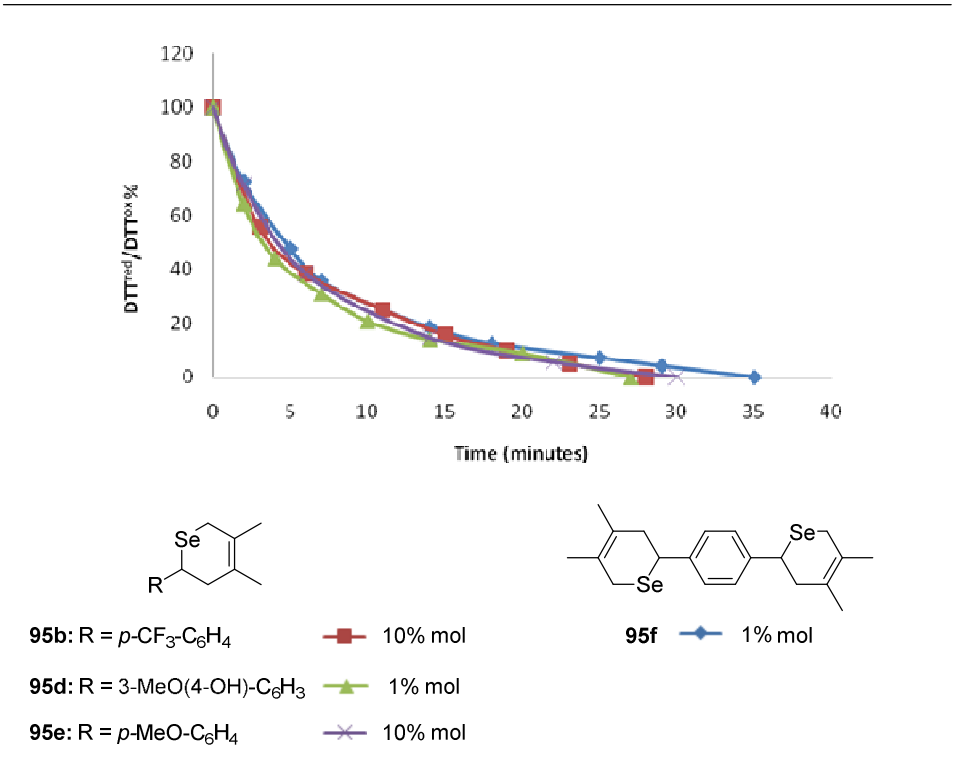
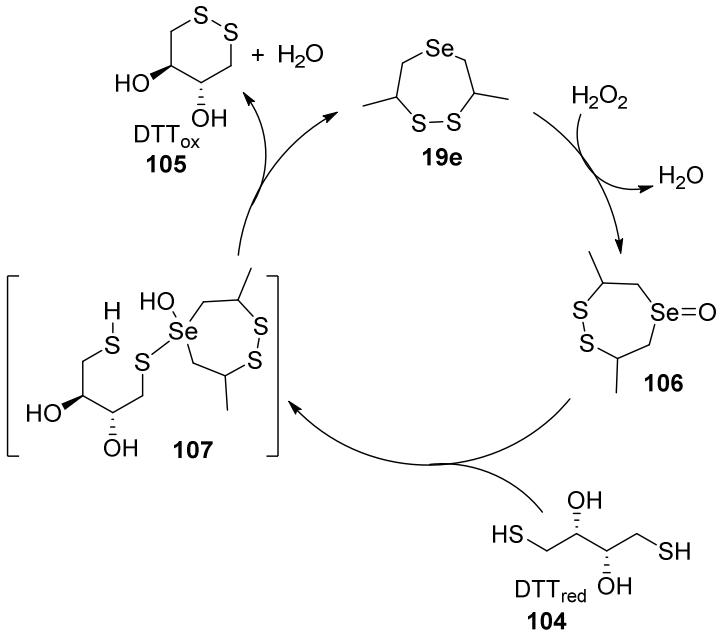


Fig. 10.4. Percentages of residual DTT_{red} as a function of the reaction time in the oxidation of DTT_{red} with H_2O_2 in the presence of 3,4-dihydro-2*H*-selenopyranes **95** as catalysts in CD_3OD

Summarising, cyclic selenides exhibited higher GPx-like than open chain organoselenium compounds. These results are not surprising and are consistent with Iwaoka's findings, where higher reactivity of cyclic systems has been related to the elevation of the HOMO energy levels.[12]

The probable catalytic cycle of **19e** is reported in the Scheme 10.2 and it follows that proposed by Iwaoka *et al.* The first step (rate determining) produce the selenoxide **106** and H_2O. **106** is highly reactive and is rapidly captured by a thiol group of DTT_{red} with the consequent formation of the intermediate selenenyl sulfide **107**. The final step, with the attack of the second thiol moiety on **107**, regenerates the catalyst **19e** and produces DTT_{ox} **105** and H_2O. A similar cycle can be proposed for the other Se-catalysts and for the dithiatellurepane **100c**.



Scheme 10.2. Catalytic cycle of **19e** for oxidation of DTT with hydrogen peroxide

10.3 Conclusions

In conclusion, we reported a preliminary evaluation of GPx-like activity of some novel organoselenium compounds. Interesting results were achieved, especially when cyclic selenides were tested. According to these assays 6- and 7-membered

selenium containing heterocycles behave as effective GPx mimics. The synthetic routes to access these compounds have been described above and its versatility may be a key to design small molecules bearing suitable moieties with the aim of improving their biological activities or important properties such as their solubility in aqueous matrices. Studies on GPx-like activity of different organoselenium compounds as well as the synthesis of new antioxidant systems are still ongoing projects in our group.

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Chapter 11

Benzoselenophenes and benzothiophenes from resveratrol: synthesis and antioxidant properties

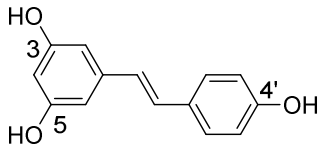
11.1 Introduction

Resveratrol ((*E*)-3,5,4'-trihydroxystilbene) is an extensively investigated polyphenolic phytoalexin of grapevines originally isolated from the roots of white hellebore.[1] Following its implication in the low incidence of heart disease purportedly associated with a high consumption of red wine –the "French paradox"[2]- it has become the focus of unabated interest over the past decades due to a broad range of beneficial activities for human health, including anticarcinogenic and antitumor properties,[3,4] protection against cardiovascular diseases,[5,6] atherosclerosis[7,8] and neurodegenerative diseases.[9] To a significant degree, most of these properties have been shown to depend on the potent antioxidant activity of this peculiar polyphenol derivative,[10-14] which has been considered as a dietary supplement and a candidate for drug development. Accordingly, considerable interest has been directed to studies of structure-activity relationships in diverse series of resveratrol derivatives, both to understand the mechanism of the powerful antioxidant activity and to provide a rational background to the design of compounds with better antioxidant properties.[15-17]

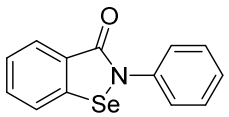
Several reports from different laboratories have demonstrated that the 4'-OH group, exhibiting a superior H-atom transfer and peroxyl radical scavenging capacity compared to resorcinol-type functionalities, and the specific geometry of the double bond are the basic structural elements underpinning the outstanding antioxidant activity of resveratrol.[12,18,19]

Based on these results, several strategies have been pursued to improve both the health impact and the absorption and bioavailability of resveratrol through rational chemical modification approaches, such as introduction of methoxy or allylic groups, metal chelating moieties or triazole rings.[20-25] Previous studies have shown that chalcogen-based functionalization represents a most useful, yet little explored,

strategy to enhance or modulate the antioxidant capacity of phenolic compounds.[26-33] In this regard, the utility of selenium-substitution to enhance the chain breaking activity of phenolic compounds via a decrease in the bond dissociation enthalpy (BDE) values of phenolic groups has been documented in the case of butylhydroxyanisole and dihydrobenzoselenophen-5-ol derivatives.[34,35] Moreover, a number of organic selenium derivatives have been shown to behave as catalytic antioxidants able to mimic the action of the Se-enzyme glutathione peroxidase (GPx-like activity),[36-38] Ebselen being the most famous member of this family of compounds.



Resveratrol



Ebselen

Selenium is moreover a nutritionally relevant trace element involved in different physiological functions and compounds containing selenium have antitumoral, antioxidant and chemopreventive properties. The formation of selenium-containing compounds, rather than the element itself, has been reported to be critical for biological activities.[39] Organoselenium compounds are less toxic than inorganic selenium derivatives, and are involved in antioxidant defense systems and in cancer prevention.[40]

We disclose a simple and straightforward entry to resveratrol modification leading to unprecedented 2-phenylbenzoselenophene derivatives with enhanced and multifunctional antioxidant activity with respect to the parent compound.

11.2 Synthesis of benzoselenophenes. Results and Discussion

11.2.1. Preparation of the benzoselenophene derivatives. Since the resveratrol structure features π-nucleophilic sites at both aromatic rings, especially at the resorcinol moiety bearing two *meta* phenolic groups, and at the stilbenic double bond, an electrophilic approach to selenenylation was deemed the most convenient

option. To this aim, the attention was directed to synthetic methodologies that allow the use of simple readily available starting materials and, above all, that avoid the need for protection of the phenolic groups, a key requirement for facile and scalable procedures. Although selenenyl electrophiles, such as Se_2Cl_2 and $SeCl_4$, are commercially available, they are not easy to handle and store and are known to disproportionate in solution to afford mono-chalcogens dihalides and oligo-chalcogens dihalides along with Se(0) and Cl_2 (reactions 1-3).[41] Reaction with $SeCl_2$ generated *in situ* by reacting Se(0) with SO_2Cl_2 as previously reported[41] (reaction 4) was therefore preferred because of the easily available reagents and expedient operational conditions.

$$SeCl_4 \rightleftharpoons SeCl_2 + Cl_2 \quad (1)$$

$$5\ Se_2Cl_2 \rightleftharpoons 2\ SeCl_2 + SeCl_4 + Cl_2 + 7\ Se \quad (2)$$

$$3\ SeCl_2 \rightleftharpoons Se_2Cl_2 + SeCl_4 \quad (3)$$

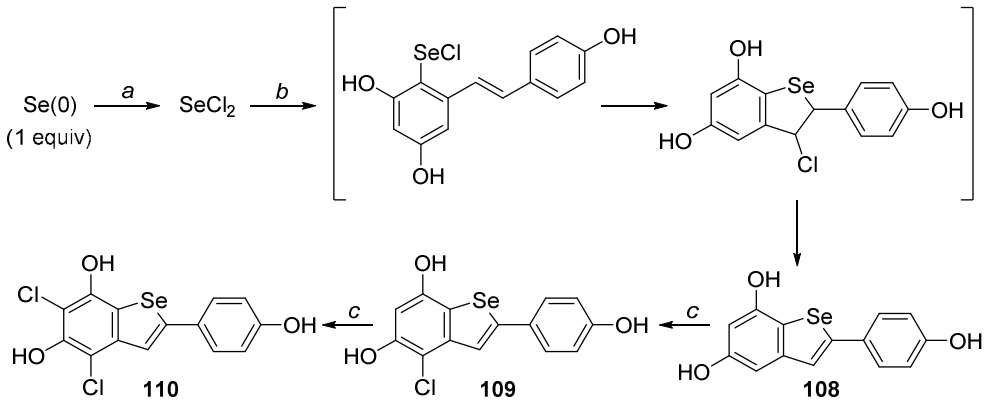
$$Se + SO_2Cl_2 \longrightarrow SeCl_2 + SO_2 \quad (4)$$

$$SO_2Cl_2 \rightleftharpoons SO_2 + Cl_2 \quad (5)$$

The solvent suggested for this transformation was THF that also minimizes the aforementioned disproportionation processes.[41] This introduced a further synthetic challenge since unprotected resveratrol is almost unsoluble in THF. After a non-trivial screening, we found out that reacting Se(0) (1 equiv) with 2 equiv of SO_2Cl_2, neat for 10 min for SO_2 evolution, then in dry THF, followed by addition of resveratrol (0.4 equiv) in dry DMF, the polyphenol was consumed after 20 h at rt. Work-up and purification by column chromatography of the dark brown crude material obtained allowed the isolation of 4,6-dichlorobenzo[*b*]selenophene **110** in 82% yield (Scheme 11.1).

Compound **110** was fully characterized by means of ^{1}H, ^{13}C and ^{77}Se NMR, showing no aliphatic but only 5 aromatic hydrogens, 12 non-equivalent aromatic carbons along with a single Se atom. ESI-MS in negative ion mode confirmed the presence of a single Se atom and indicated the presence of two chlorine atoms.

In the light of the other benzoselenophenes we were able to isolate varying the reaction conditions, *vide infra*, a mechanism can be proposed for the formation of **110** involving *in situ* formation of selenium dichloride ($SeCl_2$, reaction 4). This latter would react with the most nucleophilic position of resveratrol on the 3,5-dihydroxysubstituted aromatic ring *via* an electrophilic aromatic substitution (S_EAr) to give an arylselenyl chloride that, in turn, would undergo an electrophilic addition to the pendant double bond affording a 2,3-dihydro-3-chlorobenzoselenophene. This latter would reasonably aromatize by HCl elimination leading to the benzo[*b*]selenophene **108** (Scheme 11.1). Due to the presence of Cl_2 in the reaction mixture[42,43] a subsequent chlorination of **108** may be envisaged to give the monochloride **109** and the dichloride **110** (Scheme 11.1).



a: i) SO_2Cl_2 (2.0 equiv), neat, 10 min, r.t., ii) dry THF, 1h, r.t.,
b: Resveratrol (0.4 equiv), dry DMF, 24h, r.t., *c*: Cl_2

Scheme 11.1. Proposed mechanism for the one-pot formation of selenophenes **108, 109** and **110** from the reaction of resveratrol with $Se(0)/SO_2Cl_2$.

The order of the two electrophilic reactions, *i.e.* the S_EAr and the addition to the double bond, was likely to be that depicted in Scheme 11.1 since the formation of **108** derivatives would reflect an *anti*-Markovnikov addition to the electron-rich stilbenic double bond, and this is much conceivable if it occurs intra-molecularly after the S_EAr, instead that inter-molecularly as the first step of the sequence. The actual intermediacy of **108** in the process has been demonstrated in separate experiments in which the formation of chlorinated selenophenes **109** and **110** was

observed by reacting isolated **108** (*vide infra*) with 1.0 equiv of Se(0) and 1.2 equivs of SO_2Cl_2 at rt overnight. However, the possibility that some **109** and **110** are formed through an initial chlorination of the resorcine moiety followed by the selenophene ring closure cannot be ruled out. Since we were unable to isolate any intermediate, we cannot rule out the possibility that species different from $SeCl_2$ generated by reaction of Se(0) with SO_2Cl_2 are involved in the formation of selenophenes. However, reacting resveratrol with commercial available Se_2Cl_2, under conditions similar to those reported in Scheme 11.1, did not allow isolation of any selenophene, either chlorinated or chlorine free. On the other hand, using $SeCl_4$ **110** was obtained *albeit* in very low yield (10-15%) demonstrating the superiority of the above adopted procedure for the synthesis of resveratrol derived selenophenones.

The possibility of transforming unprotected resveratrol into a chlorinated trihydroxy benzo[*b*]selenophene **110** under one-pot conditions is certainly interesting both for the simplicity of the synthetic procedure, when compared with those available for the preparation of benzoselenophenes, and for the possible antioxidant activity of the Se-resveratrol derivatives. In fact, although several methods are described for the synthesis of benzoselenophene derivatives,[44-47] the most efficient ones are based on electrophilic intramolecular cyclization of alkynyl-selenoarenes.[48,49] To the best of our knowledge no example is reported on the reaction of stilbenes with an electrophilic selenenyl species to obtain benzoselenophenes.

Considering the potential utility of resveratrol-selenium derivatives as multifunctional antioxidants, the presence of two chlorine atoms in *ortho* position to the phenolic groups was not ideal since they would be expected to increase the bond dissociation enthalpy (BDE) of phenolic OH's by accepting intramolecular H-bond, thus decreasing their ability as hydrogen radical donors and hence their aptitude as chain breaking antioxidant in lipid peroxidation.[50] Thus we decided to study in more details the reaction reported in Scheme 11.1 trying to optimize the conditions that maximize the formation of mono-chlorinated **109** or, even better, non-chlorinated selenophene **108**. Modification of parameters as time, solvent, and temperature, gave poor results, while the stoichiometry ratio between Se(0) and

SO_2Cl_2 proved to be crucial for modulating the relative amount of the various benzoselenophenes. As reported in Table 11.1, using a 1:1 ratio between Se(0) and SO_2Cl_2 and again 0.4 equiv of resveratrol, **109** became the major product and could be isolated in 71% yield after column chromatography. On the other hand, working with [Se:SO_2Cl_2:resveratrol] at molar ratios as [1:0.8:0.4], the bis-chlorinated derivative was formed only in trace amounts, the non-chlorinated derivative **108** being the major product isolated in almost 50% yield (Table 11.1). Decreasing further the amount of SO_2Cl_2, even for longer reaction times, the residual starting resveratrol becomes significant with no real advantages in terms of **109**:**108** ratio and final yields.

Table 11.1. Optimized Stoichiometry Ratios for the Isolation of 110, 109 and 108.

Entry	Se(0) equiv	SO_2Cl_2 Equiv	Resveratrol equiv	Products	Yield (%)[a]
1	1.0	2.0	0.4	**110**	82
2	1.0	1.0	0.4	**109:110** = 85:15	71
3	1.0	0.8	0.4	**108:109**= 70:30	48

[a]Isolated yields of major product

Selenophenes **109** and **108** were fully structurally characterized by NMR (^1H, ^{13}C, ^{77}Se) and with **110** considered for their antioxidant activities as reported in the next paragraphs.

11.2.2. 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. The hydrogen donor capacity of the selenophenes **108**, **109**, **110** was assessed through the DPPH assay,[51] which measures the ability of the test compound to reduce the colored and stable DPPH radical against a suitable reference donor (typically Trolox, i.e 6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid). The time course experiments of DPPH bleaching, reported in Figure 11.1, show that all the selenophene derivatives

are more efficient than resveratrol tested under the same conditions. Notably, the percentage of DPPH reduced after 10 min in the case of **108** was nearly comparable to that obtained with Trolox. The superior activity of selenophenes is apparent also from the data analysis (Table 11.2), with a ca. four-fold increase of the rate constant for the H-atom transfer in the fast step (k_1 value) in the case of **108** with respect to resveratrol. As in methanol the reaction between DPPH and phenols is mainly governed by a sequential proton loss-electron transfer mechanism,[52] we suppose that the facilitated reaction with DPPH is due to a combined effect of the Se and Cl-atoms on the oxidation potentials of the selenophenes. The stoichiometry for DPPH trapping provides information about the fate of the oxidized products of **108** and Trolox, the only instances in which the reaction is complete after 10 minutes (see Figure 11.1). The "classical" antioxidant mechanism (*vide infra*) requires that each phenolic ring traps two radicals, so we suggest that the stoichiometry of 3.68 and 3.54 found for Trolox and **108** indicates that the products are still capable of reacting with DPPH.[53]

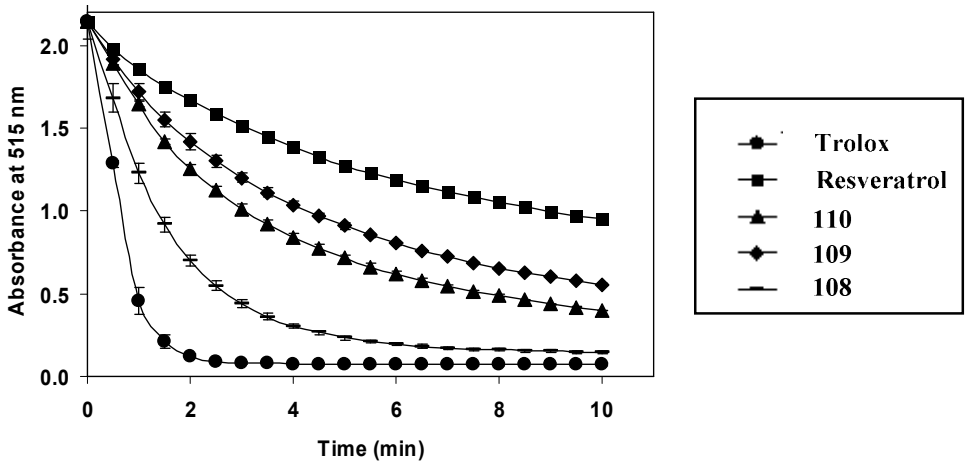


Figure 11.1. Decrease in the absorbance at 515 nm of 200 μM DPPH in the presence of 50 μM selenophene compounds, resveratrol or Trolox in methanol. Reported are the mean ± SD values for three separate experiments.

11.2.3. Ferric reducing/antioxidant power (FRAP) assay. The reducing capacity of the selenophene derivatives was measured by the FRAP assay.[54] Table 11.3 reports the results expressed as Trolox equivalents. **108** again showed activity comparable to that of Trolox, while the chlorinated derivatives **109** and **110** proved less efficient as expected, although still more active than resveratrol.

Table 11.2. H-atom Transfer Reaction from Selenophenes (50 μM each) to DPPH (200 μM) in comparison to resveratrol and Trolox.[a]

Antioxidant	DPPH reduced (%)[b]	k_1 (M^{-1} s^{-1})[c]	n_{tot}[d]
110	81.3 ± 0.1	142 ± 13	3.10 ± 0.01
109	74.1 ± 0.4	146 ± 21	2.82 ± 0.02
108	93.1 ± 0.1	340 ± 16	3.54 ± 0.01
Resveratrol	55.6 ± 0.9	87 ± 3	2.12 ± 0.27
Trolox	96.5 ± 0.4	491 ± 5	3.68 ± 0.02

[a]Values are means ± SD (n=3).

[b]Calculated after 10 min of reaction.

[c]Rate constant for the fast step.

[d]Number of H-atoms transferred after 10 min.

Table 11.3. Fe^{3+} Reducing Activity of the Selenophene Derivatives in Comparison to Resveratrol. Results are expressed as Trolox equivalents.

Antioxidant	Trolox equivalents[a]
110	0.63
109	0.84
108	0.94
Resveratrol	0.56

[a]Values are means of two separate experiments (SD≤5%).

11.2.4. Inhibited autoxidation studies. The chain-breaking antioxidant activity of the title compounds was assessed by evaluating the ability to inhibit the autoxidation of an organic substrate (reactions (6)-(11).[55] Among the methods used to quantify antioxidant efficacy, inhibited autoxidation studies more closely mimic the reactions involved in the oxidative degradation of biological molecules such as unsaturated lipids in membranes.[55] The experiments were performed by studying the inhibited autoxidation of styrene in chlorobenzene or acetonitrile (50% v/v) at 303 K, initiated by AIBN (0.05 M), in the presence of variable amounts of the compounds **108**, **109**, **110** and resveratrol (indicated as ArOH in eqs (10)- (11)). These measures afforded the rate constants for the reaction with peroxyl radicals (reaction (10), k_{inh}) and the number of radicals trapped by each antioxidant molecule, that is the stoichiometric coefficient *n*. 2,2,5,7,8-Pentamethyl-6-chromanol (α-TOH), an α-tocopherol analogue lacking the phytyl tail, was used as reference antioxidant.[55]

$$\text{Initiator} \xrightarrow{R_i} \text{R}\cdot \qquad (6)$$

$$\text{R}\cdot + \text{O}_2 \longrightarrow \text{ROO}\cdot \qquad (7)$$

$$\text{ROO}\cdot + \text{RH} \xrightarrow{k_p} \text{ROOH} + \text{R}\cdot \qquad (8)$$

$$\text{ROO}\cdot + \text{ROO}\cdot \xrightarrow{2k_t} \text{Non-radical products} \qquad (9)$$

$$\text{ROO}\cdot + \text{ArOH} \xrightarrow{k_{inh}} \text{ROOH} + \text{ArO}\cdot \qquad (10)$$

$$\text{ROO}\cdot + \text{ArO}\cdot \longrightarrow \text{Non-radical products} \qquad (10)$$

The autoxidation was followed by monitoring the oxygen consumption in an oxygen uptake apparatus based on a differential pressure transducer (Figure 11.2). The slope of the oxygen consumption trace during the inhibited period afforded k_{inh} values, while its length allowed the determination of the stoichiometric coefficient (Table 11.4).

In the apolar solvent chlorobenzene, the k_{inh} values of the selenophene derivatives are larger than that of resveratrol, the order being **108**>**109**>**110**>resveratrol. This reactivity order is believed to derive from two overlapping effects: the electron-donating activity of the Se-atom, which causes a lowering of the BDE of the phenolic OH groups, and the H-bond accepting ability of chlorine atoms which increases the BDE of the nearby OH groups.[57]

To explore the effect of solvent polarity, autoxidation experiments were performed in acetonitrile. Compared to chlorobenzene, a reactivity decrease was observed, showing that the reaction between resveratrol derivatives and ROO• is a H-atom transfer reaction which occurs only with the OH groups that are not H-bonded to the solvent.[57] In acetonitrile the reactivity order is **109** ≥ **110** > **108** > resveratrol, reasonably because in the chlorinated derivatives the OH groups are protected from the solvent by the intramolecular H-bond with the Cl-atom.[57]

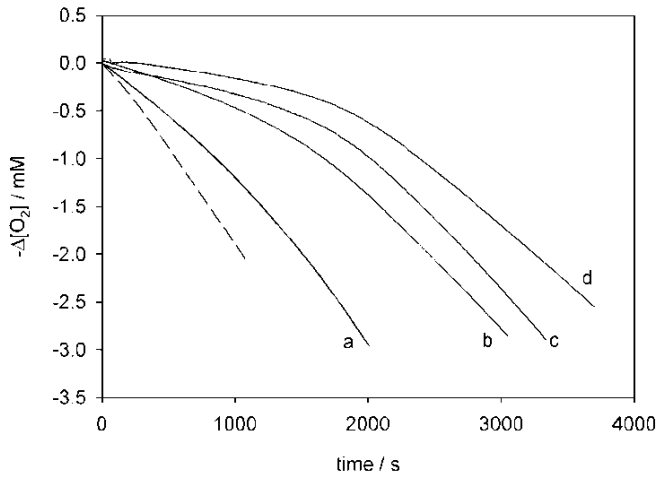


Figure 11.2. Oxygen consumption measured during the autoxidation of styrene (4.3 M) in chlorobenzene initiated by AIBN (0.05 M) at 30°C in the absence of antioxidants (dashed line) and in the presence of: a) resveratrol 7×10^{-6} M; b) **110** 1.5×10^{-5} M; c) **109** 1.9×10^{-5} M; d) **108** 1.9×10^{-5} M.

Autoxidation experiments in chlorobenzene also provided the stoichiometry of the radical trapping, which in all the Se-containing compounds was significantly smaller than 2, that is the value expected for antioxidants acting by reactions (10) and (11) (i.e. by H-atom transfer followed by radical-radical recombination).[55] It may be suggested that under autoxidation conditions, i.e. in the presence of peroxyl radicals and hydroperoxides, the selenated compounds are partially converted into Se-oxides, which are expected to be poor antioxidants (*vide infra*).

Table 11.4. Results from Autoxidation Studies in Chlorobenzene and Acetonitrile: Rate Constants for the Reaction with Peroxyl Radicals (k_{inh}) at 30 °C and Number of Radicals trapped (n).

Antioxidant	$k_{inh}/10^5$ ($M^{-1}s^{-1}$)		n^a
	Chlorobenzene	Acetonitrile	Chlorobenzene
108	8.8 ± 1.8	0.24 ± 0.02	0.66 ± 0.06
109	4.9 ± 0.4	0.48 ± 0.05	0.83 ± 0.13
110	3.5 ± 0.5	0.44 ± 0.04	0.85 ± 0.09
Resveratrol	1.8 ± 0.2	0.10 ± 0.02	1.6 ± 0.2
α-TOH	32[b]	6.8[c]	2[b]

[a] n values were measurable only in chlorobenzene

[b] From ref. [55]

[c] From ref. [56]

Kinetic data with peroxyl radicals in chorobenzene are in agreement with the results of the DPPH assay in indicating that the selenophenes are more reactive than resveratrol, but less than the α-tocopherol derivatives. However, the reactivity order among the selenophenes varies with the solvent, as effect of the interplay between the solvent characteristics and the different reaction mechanisms for the reaction with ROO• and DPPH radicals.

11.2.5. DFT calculations. To obtain deeper insight into the antioxidant activity of the title compounds, the BDE of the phenolic O-H bonds was investigated by DFT calculations at the B3LYP/LANL2DZdp level. The BDE(OH) values were obtained by using an isodesmic approach, that consists of calculating the ΔBDE between the investigated compounds and phenol, and by adding this value to the known experimental BDE(OH) of phenol in benzene (86.7 kcal mol^{-1}).[58,59]

This procedure has been previously tested with phenols having alkyl-selenium substituents in *ortho* or *para* positions, and it reproduced experimental BDE(OH) values within ± 0.3 kcal/mol, so it was expected to provide accurate BDE values for

the 3-OH and 5-OH groups.[34] On the other hand, when comparing the calculated 4'-OH BDE of resveratrol to the experimental value (82.6 kcal mol^{-1} in benzene),[12] it was found that this BDE value was underestimated by 1.8 kcal/mol (similarly to what previously obtained with other DFT-based methods),[12] so the values for the 4'-OH reported in Table 11.5 were scaled by adding 1.8 kcal/mol.

The results reported in Table 11.5 show that the introduction of the Se-atom causes a significant decrease of the 3-OH and 5-OH BDEs, and an increase of the 4'-OH BDE. The effect on the 3 and 5 positions can be interpreted as deriving from the electron-releasing, radical-stabilizing effect of the chalcogen atom.[34] Calculation showed that significant spin density is delocalized on selenium (see Figure 11.3, structures c and d). However, for the 3 position a larger BDE would be expected because the 3-OH should be H-bonded to the Se-atom, as previously reported for 2-alkylselenophenols.[34] Phenolic OH groups in *ortho* position to hydrogen bond-accepting groups possess larger BDEs than free ones because the cleavage of the O-H bond also involves the loss of the intramolecular H-bond. Although the Se-atom is not considered a strong H-bond acceptor, nevertheless it has been reported that an *ortho* octyl-seleno substituent raises the BDE of a phenolic OH by about 3 kcal/mol.[34] Notably, calculations show that there is no H-bond between Se and the 3-OH, as the most stable structures have always the 3-OH group pointing away from the Se-atom (see Figure 11.3).

Table 11.5. Calculated BDE(OH) in the Gas-Phase at the B3LYP/LANL2DZdp.

Phenol	BDE(O-H) (kcal/mol)[a]		
	4'-OH	3-OH	5-OH
Resveratrol	82.6	85.0	85.3
108	83.8	82.4	83.0
109	84.5	82.0	84.4
110	84.8	83.5	83.4
108 oxide	85.1	90.7	87.3

[a] For the numbering of the OH groups, see Figure 11.3

In the case of **108**, for instance, the 3-OH "away" isomer is more stable by 1.5 kcal mol^{-1} than the "toward" one. This result, however, is not entirely unexpected as it is reported that, in the case of *ortho* alkylthio substituents, a strong intramolecular H-bond can only be formed when the S-R bond is oriented perpendicularly to the aromatic plane (Figure 11.4, structure (a)). When the ortho S-R substituent was coplanar to the phenolic ring, for instance by inclusion in a six membered cycle, the intramolecular H-bond was absent and the reactivity of the phenolic OH group toward ROO• radicals greatly enhanced (Figure 11.4, structure (b)).

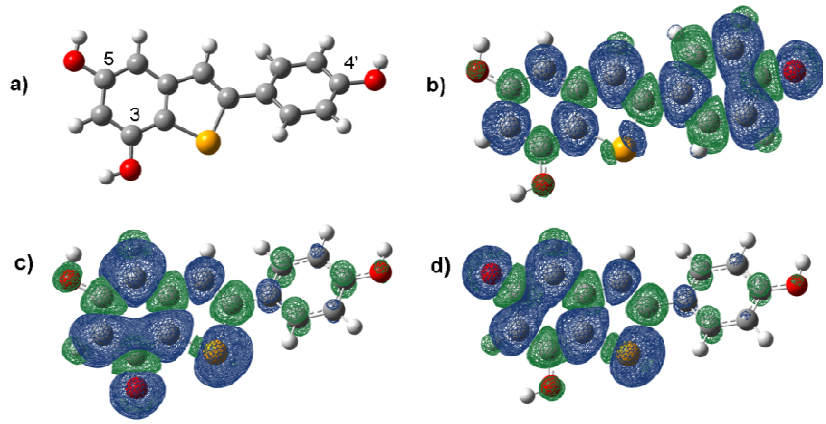


Figure 11.3. Optimized geometry for the most stable conformations of **108** (a) and of the phenoxyl radicals obtained from the abstraction of the H-atom from the 4'OH (b), 3-OH (c) and 5-OH (d); spin density in the radicals is also shown.

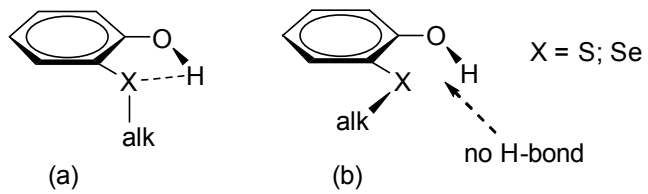


Figure 11.4. Conformational effects on the intramolecular H-bond strength in *ortho* alkyl thio- or selenophenols.

For what concerns the 4'-OH, the small increase of the BDE(OH), observed on moving from resveratrol to selenophenes, may be explained as due to the

perturbation of the stilbene caused by the Se-atom, which causes a decrease of spin delocalization (see Figure 11.5).

The introduction of a Cl-atom in **109** had a small BDE-lowering effect on the 3-OH, in line with the reported effect of chlorine on the BDE of phenols,[60] while it increased the BDE of the 5-OH by 1.4 kcal mol^{-1} because of the formation of a weak intra-molecular H-bond, as Cl-atoms are not good H-bond acceptors. Similarly, the BDE of the 3-OH and 5-OH in **110** are larger than those in **108** because both OH are involved in weak intramolecular H-bonds with the Cl-atoms.

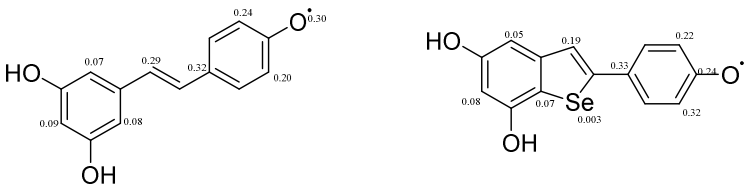


Figure 11.5.. Spin densities calculated at the B3LYP/LANL2DZdp level for the 4'-OH radicals of resveratrol (left) and **108** (right)

We also investigated the BDE in the Se-oxide of **108**, as such derivatives might be formed during the antioxidant activity of the title compounds. In Table 11.5, it can be seen that the presence of a Se=O group significantly increases all the BDE(OH), because of its electron-withdrawing effect. The BDE(OH) of the 3-OH is also raised by the formation of an intramolecular H-bond with the Se=O group.

DFT calculations therefore show that the introduction of the Se-atom causes a significantly decrease of the BDE values of the 3-OH and 5-OH, and a small increase of the 4'-OH BDE and provide a justification to explain the results of the antioxidant assays. Selenophenes appear to be more reactive than resveratrol because they have a higher number of phenolic OH groups reactive toward free radicals. On the other hand, the increased BDE values for all the OH groups predicted for the selenoxide derivative likely formed under the conditions of the autoxidation inhibition experiments is in line with the lower stoichiometric efficiency of the selenoderivatives in the reaction with peroxyl radicals.

11.2.6. Preliminary evaluation of the glutathione peroxidase (GPx)-like activity. In order to explore the potential of the title compounds as catalytic antioxidants able to mimic the action of the Se-enzyme GPx, the catalytic effect on the reduction of H_2O_2 by glutathione (GSH) was investigated.[61] **108** was reacted at 30-150 μM concentration with GSH (5 mM) and H_2O_2 (2 mM) in 0.1 M phosphate buffer (pH 7.4) and the consumption of GSH was periodically determined according to the Ellman's method.[62] Under these conditions the chlorinated benzoselenophenes **109** and **110** did not show any significant activity and were not further investigated. A dose-dependent catalytic effect of **108** on H_2O_2 decomposition was observed. Figure 11.6 shows GSH consumption in the presence of different concentrations of the compound relative to the consumption observed in the absence of **108**. Relative activity of **108** in comparison to that determined for reference GPx mimics such as diphenyl diselenide and selenocystine[63] under the same experimental conditions is reported in Table 11.6.

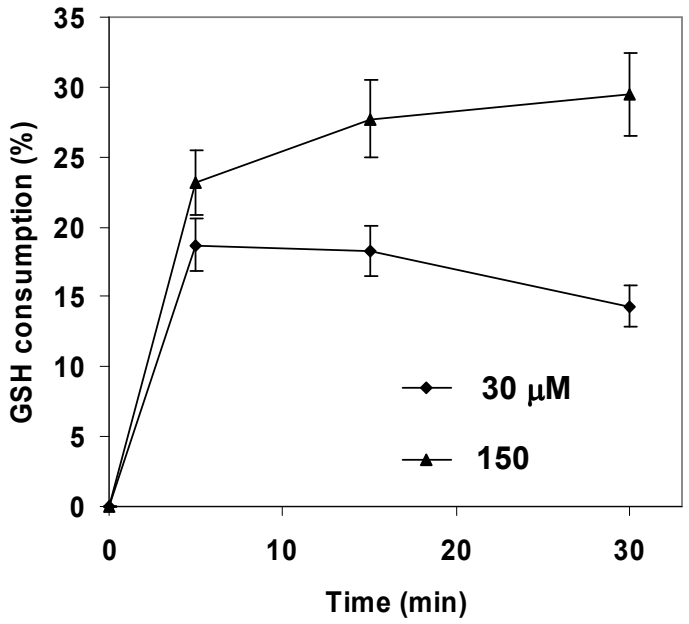


Figure 11.6. GSH consumption (%) induced by 30 or 150 μM 108 relative to the consumption observed in blank experiments (no additive). Reported are the mean ± SD values for three separate experiments.

Although still preliminary, these results clearly demonstrate that selenium incorporation into the resveratrol skeleton does not alter its known hydroperoxide scavenging properties. The complete characterization of the GP_X-like activity of **108** will be the subject of further investigation.

Table 11.6. H_2O_2 Reduction by GSH in the Presence of 150 μM **108** versus Selenium Antioxidants at the Same Concentrations as Reference.

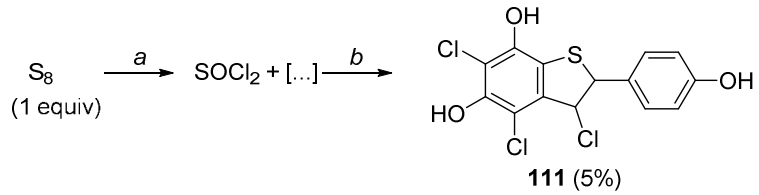
Compound	$t_{1/2}$(min)[a]	Activity[b]
No additive	26	1.0
108	8	3.3
Selenocystine	16	1.6
Diphenyldiselenide	16	1.6

[a]Time to achieve 50% GSH consumption.

[b]With respect to control with no additive.

11.3. Synthesis of benzothiophenes. Results and discussion

Having developed an effective synthetic route for the synthesis of benzoselenophene derivatives **108**, **109** and **110**, we wondered whether this protocol could be a valuable access also to the related benzothiophenes through the reaction of resveratrol with sulfur electrophilic species. Thus, sulfur - S_8 - and SO_2Cl_2 were reacted in THF at r.t.,[64] with the aim to generate sulfur chlorides, and treated *in situ* with resveratrol (Scheme 11.2).



111 (5%)

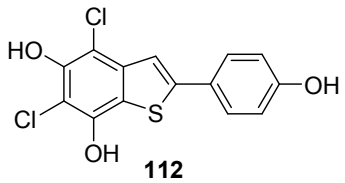
a: i) SO_2Cl_2 (6.0 equiv), neat, 10 min, r.t., ii) dry THF, 1h, r.t.
b: Resveratrol (0.4 equiv), dry DMF, 24h, r.t.

Scheme 11.2. Reaction of resveratrol with S_8/SO_2Cl_2.

S(0) proved to be less reactive than Se(0) in these conditions and its complete consumption was not observed. Nonetheless, when the reaction was performed with a large excess of SO_2Cl_2 (6.0 equiv) a complex mixture of products was formed.

The presence of **111** in the crude mixture was clearly detected by means of ^1H NMR spectroscopy. The two protons signals of the chlorinated pentaatomic ring have a resonance frequency at 5.85 ppm (doublet, J=9.6 Hz) and 5.22 ppm (doublet, J=9.6 Hz).

Isolation and characterization of the products **111** revealed to be quite tricky, because elimination of HCl occurs on SiO_2 leading to the formation of the benzothiophene **112** (Fig 11.7).



112

Fig. 11.7

Intriguingly, addiction of Lewis acid such as BF_3 or $AlCl_3$ in the reaction mixture did not afford to HCl eliminaion.

Isolation of the product **112** was achieved in very poor yield, despite optimization of reaction parameters (time, temperature, stoichiometry) was studied.

On the base of this failure, we sought for an alternative approach to the title resveratrol derivatives.

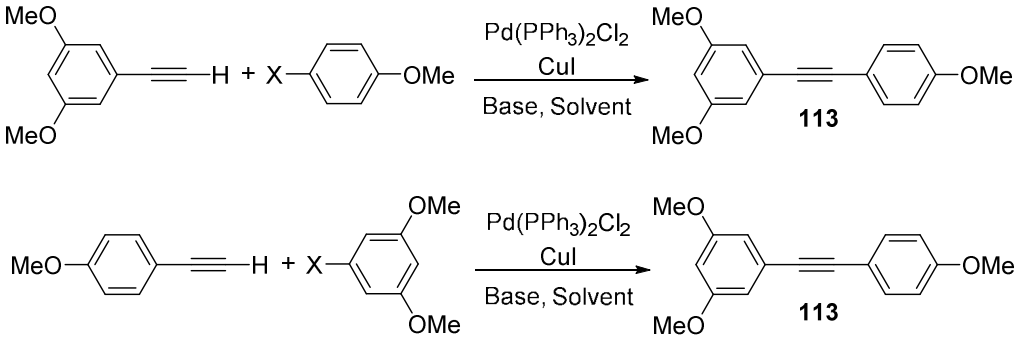
PhtNSCl (1,3-dioxoisoindolin-2-yl hypochlorothioite) proved to be a versatile reagent in sulfur functionalities delivery.

Addiction of PhtNCl to triple bonds of a bis aryl acetylenes has been reported [65,66] and Lewis acid promoted cyclization to the corresponding benzothiophenes has been described.

Thus, reaction of PhtNCl with conveniently substituted alkyne could be a synthetic route to access benzothiophenes having the resveratrol skeleton.

The synthesis of 5-((4-hydroxyphenyl)ethynyl)benzene-1,3-diol **113** bearing OH groups at the resveratrol positions, through the Sonogashira cross coupling [67] was then studied (Scheme 11.3).

The reaction of 1-ethynyl-3,5-dimethoxybenzene with 1-bromo- or 1-iodo-4-methoxybenzene, catalyzed by $Pd(PPh_3)_2Cl_2$ and CuI, was carried out in presence of different bases and solvents (Table 11.7).



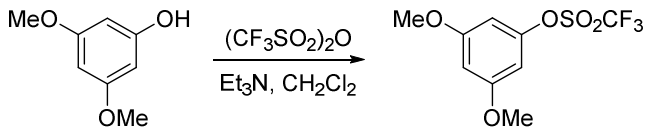
Scheme 11.3. Sonogashira *cross coupling* for the synthesis of **113**

The wanted alkyne was isolated only in poor yield, being the 1,4-diaryl 1,3-diine - arising from a self-coupling reaction on the acetylenic starting material - isolated as the major product.

Reaction between the *p*-methoxyphenyl acetylene and the 1-halo-3,5-dimethoxybenzene under different conditions allowed to reach only slightly yield improvements.

Thus, taking into account that trifluoromethanesulfonates have been reported as very effective reagent in Pd catalyzed cross coupling process, we wondered whether a conveniently substituted aryl triflate could enhance the outcome of this transformation.

114 was synthesized treating 3,5-dimethoxyphenol with trifluoromethanesulfonic anhydride in presence of Et_3N (Scheme 11.4).



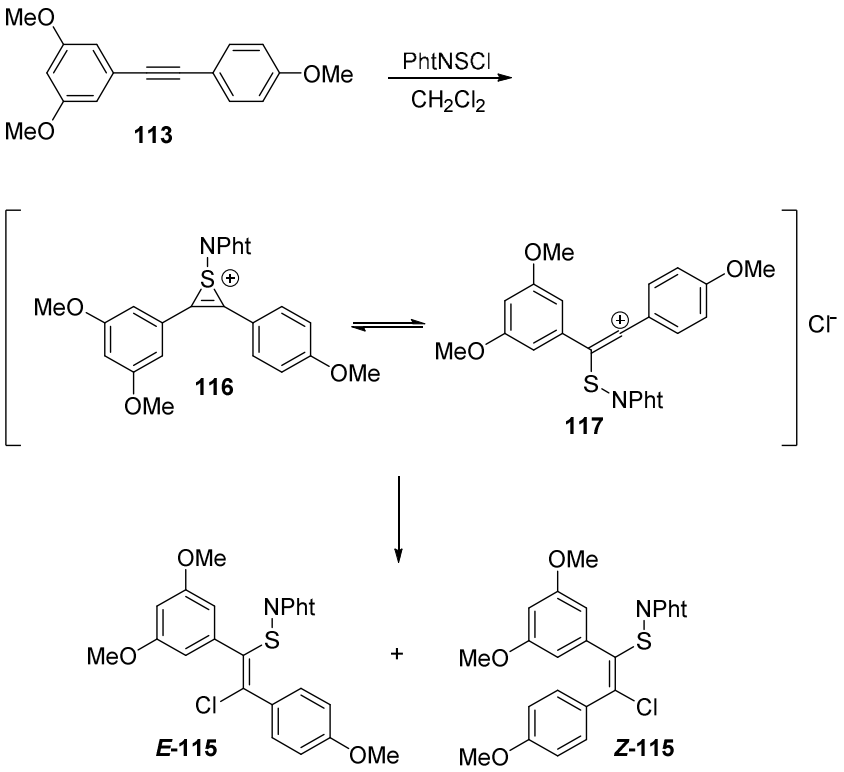
Scheme 11.4

Thus, the desired alkine **113** was achieved in good yield through Sonogashira cross coupling, reacting **114** with 4-ethynylanisole under the condition described in Table 11.7 (entry 7).

The addiction of PhtNSCl to **113** led to the formation of a 2:1 mixture of the products ***E*-115** and ***Z*-115** (Scheme 11.5). A thiirenium ion **116** intermediate is formed by addiction of $PhtNS^+$ to the triple bond. **116** is in equilibrium with the carbocationic species **117**, where the positive charge on the vinylic carbon is stabilised by the presence of an EDG at position 4' of the aromatic ring.

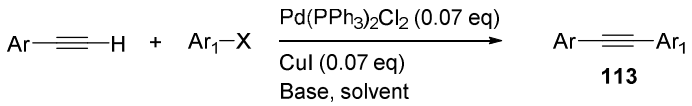
The nucleophilic attack of Cl^- on the thiirenium ion **116** gives *anti* selectivity, forming the *E* adduct **115**.

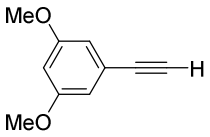
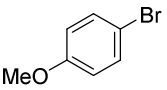
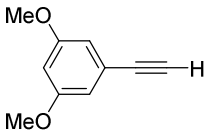
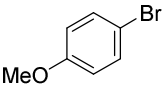
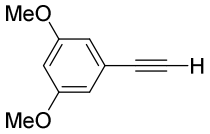
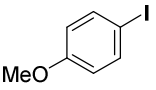
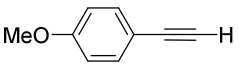
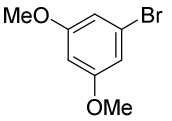
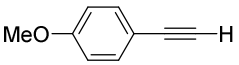
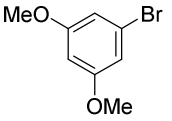
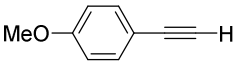
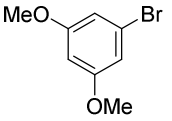
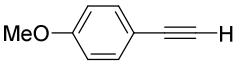
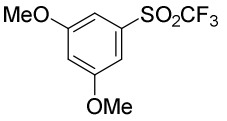
On the contrary, chlorination of the carbocationic species **117** leads to a mixture of *E* and *Z* isomers.



Scheme 11.5

Table 11.7. Synthesis of alkyne **113**



Entry	Ar—≡—H	Ar_1—X	Base	Solvent	Yield (%)[a]
1			Cs_2CO_3	DMSO	14
2			Et_3N	-	<10[b]
3			$^iPr_2NH$	-	23
4			Cs_2CO_3	DMSO	30
5			$^iPr_2NH$	-	<10[b]
6			$^iPr_2NEt$	-	21[b]
7			$^iPr_2NEt$	THF	67

[a] Refers to isolated chromatographically pure material
[b] Self-coupling product (Ar—≡—≡—Ar) was largely predominant

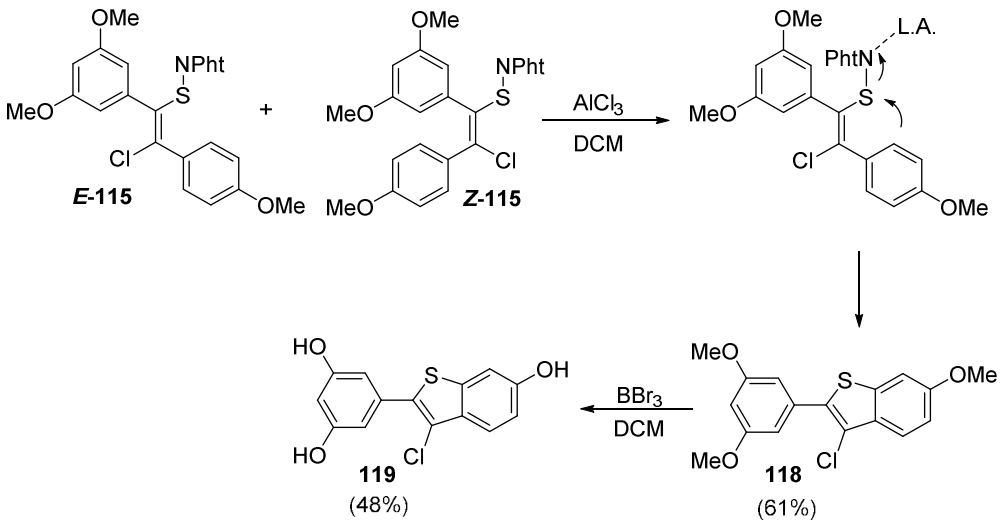
Thus, the open intermediate **117** causes the formation of an *E/Z* mixture of diastereomeric thiophthalimides **115**, but makes certain the complete regioselectivity

of the reaction for the favoured attack of the chloride ion to the most stabilized vinyl cation (Scheme 11.5).

Having in our hands the thiophthalimides ***E*-115** and ***Z*-115** the ring closure to the corresponding thiofenes through intramolecolar S_EAr was then investigated.

Lewis acid promoted cyclizations on similar substrates have been described,[68] therefore the ***E*-115** and ***Z*-115** mixture was treated with $AlCl_3$ and formation of the desired benzothiophene **118** was observed (Scheme 11.6).

The intramolecular ring closure to benzothiophene requires that the sulfenamide sulfur and the aromatic ring lay *cis* to each other (see Scheme 11.6), hence, only the *E* isomer should be consumed in the Lewis acid catalyzed intramolecular S_EAr. In spite of this, reacting the crude *E*/*Z* mixtures of derivatives **115** with 4 equivalents of $AlCl_3$ in DCM at room temperature, we observed complete consumption of the starting material and the thiophene **118** was isolated in 61% overall yield. This can be rationalized considering that, under the reaction conditions required for the cyclization, a *Z*/*E* isomerization takes place allowing the complete consumption of the *Z* isomer as well.



Scheme 11.6

A final deprotection step with BBr_3 is required to isolate the wanted benzothiophene **119** (48% yield).

The chlorine atom on the pentaatomic ring may be considered as a resource for further functionalization.

Then, the antioxidant activity was studied, and preliminary results showed a lower value of K_{inh} of **119** ($0.8 \cdot 10^5$) with respect to both selenated derivatives and resveratrol itself (see Table 11.4). This behaviour was indeed expected as the sulfurated pentaatomic cycle is condensed with the 4'-hydroxy substituted ring. The radical formed by the H-atom transfer from an oxydril group placed on the resorcinol moiety is not stabilised by conjugating with the heteroatom.

The stoichiometric factor measured (n= 2.2) is lower with respect to the expected value.

A more reliable evaluation of the heteroatom effect on the antioxidant properties of resveratrol derived benzo-thiophenes and selenophenes can be carried out only comparing structures different just for the heteroatom in the cyclocondensed ring.

Thus synthesis of benzothiophenes and benzoselenophenes reported in Fig. 11.8 would be required for a deeper insight into the role of chalcogen.

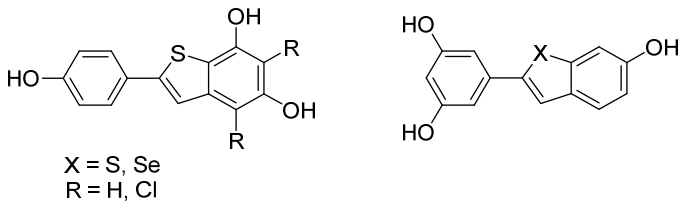


Fig. 11.8

11.4 Conclusions

Resveratrol-based scaffolds are the focus of continuing interest as a source of inspiration for new bioactive derivatives for biomedical applications. Herein, we have disclosed a new entry to resveratrol manipulation based on the rational use of selenium chemistry to obtain an unprecedented set of benzoselenophene derivatives as promising lead structures for the development of innovative antioxidants inspired to natural products. Ring closure with installment of the selenium center onto the resorcinol moiety allowed to achieve the dual goal of: *a)* enhancing the H-atom transfer ability of the *meta* OH groups in resveratrol with respect to the 4'-OH group

via a consistent decrease of the BDE (DFT evidence); and *b)* imparting additional antioxidant properties, such as GPx-like activity, to the resveratrol scaffold.

In particular, all the benzoselenophene derivatives, especially the parent **110**, exhibited H-atom donor and peroxyl radical scavenging activity far superior to that of resveratrol and comparable to that of Trolox, as a reference compound. A peculiar role of the chlorine atoms on the chain-breaking antioxidant activity in polar medium was also apparent, due to a marked "protection" against the deactivating effect of hydrogen bonding with the solvent on the H-atom donor capacity. Overall, these results provide a convenient synthetic entry to 2-phenylbenzoselenophene derivatives and point to seleno-substitution as an expedient tool to tailor antioxidant and chain breaking properties in polyphenol derivatives.

Preliminary results on the synthesis of benzothiophenes from resveratrol have been achieved. Further studies aimed to better understand the effect of the chalcogen insertion in the resveratrol core on the antioxidant properties are currently under investigation, through the synthesis and the study of new compounds.

11.5 References

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Chapter 12

Synthesis of ascorbyl derivatives: towards new nanosystems

12.1 Introduction

Ascorbic acid is one of the most powerful natural antioxidants, but due to its poor solubility in hydrophobic media, can only be used in aqueous environments. Its molecule possesses four different hydroxyl groups that can be selectively modified to produce a wide variety of derivatives, such as ethers and esters with aliphatic chains that increase the hydrophobicity of the molecule.[1] When the - OH groups of the ascorbate ring (in C2 and C3) are not modified, the final product keeps the same extraordinary radical scavenging activity, and behaves as a surfactant, producing supramolecular assemblies in water dispersions, or coagels, depending on concentration and temperature.[1,2]

Vitamin C can be used as a versatile headgroup for the synthesis of surfactants. These surfactants provide ideal candidates for exploring the effects of chirality on self-assembly. The headgroups possess two stereogenic centers, in positions 4 and 5, which generate four different epimers. Of these, L-(+)-ascorbic acid is the most familiar.

Although L-ascorbic acid is soluble essentially only in water, methanol, and ethanol, 6-O-Ascorbic acid alkanoates can also be dispersed in hydrophobic environments. There they act as excellent antioxidant agents, and they can be used to solubilize and protect lipophilic ingredients (drugs, vitamins, etc.) against radical attack.

D-(-)-Isoascorbic acid is an epimer of L-(+)-ascorbic acid with an inversion of the configuration at C5. It is an active antioxidant agent. However, it possesses only 1/20 of the biological activity of Vitamin C. This is because the reducing and acidity properties of the ascorbic epimers are due to the furan ring, the enediol group, and the carbonyl in position 1, whereas the biological effect is related to the side chain. Different configurations of the two headgroups produces a different set of inter- and intramolecular interactions that largely affect the thermodynamics of self-assembly greatly and particularly through hydration.[3]

6-O-Ascorbic acid alkanoates possess both a hydrophobic moiety (aliphatic chain) and a polar group (ascorbic acid) and behave as amphiphilic molecules in water, and consequently it is expected that they would show enhancing properties.

120 L-ascorbic acid

121 D-isoascorbic acid

Fig. 12.1

These derivatives have been previously synthesised with the main aim of obtaining amphiphiles that could combine the powerful antioxidant properties of ascorbic acid with the capacity to produce supramolecular aggregates. They proved to be interesting both on account of their phase behaviour, and of the properties of the supramolecular assemblies they form. When dispersed in water at room, or lower, temperatures above ca. 5% w/w concentration, they form coagels. At higher temperatures, the microstructure changes to micellar solutions for surfactants of low hydrocarbon chain length.[4]

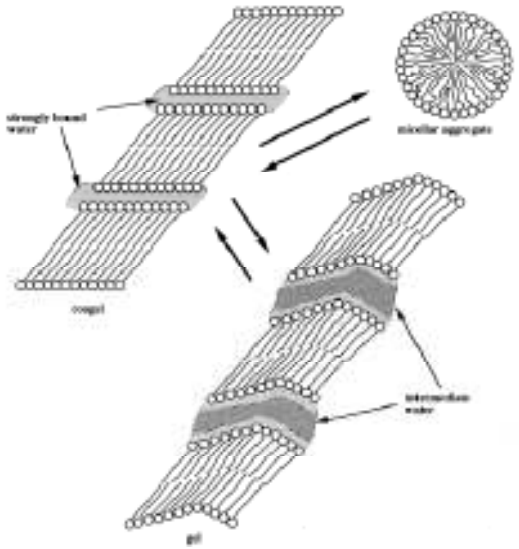


Fig. 12.2. Schematic structure of a coagel, a gel, and a micellar aggregate. The dark areas indicate the water molecules that surround the polar headgroups (light gray represents strongly bound water; darker gray corresponds to intermediate water)

It is demonstrated that chirality and other structural features determine the architecture and biological activity of supramolecular self-assemblies.[5,6,7]

These systems, acting as surfactants and organogels,[8] would be very useful by improving the biopharmaceutical properties of a great variety of therapeutically relevant drugs to be administrated by different routes, where permeation of lipophilic drugs and its absorption is required.[9] Since ascorbic acid derivatives possess the same antioxidant properties of their parent molecule, these aggregates provide an ideal environment for the solubilization of hydrophobic and sensitive drugs that might be degraded and oxidized when exposed to light, heat, dissolved oxygen, and other radical-producing species.[10-13]

In this context, an example is represented by the solubilization of a natural drug, artemisinin (QHS), in an aqueous micellar dispersion of octanoyl-6-O-ascorbic acid.[14] The rheological behavior is a crucial factor for the use of 6-O-ascorbic acid alkanoates coagels as efficient and stabilizing drug carriers, especially for rather hydrophobic and easily degradable products.[15]

Properties at the gas/water interface of mixtures of ascorbyl-stearate with vitamin D_3,[16] α-Tocopherol[17] or Vitamin K_1[18] have been studied.

Vitamin C esters show also interesting effects against leukemia cells[20] and perform some anti-tumor activity.[19]

12.2 Results and discussion

12.2.1. Synthesis of ascorbyl esters. We began our research with the aim to optimize a method to obtain ascorbyl- 5-O- or 6-O- alkanoates and ascorbyl-5-O-,6-O-dialkanoates, with different length of the saturated or unsaturated aliphatic chain. The synthesis of derivatives of ascorbic acid and oleic acid was also investigated.

To the best of our knowledge very few examples of ascorbyl-5-O-,6-O-dialkanoates are reported whereas only one report (patent)[21] is described for synthesis of ascorbyl-5-O-alkanoates.

Acetic anhydride and H_2SO_4 or $KHSO_4$ are used as catalysts in the formation of L-ascorbyl-5-O-6-O-diacetate. Tri- and tetra-esterification derivatives represent common by-products in this reaction.[22]

Recently, L-ascorbyl-5-O-,6-O- diacetate has been used as an intermediate for the synthesis of some patented compounds.[22]

Two examples about the synthesis of long chain L-ascorbyl dialkanoates and their application as antioxidant compounds in foods or in liposomal membranes, as such or in combination with α-tocopherol are reported.[23] It is literature described that their activity depends on the aliphatic chain length.

Of particular interest could be the synthesis of ascorbil oleates. These systems bear on the same molecular skeleton both oleic acid and ascorbic acid moieties, that can sinergically exhibit antioxidant properties. These compounds are nowadays studied as antioxidant additives in the field of Food technologies (E340).[24]

Although the application of such molecules could be very interesting, their synthesis is quite difficult, especially in large scale, because of the presence of labile functional groups and the high instability of the ascorbic acid core.

The general synthetic approach includes the use of an enzymatic catalysis (*Candida antarctica* Lipase B solid-phase supported) in the reaction between oleic acid and ascorbic acid.

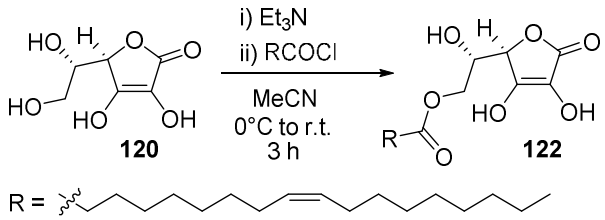
Only an example of reaction with different catalyst (boron trifluoride in dioxane) is described in literature.[25] This procedure allows only the esterification at C-6 and make use of a toxic gas, difficult to handle for large scale purpose. The study of alternative methods to obtain this molecules is an actual topic in literature.

In a series of screening reactions L-ascorbic acid and oleic acid were treated with several acid (protic: H_2SO_4, Lewis: BF_3, BCl_3) under different conditions. In our hands, the wanted product was not formed or obtained only in traces together with a complex mixture of by-products.

We though then to use the oleoyl chloride, more reactive than the corresponding acid. Thus, L-ascorbic acid was treated with oleoyl chloride in the presence of different bases (Et_3N, pyridine, K_2CO_3, Cs_2CO_3/TBAI) and in different solvents (DMF, MeCN, THF, dioxane). The wanted product **122** was isolated in moderate

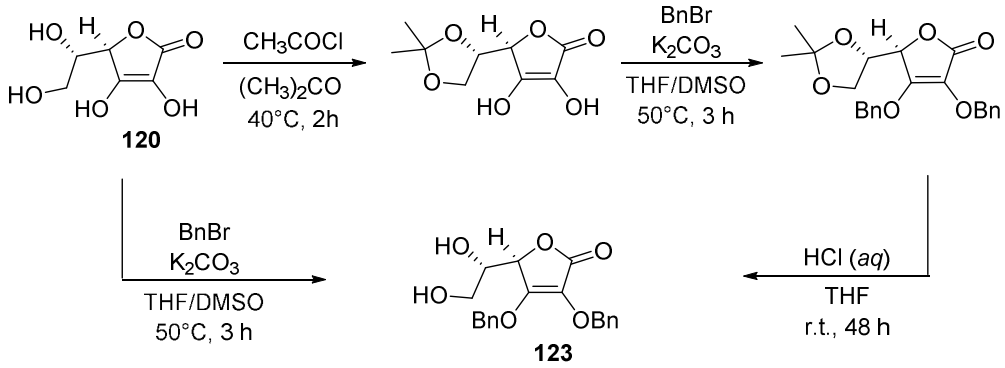
yield under the conditions described in Scheme **12.1**. The reaction did not work under acid catalysis (BF_3, H_2SO_4).

We considered that low yields could be due to a possible interaction between the oxydriles at position 2 and 3 (pK_a = 11.6 and pK_a = 4.2, respectively) and the base. Thus, esterification reaction on the 2,3-benzyl derivative of L-ascorbic acid **123** was carried out and the cleavage of the protecting group was investigated.



Scheme 12.1. Esterification of L-ascorbic acid with oleoyl chloride

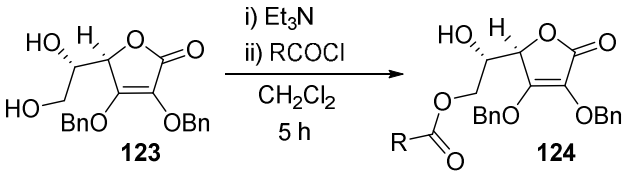
Synthesis of **123** is literature known and the procedure includes a protection of 5,6-OH-groups as acetonide, formation of the benzyl ethers at positions 2 and 3 and cleavage of the acetonide under acid conditions (Scheme 12.2).[26] We found out that **123** could be directly achieved in comparable yields through a one-pot treatment of L-ascorbic acid with benzyl bromide, thence reducing the number of steps from three to one.



Scheme 12.2

On the substrate **123** esterification at position 6 could be easily achieved in good yields by treatment with oleoyl chloride in the presence of Et_3N. Further cleavage of

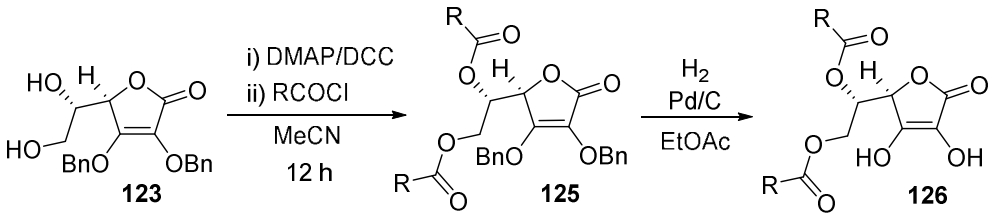
benzyl ether is required to access the desired products. The incompatibility of H_2-Pd/C conditions with olefins prompted us to seek for an alternative milder method to cleave the benzyl ether. Unfortunatly, Chlorosulfonyl-isocyanate (CSI) and Na_2CO_3 in CH_2Cl_2[27] - to the best of our knowledge the mildest procedure reported in literature - proved to be ineffective on **124**, a complex mixture of by-products being detected.



R = $(CH_2)_7CH=CH(CH_2)_7CH_3$ (*cis*)

Scheme 12.3

When **123** was treated with 2 equivalents of saturated acyl chloride in the presence of DMAP/DCC using MeCN as the solvent, a clear access to L-ascorbyl-5-O-,6-O-dialkanoates was found. The cleavage of protecting group at positions 2 and 3 led to the formation of the wanted products (Scheme 12.4).

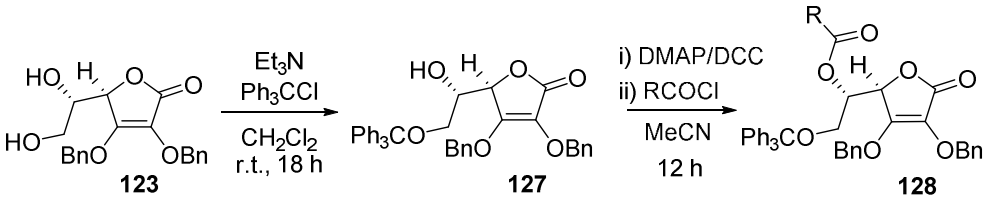


a: R = $(CH_2)_{10}CH_3$
b: R = $(CH_2)_8CH_3$
c: R = $(CH_2)_6CH_3$

Scheme 12.4

Having developed an efficient protocol to obtain L-ascorbyl-5-O-,6-O-dialkanoates, we turned our attention on the synthesis of ascorbyl-5-O-alkanoates. Acylation of unprotected L-ascorbic acid occurs at first at position 6 and later at positions 2, 5 and 3 (in this order). On the basis of these consideration we reacted **123** with trityl chloride in the presence of Et_3N to obtain **127**, protected at position 6,

in such a way that the esterification occurs only on the C5-OH. Treatment of **127** with acyl chlorides in the presence of DMAP/DCC afforded **128** in good yields (Scheme 12.5). Cleavage of the protecting groups of **128** proved to be tricky. Decomposition of the structure was always observed whether the final step was the H2-Pd/C treatment (cleavage of benzyl ether) or the BF_3 one (cleavage of trityl group).



a: R = $(CH_2)_6CH_3$
b: R = $(CH_2)_8CH_3$

Scheme 12.5

Antioxidant properties of ascorbyl-5-O-6-O-dialkanoates **126a-c** were preliminary investigated through the above described DPPH test (Table 12.1).

Table 12.1. H-atom Transfer Reaction from ascorbyl-5-O-6-O-dialkanoates to DPPH[a]

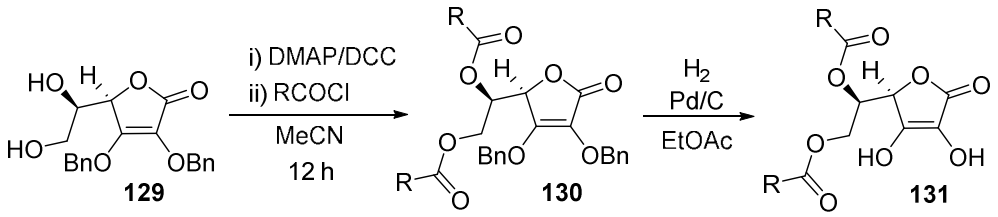
Product	%Inibition[b]
126a	93.40%
126b	90.70%
126c	94.09%

[a]50mmol of ascorbyl-5-O-6-O-dialkanoates and 50 mmol of DPPH

[b]Calculated after 20 min

All the products showed short reaction times (< 1 min) and an high activity in terms of reduced DPPH after 20 minutes, confirming their efficacy against free radicals.

This synthetic path proved to be efficient also in the obtaining the analogues D-(-)-isoascorbic acid derivatives (Scheme 12.6).



Scheme 12.6

12.2.2. Chemical-physical properties. In order to evaluate a possible role of vitamin C derivatives in the formation of self-assembling nanostructures in a aqueous environment, some chemical-physical properties of the synthesized diesters were analyzed.

These results were also compared with those obtained from the analysis of structures mono-substituted on OH at C-6 previously studied.

DSC and SAXS measures were performed on solid compounds to acquire structural and morphological information.

DSC measures (Differential Scansion Calorimetry). DSC experiments were performed to detect the phase-transition temperature and enthalpy change of **126a-c**. The observed melting points were lower than those of mono-substituted derivatives (Table 12.2).

Table 12.2. Melting point for ascorbyl- 5-O-,6-O-dialkanoates and 6-O-alkanoates

	5-O-,6-O-dialkanoates (Melting point - °C)	**6-O-alknoates (Melting point - °C)**
126a	46.2-46.6	105.5-106.5
126b	43.2-45.2	96.0-98.0
126c	63.5-64.0	87.0-88.0
131	72.3-73.4	--

This could be due to a decreased dipole-dipole interaction. In the double chain derivatives the lack of the free OH at C-5 causes probably a reduction in the dipolar interactions, both inter and intra molecular. Thus, it is possible to hypothesize a less ordered structure within disubstitued compounds.

Table 12.3. State of ascorbyl 5-O-,6-O-dialkanoates in different solvents

Product	Solvent	Solution weigh (mg)	%Weigh	State
126a	H_2O	100	0.5	Insoluble
	H_2O	200	1	Insoluble
	H_2O	500	2	Insoluble
	H_2O	500	5	Insoluble
	Isooctane	300	1	Gel
	Ciclohexane	300	3	Gel
	Ciclohexane	300	5	Gel
	Ciclohexane+H_2O	300	5-1-94	Gel
	Isooctane+H_2O	300	5-1-94	Gel
	Ciclohexane	300	8	Gel
	Ciclohexane+H_2O	500	5-1-94	Insoluble
	Ciclohexane	500	8	Gel
	Ciclohexane	300	15	Gel
	Ciclohexane+H_2O	300	8-1-91	Gel
126b	H_2O	100	0.5	Insoluble
	H_2O	200	1	Insoluble
	H_2O	500	2	Insoluble
	H_2O	500	5	Insoluble
	Ciclohexane	300	1	Sol./ no gel
	Isooctane	300	1	Sol./ no gel
	Ciclohexane	300	3	Sol./ no gel
	Isooctane	300	3	Sol./ no gel
	Cloroform	300	3	Sol./ no gel
	Ciclohexane	300	3	Sol./ no gel
	Ciclohexane+H_2O	300	5-1-94	Sol./ no gel
	Isooctane+H_2O	300	5-1-94	Sol./ no gel
126c	H_2O	500	1	Insoluble
	Ciclohexane	300	5	Sol./ no gel
	Isoctane	300	5	Sol./ no gel
	Isooctane+H_2O	300	5-1-94	Sol./ no gel
	Ciclohexane+H_2O	300	5-1-94	Sol./ no gel
	Cloroform	300	3	Sol./ no gel

The molecular dimensions and the aliphatic chain length of the fatty acid may influence the melting point in the two series of vitamin C.

The nanostructural organization of compounds **126a-c** in water, organic solvents and H_2O/organic solvent mixtures was then investigated. Results are summarized in Table 12.3.

Double chain derivatives are insoluble in water. All products well dissolve in organic solvent. **126a** gave a gel in cyclohexane (5%, 8%, 15% in weight) and cyclohexane/water (solid: water : cyclohexane ratio 5:1:94 and 8:1:91).

Also in a mixture of isooctane-water (solid : water : isooctane ratio 5:1:94) the formation of a gel was observed.

The procedure to obtain the gel includes the sample heating at 30°C for 5 minutes, followed by a slow cooling at 10-11°C. **126c** and **126b** derivatives did not afford the gel.

SAXS measures (small angle X Ray scattering). 126a shows a thin-layers structure, in analogy with what previously observed for the single chain derivatives. The same structure can be supposed also for the **126c** derivative, even if the crystalline phase is different. **126b** is a crystalline solid too and the structure is not lamellar.

SAXS experiments were also performed on the gel samples as a function of temperature. Fig 12.3 shows the profiles obtained for **126a**/ciclohexane (15:85 w/w). The measures were carried out on the solid phase gel (red curve, *a*) then the gel was melted by heating (blue curve, *b*) and again cooled (green curve, *c*).

In order to extract the structural parameters, several fitting procedures for different models were checked.

126a gel in cyclohexane (15% w/w) is formed by solid fibres with a 10 nm diameter. These are formed by cylindrical sub unities, observable after the gel formation. The behaviour of the gel is reversible and the structure is restored after the cooling.

The distance between thin-layer chains is approx 36Å in **126a** while it is ≈17Å in **126b**. Structure of **126c** derivative is still ordered and the distance between thin-layer, chains is shorter, in agreement with the presence of shorter chains and similar to those of the single chain derivatives.

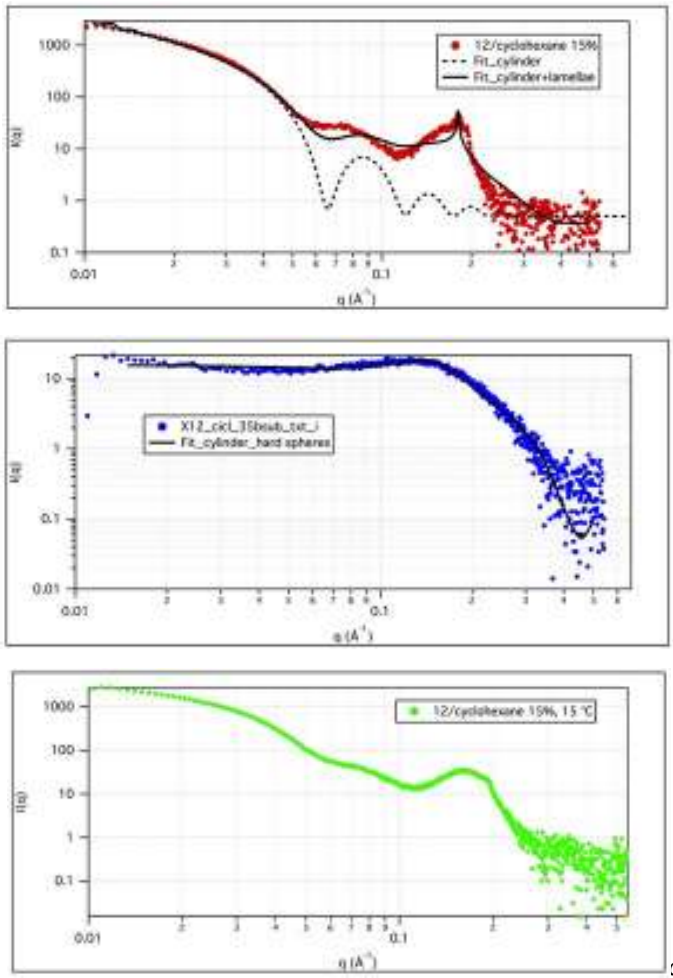


Fig. 12.3. SAXS intensity distribution for an **126a**/ciclohexane (15:85 w/w) organogel at different temperature. Best fit is represented by lines.

12.3. Conclusions

In conclusion, ascorbyl- 5-O-,6-O-dialkanoates were synthesised and preliminary results on their physicochemical properties have been achieved. Formation of organogels containing a vitamin C-based surfactants that bear aliphatic chains linked to the L-ascorbic or D-isoascorbic ring. Organogels are produced in the presence of hydrocarbons with or without water. The presence of a redox active polar head

group in the surfactant adds an important and new functionality to the final organogels that can be used to solubilize and protect sensitive organic molecules.

Preliminary results showed the possibility to introduce unsaturated chains through an easy and direct procedure. Optimization of this route toward the synthesis of single or double unsaturated chain derivatives of vitamin C, as well as the evaluation of their physicochemical properties is currently under investigation. Synthesis of sulfur- and selenium- containing systems from ascorbic acid is also ongoing project in our group.

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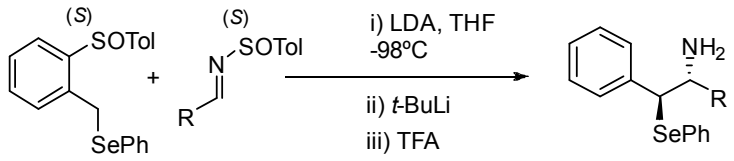
Chapter 13

Synthesis and reactivity of silylated chiral o-sulfinylbenzyl carbanions

13.1 Introduction

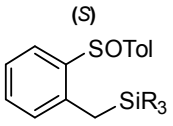
During the study of organoselenium derivatives as interesting compounds with antioxidant, antitumoral and antimicrobial activities it was found a convenient and selective access to diastereomerically pure 1,2-selenoamines.[1] The procedure was based on the reactivity of a selenyl benzylcarbanion stabilized by an (*S*)-2-*p*-tolylsulfinyl group which was able to react with chiral imines to afford the desired enantioenriched *vic*-selenoamines, after *C*- desulfinylation with *t*-BuLi followed by reaction with TFA (for *N*-desulfinylation).



Scheme 13.1

13.2. Results and discussion

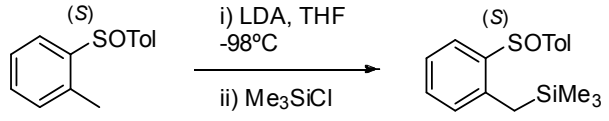
On the basis of these findings we moved to consider the behaviour of the corresponding silylated *o*-sulfinyl benzylcarbanions, which can be obtained from benzylsilanes **132** (Fig. 13.1), with electrophiles, either to evaluate the stereochemical outcome of the reactions and also to study the possible further functionalization of the C-Si bond under suitable conditions.



132

Fig. 13.1

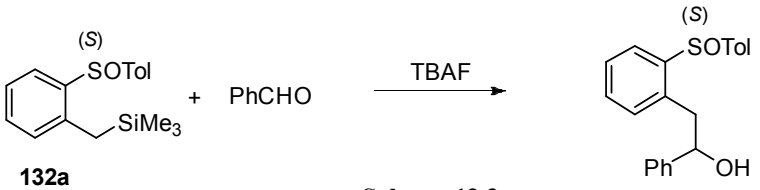
Only one example is described in the literature to synthesize the trimethylsilyl derivative (R = Me), as reported in Scheme 13.2.[2]



132a

Scheme 13.2

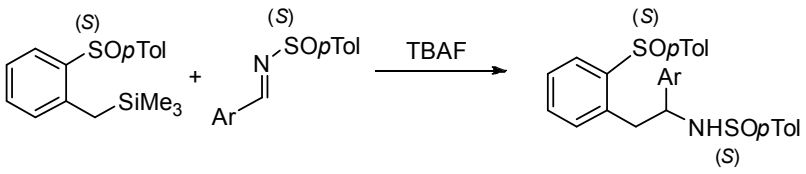
With the aim to assess whether the *o*-sulfinyl group could influence the stereochemistry of the reaction with prochiral electrophiles through the functionalization of the C-Si bond, as model reaction the silyl-sulfoxide was treated with benzaldehyde and TBAF. The carbodesilylation reaction was efficient in transferring the nuclephilic system on the aldehyde, but a 1:1 diastereomeric mixture of the oxydrilated adduct was evidenced (Scheme 13.3).



132a

Scheme 13.3

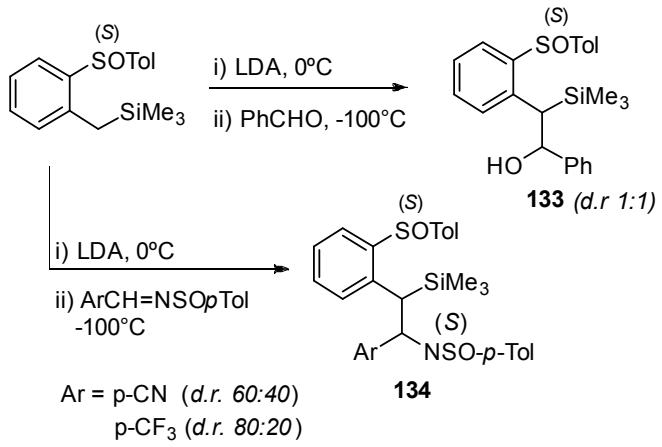
We moved to consider different electrophiles, bearing a chiral group, such as different aromatic (*S*)-*N*-2-*p*-tolylsulfinylimines, which were demostrated very good reagents when treated with the selenated sulfinyl carbanions, as described above. Unfortunately, performing the reaction under analogue conditions, also in this case an equimolar mixture of diastereoisomers was isolated (Scheme 13.4).



Ar = C_6H_5, pCH_3O-C_6H_4,
pCF_3-C_6H_4

Scheme 13.4

Then we focused our attention on the behaviour of carbanions of the *o*-sulfinyl benzylsilanes with electrophiles, to evaluate the efficiency and the stereochemical outcome of this reaction.

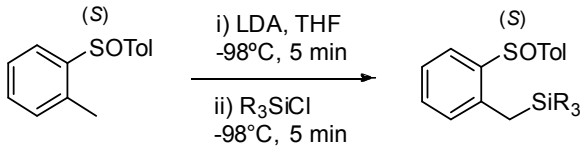


Scheme 13.5

In fact previous results obtained in our laboratory showed that the reaction of the trimethylsilyl derivative **132a** with aldehydes and aromatic chiral imines was able to afford β-silylated ethanol **133** and silyl-β-phenylethylamines **134**, which can be further functionalized.

No induction was observed in the reaction with benzaldehyde, while in the case of imines a slghtly better d.r. was evindeced (Scheme 13.5).

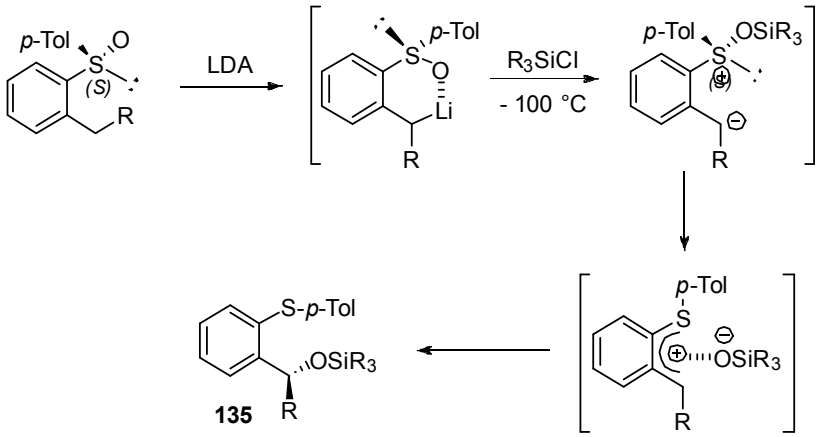
Thus we reasoned that more sterically hindered silyl groups could induce higher stereochemical control on the desired products. Compounds **132b,c,d** were synthesized in a similar way as described above, by treatment of the *o*-sulfinyl toluene with LDA followed by reaction with the suitable silyl chloride (Scheme **13.6**). Only for the TBDMS-derivative the electrophile was added at higher temperature (-78°C).[3]



13b: (R_3 = $MePh_2$) (45%)
13c: (R_3 = Me_2Ph) (10%)
13d: (R_3 = Me_2t-Bu) (18%)

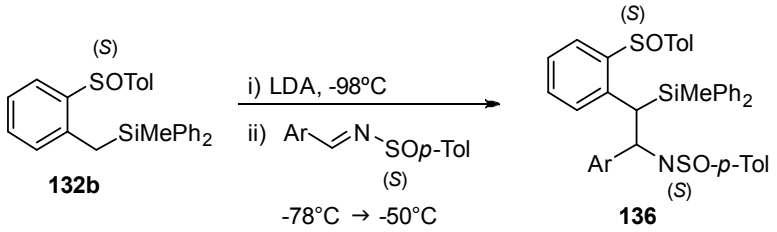
Scheme 13.6

The yields were quite low, even under different conditions, as far as appreciable amounts of the corresponding (2-(*p*-tolylthio)benzyloxy)silanes **135** were formed (Scheme 13.7), as already reported for the TMS-derivative.[2]



Scheme 13.7

The *o*-sulfinyl benzyl-(methyldiphenyl) and -(dimethyl-*t*butyl)-silanes **132b** and **132c** were then reacted with chiral aryl imines, to estimate whether bulkier silyl-groups can affect the stereochemical outcome of this kind of functionalition. Optimization of the conditions were indeed required for these substrates. In fact preliminary results showed that higher temperature (-78°C→-50°C) was necessary for the reaction of the α-silyl benzylcarbanions with the imines. It is intersting to observe that, while for the -$SiMe_2tBu$ derivative no reaction was obtained, reaction of the -$SiMePh_2$ derivative with imines showed an appreciable diastereomeric control.



Ar = *p*-CH_3 (d.r. 70:30)
p-CN (d.r. > 98:2)
p-CF_3 (d.r. > 98:2)

Scheme 13.8

In fact treatment with the substitued *N*-(4-methyl)-, (4-cyano)- and (4-trifluoromethyl)benzilidene-(*S*)-sulfinyl-imines led to the formation of two of the four diastereoisomers, with a ratio 70:30 for the 4-methyl-substituted imine, while when EWG were present, a d.r.>98:2 was obtained (Scheme 13.8).[3]

Nonetheless the products were formed in quite low yields (15%-25%), and additional reactions will be necessary to evaluate a possible optimization of such procedure.

It is anyway interesting to underline that the so obatined results with the EWG on imines allow to consider a stereocontrol on both the new formed stereogenic centers, showing how the diphenyl(methyl)silyl) moiety is more efficient with respect the other silyl groups.

These results seem to evidence that higher steric hindrance close to the sulfinyl group on the aromatic ring can direct the attack of the carbanion on a preferred face of the C-N double bond of the imine.

This control can also be ascribed to the presence of two phenyl groups, which can assume a precise position in the space, able to produce efficient π-π stacking interactions in the final products.

NMR analysis seems to confirm this hypothesis, as far as chemical shifts of aromatic protons were shielded (6.6 and 7.0 ppm) with respect the TMS-derivative (values over 7.0 ppm). Also the resonance frequence of the NH appears at lower values in comparison with the expected chemical shift of sulfinamides (3.48 and 3.76 ppm).

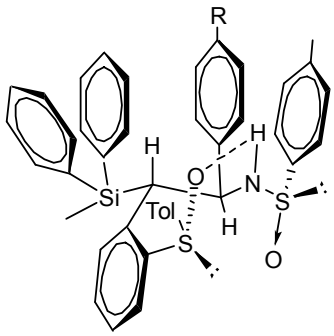


Fig. 13.2

These results allow to suppose a rather rigid structure, with a limited rotation around the single bonds, presumably due to the formation of hydrogen bonds between NH and S=O on the aromatic ring. This should generate a deshielding on the proton of NH, but probably at the same time this interaction could place the proton in a space with a strong shielding effect due to interactions between π-orbitals of aromatic rings (Fig. 13.2).

13.3 References

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Chapter 14

Copper-catalysed hydroboration of inactivated terminal olefins

14.1 Introduction

Since its discovery in 1956, the unique olefin hydroboration reaction has became one of the most widely used synthetic reactions.[1] Boronic esters are extremely functional building blocks as the C-B bond can be easily transformed with retention of configuration into a CN, CO, or CC bond.[2] In this context, hydroboration proved to be a versatile and useful tool in organic synthesis and many new types of reagents have been introduced, including some which have shown enantioselectivities as high as 100% with certain olefins.[3] When Noth and Mannig[4] reported a catalysed hydroboration for the first time, a new facet of such reaction was revealed. Of particular interest is the possibility to access regioselectively and enantioselectively the branched isomer through hydroboration process (Scheme 14.1). Transition metal catalysed regioselective hydroboration of alkenes have attracted much interest, as it provides opportunities for unique regio- and enantioselectivity.

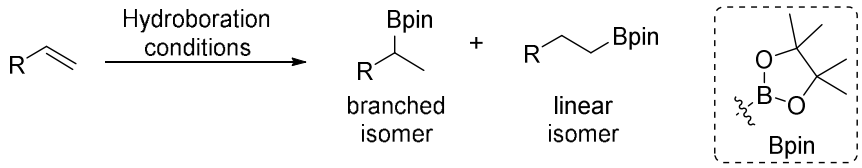


Fig. 14.1. Regiochemistry of hydroboration of alkenes

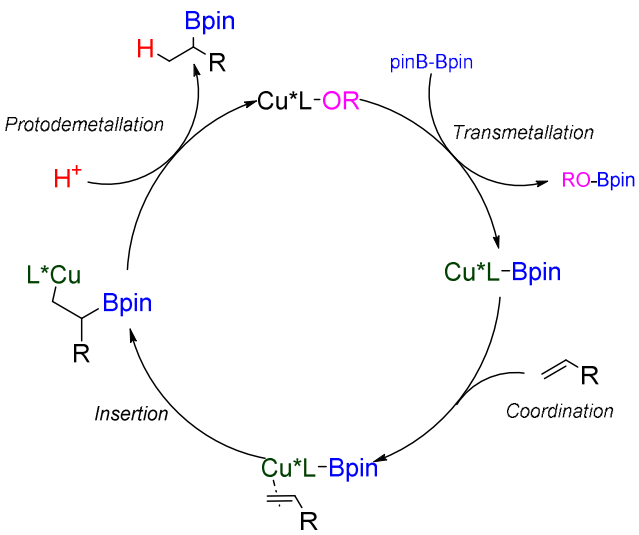
The Rh-catalysed asymmetric reaction has advanced considerably since Hayashi's seminal paper describing the BINAP/[$Rh(COD)_2$]- BF_4-catalyzed reaction in 1989.[5] Brown and co-workers reported that cyclic secondary boranes derived from ephedrine and pseudoephedrine undergo rhodium complex-catalysed hydroboration of styrene derivatives. Regio- and enantio- selectivities were both strongly depending from the catalyst and the substrate.[6] Zhang *et al*. reported a regioselective asymmetric synthesis of the Markovnikov isomer by hydroboration reaction catalysed by neutral Rhodium complexes.[7] More recently chiral phosphites and phosphoramidites have been used as ligands in the Rh-catalysed hydroboration

of a number of styrenes with pinacol borane, allowing to reach good enantioselectivities.[8]

Although many other catalytic systems, including ruthenium,[9] nickel,[10] samarium,[11] and lanthanum[12] catalysts, have been employed for the transformation, the development of a highly regio- and enantioselective hydroboration still remains as a challenge. Moreover, these reactions have been reported for styrene derivatives only. In this scenario a broadening of the scope is highly desirable. On the other hand, only a few example of Cu-catalysed hydroboration reaction has been described[13] and the scope is still limited to styrene derivative.

14.2 Results and discussion

On the basis of these considerations, we decided to investigate the Cu(I)-catalysed hydroboration of alkenes with the aim to disclose a novel procedure to synthesise nonracemic borylated products from inactivated terminal olefins. The possibility to react alkenes different from styrenes would greatly enlarge the scope of the process.

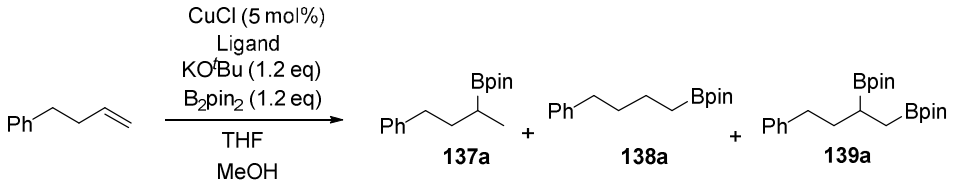


Scheme 14.2. Proposed mechanism

The proposed mechanism for the Cu(I)-catalysed hydroboration is reported in Scheme 14.2.

With the aim to verify whether this copper catalysed transformation was possible, a first set of reactions on 4-phenylbut-1-ene was performed under conditions described in Table 14.1 with different ligands. Despite hydroboration of the alkene was achieved, a mixture of the Markovnikov and anti-Markovnikov products was always detected. Despite the use of chiral ligands an enantiomeric excess for **137a** was not obtained (Table 14.1, entries 1,2,4). These findings prompted us to systematically investigate the reaction conditions. Optimal temperature was found to be 50°C, being the reaction too slow at r.t. or 35°C. Major amount of undesired diboronic ester **139a** was observed at higher temperature.

Table 14.1. Ligand screening for hydroboration of 4-phenylbut-1-ene



Entry	Ligand	%mol	% Conv	**137a:138a:139a**[a]	ee%
1	(*R*)-Tol-BINAP	5	n.d.	56:21:23 (69:31)	0
2	(*R*)-Josiphos	5	n.d.	75:25:0 (75:25)	0
3	SPhos	10	n.d.	77:18:5 (80:20)	--
4	(*S*)-BINAP	5	n.d.	39:15:46 (72:28)	0

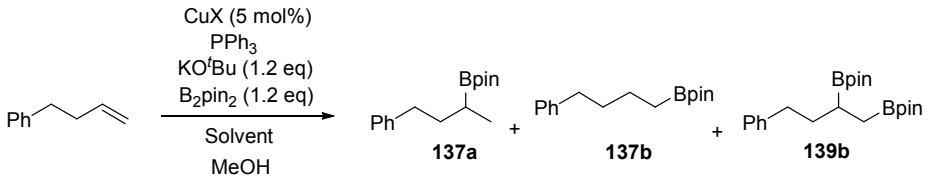
[a] **137a:138a** ratio is reported in the brackets

The variables involved in this transformation are i) the copper source, ii) the ligand, iii) the solvent, iv) the substrate and v) the proton source.

We began our studies with a screening of Cu(I) sources and we found that using the species reported in Table 14.2 under the described conditions, selective formation of **137a** could not be achieved. On the contrary, a **137a**:**138a**:**139a** mixture was formed in a variable ratio as function of the solvent. Thus, we

performed the hydroboration reaction of 4-phenylbut-1-ene in different organic solvents, using (*S*)-BINAP as a ligand and CuBr as a Cu(I) source.

Table 14.2. Copper source screening for hydroboration of 4-phenylbut-1-ene



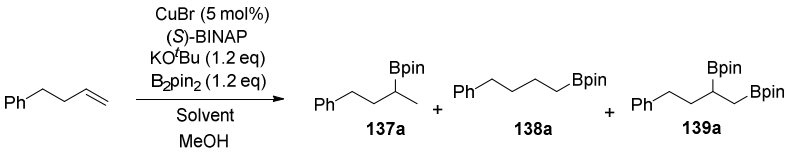
Solvent		CuCl	CuI	CuBr	$Cu(NCCH_3)_4^+ CF_3SO_3^-$
THF	Conversion%	41	77	57	72
	137a:138a:139b	64:36:0	10:4:86	7:6:87	4:4:92
PhMe	Conversion%	80	67	67	72
	137a:138a:139a	22:78:0	44:18:38	20:27:53	17:47:36
MeOH		n.r.	n.r.	n.r.	n.r.
MeCN	Conversion%	79	79	83	76
	137a:138a:139a	13:2:85	10:2:88	6:1:93	5:2:93
DCM		n.r.	n.r.	n.r.	n.r.

The results are reported in Table 14.3. In some of these solvents the reaction did not work at all (entries 14-23) and when DMSO was used only diboration process occurred (likely not metal catalysed, see ref 14). In all the other cases mixture of Markovnikov and anti-Markovnikov products was formed together with the diboronic ester **139a**. Intriguingly, in Et_3N **137a**:**138a** were formed in 97:3 ratio without detecting **139a**, despite with a quite low conversion (25%).

Thus, we went through a deep investigation about the ligand effect and two set of reactions were carried out. The conditions are described in Table 14.4. The first and the second set were different for the copper source and for the solvent (CuCl in THF vs CuBr in MeCN). With the aim to promote an enantioselective transformation, several chiral phosphines and bis(oxazoline) derivatives (Box) were tested as ligands. Unfortunately, only a poor ee could be achieved using *R*,*R*-MeDuphos in THF and (*S*)-DM-Segphos in MeCN (Table 14.4, entries 2 and 6). Similar or more hindered phosphines such as (*R*)-Fluorophos or (*R*)-DTBM-Segphos (Table 14.4, entries 7 and 8) did not afford any enantioselectivities. Nonetheless, some ligands in

CuBr/MeCN conditions proved to make the process highly regioselective (Table 14.4, entries 1, 6, 7).

Table 14.3. Solvent screening for hydroboration of 4-phenylbut-1-ene



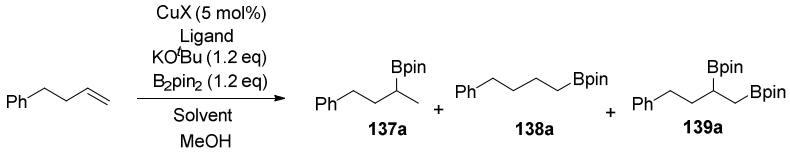
Entry	Solvent	conv (%)	137a:138a:139a[a]	*ee*%	Entry	Solvent	conv (%)
1	Et_3N	25	97:3	0	13	DMSO	41[b]
2	^{t}BuCN	84	30:8:62 (79:21)	0	14	PhCN	n.r.
3	^{n}PrCN	61	49:15:36 (77:23)	0	15		n.r.
4	DME	82	27:12:61 (70:30)	0	16	$CHCl_3$	n.r.
5	$^iPr_2O$	16	57:25:18 (69:31)	0	17	Nitromethane	n.r.
6	1,4 Dioxane	57	57:32:11 (64:36)	0	18	DCE	n.r.
7	$PhCF_3$	49	58:37:4 (61:39)	0	19	Acetone	n.r.
8	2-Me-THF	75	35:25:40 (58:42)	0	20	C_6F_6	n.r.
9	Fluorobenzene	49	53:41:6 (57:43)	0	21	Pyridine	n.r.
10	Chlorobenzene	68	52:45:3 (54:46)	0	22	$ClCH_2CN$	n.r.
11		75	13:6:81	0	23	NMP	n.r.
12	Hexane:Tol (1:1)	65	61:39	0			

[a] **137a:138a** ratio is reported in the brackets
[b] Only diboronic ester **139a** was formed

Taking into account difficulties encountered in promoting an enantioselective synthesis, we turned our attention on the regioselective access to racemic mixture of Markovnikov hydroboration product of unactivated terminal olefins.

On the basis of these considerations we reacted 1-octene in the presence of those ligands that gave major **137**:**138** ratio when 4-phenylbut-1-ene was used as the substrate. Under these conditions **137b** and **138b** were formed in variable ratio without clear regioselective access to the Markovnikov product, showing a strong substrate effect in this transformations (Table 14.5).

Table 14.4. Ligand screening for hydroboration of 4-phenylbut-1-ene[a]



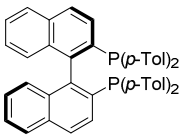
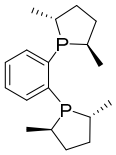
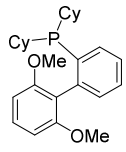
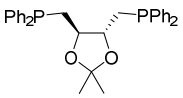
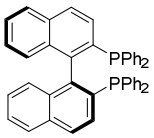
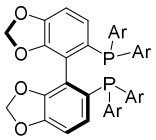
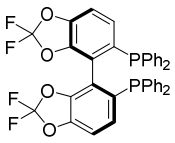
Entry	Ligand	%mol	CuCl/THF % Conv	**137a:138a**	ee%	CuBr/MeCN % Conv	**137a:138a**	ee %
1	 (*R*)-Tol-BINAP	5	n.d	69:31	0	43	97:3	0
2	 (*R,R*)-MeDuphos	5	n.d.	49:51	28	28	83:17	0
3	 SPhos	10	n.d.	80:20	0	38	94:6	0
4	 (*R*)-DIOP	5	n.d.	11:89	0	51	61:39	0
5	 (*S*)-BINAP	5	n.d.	72:28	0	76	91:9	0
6	 Ar = 3,5-Me-C_6H_3 (*S*)-DM-Segphos[a]	5	n.d.	52:48	0	38	98:2	20
7	 (*R*)-Fluorophos	5	n.d.	52:48	0	78	93:7	0

Table 14.4. | Continued

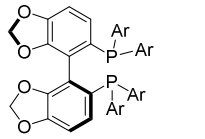
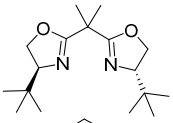
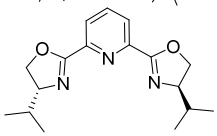
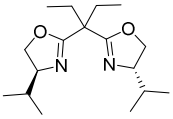
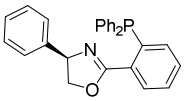
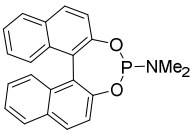
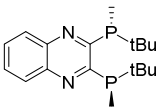
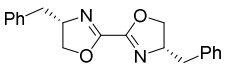
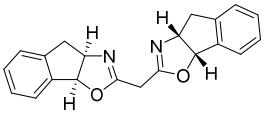
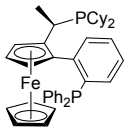
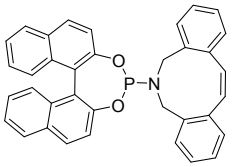
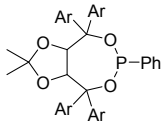
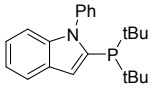
Entry	Ligand	%mol	CuCl/THF % Conv	CuCl/THF **137a:138a**	CuCl/THF ee%	CuBr/MeCN % Conv	CuBr/MeCN **137a:138a**	CuBr/MeCN ee %
8	 Ar = 3,5-^{t}Bu-4-MeO-C_6H_2 (*R*)-DTBM-Segphos	5	n.d.	n.d.	0	n.d.	81:19	0
9		5	69	74:16	0	n.d.	n.d.	n.d.
10		5	47	82:18	0	66	79:21	0
11		5	55	85:15	0	n.d.	n.d.	n.d.
12		5	45	82:18	0	70	86:14	0
13		10	16	82:18	0	n.d.	n.d.	n.d.
14		10	33	90:10	0	6	80:20	**0**
15		5	57	22:78	**0**	<15	84:16	0
16		5	36	93:7	0	41	81:19	0
17		5	72	80:20	0	<15	85:15	0

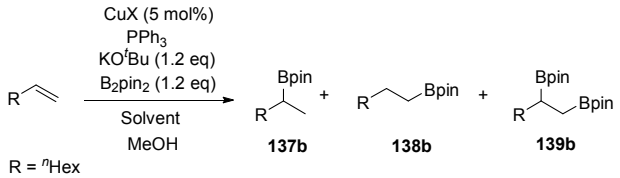
Table 14.4 | Continued

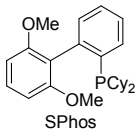
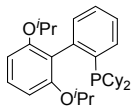
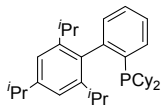
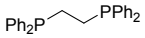
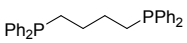
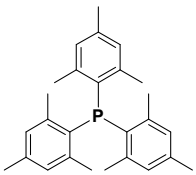
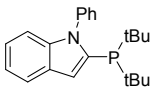
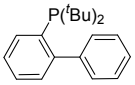
Entry	Ligand	%mol	CuCl/THF			CuBr/MeCN		
			% Conv	**137a:138a**	ee%	% Conv	**137a:138a**	ee %
18		5	33	86:14	0	33	88:12	0
19		10	25	89:11	0			
20		10	76	76:24	--			
21		10	n.d.	75:25	--			
22	PCy_3	10	n.d.	74:26	--	--	--	--

[a] A variable amount of the diboronic ester 139a was always detected

Looking at the results achieved, we hypothesized a relation between the cone angle of trisubstituted phosphines and the branched/linear isomer ratio (Table 14.5). The cone angle of PPh_3, P(*p*Tol)$_3$, P^{t}Bu$_3$, and P(*o*Tol)$_3$ is 145°, 145°, 182° and 194° respectively. A semi-linear increasing of the **137b:138b** ratio was observed moving from PPh_3 to P(*o*Tol)$_3$ in THF. Unfortunately, trimesitylphosphine (cone angle 212°) gave only 73:27 **137b:138b** ratio (Table 14.5, entry 10). Reactivity of 1-hexadecene led generally to the same considerations. Nonetheless, using DM-Segphos as the ligand, 95% of regioselectivity for the branched isomer was achieved. As a further step we evaluated the effect of the proton source on the outcome of the reaction. Several compounds were tested but, beyond methanol, only hexafluoroisopropanol and trifluoroethanol proved to be effective in promoting the trasformation, despite with a low conversion and without advantages in the regioselectivity. Compounds tested as proton sources are ordered in Table 14.6 as increasing pK_a values.

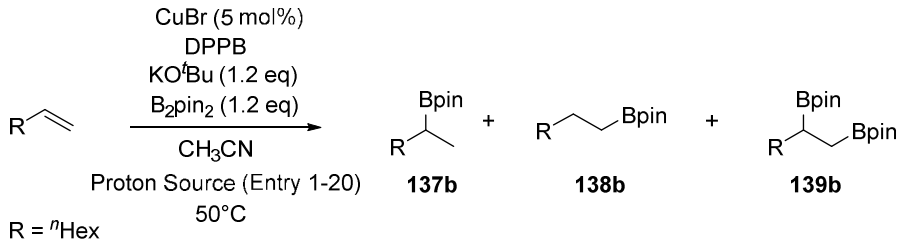
Table 14.5. Ligand screening for hydroboration of 1-hexene

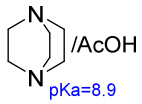
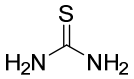
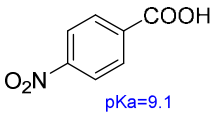
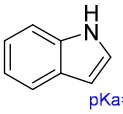
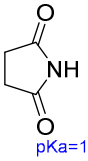
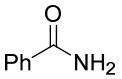
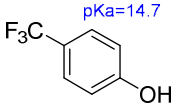
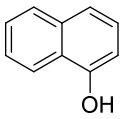
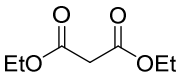
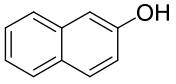


Entry	Ligand	%mol	CuCl/THF		CuBr/MeCN	
			% Conv	**137b:138b:139b**[a]	% Conv	**137b:138b:139b**[a]
1	 SPhos	10	n.d.	16:6:78 (73:27)	n.d.	0:0:100
2	 Ruphos	10	n.d.	31:14:55 (68:32)	23	16:4:80 (80:20)
3	 XPhos	10	n.d.	0:0:100	81	6:3:91 (67:33)
4	 DPPE	5	n.d	43:56:1 (43:57)	n.d.	7:3:90 (71:29)
5	 DPPB	5	n.d.	42:20:38 (68:32)	n.d.	26:5:69 (85:15)
6	PPh3	10	n.d.	25:54:21 (31:69)	n.d.	57:17:26 (77:23)
7	(*S*)-DM-Segphos	5			n.d.	(78:22:0) 78:22
8	P(*o*-Tol)$_3$	10	n.d.	39:8:53 (83:17)	n.d.	63:17:21 (79:21)
9	P(*p*-Tol)$_3$	10	n.d.	28:46:26 (38:62)	n.d.	38:8:56 (81:19)
10		10	19	69:18:33 (73:27)	n.d.	43:15:42 (74:26)
11	P^{t}Bu$_3$	10	n.d.	32:12:57 (73:27)	n.d.	24:5:71 (83:17)
12		10	n.d.	38:14:48 (74:26)	n.d.	36:10:54 (78:22)
13	 Johnphos	10	n.d.	44:15:41 (74:26)	n.d.	15:2:83 (87:12)

[a] **137b:138b** ratio is reported in brackets

Table 14.6. Proton source screening in hydroboration reaction



Entry	H^+ Source	137b:138b	Entry	H^+ Source	137b:138b
1	 /AcOH pKa=8.9	n.r.	11	 pKa=21.0	n.r.
2	 pKa=9.1	n.r.	12	 pKa=21.0	n.r.
3	AcOH pKa=12.6	n.r.	13	 pKa=23.0	n.r.
4	 pKa=14.7	n.r.	14	 pKa=23.3	n.r.
5	 pKa=15.3	n.r.	15	CF_3CH_2OH pKa=23.5	86:14[a]
6	 pKa=16.2	n.r.	16	 pKa=25.2	n.r.
7	 pKa=16.4	n.r.	17	EtOH pKa=29.8	n.r.
8	 pKa=17.2	n.r.	18	^{i}PrOH pKa=30.3	n.r.
9	$(CF_3)_2CHOH$ pKa=17.9	72:28[a]	19	tBuOH pKa=32.2	n.r.
10	PhOH pKa=18.0	n.r.			

[a] Traces of product, diboronic ester was observed as main product (76%)

[b] Conversion: 28%. Diboronic ester was not formed

14.3 Conclusions

In conclusion, we investigated the unexplored Markovnikov Cu(I) catalysed hydroboration of unanctivated terminal olefins. A series of factors were evaluated to optimise the outcome of the reaction and, despite enantioselective transformations could not be achieved (best result 65:35 er), interesting results about the formation of the Markovnikov isomer were obtained. Branched isomers of the substrates examined were synthesised together with a 2-12% of the linear product arose from anti-Markovnikov addition.

14.4 References

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Chapter 15

Stereoselective synthesis of 1,2-diboronic esters through *lithiation-borylation* and their functionalization

15.1 Introduction

Optically active 1,2-diols are an important class of organic compounds used for synthetic intermediates of bioactive or pharmaceutical compounds.[1] They have commonly been synthesized by direct asymmetric dihydroxylation of alkenes with osmium reagents,[2] asymmetric hydrogenation of α-hydroxyketones,[3] asymmetric hydrolytic kinetic resolution of epoxides,[4] and enzymatic reactions,[5] to name a few.

Besides these methods, direct dihydroxylation of alkenes with osmium-free catalysts has recently attracted attention[6] and some iron catalysts have also been explored.[7] Asymmetric 1,2-diboration of alkenes and subsequent oxidation can provide optically active 1,2-diols.[8-11] Moreover, C-B bond of boronic esters can be conveniently transformed into a number of functionalities making the synthesis of these compounds even more attracting.

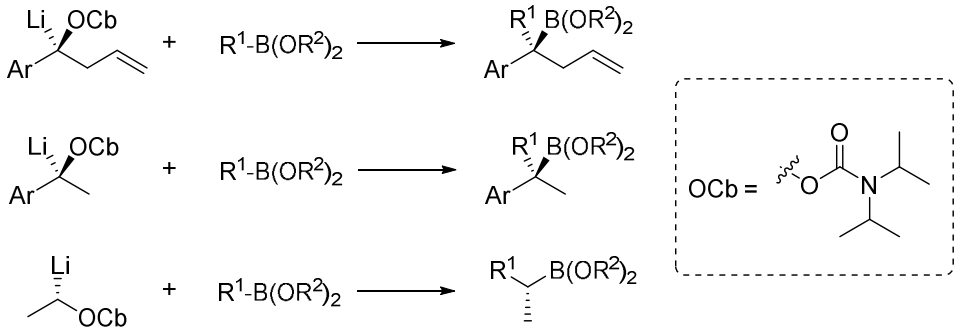
Efficient, reliable, and practical synthetic methods of optically active 1,2-diols (and 1,2-diboronic esters) are still in demand to solve challenging subjects such as expanding substrate scope (i.e. tertiary alcohols), attaining a high level of enantioselectivity, or making the reaction environmentally more benign.

Taking into account these considerations, we envisioned a novel route to access 1,2-diboronic esters through lithiation-borylation methodology.

15.2 Results and discussion

In recent years, Aggarwal and co-workers have developed lithiation–borylation methodology of primary[12] and secondary[13] carbamates for the stereocontrolled synthesis of secondary and tertiary boronic esters (Scheme 15.1). The process is

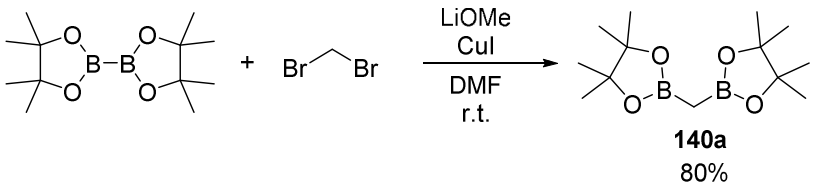
related to Blakemore's reactions of α-lithiated alkylchlorides[14] and follows the fundamental work of Matteson on 1,2-metallate rearrangements of boronic esters.



Scheme 15.1. Reaction of lithiated carbamates with bronic esters

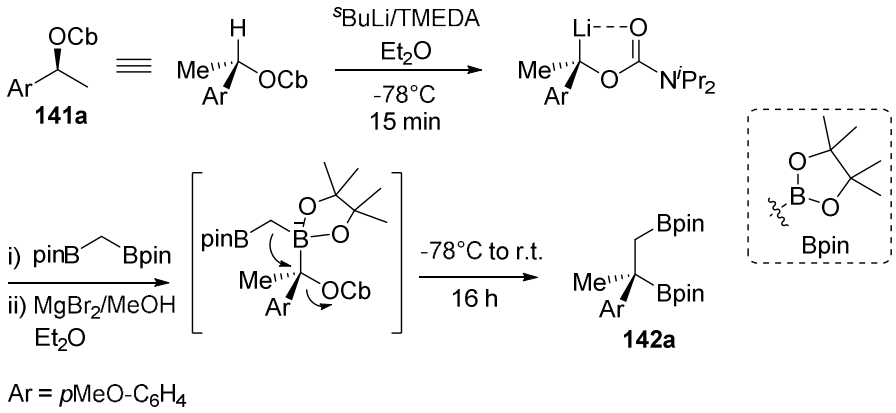
Secondary *N*,*N*-diisopropyl carbamates could be achieved from the enantioenriched secondary alcohols. These could be obtained from commercial sources, prepared from the corresponding acetophenones by Noyori asymmetric transfer hydrogenation or by enzymatic resolution of the racemate. *N*,*N*-diisopropyl carbamates could be deprotonated with ^{s}BuLi in Et_2O at –78 °C, and then reacted with a boronic ester (–78 °C). On warming, the intermediate 'ate' complexes underwent 1,2-migration to give the corresponding homologated boronic esters in good yields and high enantioselectivities. Primary carbamates could be easily obtained from the corresponding primary alcohols and their asymmetric deprotonation could be induced by using of ^{s}BuLi/(-)-spartein.[15] Product of opposite enantioselectivity could be obtained by replacing (-)-spartein with (+)-spartein or with O'Brien's (+)-spartein surrogate.[16] The boronic esters could be *in situ* oxidised to afford chiral alcohols or utilized in further omologations.

We considered the use of this reaction with a suitable symmetric diboronic ester for the synthesis of the title 1,2-diboronic esters. Thus, bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane **140a** was obtained following literature procedure[17] from bis(pinacolato)diboron and CH_2Br_2 (Scheme 15.2).



Scheme 15.2: Synthesis of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane

To test this reactivity, (*S*)-1-(4-methoxyphenyl)ethyl diisopropylcarbamate (**(*S*)-141a**, 98:2 er) was synthesized from (*S*)-1-(4-methoxyphenyl)ethan-1-ol, obtained following one of the methods described above. Then, lithiation of the carbamate was performed using ^{s}BuLi/TMEDA in Et_2O at -78°C (Scheme 15.3).



Scheme 15.3. Proposed lithiation-borylation route to 1,2-diboronic esters

The reaction was conducted under two conditions: (i) conditions **A**: addition of the boronic ester to the lithiated carbamate at -78 °C followed by warming to room temperature for 16 h; (ii) conditions **B**: addition of the boronic ester to the lithiated carbamate at -78 °C followed after 2 h by addition of 1.7 equivalents of a solution of $MgBr_2$ in MeOH and subsequent warming to room temperature for 16 h. Under conditions **B**, the reaction gave tertiary boronic ester **142a** in higher yield (81%) and enantiospecificity (100 es, 98:2 er). $MgBr_2$ in MeOH as additive is known to have two distinct effects on lithiation-borylation reactions: (i) it increases the relative rate of 1,2-migration of the intermediate boronate complex over reversibility back to the starting components and (ii) any anions formed from reversibility are quenched, thus preventing re-addition.[13b,18] In almost all cases studied, the yield of the boronic

ester was significantly increased with this additive, thus demonstrating its ability in promoting 1,2-migration over reversal. Without this additive, the lower yield is likely to be due to decomposition of the boronate complex back to the starting materials.

The reaction proceeds with almost complete retention of the stereochemistry because of the oxygen of the ester complexes with the lithium of the metallated carbamate and so is delivered on the same face as the metal (Figure 15.1).

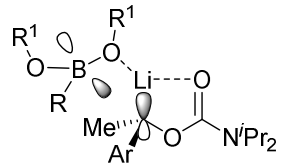
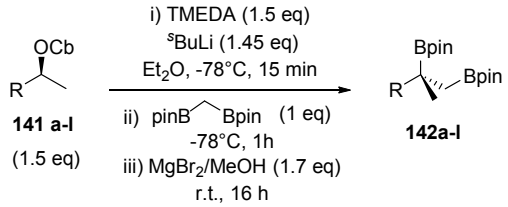


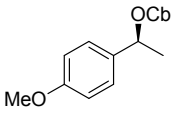
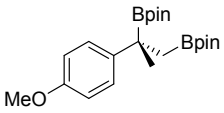
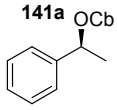
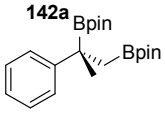
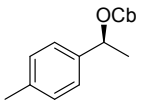
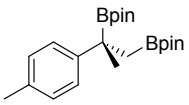
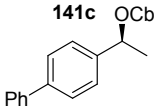
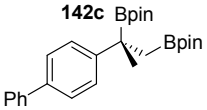
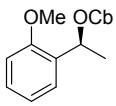
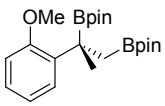
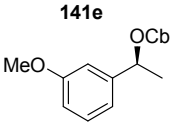
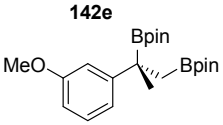
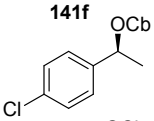
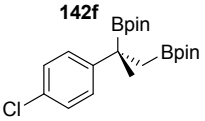
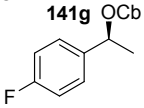
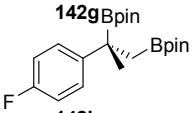
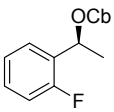
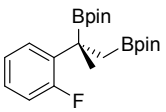
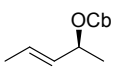
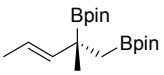
Figure 15.1. Retention of configuration in the reaction of lithiated carbamates with boronic esters

Having demonstrated the possibility to access enantioenriched 1,2-diboronic esters, we went through an exploration of the scope and limitations of this methodology. Thus, different tertiary benzylic carbamates were reacted with **140a** under the described conditions (Table 15.1, entries 1-9) to afford the corresponding 1,2-diboronic esters differently substituent on the aromatic ring. We examined carbamates bearing both electron-rich (*p*MeO-C_6H_4, *p*Me-C_6H_4, *o*MeO-C_6H_4, *m*MeO-C_6H_4, Table 15.1, entries 1,3,5,6) and electron-deficient (*p*Cl-C_6H_4, *p*F-C_6H_4, *o*F-C_6H_4, Table 15.1, entries 7, 8, 9) aromatics. The 1,2 diboronic esters were generally isolated in good yields for the *p*-substituted derivatives, while a decreasing was noticed for the *o*-substituded. In all cases the enantiospecificities observed were high (es 98-100%).

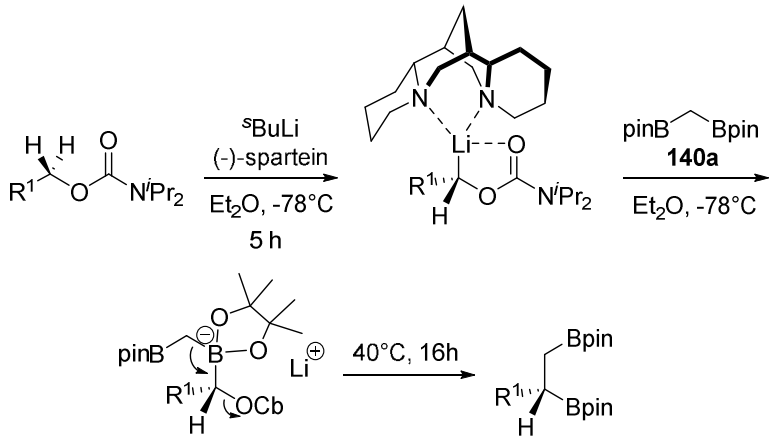
The secondary allylic carbamate **141l** proved as well effective in this transformation and the diboronic ester **142l** was isolated in good yield and with a good er (Table 15.1, entry 10). Having studied the reactivity of secondary carbamates, we moved to explore the behavior of primary carbamates using this methodology. As discussed above, symmetric deprotonation on these substrate can be achieved by using chiral amines such as (+)- or (-)-spartein (Scheme 15.4).

Table 15.1. Synthesis of 1,2-diboronic ester through lithiation-borylation of secondary diisopropylcarbamates



Entry	Diisopropylcarbamate	1,2-diboronic ester	er	Yield (%)
1	 **141a**	 **142a**	98:2	81
2	 **141b**	 **142b**	98:2	76
3	 **141c**	 **142c**	98:2	68
4	 **141d**	 **142d**	95:5	67
5	 **141e**	 **142e**	>99:1	45
6	 **141f**	 **142f**	87:13	62
7	 **141g**	 **142g**	98:2	73
8	 **141h**	 **142h**	>99:1	75
9	 **141i**	 **142i**	99:1	46
10	 **141l**	 **142l**	99:1	73

In this context, primary carbamates **141m,n** were reacted under lithiation-borylation conditions with **140a**. Reaction performed in the presence of (+) spartein afforded **(2*S*)-142m** and **(2*S*)-142n** while (-)-spartein induced the synthesis of the diastereoisomers at C-2 **(2*R*)-142m** and **(2*R*)-142n** (Table 15.2, entries 1-4).



Scheme 15.4: Lithiation of primary carbamates in the synthesis of diboronic esters

The reaction proved to be efficient and the d.r. observed was higher than 20:1, revealing that a matched/mis-matched effect is not detectable, despite products **(2*R*)-142m** and **(2*R*)-142n** were isolated in lower yields.

Aggarwal and co-workers reported 2,4,6-triisopropylbenzoates (TIB esters) as a more reactive substrates in lithiation-borylation, showing an increase in the rate of 1,2-migration compared with *N*,*N*-diisopropylcarbamates. This achievement was particolary interesting to broad the scope of lithiation borylation methodology to the synthesis and homologation of challenging boronic esters.

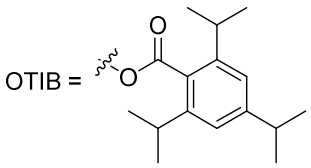
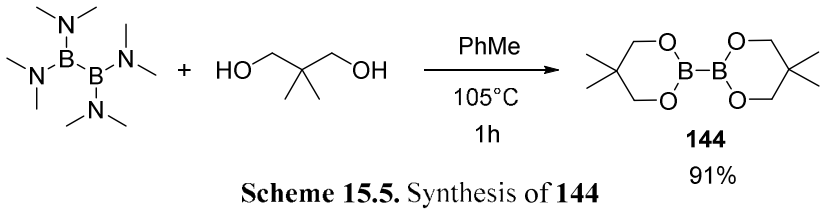


Figure 15.2

Primary TIB esters were easily obtained from their corresponding alcohols by direct acylation with 2,4,6-triisopropylbenzoyl chloride (TIBCl).[19]

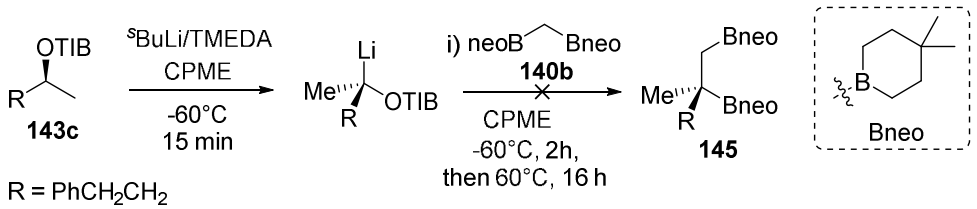
In this context, 2,4,6-triisopropylbenzoates **143a,b** were lithiated in presence of (+)-spartein and treated with **140a** under the conditions described above affording the corresponding 1,2-diboronic esters in good yields and with good enantioselectivities (Table 15.2, entries 5, 6).

The only limitation of the present methodology was found in secondary alkyl 2,4,6-triisopropylbenzoates **143c** (Table 15.2, entry 7) that proved to be unreactive despite the reaction was performed in different conditions (Cyclopentyl methyl ether - CPME - as the solvent and raising the temperature at -60°C). Previously study reported by Aggarwal demonstrated a higher reactivity of neopentyl boronic esters with respect to their pinacol analogues, especially for hindered and challenging substrates.[18] Thus, we sought for a possible use of the diboronic ester **140b** in this methodology. 5,5,5',5'-Tetramethyl-2,2'-bi(1,3,2-dioxaborinane) **144** was synthesized following literature procedure[20] (Scheme 15.5) and then reacted with dibromomethane as described above in the Scheme 15.2 affording **140b**.



Scheme 15.5. Synthesis of **144**

Unfortunately, when **140b** was used in lithiation borylation under the described conditions the wanted diboronic ester **145** was not achieved.



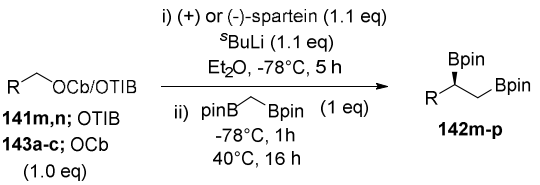
Scheme 15.6

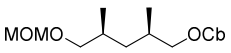
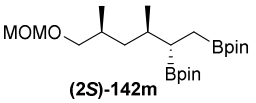
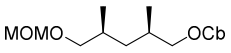
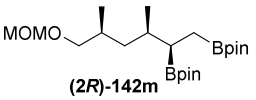
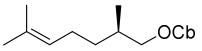
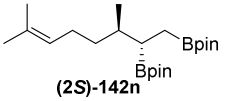
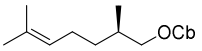
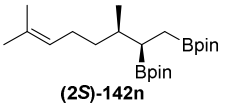
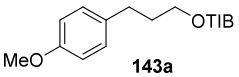
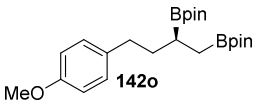
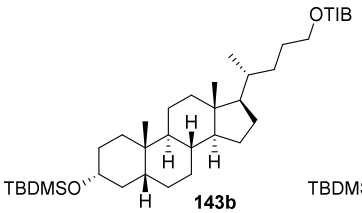
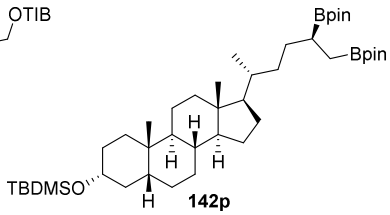
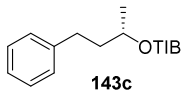
Having found a general procedure for the synthesis of enantioenriched 1,2 diboronic esters and having demonstrated its wide scope, we wished to demonstrate

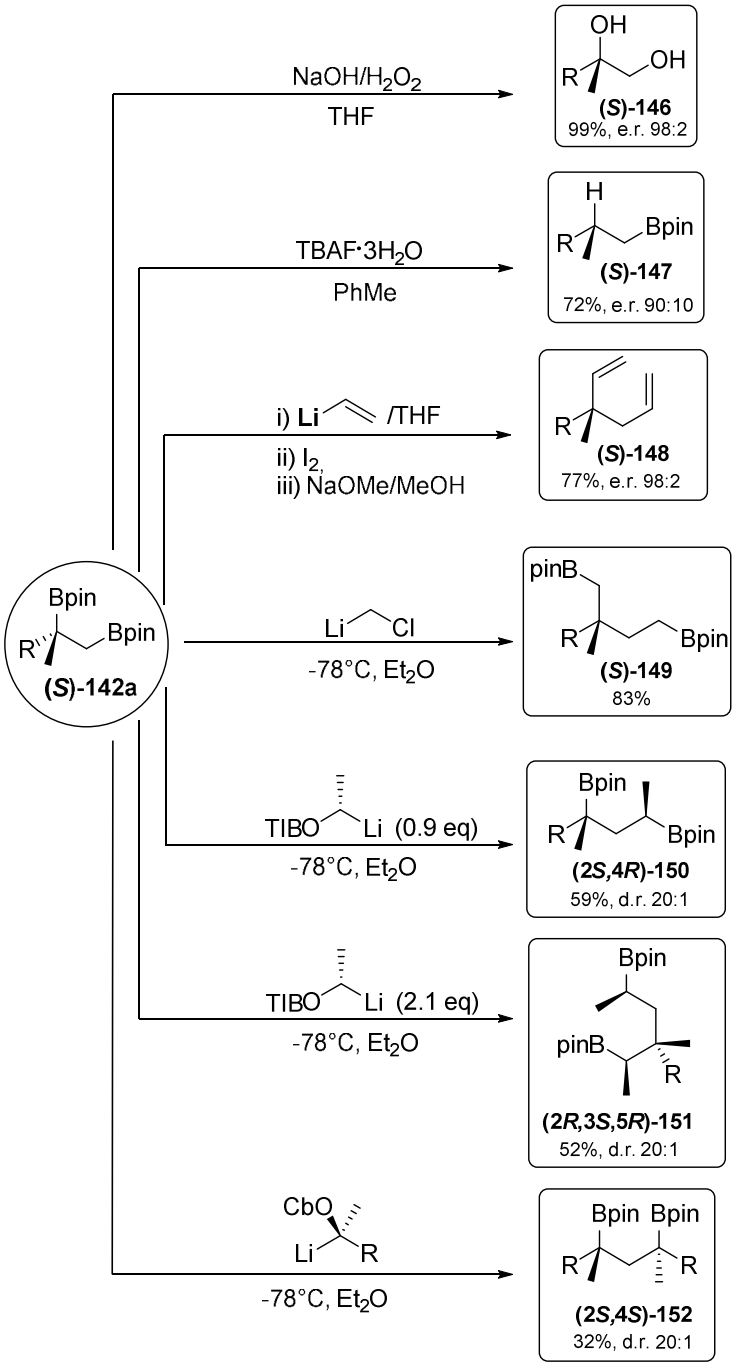
the synthetic utility of the these boronic esters by conversion to other functional groups.

Thus, **(*S*)-142a** was oxidised with an excess of alkaline hydrogen peroxide to afford the chiral tertiary diol **(*S*)-146** in good yields and high enantioselectivity.

Table 15.2. Synthesis of 1,2-diboronic ester through lithiation-borylation of primary diisopropylcarbamates and triisopropylbenzoates



Entry	Substrate	1,2-diboronic ester	e.r. or d.r.	Yield (%)
1	 **141m**	 **(2*S*)-142m**	>20:1	69
2	 **141m**	 **(2*R*)-142m**	>20:1	31
3	 **141n**	 **(2*S*)-142n**	>20:1	39
4	 **141n**	 **(2*S*)-142n**	>20:1	36
5	 **143a**	 **142o**	97:3	71
6	 **143b**	 **142p**	>20:1	73
7	 **143c**	--	--	--



Scheme 15.7. Functionalization of 1,2-diboronic esters

TBAF promoted protodeboronation[21] of **(*S*)-142a** led to the formation of the enantioenriched boronic ester **(*S*)-147** in 72% yield. The e.r. of the product could be increased under slightly modified conditions.

Diboronic ester **(*S*)-142a** was reacted under Zweifel olefination conditions[22] with vinyl lithium (generated *via* tin−lithium exchange) to give the enantioenriched diene **(*S*)-148** in 77% yield and 98:2 e.r. (Scheme 15.7). **(*S*)-142a** was also one-carbon homologated under Matteson conditions[23] with chloromethyllithium (generated *in situ* from bromochloromethane and ^{n}BuLi) to form the corresponding 1,4 diboronic ester **(*S*)-149** in 83% yield and complete enantiospecificity.

Homologation based on lithiation borylation methodology[12c,24] under different conditions afforded products **150** and **151**. Slowly adding a solution of (*S*)-(1-((2,4,6-triisopropylbenzoyl)oxy)ethyl)lithium (generated *via* tin-lithium exchange) in Et_2O at -78°C to **(*S*)-142a** (Et_2O solution at -78°C) primary boronic ester is selectively homologated, leaving untouched the tertiary function, to afford the product **150** with two controlled stereocenters and two boronic esters which can be further functionalized.

When an excess of the same lithium derivative is used both the esters are homologated leading to the corresponding 1,4-diboronic ester **151** with three controlled (two contiguous) stereocenters.

Selective homologation of the primary function with the lithium species generated from **141a** led to the formation of the scarcely accessible 1,3-diboronic ester **152**, bearing two stereocontrolled tertiary esters that could be easily oxidised to the corresponding enantioenriched hindered 1,3-diol.

15.3 Conclusions

In conclusion we developed an efficient and versatile methodology to access enantioenriched 1,2-diboronic esters through lithiation borylation. The wide scope of such process allows its possible application in the synthesis of chiral building blocks that could be assembled to obtain natural or biologically active molecules. Further functionalization of diboronic esters were demonstrated, hence showing a possible use of these compounds as a useful intermediates in highly enantioselective

synthesis of complex molecules. Lithiation borylation on 1,2-diboronic esters allowed the enantioselective homologation disclosing a possible their application in assembly-line synthesis.

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Chapter 16

Experimental part

General

NMR spectra were recorded in $CDCl_3$ or CD_3OD with Varian Gemini 200, Mercury 400 and Inova 400 spectrometers operating at 200 and 400 MHz (^1H), 50 and 100 (^{13}C), 38 MHz (^{77}Se NMR). NMR signals were referenced to non deuterated residual solvent signals of chloroform (7.26 ppm for ^1H, 77.0 ppm for ^{13}C) or methanol (3.31 ppm for ^1H, 44.9 ppm for ^{13}C). For 77Se spectra, $(PhSe)_2$ was used as external reference (461 ppm).

Mass spectra (MS) were obtained at 70eV ionization potential and by ESI.

High resolution mass spectra (HRMS) were recorded on a VG Analytical Autospec by Electron Ionisation (EI) or Chemical Ionisation (CI) or on a Brüker Daltonics Apex IV by Electrospray Ionisation (ESI). IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR as a thin film. Only selected absorption maxima (νmax) are reported in wavenumbers (cm^{-1}).

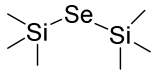
Optical rotation $[\alpha]_D^T$ was measured on a Bellingham and Stanley Ltd. ADP220 polarimeter.

Chiral SFC was performed on a Waters TharSFC system and monitored by DAD (Diode Array Detector).

Compound names are those generated by ChemBioDraw 13.0 software (PerkinElmer), following the IUPAC nomenclature.

Solvent were dried using a solvent purification system (Pure-Solv™). Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Flash column chromatography was performed, if not specified, using silica gel (230-400 mesh). Where not specified products were commercially available or obtained through reported procedures.

Synthesis of bis(trimethylsilyl)selenide (2)



bis(trimethylsily)selenide - HMDSS - was obtained through a modified standard procedure.[1] Se(0) (19 mmol, 1 eq.) was portionwise added to a suspension of $NaBH_4$ (42 mmol, 2.2 eq.) in 35 mL of dry THF at room temperature in a schlenk tube under inert atmosphere. The reaction was stirred for 24 h and then Me_3SiCl (47.5 mmol, 2.5 eq.) was slowly added. After 3 h the mixture was diluted with pentane and filter through celite under N_2. Elimination of the solvents under reduced pressure gave **2**, pure enough to be used without a further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.46 (18H, s) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 4.7 ppm.

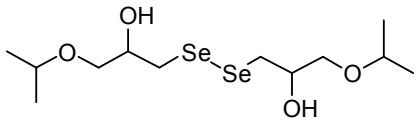
^{77}Se NMR (38 MHz, $CDCl_3$): δ = -337.2 ppm.

MS (EI) *m/z* (%): 226 (27, $M^{+\cdot}$), 211 (56), 73 (100).

Synthesis of β-hydroxy diselenides (4). General procedure

A solution of epoxide **3** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1.6 mmol) in dry THF (3 mL), was treated under inert atmosphere with TBAF (0.64 mL of 1M THF solution, 0.64 mmol). After stirring for 4 h, the solution was diluted with diethyl ether, washed with water and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford a crude product, which was purified on silica gel as described for each product.

3,3-Diselanediylbis(1-isopropoxypropan-2-ol) (4a)



Following the general procedure, starting from 2-(isopropoxymethyl)oxirane (100 mg, 0.86 mmol), after purification (petroleum ether/ethyl acetate 1:1), 3,3-diselanediylbis(1-isopropoxypropan-2-ol) was obtained as a 3:2 mixture of two diastereoisomers (129 mg, 68%).

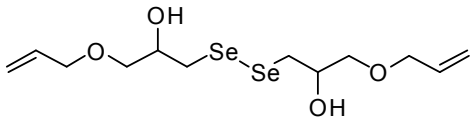
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (12H, d, *J*=6.0 Hz), 1.17 (12H, d, *J*=6.0 Hz), 2.47 (4H, bs), 3.06-3.19 (4H, m), 3.40-3.66 (16H, m), 3.87-3.94 (2H, m, major diastereoisomer), 3.96-4.03 (2H, m, minor diastereoisomer) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 34.1, 70.3, 70.9, 71.2, 72.2, 72.3 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 279.8, 280.4 ppm.

MS (EI) *m/z* (%): 394 (2.60, $M^{+\cdot}$), 99 (19), 75 (42), 73 (15), 59 (6), 58 (11), 57 (75), 43 (100), 41 (24), 39 (4).

3,3'-Diselanediylbis(1-(allyloxy)propan-2-ol) (4b)



Following the general procedure, starting from 2-((allyloxy)methyl)oxirane (100 mg, 0.88 mmol), after purification (petroleum ether/ethyl acetate 2:1), 3,3'-diselanediylbis(1-(allyloxy)propan-2-ol) was obtained as a mixture of diastereoisomers (104 mg, 61%).

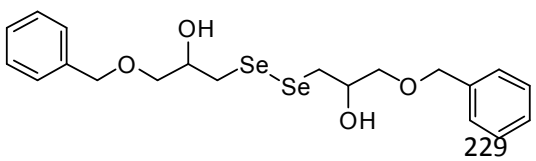
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.63 (4H, bs), 3.09 (4H, dd, *J*=7.2, 12.8 Hz), 3.16 (4H, dd, *J*=5.2, 12.8 Hz), 3.44-3.58 (8H, m), 4.02-4.06 (12H, m), 5.21-5.31 (8H, m), 5.82-5.96 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.9, 34.0, 35.7, 69.7, 70.2, 72.4, 72.9, 73.2, 117.4, 134.3 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 279.4 ppm.

MS (EI) *m/z* (%): 390 (1, $M^{+\cdot}$), 195 (7), 97 (12), 71 (6), 58 (9), 57 (26), 45 (5), 43 (21), 41 (100), 39 (13).

3,3'-Diselanediylbis(1-(benzyloxy)propan-2-ol) (4c)



Following the general procedure, starting from 2-

((benzyloxy)methyl)oxirane (100 mg, 0.61 mmol), after purification (petroleum ether/ethyl acetate 2:1), 3,3'-diselanediylbis(1-(benzyloxy)propan-2-ol) was obtained as a mixture of two diastereoisomers (137 mg, 92%).

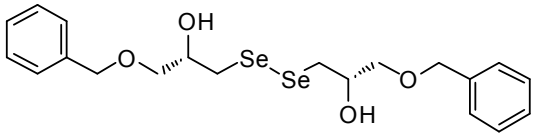
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (4H, bs), 3.03-3.19 (8H, m), 3.48-3.65 (8H, m), 4.01-4.09 (4H, m), 4.56 (8H, m), 7.28-7.39 (20H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.1, 70.2, 72.9, 73.5, 127.6, 127.7, 128.3, 137.6 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 277.5, 280.3 ppm.

MS (EI) *m/z* (%): 488 (1, $M^{+\cdot}$), 367 (17), 244 (52), 91 (100).

(2*S*,2'*S*)-3,3'-Diselanediylbis(1-(benzyloxy)propan-2-ol) ((2*S*,2'*S*)-4c)



Following the general procedure, starting from (2*R*)-2-((benzyloxy)methyl)oxirane (60 mg, 0.37 mmol), after purification (petroleum ether/ethyl acetate 2:1), (2*S*,2'*S*)-3,3'-diselanediylbis(1-(benzyloxy)propan-2-ol) was obtained (78 mg, 83%).

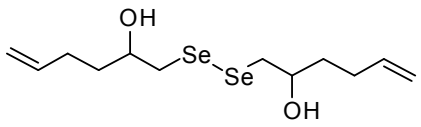
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (2H, bs), 3.09 (2H, dd, *J*=4.8, 12.8 Hz), 3.16 (2H, dd, *J*=7.6, 12.8 Hz), 3.50-3.62 (4H, m), 4.01-4.12 (2H, m), 4.56 (4H, ap s), 7.30-7.36 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.1, 70.2, 72.9, 73.5, 127.6, 127.7, 128.3, 137.6 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 277.5 ppm.

MS (EI) *m/z* (%): 488 (1, $M^{+\cdot}$), 367 (17), 244 (52), 91 (100).

1,1'-Diselanediylbis(hex-5-en-2-ol) (4d)



Following the general procedure, starting from 2-(but-3-en-1-yl)oxirane (60 mg, 0.61 mmol), after purification (petroleum ether/ethyl acetate 3:1), 1,1'-diselanediylbis(hex-5-en-2-ol) was obtained as a 3:2 mixture of two diastereoisomers (104 mg, 61%).

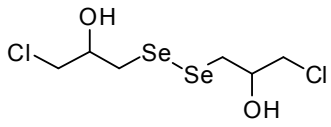
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58-1.71 (8H, m), 2.11-2.30 (8H, m), 2.41 (4H, bs), 2.58-2.65 (2H, m), 2.81-2.86 (2H, m), 2.95-3.03 (2H, m), 3.13-3.19 (2H, m), 3.68-3.78 (2H, m, minor diastereoisomer), 3.81-3.89 (2H, m, major diastereoisomer), 4.97-5.10 (8H, m), 5.75-5.88 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.0, 30.1, 35.6, 36.0, 38.5, 38.7, 69.9, 70.4, 115.1, 137.9; 138.0 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 267.6, 268.6 ppm.

MS (EI) *m/z* (%): 258 (10), 97 (16), 83 (30), 67 (54), 55 (67), 43 (100), 41 (84), 39 (69).

3,3'-Diselanediylbis(1-chloropropan-2-ol) (4e)



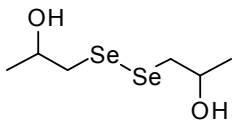
Following the general procedure, starting from 2-(chloromethyl)oxirane (30 mg, 0.31 mmol), after purification (petroleum ether/ethyl acetate 2:1), 3,3'-diselanediylbis(1-chloropropan-2-ol) was obtained as a mixture of two diastereoisomers (23 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.85-3.12 (12H, m), 3.65 (8H, bd, *J*=5.2 Hz), 3.96-4.09 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.8, 48.3, 71.0, 71.1 ppm.

MS (ESI, positive) *m/z*: 368 ($[M+Na]^+$).

1,1'-Diselanediylbis(propan-2-ol) (4f)



Following the general procedure, starting from **3f** (58 mg, 1.00 mmol), after purification (petroleum ether/ethyl acetate 2:1), 1,1'-diselanediylbis(propan-2-ol) was obtained as a mixture of two diastereoisomers (71 mg, 61%).

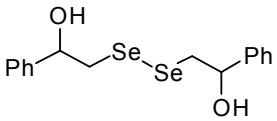
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (12H, d, *J*=6.2 Hz), 2.38 (4H, bs), 2.94-3.01 (4H, m), 3.12 (2H, dd, *J*=3.6, 4.8 Hz), 3.15 (2H, dd, *J*=3.6, 4.8 Hz), 4.00-4.08 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5, 39.8, 67.1 ppm.

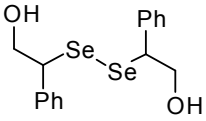
^{77}Se NMR (38 MHz, $CDCl_3$): δ = 268.0 ppm.

MS (EI) *m/z* (%): 278 (9, $M^{+\cdot}$), 219 (1), 160 (14), 121 (3), 93 (4), 59 (100).

2,2'-Diselanediylbis(1-phenylethanol) (4g)



Major



Minor

Following the general procedure, 2-phenyloxirane (40 mg, 0.33 mmol) gave, after purification (petroleum ether/ethyl acetate 4:1), the *major* regioisomer 2,2'-diselanediylbis(1-phenylethanol) as a mixture of two diastereoisomers (49 mg, 64%), together with a 20% of a distereoisomeric mixture of the *minor* regioisomer 1,1'-diselanediylbis(2-phenylethanol).

Major regioisomer (**4g**-*major*)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.83 (4H, bs), 3.17-3.37 (8H, m), 4.89-4.98 (4H, m), 7.21-7.48 (20H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.6, 39.8, 73.2, 73.3, 125.8, 128.0, 128.6, 142.3 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 279.2, 279.8 ppm.

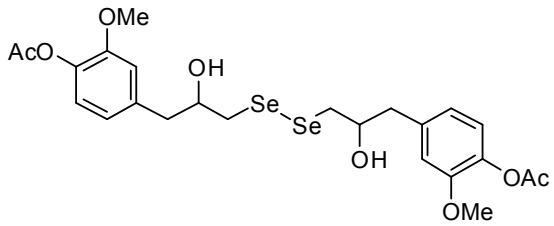
Minor regioisomer (**4g**-*minor*)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.83 (4H, bs), 3.35-3.61 (8H, m), 4.99-5.11 (4H, m), 7.21-7.48 (20H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.4, 72.6, 125.8, 128.0, 128.6, 142.3 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 262.5, 264.5 ppm.

(Diselanediylbis(2-hydroxypropane-3,1-diyl))bis(2-methoxy-4,1-phenylene) diacetate (4h)



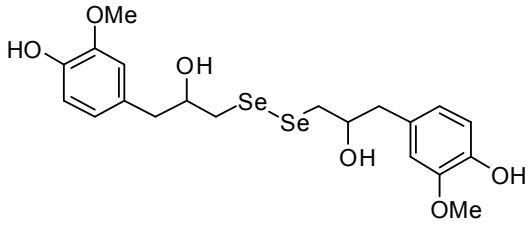
Following the general procedure, starting from **3h** (40 mg, 0.18 mmol), after purification (petroleum ether/ethyl acetate 2:1), **4h** was obtained as a mixture of two diastereoisomers (37 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (12H, s), 2.84 (8H, ap d, ls=6.8 Hz), 2.91-3.02 (4H, m), 3.10-3.20 (4H, m), 3.82 (12H, s), 3.99-4.18 (4H, m), 6.78-6.87 (8H, m), 6.92-7.00 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.7, 37.4, 42.8, 42.9, 55.9, 71.8, 71.9, 111.9, 113.5, 121.5, 122.7, 136.6, 138.3, 150.9, 169.1 ppm.

MS (ESI, positive) *m/z*: 629 $[M+Na]^{+\cdot}$.

4,4'-(Diselanediylbis(2-hydroxypropane-3,1-diyl))bis(2-methoxyphenol) (4i)



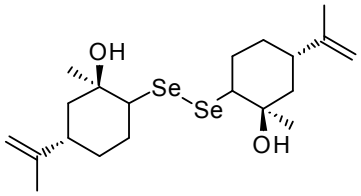
Following the general procedure, starting from 2-methoxy-4-(oxiran-2-ylmethyl)phenol (40 mg, 0.22 mmol), after purification (petroleum ether/ethyl acetate 2:1), **4i** was obtained as a mixture of two diastereoisomers (36 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (4H, bs), 2.63-2.96 (16H, m), 3.87 (6H, s), 3.88 (6H, s), 3.87-3.93 (2H, m), 3.95-4.09 (2H, m), 5.55 (4H, bs), 6.67-6.74 (8H, m), 6.84-6.87 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.6, 33.7, 42.9, 43.1, 56.0, 71.8, 112.1, 114.6, 122.2, 129.6, 144.2, 146.7 ppm.

MS (ESI, positive) *m/z*: 545 $[M+Na]^{+\cdot}$.

(1*R*,4*R*)-2-(((2*R*,4*S*)-2-Hydroxy-2-methyl-4-(prop-1-en-2-yl)cyclohexyl)diselanyl)-1-methyl-4-(prop-1-en-2-yl)cyclohexanol (4l)

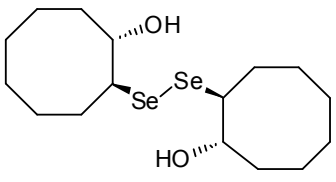


Following the general procedure, starting from (1*R*,4*R*)-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptane (30 mg, 0.2 mmol), after purification (petroleum ether/ethyl acetate 4:1), (1*R*,4*R*)-2-(((2*R*,4*S*)-2-Hydroxy-2-methyl-4-(prop-1-en-2-yl)cyclohexyl)diselanyl)-1-methyl-4-(prop-1-en-2-yl)cyclohexanol was obtained as a mixture of two diastereoisomers (24 mg, 51%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (12H, s), 1.45-1.71 (24H, m), 1.74 (12H, s), 2.05-2.38 (4H, m), 3.41 (2H, bs), 3.63 (2H, bs), 4.77 (8H, ap s) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3, 26.3, 29.5, 33.4, 33.7, 35.2, 35.6, 39.3, 39.4, 56.3, 58.1, 72.4, 109.5, 148.6 ppm.

2,2'-Diselanediyldicyclooctanol (4m)



Following the general procedure, starting from 9-oxabicyclo[6.1.0]nonane (37 mg, 0.29 mmol), after purification (petroleum ether/ethyl acetate 3:1), 2,2'-Diselanediyldicyclooctanol was obtained as a mixture of two diastereoisomers (37 mg, 56%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98-1.52 (24H, m), 1.53-1.79 (16H, m), 1.98-2.22 (8H, m), 2.53-3.05 (8H, m), 3.23-3.78 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.5, 26.7, 27.1, 44.6, 33.3, 34.6, 52.1, 52.5, 75.5 ppm.

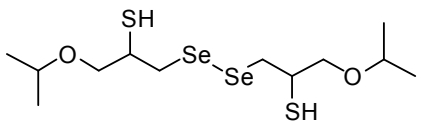
^{77}Se NMR (38 MHz, $CDCl_3$): δ = 299.2, 302.0 ppm.

MS (EI) *m/z* (%): 414 (4, $M^{+\cdot}$), 127 (35), 81 (100), 41 (20).

Synthesis of β-mercapto diselenides (8). General procedure

A solution of thiirane **5** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1.6 mmol) in dry THF (3 mL) was cooled under inert atmosphere at -15°C, and treated with TBAF (0.48 mL of 1M THF solution, 0.48 mmol). After stirring for 1 h, the solution was treated with 50% aqueous solution of citric acid, extracted with diethyl ether, washed with 20% aqueous citric acid, and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford the crude product.

3,3'-Diselanediylbis(1-isopropoxypropane-2-thiol) (8a)



Following the general procedure, starting from 2-(isopropoxymethyl)thiirane (30 mg, 0.23 mmol), after purification (petroleum ether/ethyl acetate 3:1), 3,3'-diselanediylbis(1-isopropoxypropane-2-thiol) was obtained as a mixture of two diastereoisomers (30 mg, 37%).

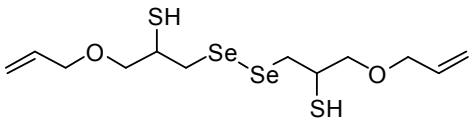
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.16 (24H, d, *J*=6.2 Hz), 2.04 (4H, d, *J*=7.2 Hz), 3.06-3.21 (8H, m), 3.23-3.46 (4H, m), 3.49-3.71 (12H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.2, 36.4, 41.1, 71.6, 72.2 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 308.6, 310.5 ppm.

MS (EI) *m/z* (%): 344 (4), 99 (28), 73 (100).

3,3'-Diselanediylbis(1-(allyloxy)propane-2-thiol) (8b)



Following the general procedure, starting from 2-((allyloxy)methyl)thiirane (50 mg, 0.38 mmol), after purification (petroleum ether/ethyl acetate 2:1), 3,3'-diselanediylbis(1-(allyloxy)propane-2-thiol) was obtained as a mixture of two diastereoisomers (46 mg, 57%).

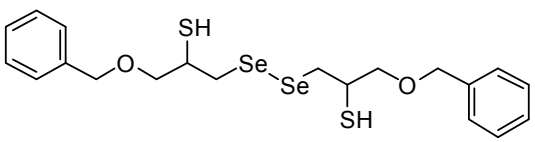
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.03 (4H, d, *J*=7.6 Hz), 2.83-3.11 (4H, m), 3.17-3.39 (8H, m), 3.51-3.69 (8H, m), 4.01-4.03 (8H, m), 5.18-5.32 (8H, m), 5.82-5.97 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 36.2, 40.7, 72.1, 73.4, 117.3, 134.3 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 310.6, 311.9 ppm.

MS (ESI, positive) *m/z*: 443 $[M+Na]^{+\cdot}$.

3,3'-Diselanediylbis(1-(benzyloxy)propane-2-thiol) (8c)



Following the general procedure, starting from 2-((benzyloxy)methyl)thiirane (50 mg, 0.28 mmol), after purification (petroleum ether/ethyl acetate 3:1), 3,3'-diselanediylbis(1-(benzyloxy)propane-2-thiol) was obtained as a mixture of two diastereoisomers (26 mg, 36%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.04 (4H, d, *J*=7.8 Hz), 3.21-3.41 (12H, m), 3.55-3.78 (8H, m), 4.55 (8H, ap s), 7.27-7.41 (20H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.1, 36.2, 73.2, 73.4, 127.7, 127.8, 128.4, 137.8 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 310.8, 311.6 ppm.

MS (ESI, positive) *m/z*: 520 $[M+H]^{+\cdot}$.

Synthesis of β-amino diselenides.

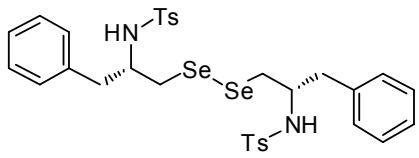
a) General procedure for *N*-Ts protected diselenides (9)

A solution of aziridine **6** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1.6 mmol) in dry THF (3 mL) was cooled under inert atmosphere at 0°C, and treated with TBAF (0.48 mL of 1M THF solution, 0.48 mmol). After warming to room temperature and stirring for ca. 1 h, the solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford a crude product, which was purified on silica gel as described for each product.

b) General procedure for *N*-Boc protected diselenides (10)

A solution of aziridine **7** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1.6 mmol) in dry THF (3 mL) was treated under inert atmosphere with TBAF (1.6 mL of 1M THF solution, 1.6 mmol). After stirring for ca. 12 h, the solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford a crude product, which was purified on silica gel as described for each product.

***N,N'*-((2*S*,2'*S*)-Diselanediylbis(1-phenylpropane-3,2-diyl))bis(4-methylbenzenesulfonamide) (9a)**



Following the general procedure, starting from (*S*)-2-benzyl-1-tosylaziridine (40 mg, 0.14 mmol), after purification (petroleum ether/ethyl acetate 4:1), *N,N'*-((2*S*,2'*S*)-diselanediylbis(1-phenylpropane-3,2-diyl))bis(4-methylbenzenesulfonamide) was obtained (37 mg, 73%).

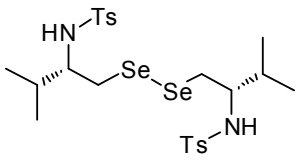
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (6H, s), 2.71 (2H, dd, *J*=7.0, 14.0 Hz), 2.87 (2H, dd, *J*=6.6, 14.0 Hz), 3.02 (2H, dd, *J*=6.4, 13.2 Hz), 3.22 (2H, dd, *J*=4.8, 13.2 Hz), 3.61-3.78 (2H, m), 5.03 (2H, d, *J*=7.4 Hz), 6.94-7.01 (6H, m), 7.15-7.22 (8H, m), 7.60 (4H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5, 35.6, 40.3, 55.5, 126.7, 127.0, 128.6, 129.2, 129.5, 136.4, 137.4, 143.1 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 283.2 ppm.

MS (ESI, negative) *m/z*: 734 $[M-H]^-$.

***N*,*N*'-((2*S*,2'*S*)-Diselanediylbis(3-methylbutane-2,1-diyl))bis(4-methylbenzene-sulfonamide) (9b)**



Following the general procedure, starting from **6b** (40 mg, 0.17 mmol), after purification (petroleum ether/ethyl acetate 3:1), **9b** was obtained (32 mg, 58%).

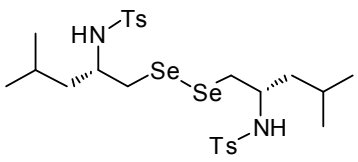
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (12H, d, *J*=6.8 Hz), 1.82-2.00 (2H, m), 2.42 (6H, s), 3.01 (2H, dd, *J*=6.0, 12.8 Hz), 3.12 (2H, dd, *J*=5.6, 12.8 Hz), 3.25-3.37 (2H, m), 5.16 (2H, d, *J*=8.4 Hz), 7.29 (4H, ap d, ls=8.0 Hz), 7.77 (4H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.3, 18.6, 21.3, 30.4, 33.5, 59.5, 126.8, 126.8, 129.2, 137.7, 142.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 288.6 ppm.

MS (ESI, negative) *m/z*: 638 $[M-H]^-$.

***N*,*N*'-((2*S*,2'*S*)-Diselanediylbis(4-methylpentane-2,1-diyl))bis(4-methylbenzene-sulfonamide) (9c)**



Following the general procedure, starting from (*S*)-2-isobutyl-1-tosylaziridine (40 mg, 0.16 mmol), after purification (petroleum ether/ethyl acetate 3:1), **9c** was obtained (32 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.62 (6H, d, *J*=6.0 Hz), 0.79 (6H, d, *J*=6.4 Hz), 1.22-1.34 (2H, m), 1.36-1.46 (4H, m), 2.42 (6H, s), 3.01 (2H, dd, *J*=6.4, 12.8 Hz),

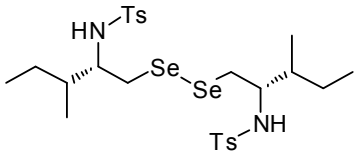
3.21 (2H, dd, *J*=4.0, 12.8 Hz) 3.46-3.56 (2H, m), 4.98 (2H, d, *J*=8.0 Hz), 7.30 (4H, ap d, ls=8.4 Hz), 7.79 (4H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5, 21.7, 22.8, 24.5, 37.2, 43.7, 52.4, 127.2, 129.7, 137.9, 143.4 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 282.3 ppm.

MS (ESI, positive) *m/z*: 667 $[M+Na]^{+\cdot}$.

***N*,*N*'-((2*S*,2'*S*)-Diselanediylbis(3-methylpentane-2,1-diyl))bis(4-methylbenzenesulfonamide) (9d)**



Following the general procedure, starting from (*S*)-2-((*S*)-sec-butyl)-1-tosylaziridine (40 mg, 0.16 mmol), after purification (petroleum ether/ethyl acetate 3:1), **9d** was obtained (31 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (6 H, d, *J*=7.2 Hz), 0.79 (6H, t, *J*=7.2 Hz), 0.90-1.04 (4H, m), 1.28-1.39 (2H, m), 2.42 (6H, s), 3.02 (4H, ap d, ls=6.0 Hz), 3.33-3.40 (2H, m), 5.10 (2H, d, *J*=8.4 Hz), 7.29 (4H, ap d, ls=8.4 Hz), 7.77 (4H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.5, 14.8, 21.5, 24.8, 32.8, 37.7, 58.6, 127.2, 129.6, 137.9, 143.3 ppm.

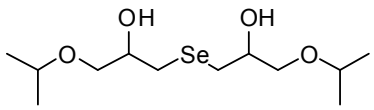
^{77}Se NMR (38 MHz, $CDCl_3$): δ = 291.4 ppm.

MS (ESI, negative) *m/z*: 666 $[M-H]^{-}$.

Synthesis of β-hydroxy selenides (11). General procedure

A solution of epoxide **3** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (0.6 mmol) in dry THF (3 mL), was treated under inert atmosphere with TBAF (0.24 mL of 1M THF solution, 0.24 mmol). After stirring for 4 h, the solution was diluted with diethyl ether, washed with water and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford a crude product, which was purified on silica gel as described for each product.

3,3'-Selenobis(1-isopropoxypropan-2-ol) (11a)



Following the general procedure, starting from 2-(isopropoxymethyl)oxirane (80 mg, 0.69 mmol), after purification (petroleum ether/ethyl acetate 3:1), 3,3'-selenobis(1-isopropoxypropan-2-ol) was obtained as a mixture of two diastereoisomers (78 mg, 72%).

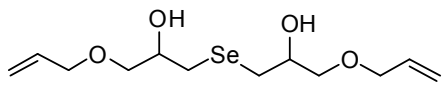
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (24H, d, *J*=6.2 Hz), 2.70 (4H, dd, *J*=6.2, 12.8 Hz), 2.71 (4H, dd, *J*=6.8, 12.8 Hz), 2.81 (4H, bs), 3.39-3.44 (4H, m), 3.45-3.50 (4H, m), 3.53-3.66 (4H, m), 3.86-3.93 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 28.9, 70.2, 70.3, 71.2, 72.2 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 67.9, 70.3 ppm.

MS (EI) *m/z* (%): 314 (1, $M^{+\cdot}$), 99 (44), 73 (12), 57 (100), 43 (86), 41 (24).

3,3'-Selenobis(1-(allyloxy)propan-2-ol) (11b)



Following the general procedure, starting from 2-((allyloxy)methyl)oxirane (60 mg, 0.53 mmol), 3,3'-selenobis(1-(allyloxy)propan-2-ol) was obtained as a mixture of diastereoisomers (62 mg, 76%).

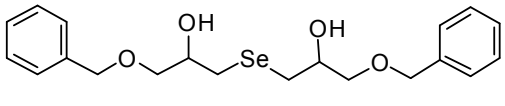
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.61-2.89 (12H, m), 3.40-3.59 (8H, m), 3.90-3.99 (4H, m), 4.00-4.09 (8H, m), 5.12-5.38 (8H, m), 5.79-6.00 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.9, 70.0, 70.1, 72.3, 76.4, 117.3, 134.3 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 68.3, 71.0 ppm.

MS (EI) *m/z* (%): 253 (4), 97 (19), 57 (17), 55 (15), 43 (15), 41 (100).

3,3'-Selenobis(1-(benzyloxy)propan-2-ol) (11c)



Following the general procedure, starting from 2-((benzyloxy)methyl)oxirane (80 mg, 0.49 mmol), 3,3'-selenobis(1-(benzyloxy)propan-2-ol) was obtained as a mixture of two diastereoisomers (91 mg, 91%).

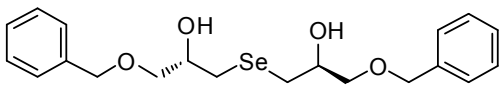
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.71 (4H, dd, *J*=7.2, 12.8 Hz), 2.81 (4H, dd, *J*=4.8, 12.8 Hz), 3.15 (4H, bs), 3.40-3.60 (8H, m), 3.90-4.00 (4H, m), 4.55 (8H, ap s), 7.20-7.40 (20H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.9, 70.0, 70.1, 73.2, 73.4, 127.7, 128.4, 137.7.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 69.1, 71.4 ppm.

MS (EI) *m/z* (%): 410 (3, $M^{+\cdot}$), 358 (73), 343 (16), 136 (21), 91 (100).

(2*S*,2'*S*)-3,3'-Selenobis(1-(benzyloxy)propan-2-ol) ((2*S*,2'*S*)-11c)



Following the general procedure, starting from (2*R*)-2-((benzyloxy)methyl)oxirane (60 mg, 0.37 mmol), after purification (petroleum ether/ethyl acetate 2:1), (2*S*,2'*S*)-3,3'-selenobis(1-(benzyloxy)propan-2-ol) was obtained (65 mg, 87%).

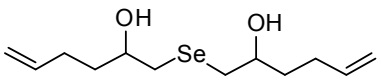
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.70 (2H, dd, *J*=7.0, 12.8 Hz), 2.82 (2H, dd, *J*=4.8, 12.8 Hz), 3.30 (2H, bs), 3.48-3.60 (4H, m), 3.91-4.06 (2H, m), 4.55 (4H, ap s), 7.27-7.41 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.9, 70.0, 73.3, 73.4, 127.7, 128.0, 128.4, 137.8 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 69.1 ppm.

MS (EI) *m/z* (%): 410 (3, $M^{+\cdot}$), 358 (73), 343 (16), 136 (21), 91 (100).

1,1'-Selenobis(hex-5-en-2-ol) (11d)



Following the general procedure, starting from 2-(but-3-en-1-yl)oxirane (80 mg, 0.82 mmol), 1,1'-selenobis(hex-5-en-2-ol) was obtained as a mixture of two diastereoisomers (89 mg, 78%).

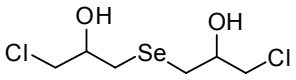
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50-1.62 (8H, m), 2.05-2.30 (8H, m), 2.50-2.65 (4H, m), 2.73-2.85 (4H, m), 3.05 (4H, bs), 3.67-3.80 (4H, m), 4.84-5.12 (8H, m), 5.68-5.90 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.1, 33.3, 33.6, 35.8, 35.9, 69.9, 70.4, 115.0, 137.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 50.9, 59.5 ppm.

MS (EI) *m/z* (%): 277 (2, $M^{+\cdot}$), 181 (3), 81 (100), 67 (25), 55 (39), 43 (56), 41 (80).

3,3'-Selenobis(1-chloropropan-2-ol (11e)



Following the general procedure, starting from 2-(chloromethyl)oxirane (50 mg, 0.54 mmol), after purification (petroleum ether/ethyl acetate 3:1), 3,3'-selenobis(1-chloropropan-2-ol was obtained as a mixture of two diastereoisomers (48 mg, 66%).

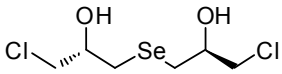
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (4H, bs), 2.82 (2H, dd; *J*=7.2, 13.2 Hz), 2.83 (2H, dd; *J*=7.2, 13.2 Hz), 2.92 (2H, dd; *J*=4.4, 13.2 Hz), 2.93 (2H, dd; *J*=4.4, 13.2 Hz), 3.64-3.66 (8H, m), 3.98-4.06 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.3, 48.3, 71.0, 71.1 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 78.9 ppm.

MS (ESI, negative) *m/z*: 265 $[M-H]^-$.

(2*S*,2'*S*)-3,3'-Selenobis(1-chloropropan-2-ol) ((2*S*,2'*S*)-11e)



Following the general procedure, starting from (2*R*)-2-(chloromethyl)oxirane (50 mg, 0.54 mmol), after purification (petroleum ether/ethyl acetate 3:1), (2*S*,2'*S*)-3,3'-selenobis(1-chloropropan-2-ol) was obtained (47 mg, 65%).

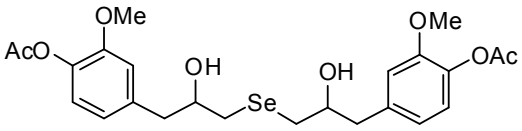
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.82 (2H, dd, *J*=7.2, 13.6 Hz), 2.93 (2H, dd, *J*=4.4, 13.6 Hz), 3.60-3.70 (4H, m), 3.98- 4.06 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.3, 48.3, 71.0 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 77.8 ppm.

MS (ESI, negative) *m/z*: 265 $[M-H]^-$.

(Selenobis(2-hydroxypropane-3,1-diyl))bis(2-methoxy-4,1-phenylene) diacetate (11f)



Following the general procedure, starting from 2-methoxy-4-(oxiran-2-ylmethyl)phenyl acetate (40 mg, 0.18 mmol), after purification (petroleum ether/ethyl acetate 2:1), (selenobis(2-hydroxypropane-3,1-diyl))bis(2-methoxy-4,1-phenylene) diacetate was obtained as a mixture of two diastereoisomers (40 mg, 84%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.30 (12H, s), 2.62-2.97 (20H, m), 3.80 (12H, s), 3.88-4.02 (4H, m), 6.62-6.88 (8H, m), 6.94 (4H, ap d, ls=7.6Hz) ppm.

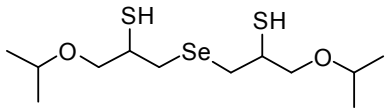
^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.7, 32.5, 43.2, 55.8, 71.9, 72.1, 113.5, 121.4, 122.6, 136.8, 138.3, 150.8, 169.1 ppm.

MS (ESI, negative) *m/z*: 524 $[M-H]^-$.

Synthesis of β-mercapto selenides (15). General procedure

A solution of thiirane **5** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (0.6 mmol) in dry THF (3 mL) was cooled under inert atmosphere at 0°C, and treated with TBAF (0.18 mL of 1M THF solution, 0.18 mmol). After stirring for 20 minutes, the solution was treated with 50% aqueous solution of citric acid, extracted with diethyl ether, washed with 20% aqueous citric acid, and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford a crude product.

3,3'-Selenobis(1-isopropoxypropane-2-thiol) (15a)



Following the general procedure, starting from 2-(isopropoxymethyl)thiirane (80 mg, 0.61 mmol), 3,3'-selenobis(1-isopropoxypropane-2-thiol) was obtained as a mixture of two diastereoisomers (93 mg, 89%).

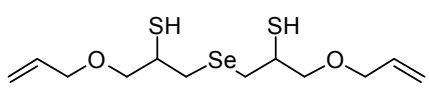
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14-1.16 (24H, m), 2.06 (2H, d, *J*=8.0 Hz), 2.07 (2H, d, *J*=8.0 Hz), 2.91-3.04 (8H, m), 3.08-3.16 (4H, m), 3.46-3.52 (4H, m), 3.56-3.68 (8H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.04; 22.07, 31.2, 40.8, 71.7, 72.1 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 123.8 ppm.

MS (EI) *m/z* (%): 344 (9, $M^{+\cdot}$), 154 (9), 133 (11), 99 (38), 91 (16), 73 (96), 57 (100), 43 (82), 41 (47).

3,3'-Selenobis(1-(allyloxy)propane-2-thiol) (15b)



Following the general procedure, starting from 2-((allyloxy)methyl)thiirane (50 mg,

0.38 mmol), 3,3'-selenobis(1-(allyloxy)propane-2-thiol) was obtained as a mixture of two diastereoisomers (68 mg, 86%).

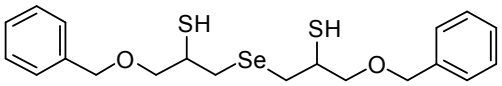
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.038 (2H, d, *J*=8.0 Hz), 2.04 (2H, d, *J*=8.0 Hz), 2.86-3.05 (8H, m), 3.12-3.18 (4H, m), 3.50-3.63 (8H, m), 3.96-4.02 (8H, m), 5.16-5.30 (8H, m), 5.82-5.94 (4H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.2, 40.4, 72.0, 73.5, 117.2, 134.2 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 124.5, 125.4 ppm.

MS (ESI, negative) *m/z*: 340 $[M-H]^-$.

3,3'-Selenobis(1-(benzyloxy)propane-2-thiol) (15c)



Following the general procedure, starting from 2-((benzyloxy)methyl)thiirane (80 mg, 0.44 mmol), 3,3'-selenobis(1-(benzyloxy)propane-2-thiol) was obtained as a mixture of two diastereoisomers (86 mg, 88%).

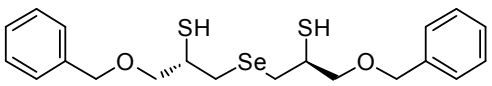
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.067 (2H, d, *J*=8.0 Hz), 2.07 (2 H, d, *J*=8.0 Hz), 2.86-3.05 (8H, m), 3.14-3.26 (4H, m), 3.54-3.76 (8H, m), 4.54 (8H, ap s), 7.20-7.42 (20H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 40.5, 73.1, 73.7, 127.6, 127.7, 128.4, 137.8 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 124.8, 126.7 ppm.

MS *m/z* (%): 442 (4, $M^{+\cdot}$), 409 (1), 181 (14), 147 (10), 107 (29), 91 (100).

(2*S*,2'*S*)-3,3'-Selenobis(1-(benzyloxy)propane-2-thiol) ((2*S*,2'*S*)-15c)



Following the general procedure, starting from (2*S*)-2-

((benzyloxy)methyl)thiirane (60 mg, 0.33 mmol), (2*S*,2'*S*)-3,3'-selenobis(1-(benzyloxy)propane-2-thiol) was obtained (64 mg, 88%).

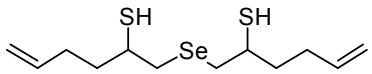
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (2H, d, *J*=8.0 Hz), 2.95-2.99 (4H, m), 3.12-3.22 (2H, m), 3.54-3.70 (4H, m), 4.53 (4H, ap s), 7.20-7.42 (10H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.2, 40.5, 73.1, 73.6, 127.6, 127.7, 128.4, 137.7 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 124.8 ppm.

MS *m/z* (%): 442 (4, $M^{+\cdot}$), 409 (1), 181 (14), 147 (10), 107 (29), 91 (100).

1,1'-Selenobis(hex-5-ene-2-thiol) (15d)



Following the general procedure, starting from 2-(but-3-en-1-yl)thiirane (60 mg, 0.53 mmol), **15d** was obtained as a mixture of two diastereoisomers (69 mg, 84%).

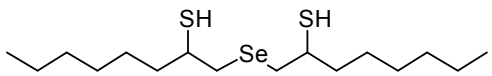
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52-1.62 (8H, m), 1.84 (4H, d, *J*=6.8 Hz), 1.88-1.96 (4H, m), 2.12-2.36 (8H, m), 2.86-2.90 (8H, m), 4.98-5.10 (8H, m), 5.66-5.82 (4H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 35.6, 36.9, 40.8, 115.0, 137.4 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 141.4, 142.2 ppm.

MS *m/z* (%): 310 (0.1, $M^{+\cdot}$), 115 (100), 101 (10), 81 (28), 59 (10), 55 (20), 41 (28), 39 (11).

1,1'-Selenobis(octane-2-thiol) (15e)



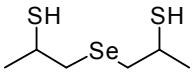
Following the general procedure, starting from 2-hexylthiirane (60 mg, 0.42 mmol), 1,1'-selenobis(octane-2-thiol) was obtained as a mixture of two diastereoisomers (61 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80-0.90 (12H, m), 1.20-1.40 (32H, m), 1.42-1.58 (8H, m), 1.85 (4H, d, *J*=6.4 Hz), 2.76-2.93 (8H, m), 3.07-3.15 (4H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.6, 27.2, 28.9, 29.1, 31.7, 34.6, 35.7, 37.8, 41.5 ppm.

MS *m/z* (%): 369 ([$M^{+\cdot}$], 13), 256 (30), 254 (18), 192 (17), 149 (11), 135 (14), 69 (100), 55 (87), 41 (99).

1,1'-Selenobis(propane-2-thiol) (15f)



Following the general procedure, starting from 2-methylthiirane (50 mg, 0.68 mmol), 1,1'-selenobis(propane-2-thiol) was obtained as a mixture of two diastereoisomers (57 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (12H, d, *J*=3.4 Hz), 1.96 (4H, d, *J*=6.0 Hz), 2.72-2.96 (8H, m), 3.05-3.18 (4H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 36.0, 36.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 157.3, 157.9 ppm.

MS *m/z* (%): 230 (4, $M^{+\cdot}$), 75 (100), 41 (87), 47 (33), 39 (21), 61 (7), 121 (6).

Synthesis of β-amino selenides.

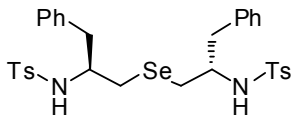
a) General procedure for *N*-Ts protected selenides (16)

A solution of aziridine **6** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (0.6 mmol) in dry THF (3 mL) was cooled under inert atmosphere at 0°C, and treated with TBAF (0.3 mL of 1M THF solution, 0.3 mmol). After warming to room temperature and stirring for about 1 h, the solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford a crude product, which was purified on silica gel as described for each product.

b) General procedure for *N*-Boc protected selenides (17)

A solution of aziridine **7** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (0.6 mmol) in dry THF (3 mL) was treated under inert atmosphere with TBAF 0.6 mL of 1M THF solution, 0.6 mmol). After stirring for about 12 h, the solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum to afford a crude product, which was purified on silica gel as described for each product.

***N*,*N*'-((2*S*,2'*S*)-Selenobis(1-phenylpropane-3,2-diyl))bis(4-methylbenzenesulfonamide) (16a)**



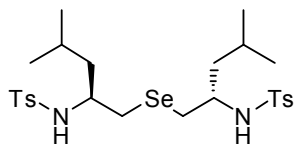
Following the general procedure, starting from (*S*)-2-benzyl-1-tosylaziridine (40 mg, 0.14 mmol), after purification (petroleum ether/ethyl acetate 3:1), **16a** was obtained (31 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (6H, s), 2.51-2.83 (8H, m), 3.44-3.71 (2H, m), 5.07 (2H, d, *J*=7.6 Hz), 6.98-7.05 (6H, m), 7.15-7.24 (8H, m), 7.55 (4H, ap d, ls=8.6 Hz) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 59.8 ppm.

MS (ESI, negative) *m/z*: 655 $[M-H]^-$.

***N*,*N*'-((2*S*,2'*S*)-Selenobis(4-methylpentane-2,1-diyl))bis(4-methylbenzenesulfonamide) (16b)**



Following the general procedure, starting from (*S*)-2-isobutyl-1-tosylaziridine (40 mg, 0.16 mmol), after purification (petroleum ether/ethyl acetate 3:1), **16b** was obtained (32 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66 (6H, d, *J*=6.4 Hz), 0.78 (6H, d, *J*=6.8 Hz), 1.15-1.30 (4H, m), 1.36-1.48 (2H, m), 2.42 (6H, s), 2.57 (2H, dd, *J*=5.2, 12.4 Hz),

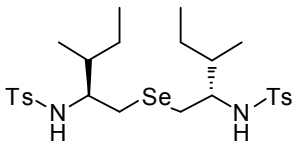
2.64 (2H, dd, *J*=4.4, 12.4 Hz), 3.37-3.47 (2H, m), 4.97 (2H, d, *J*=8.8 Hz), 7.29 (4H, ap d, ls=8.8 Hz), 7.76 (4H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6, 21.9, 22.8, 24.5, 33.3, 44.3, 51.7, 126.9, 129.6, 138.0, 143.3 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 38.2 ppm.

MS (ESI, negative) *m/z*: 587 $[M-H]^-$.

_N_,_N_'-((2_S_,2'_S_)-Selenobis(3-methylpentane-2,1-diyl))bis(4-methylbenzenesulfonamide) (16c)



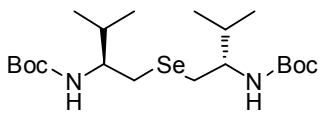
Following the general procedure, starting from (*S*)-2-((*S*)-sec-butyl)-1-tosylaziridine (40 mg, 0.16 mmol), after purification (petroleum ether/ethyl acetate 3:1), **16c** was obtained (32 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71-0.78 (12H, m), 1.16-1.22 (4H, m), 1.23-1.38 (2H, m), 2.41 (6H, s), 2.40-2.60 (4H, m), 3.15-3.25 (4H, m), 5.18 (2H, d, *J*=8.4 Hz), 7.28 (4H, ap d, ls=8.4 Hz), 7.75 (4H, ap d, ls=8.4 Hz) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 48.0 ppm.

MS (ESI, negative) *m/z*: 587 $[M-H]^-$.

Di-*tert*-butyl((2_S_,2'_S_)-selenobis(3-methylbutane-2,1-diyl))dicarbamate (17a)



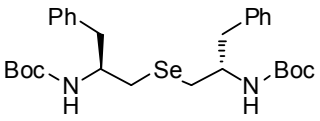
Following the general procedure, starting from (*S*)-*tert*-butyl 2-isopropylaziridine-1-carboxylate (40 mg, 0.22 mmol), after purification (petroleum ether/ethyl acetate 5:1), di-*tert*-butyl((2*S*,2'*S*)-selenobis(3-methylbutane-2,1-diyl))dicarbamate was obtained (27 mg, 56%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (6H, d, *J*=6.6 Hz), 0.94 (6H, d, *J*=6.6 Hz), 1.50 (18H, s), 1.65-1.86 (2H, m), 2.88 (2H, dd, *J*=8.8, 12.8 Hz), 3.01 (2H, dd, *J*=2.4, 12.8 Hz), 3.52-3.74 (2H, m), 4.64 (2H, bd, *J*=9.2 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.8, 18.9, 28.1, 29.9, 32.4, 56.0, 78.9, 155.7 ppm.

MS (ESI, negative) *m/z*: 451 $[M-H]^-$.

Di-*tert*-butyl((2*S*,2'*S*)-selenobis(1-phenylpropane-3,2-diyl))dicarbamate (17b)



Following the general procedure, starting from (*S*)-*tert*-butyl 2-benzylaziridine-1-carboxylate (40 mg, 0.17 mmol), after purification (petroleum ether/ethyl acetate 5:1), di-*tert*-butyl((2*S*,2'*S*)-selenobis(1-phenylpropane-3,2-diyl))dicarbamate was obtained (43 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (18H, s), 2.62-2.73 (4H, m), 2.76-2.88 (4H, m), 3.87-4.07 (2H, m), 4.70 (1H, bs) ppm.

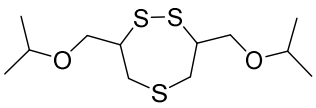
^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.4, 30.0, 40.5, 51.6, 79.5, 126.5, 128.5, 128.3, 137.5, 155.1 ppm.

MS (ESI, negative) *m/z*: 547 $[M-H]^-$.

Synthesis of 1,2,5-trithiepanes 18. General procedure.

A solution of thiirane **5** (2 mmol) and bis(trimethylsilyl)sulfide (HMDST) (1 mmol) in distilled THF (3 mL) was treated under inert atmosphere at room temperature with TBAF (0.2 mL of 1M THF solution, 0.2 mmol). After stirring at r.t. for about 24 h, the solution was diluted with diethyl ether, washed with water, then with brine and dried over Na_2SO_4. The solvent was evaporated under vacuum affording a crude product, which was purified on silica gel (petroleum ether/diethyl ether).

3,7-Bis(isopropoxymethyl)-1,2,5-trithiepane (18a)



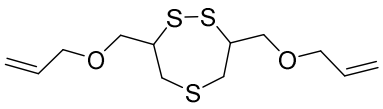
Following the general procedure, 2-(isopropoxymethyl)thiirane (50 mg, 0.38 mmol) and bis(trimethylsilyl)sulfide (34 mg, 0.19 mmol) gave 3,7-bis(isopropoxymethyl)-1,2,5-trithiepane as a equimolar mixture of two diastereoisomers (61%, 34 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11-1.15 (12H, m), 2.93-3.41 (6H, m), 3.48-3.77 (6H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8, 21.9, 22.0, 34.1, 34.5, 50.5, 52.8, 69.2, 69.8, 72.2 ppm.

MS (EI) *m/z* (%): 296 [$M^{+\cdot}$, (3)], 236 (2), 196 (1), 136 (3), 99 (56), 73 (28), 57 (100).

3,7-bis((allyloxy)methyl)-1,2,5-trithiepane (18b)



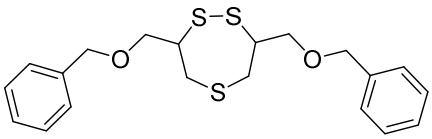
Following the general procedure, 2-(allyloxymethyl)thiirane (50 mg, 0.38 mmol) and bis(trimethylsilyl)sulfide (34 mg, 0.19 mmol) gave, after purification on silica gel chromatography (petroleum ether/diethyl ether 15:1), **18b** as a equimolar mixture of two diastereoisomers (64%, 26 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.96-3.25 (6H, m), 3.50-3.75 (4H, m), 3.97-4.03 (4H, m), 5.17-5.31 (4H, m), 5.78-5.98 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.2, 34.3, 46.8, 47.1, 71.7, 72.1, 117.1, 134.6 ppm.

MS (EI) *m/z* (%): 292 [$M^{+\cdot}$, (2)], 235 (32), 177 (8), 105 (18), 97 (100), 73 (64), 55 (71).

3,7-Bis((benzyloxy)methyl)-1,2,5-trithiepane (18c)



Following the general procedure, 2-(benzyloxymethyl)thiirane (50 mg, 0.28 mmol) and bis(trimethylsilyl)sulfide (25 mg, 0.14 mmol) gave, after purification on silica gel chromatography (petroleum ether/diethyl ether 15:1), **18c** as a equimolar mixture of two diastereoisomers (64%, 25 mg).

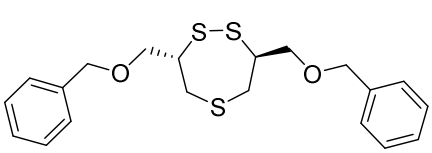
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93-3.42 (6H, m), 3.58-3.79 (4H, m), 4.50-4.55 (4H, m), 7.28-7.36 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.9, 50.6, 70.1, 73.2, 127.7, 128.6, 129.7, 137.9 ppm.

MS (EI) *m/z* (%): 392 [$M^{+\cdot}$, (2)], 301 (1), 284 (1), 195 (2), 147 (9), 105 (5), 91 (100).

Elemental analysis: calculated for $C_{20}H_{24}S_2O_3$: C, 61.19; H, 6.16. Found: C, 61.34; H, 6.34.

(3*S*,7*S*)-3,7-Bis((benzyloxy)methyl)-1,2,5-trithiepane ((3*S*,7*S*)-18c)



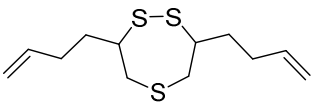
Following the general procedure, (2*R*)-2-(benzyloxymethyl)thiirane gave, after purification by flash column chromatography (petroleum ether/diethyl ether 15:1), (3*S*,7*S*)-3,7-bis((benzyloxy)methyl)-1,2,5-trithiepane (65%, 26 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.98-3.39 (6H, m), 3.60-3.78 (4 H, m), 4.53-4.55 (4H, m), 7.32-7.36 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.2, 50.2, 71.2, 71.7, 73.2, 127.7, 128.1, 128.4, 137.8 ppm.

MS (EI) *m/z* (%): 392 [$M^{+\cdot}$, (2)], 301 (1), 284 (1), 195 (2), 147 (9), 105 (5), 91 (100).

3,7-Di(but-3-en-1-yl)-1,2,5-trithiepane (18d)



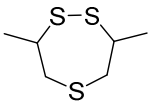
Following the general procedure, 2-(but-3-enyl)thiirane (50 mg, 0.44 mmol) and bis(trimethylsilyl)sulfide (39 mg, 0.22 mmol) gave 3,7-di(but-3-en-1-yl)-1,2,5-trithiepane as a equimolar mixture of two diastereoisomers (86%, 49 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46-1.75 (4H, m), 2.01-2.38 (4H, m), 2.68-3.15 (3H, m), 4.95-5.06 (4H, m), 5.66-5.85 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9, 24.0, 30.9, 31.2, 32.7, 33.0, 41.2, 115.4, 137.4 ppm.

MS (EI) *m/z* (%): 260 [$M^{+\cdot}$, (9)], 227 (3), 178 (5), 159 (6), 145 (10), 113 (39), 105 (12), 99 (18), 85 (15), 73 (17), 67 (29), 53 (24), 81 (100).

3,7-Dimethyl-1,2,5-trithiepane (18e).

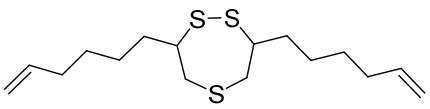


Following the general procedure, 2-(methyl)thiirane (20 mg, 0.27 mmol) and bis(trimethylsilyl)sulfide (24 mg, 0.14 mmol) gave 3,7-dimethyl-1,2,5-trithiepane as a equimolar mixture of two diastereoisomers (85%, 21 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24-1.42 (6H, m), 2.58-3.31 (6H, m) ppm.

MS (EI) *m/z* (%): 180 [$M^{+}\cdot$, (68)], 147 (11), 138 (33), 115 (23), 64 (21), 74 (85), 64 (21), 59 (32), 41 (100).

3,7-Di(hex-5-en-1-yl)-1,2,5-trithiepane (18f).



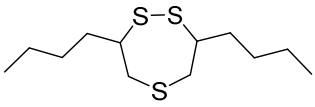
Following the general procedure, 2-(hex-5-en-1-yl)thiirane (30 mg, 0.2 mmol) and bis(trimethylsilyl)sulfide (18 mg, 0.1 mmol) gave 3,7-di(hex-5-en-1-yl)-1,2,5-trithiepane as a equimolar mixture of two diastereoisomers (83%, 26 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27-1.55 (12H, m), 2.01-2.10 (4H, m), 2.75-2.98 (2H, m), 3.00-3.27 (4H, m), 4.91-5.03 (4H, m), 5.65-5.88 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.7, 28.6, 33.5, 33.8, 41.2, 42.7, 114.5, 138.6 ppm.

MS (EI) *m/z* (%): 316 [$M^{+}\cdot$, (15)], 206 (18), 141 (30), 109 (31), 95 (11), 87 (27), 79 (23), 67 (99), 55 (54), 41 (100).

3,7-Dibutyl-1,2,5-trithiepane (18g)



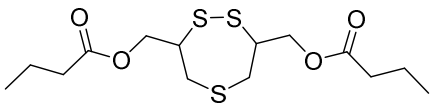
Following the general procedure, 2-butylthiirane (50 mg, 0.43 mmol) and bis(trimethylsilyl)sulfide (38 mg, 0.22 mmol) gave 3,7-dibutyl-1,2,5-trithiepane as a equimolar mixture of two diastereoisomers (75%, 44 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85-0.96 (6H, m), 1.24-1.65 (12H, m), 2.64-3.33 (6H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6, 13.9, 19.7, 22.4, 23.9, 29.4, 33.3, 33.7, 42.2, 51.1, 58.7 ppm.

MS (EI) *m/z* (%): 264 ($M^{+}\cdot$, 16), 231 (3), 199 (10), 180 (21), 115 (31), 87 (17), 83 (38), 55 (90), 41 (100).

(1,2,5-Trithiepane-3,7-diyl)bis(methylene) dibutyrate (18h)



Following the general procedure, 2-(methylene butyrate)thiirane (40 mg, 0.25 mmol) and bis(trimethylsilyl)sulfide (22 mg, 0.13 mmol) (1,2,5-trithiepane-3,7-diyl)bis(methylene) dibutyrate as a equimolar mixture of two diastereoisomers (68%, 30 mg).

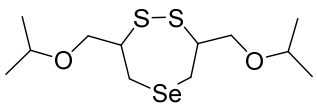
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92-0.97 (6H, m), 1.57-1.74 (4H, m), 2.26-2.35 (4H, m), 2.79-3.41 (6H, m), 4.07-4.37 (4H, m) ppm.

MS (EI) *m/z* (%): 352 [$M^{+\cdot}$, (5)], 264 (10), 224 (6), 176 (14), 136 (92), 104 (15), 71 (98), 43 (100).

Synthesis of 1,2,5-dithiaselenepanes 19. **General procedure**.

A solution of thiirane **5** (2 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1 mmol) in dry THF (3 mL) was cooled under inert atmosphere at 0°C, and treated with TBAF (0.2 mL of 1M THF solution, 0.2 mmol). After warming to room temperature and stirring for about 12 h, the solution was diluted with diethyl ether, washed with water, then with brine, and dried over Na_2SO_4. The solvent was evaporated under vacuum affording a crude product, which was purified on silica gel (petroleum ether/diethyl ether).

3,7-Bis(isopropoxymethyl)-1,2,5-dithiaselenepane (19a)



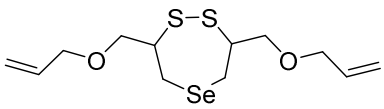
Following the general procedure, 2-(isopropoxymethyl)thiirane (50 mg, 0.38 mmol) and bis(trimethylsilyl)selenide (43 mg, 0.19 mmol) gave 3,7-bis(isopropoxymethyl)-1,2,5-dithiaselenepane as a equimolar mixture of two diastereoisomers (71%, 46 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.14 (12H, ap d, ls=6.4 Hz), 2.91-3.28 (6H, m), 3.40-3.68 (6H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 29.7, 49.5, 69.9, 70.1, 72.2 ppm.

MS (EI) *m/z* (%): 344 [$M^{+\cdot}$, (5)], 244 (6), 137 (5), 121 (7), 99 (31), 73 (33), 59 (12), 57 (100), 43 (93).

3,7-Bis((allyloxy)methyl)-1,2,5-dithiaselenepane (19b)



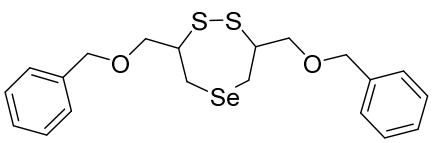
Following the general procedure, 2-(allyloxymethyl)thiirane (50 mg, 0.28 mmol) and bis(trimethylsilyl)selenide (32 mg, 0.14 mmol) gave, after purification on silica gel chromatography (petroleum ether/diethyl ether 8:1), 3,7-bis((allyloxy)methyl)-1,2,5-dithiaselenepane as a equimolar mixture of two diastereoisomers (73%, 35 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.01-3.22 (6H, m), 3.37-3.76 (4H, m), 3.97-4.05 (4H, m), 5.18-5.30 (4H, m), 5.81-5.98 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.6, 49.1, 71.9, 72.2, 72.8, 117.4, 134.5 ppm.

MS (EI) *m/z* (%): 340 [$M^{+\cdot}$ (6)], 283 (8), 242 (9), 225 (5), 185 (7), 151 (6), 129 (15), 121 (21), 97 (60), 73 (100), 55 (58)

3,7-Bis((benzyloxy)methyl)-1,2,5-dithiaselenepane (19c)

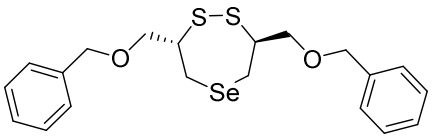


Following the general procedure, 2-(benzyloxymethyl)thiirane (50 mg, 0.28 mmol) and bis(trimethylsilyl)selenide (32 mg, 0.14 mmol) gave 3,7-bis((benzyloxy)methyl)-1,2,5-dithiaselenepane as a equimolar mixture of two diastereoisomers (74%, 45 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.89-3.31 (6H, m), 3.47-3.91 (4H, m), 4.53-4.55 (4H, m), 7.28-7.35 (10H, m) ppm.

MS (EI) *m/z* (%): 440 [$M^{+\cdot}$ (2)], 292 (2), 147 (4), 107 (7), 91 (100), 73 (7), 65 (9).

(3*S*,7*S*)-3,7-Bis((benzyloxy)methyl)-1,2,5-dithiaselenepane ((3*S*,7*S*)-19c)



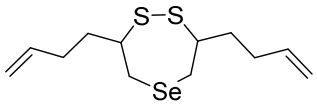
Following the general procedure, (2*R*)-2-(benzyloxymethyl)thiirane gave (3*S*,7*S*)-3,7-bis((benzyloxy)methyl)-1,2,5-dithiaselenepane (71%, 44 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.91-3.32 (6H, m), 3.61-3.78 (4H, m), 4.54 (4H, ap s), 7.31-7.36 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.6, 49.2, 72.1, 73.3, 127.6, 127.7, 137.9 ppm.

MS (EI) *m/z* (%): 440 [$M^{+\cdot}$ (2)], 292 (2), 147 (4), 107 (7), 91 (100), 73 (7), 65 (9).

3,7-Di(but-3-en-1-yl)-1,2,5-dithiaselenepane (19d)

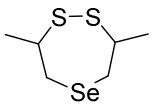


Following the general procedure, 2-(but-3-enyl)thiirane (50 mg, 0.44 mmol) and bis(trimethylsilyl)selenide (50 mg, 0.22 mmol) gave 3,7-di(but-3-en-1-yl)-1,2,5-dithiaselenepane as a equimolar mixture of two diastereoisomers (68%, 46 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48-1.73 (4H, m), 1.98-2.35 (4H, m), 2.65-3.18 (6H, m), 4.96-5.11 (4H, m), 5.61-5.84 (2H, m) ppm.

MS (EI) *m/z* (%): 308 [$M^{+\cdot}$, (9)], 226 (5), 194 (8), 145 (15), 113 (47), 81 (100), 41 (73).

3,7-Dimethyl-1,2,5-dithiaselenepane (19e)

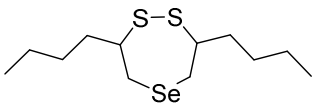


Following the general procedure, 2-(methyl)thiirane (20 mg, 0.27 mmol) and bis(trimethylsilyl)selenide (31 mg, 0.14 mmol) gave, after purication by flash column chromatography (petroleum ether/diethyl ether 25:1), 3,7-dimethyl-1,2,5-dithiaselenepane as a equimolar mixture of two diastereoisomers (67%, 22 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24-1.43 (6H, m), 2.93 (2H, dd, *J*=6.4, 13.8 Hz), 3.14 (2H, dd, *J*=3.8, 13.8 Hz), 3.18-3.42 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.1, 20.8, 34.6, 38.3, 41.2 ppm.

3,7-Dibutyl-1,2,5-dithiaselenepane (19f)



Following the general procedure, 2-butylthiirane (50 mg, 0.43 mmol) and bis(trimethylsilyl)selenide (49 mg, 0.22 mmol) gave 3,7-dibutyl-1,2,5-dithiaselenepane as a equimolar mixture of two diastereoisomers (78%, 54 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86-0.93 (6H, m), 1.23-1.75 (12H, m), 2.58-3.23 (6H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 22.3, 24.7, 26.6, 28.9, 29.2, 32.3, 32.6, 34.1 ppm.

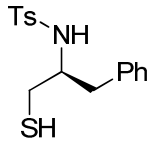
Synthesis of *N*-Tosyl β-aminothiols 22. **General procedure**.

A solution of aziridine **6** (1 mmol) and bis(trimethylsilyl)sulfide (HMDST) (1.2 mmol) in dry THF (3 mL) was cooled under inert atmosphere at 0°C, and treated with TBAF (0.24 mL of 1M THF solution, 0.24 mmol). The reaction was stirred for 20 min and then citric acid (50% *aq* solution) was added. The solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum affording a crude product pure enough so that it could be used without further purification.

Synthesis of *N*-Boc β-aminothiols 23. **General procedure**.

A solution of aziridine **7** (1 mmol) and bis(trimethylsilyl)sulfide (HMDST) (1.2 mmol) in dry THF (3 mL) was treated with TBAF (1.2 mL of 1M THF solution, 1.2 mmol). The reaction was stirred for 1 h and then citric acid (50% *aq* solution) was added. The solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum affording a crude product pure enough so that it could be used without further purification.

(*S*)-*N*-(1-Mercapto-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (22a)



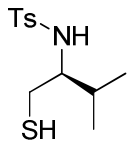
Following the general procedure, (*S*)-2-benzyl-1-tosylaziridine (33 mg, 0.11 mmol), bis(trimethylsilyl)sulfide (31 mg, 0.17 mmol) and TBAF (35 uL, 1M THF solution) gave (*S*)-*N*-(1-mercapto-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (98%, 35 mg) as a yellowish oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (1H, ap t, *J*=8.8 Hz, S**H)**, 2.42 (3H, s),2.54 (1H, ddd, *J*=4.0, 8.5, 14.0 Hz, C**H$_a$**H$_b$SH), 2.59-2.68 (1H, m, CH$_a$**H$_b$**SH), 2.70-2.85 (2H, m), 3.53-3.75 (1H, m), 4.71 (1H, d, *J*=8.0 Hz, N**H**), 6.98-7.03 (2H, m), 7.17-7.24 (5H, m), 7.61 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (CH_3), 28.7 (CH_2), 38.9 (CH_2), 55.5 (CH), 126.8 (CH), 128.7 (CH), 129.1 (CH), 129.2 (CH), 129.6 (CH), 136.4 (C), 137.2 (C), 143.4 (C) ppm.

MS (EI) *m/z* (%): 274 [$M^{+\cdot}$-CH_2SH, (27)], 230 [$M^{+\cdot}$-Bn, (40)], 155 (39), 91 [Bn^+, (100)], 74 (33), 65 (24).

(*S*)-*N*-(1-Mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (22b)



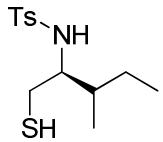
Following the general procedure, (*S*)-2-isopropyl-1-tosylaziridine (119 mg, 0.5mmol), bis(trimethylsilyl)sulfide (133 mg, 0.75mmol) and TBAF (150uL, 1M THF solution) gave (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (93%, 127 mg) as a yellowish oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.78 (3H, d, *J*=6.6 Hz, (C**H$_3$**)$_2$CH), 0.80 (3H, d, *J*=7.0 Hz, (C**H$_3$**)$_2$CH), 1.15 (1H, dd, *J*=8.0, 9.4 Hz, S**H**), 1.79-1.93 (1H, m, C**H**$(CH_3)_2$), 2.42 (3H, s), 2.50 (1H, dd, *J*=5.6, 9.4 Hz, C**H$_a$**H$_b$SH), 2.61 (1H, dd, *J*=5.6, 8.0 Hz, CH$_a$**H$_b$**SH), 3.04-3.15 (1H, m, C**H**NH), 4.94 (1H, bd, *J*=8.8 Hz, N**H**), 7.29 (2H, ap d, ls=8.0 Hz), 7.76 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.1 (CH_3), 18.9 (CH_3), 21.5 (CH_3), 27.2 (CH_2), 29.5 (CH), 60.0 (CH), 127.0 (CH), 129.6 (CH), 137.9 (C), 143.4 (C) ppm.

MS (EI) *m/z* (%): 226 [$M^{+\cdot}$-CH_2SH,(69)], 155 (58), 91 [Bn^+, (100)], 65 (22).

***N*-((2*S*,3*S*)-1-Mercapto-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (22c)**

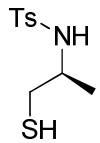


Following the general procedure, (*S*)-2-((*S*)-sec-butyl)-1-tosylaziridine (127 mg, 0.5 mmol), bis(trimethylsilyl)sulfide (133 mg, 0.75 mmol) and TBAF (150 uL, 1M THF solution) gave *N*-((2*S*,3*S*)-1-mercapto-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (92%, 132 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.75-0.83 (6H, m), 1.13 (1H, dd, *J*=7.9, 9.3 Hz, S**H**), 0.90-1.10 (1H, m), 1.37-1.66 (2H, m), 2.42 (3H, s), 2.45-2.67 (2H, m), 3.12-3.24 (1H, m), 4.94 (1H, d, *J*=8.8 Hz), 7.30 (2H, ap d, ls=8.4 Hz), 7.76 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.2 (CH_3), 14.9 (CH_3), 21.5 (CH_3), 24.7 (CH_2), 26.7 (CH_2), 36.3 (CH), 58.6 (CH), 127.0 (CH), 129.7 (CH), 137.8 (C), 143.4 (C) ppm.

(*S*)-*N*-(1-Mercaptopropan-2-yl)-4-methylbenzenesulfonamide (22d)



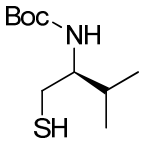
Following the general procedure, (*S*)-2-methyl-1-tosylaziridine (106 mg, 0.5 mmol), bis(trimethylsilyl)sulfide (133 mg, 0.75 mmol) and TBAF (150 uL, 1M THF solution) gave (*S*)-*N*-(1-mercaptopropan-2-yl)-4-methylbenzenesulfonamide (86%, 105 mg) as a yellowish oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (1H, dd, *J*=7.0, 8.4 Hz, S**H**), 1.10 (3H, d, *J*=6.6 Hz), 2.43 (3H, s), 2.52-2.59 (2H, m), 3.42-3.61 (1H, m), 5.10 (1H, bs), 7.31 (2H, ap d, ls=8.2 Hz), 7.77 (2H, ap d, ls=8.2 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.6 (CH_3), 21.5 (CH_3), 34.6 (CH_2), 35.7 (CH), 127.7 (CH), 129.6 (CH), 135.2 (C), 144.3 (C) ppm.

MS (EI) *m/z* (%): 198 [$M^{+\cdot}$-CH_2SH, (67)], 155 (65), 91 [Bn^+, (100)], 65 (22).

(*S*)-*Tert*-butyl (1-mercapto-3-methylbutan-2-yl)carbamate (23a)

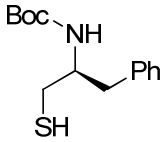


Following the general procedure, (*S*)-*tert*-butyl 2-isopropylaziridine-1-carboxylate (93 mg, 0.5 mmol), bis(trimethylsilyl)sulfide (133 mg, 0.75 mmol) and TBAF (150 uL, 1M THF solution) gave (*S*)-*tert*-butyl (1-mercapto-3-methylbutan-2-yl)carbamate (91%, 99 mg) as a yellowish oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (6H, ap t, *J*=7.0 Hz, (C**H$_3$**)$_2$CH), 1.29 (1H, dd, *J*=7.9, 10.8 Hz, S**H**), 1.44 (9H, s), 1.76-1.92 (1H, m, C**H**(CH_3)$_2$), 2.65 (2H, bd, *J*=6.2, C**H$_2$**SH), 3.42-3.61 (1H, m, C**H**NH), 4.60 (1H, bd, *J*=9.0 Hz, N**H**) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.4 (CH_3), 19.5 (CH_3), 28.4 (CH_3), 31.2 (CH), 35.9 (CH_2), 54.9 (CH), 79.1 (C), 155.8 (CO) ppm.

(*S*)-*Tert*-butyl (1-mercapto-3-phenylpropan-2-yl)carbamate (23b)



Following the general procedure, (*S*)-*tert*-butyl 2-benzylaziridine (117 mg, 0.5 mmol), bis(trimethylsilyl)sulfide (133 mg, 0.75 mmol) and TBAF (150 uL, 1M THF solution) gave (*S*)-*tert*-butyl (1-mercapto-3-phenylpropan-2-yl)carbamate (92%, 123 mg) as a yellowish oil.

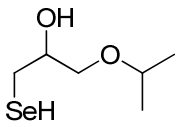
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (1H, ap t, *J*=8.8 Hz, S**H)**, 1.42 (9H, s), 2.51-2.77 (2H, m), 2.86 (2H, bd, *J*=7.2 Hz),3.87-4.08 (1H, m), 4.76 (1H, d, *J*=8.0 Hz, N**H**), 7.17-7.37 (5H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.4 (CH_3), 37.0 (CH_2), 38.8 (CH_2), 52.6 (CH), 79.5 (C), 126.5 (CH), 128.4 (CH), 129.4 (CH), 137.4 (C), 155.1 (C) ppm.

Synthesis of β-hydroxyselenols 24. **General procedure**.

A solution of epoxide **3** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1.6 mmol) in dry THF (3 mL) was cooled under inert atmosphere at 0°C, and treated with TBAF (0.32 mL of 1M THF solution, 0.32 mmol). The reaction was stirred for 10 min and then solid citric acid was added. The solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum affording a crude product pure enough so that it could be used without further purification.

1-Hydroseleno-3-isopropoxypropan-2-ol (24a)

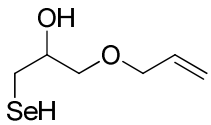


Following the general procedure, 2-(isopropoxymethyl)oxirane (58 mg, 0.50 mmol), bis(trimethylsilyl)selenide(192 mg, 0.85mmol) and TBAF (255uL, 1M THF solution) gave1-hydroseleno-3-isopropoxypropan-2-ol (62%, 61 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.58 (1H, t, *J*=7.6 Hz, Se**H**), 1.16 (6H, d, *J*=6.2 Hz), 2.68-2.76 (2H, m, C**H$_2$**Se), 3.39-3.68 (3H, m), 3.94-4.02 (1H, m) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -78.6 ppm.

1-(Allyloxy)-3-hydroselenopropan-2-ol (24b)



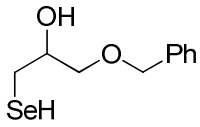
Following the general procedure, 2-((allyloxy)methyl)oxirane (30 mg, 0.26 mmol), bis(trimethylsilyl)selenide (100 mg, 0.44 mmol) and TBAF (132 uL, 1M THF solution) gave 1-(allyloxy)-3-hydroselenopropan-2-ol (55%, 28 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.58 (1H, t, *J*=7.6 Hz, coupling with ^{77}Se: dt, $^1J_{Se\text{-}H}$=46.4 Hz, Se**H**), 2.55-2.79 (2H, m, C**H$_2$**Se),3.49 (2H, ap dd, *J*=4.1, 5.0 Hz), 3.78-3.92 (1H, m), 4.02 (2H, d, *J*=5.4 Hz), 5.13-5.32 (2H, m), 5.88 (1H, ddd, *J*=5.7, 10.8, 22.7 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3 (CH_2), 70.9 (CH), 72.3 (CH_2), 73.6 (CH_2), 117.4 (CH_2), 134.3 (CH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -78.5 ppm.

1-(Benzyloxy)-3-hydroselenopropan-2-ol (24c)



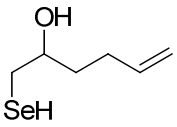
Following the general procedure, 2-((benzyloxy)methyl)oxirane (82 mg, 0.50 mmol), bis(trimethylsilyl)selenide (192 mg, 0.85 mmol) and TBAF (255 uL, 1M THF solution) gave 1-(benzyloxy)-3-hydroselenopropan-2-ol (86%, 105 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.60 (1H, t, *J*=7.6 Hz, coupling with ^{77}Se: dt, $^{1}J_{Se\text{-}H}$=46.2 Hz, Se**H**), 2.57-2.82 (2H, m, C**H**$_2$Se), 3.51-3.59 (2H, m), 3.81-3.94 (1H, m), 4.56 (2H, ap s), 7.29-7.38 (5H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3 (CH_2), 70.9 (CH), 72.6(CH_2), 73.4 (CH_2), 127.8 (CH), 127.9 (CH), 128.5 (CH), 137.8 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -79.4 ppm.

1-Hydroselenohex-5-en-2-ol (24d)



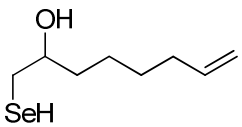
Following the general procedure, 2-(but-3-en-1-yl)oxirane (49 mg, 0.50 mmol), bis(trimethylsilyl)selenide (192 mg, 0.85mmol) and TBAF (255uL, 1M THF solution) gave 1-hydroselenohex-5-en-2-ol (71%, 64 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.68 (1H, t, *J*=7.6 Hz, Se**H**), 1.56-1.72 (2H, m), 2.09-2.12 (2H, m), 2.49-2.68 (1H, m), 2.38 (1H, bs), 2.79 (1H, ddd, *J*=3.5, 7.6, 11.8 Hz), 3.57-3.78 (1H, m), 4.92-5.11 (2H, m), 5.73-5.91 (1H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.3 (CH_2), 30.0 (CH_2), 35.8 (CH_2), 70.4 (CH), 115.0 (CH_2), 138.0 (CH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -88.5 ppm.

1-Hydroselenooct-7-en-2-ol (24f)



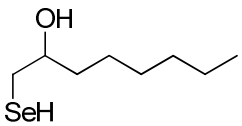
Following the general procedure, 2-(hex-5-en-1-yl)oxirane (63 mg, 0.50 mmol), bis(trimethylsilyl)selenide (192 mg, 0.85 mmol) and TBAF (255 uL, 1M THF solution) gave 1-hydroselenooct-7-en-2-ol (44%, 45 mg) in a mixture with 30% of the corresponding diselenide.

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.69 (1H, ap t, *J*=8.0 Hz, Coupling with ^{77}Se: dt, $^{1}J_{Se-H}$=45.2 Hz, Se**H**), 1.34-1.61 (6H, m), 2.01-2.11 (2H, m), 2.50-2.64 (1H, m), 2.82 (1H, ddd, *J*=3.7, 8.0, 12.6 Hz), 3.55-3.89 (1H, m), 4.91-5.05 (2H, m), 5.80 (1H, ddt, *J*=5.8, 6.7, 10.1 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.2 (CH_2), 28.8 (CH_2), 33.6 (CH_2), 36.4 (CH_2), 38.7 (CH_2), 70.9 (CH), 114.5 (CH_2), 138.7 (CH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -90.5 ppm.

1-Hydroselenooctan-2-ol (24g)



Following the general procedure, 2-hexyloxirane (64 mg, 0.50 mmol), bis(trimethylsilyl)selenide (192 mg, 0.85mmol) and TBAF (255uL, 1M THF solution) gave 1-hydroselenooctan-2-ol (62%, 65 mg) in a mixture with 20% of the corresponding diselenide.

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.70 (1H, t, *J*=8.0 Hz, coupling with ^{77}Se, dt, $^{1}J_{Se-H}$=46.0 Hz, Se**H**), 0.87 (3H, ap t, *J*=6.5 Hz), 1.24-1.36 (8H, m), 1.42-1.58 (2H, m), 2.33 (1H, bs), 2.49-2.65 (1H, m), 2.81 (1H, ddd, *J*=3.7, 8.0, 12.6 Hz), 3.55-3.68 (1H, m) ppm.

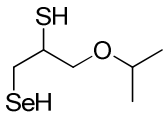
^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6 (CH_2), 25.9 (CH_2), 26.4 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 36.3 (CH_2), 71.8 (CH). ppm

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -90.3 ppm.

Synthesis of β-mercaptoselenols 25. **General procedure**.

A solution of thiirane **5** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1.6 mmol) in dry THF (3 mL) was cooled under inert atmosphere at -15°C, and treated with TBAF (0.16 mL of 1M THF solution, 0.16 mmol). The reaction was stirred for 5 min and then solid citric acid was added. The solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum affording a crude product pure enough so that it could be used without further purification.

1-Hydroseleno-3-isopropoxypropane-2-thiol (25a)



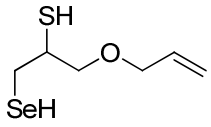
Following the general procedure, 2-(isopropoxymethyl)thiirane (100 mg, 0.76 mmol), bis(trimethylsilyl)selenide (291 mg, 1.29 mmol) and TBAF (257uL, 1M THF solution) gave 1-hydroseleno-3-isopropoxypropane-2-thiol (86%, 140mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.49 (1H, t, *J*=7.6 Hz, Se**H**), 1.11 (6H, d, *J*=6.2 Hz), 1.90 (1H, d, *J*=8.4 Hz, S**H**), 2.88-2.94 (2H, m, C**H$_2$**Se), 2.95-3.17 (1H, m, C**H**SH), 3.38-3.63 (3H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0 (CH_3), 22.1 (CH_3), 23.5 (CH_2Se), 41.8 (CHSH), 71.2 (CH_2), 72.0 (CH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -58.1 ppm.

1-(Allyloxy)-3-hydroselenopropane-2-thiol (25b)



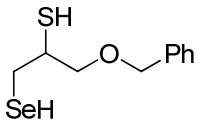
Following the general procedure, 2-(allyloxymethyl)thiirane (90 mg, 0.69 mmol), bis(trimethylsilyl)selenide (267 mg, 1.17 mmol) and TBAF (234uL, 1M THF solution) gave 1-(allyloxy)-3-hydroselenopropane-2-thiol (71%, 105 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.44 (1H, t, *J*=7.4 Hz, Se**H**), 1.93 (1H, d, *J*=8.6 Hz, S**H**), 2.90-2.94 (1H, m, C**H**$_2$Se), 2.95 (1H, d, *J*=7.5 Hz, C**H**$_2$Se),3.01-3.19 (1H, m, C**H**SH), 3.51 (1H, dd, *J*=6.0, 10.0 Hz), 3.64 (1H, dd, *J*=4.0, 10.0 Hz), 5.14-5.38 (2H, m), 5.89 (1H, ddt, *J*=1.4, 2.8, 5.6 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.5 (CH_2Se), 41.6 (CHSH), 72.0 (CH_2), 73.2 (CH_2), 117.3 (CH_2), 134.4 (CH). ppm

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -55.2 ppm.

1-(Benzyloxy)-3-hydroselenopropane-2-thiol (25c)



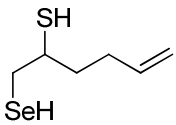
Following the general procedure, 2-(benzyloxymethyl)thiirane (100 mg, 0.56 mmol), bis(trimethylsilyl)selenide (214 mg, 0.94 mmol) and TBAF (188 uL, 1M THF solution) gave 1-(benzyloxy)-3-hydroselenopropane-2-thiol (93%, 136 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.49 (1H, t, *J*=7.8 Hz, Se**H**), 1.97 (1H, d, *J*=8.8 Hz, S**H**), 2.91-2.99 (2H, m, C**H$_2$**Se), 3.04-3.26 (1H, m, C**H**SH), 3.55 (1H, dd, *J*=6.0, 10.0 Hz), 3.69 (1H, dd, *J*=6.0, 10.0 Hz), 4.55 (2H, ap s), 7.28-7.41 (5H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.5 (CH_2Se), 41.5 (CHSH), 72.9 (CH_2), 73.0 (CH_2), 127.6 (CH), 127.7 (CH), 128.4 (CH), 137.8 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -55.4 ppm.

1-Hydroselenohex-5-ene-2-thiol (25d)



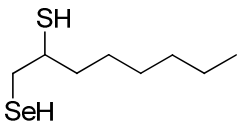
Following the general procedure, 2-(but-3-enyl)thiirane (90 mg, 0.79 mmol), bis(trimethylsilyl)selenide (303 mg, 1.34 mmol) and TBAF (268uL, 1M THF solution) gave 1-hydroselenohex-5-ene-2-thiol (67%, 103 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.39 (1H, t, *J*=7.0 Hz, Se**H**), 1.74 (1H, d, *J*=6.8 Hz, S**H**), 1.48-1.67 (1H, m), 1.77-1.98 (1H, m), 2.06-2.38 (2H, m), 2.80-2.97 (2H, m, C**H$_2$**Se), 2.98-3.19 (1H, m, C**H**SH), 4.96-5.10 (2H, m), 5.66-5.88 (1H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.5 (CH_2Se), 31.2 (CH_2), 36.4 (CH_2), 42.3 (CHSH), 115.5 (CH_2), 137.3 (CH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -44.1 ppm.

1-Hydroselenooctane-2-thiol (25e)



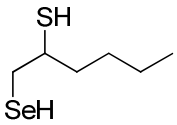
Following the general procedure, 2-hexylthiirane (60 mg, 0.42 mmol), bis(trimethylsilyl)selenide (160 mg, 0.71 mmol) and TBAF (142uL, 1M THF solution) gave 1-hydroselenooctan-2-thiol (42%, 39 mg) in a mixture 3:1 with the corresponding diselenide.

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.41 (1H, t, *J*=7.2 Hz, Se**H**), 0.89 (3H, ap t, *J*=4.4 Hz), 1.25-1.39 (6H, m), 1.39-1.59 (2H, m), 1.74 (1H, d, *J*=6.9 Hz, S**H**), 1.73-1.91 (1H, m), 2.79-2.86 (2H, m, C**H$_2$**Se), 2.87-3.01 (1H, m, C**H**SH) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.4 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 33.7 (CH_2), 37.2 (CH_2), 60.5 (CH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -43.1 ppm.

1-Hydroselenohexane-2-thiol (25f)



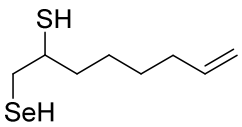
Following the general procedure, 2-butylthiirane (100 mg, 0.86 mmol), bis(trimethylsilyl)selenide (330 mg, 1.46 mmol) and TBAF (292uL, 1M THF solution) gave 1-hydroselenohexan-2-thiol (43%, 73 mg) in a mixture 2:1 with the corresponding diselenide.

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.43 (1H, t, *J*=7.0 Hz, Se**H**), 0.88 (3H, ap t, *J*=6.4 Hz), 1.21-1.53 (4H, m), 1.74 (1H, d, *J*=6.8 Hz, S**H**), 1.75-1.90 (2H, m), 2.80-3.01 (3H, m, C**H$_2$**Se overlapped with C**H**SH) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.3 (CH_2), 27.5 (CH_2), 29.2 (CH_2), 36.9 (CH_2), 43.0 (CHSH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -42.4. ppm

1-Hydroselenooct-7-en-2-thiol (25h)



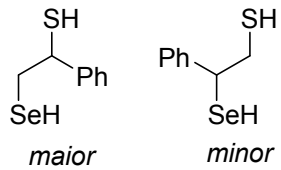
Following the general procedure, 2-(hex-5-en-1-yl)thiirane (56 mg, 0.40 mmol), bis(trimethylsilyl)selenide (154 mg, 0.68 mmol) and TBAF (135 uL, 1M THF solution) gave 1-hydroselenooct-7-en-2-thiol (76%, 68 mg) in a mixture 9:1 with the corresponding diselenide.

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.40 (1H, t, $^{3}J_{H\text{-}H}$=7.2 Hz; coupling with ^{77}Se: ap dt, $^{1}J_{Se\text{-}H}$=44.8 Hz, Se**H**), 1.34-1.55 (6H, m), 1.75 (1H, d, *J*=6.8 Hz, S**H**), 2.01-2.10 (2H, m), 2.79-2.86 (2H, m, CH_2Se), 2.86-3.01 (1H, m, C**H**SH), 4.91-5.05 (2H, m), 5.68-5.90 (1H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.5 (CH_2), 27.6 (CH_2), 28.4 (CH_2), 33.5 (CH_2), 37.0 (CH_2), 43.0 (CH), 114.6 (CH_2), 138.6 (CH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -42.1 ppm.

2-Hydroseleno-1-phenylethanethiol (25g)



Following the general procedure, 2-phenylthiirane (70 mg, 0.51mmol), bis(trimethylsilyl)selenide (197 mg, 0.87mmol) and TBAF (174uL, 1M THF solution) gave 2-hydroseleno-2-phenylethanethiol (*major* regioisomer) with 40% of the *minor* regioisomer2-hydroseleno-1-phenylethanethiol.

^{1}H NMR (300 MHz, $CDCl_3$): δ = -0.45 (1H, dd, *J*=6.0, 7.8 Hz, coupling with ^{77}Se:$^{1}J_{Se\text{-}H}$=46.5 Hz, Se**H** *major* regioisomer), 0.70 (1H, d, *J*=4.5 Hz, Se**H** *minor* regioisomer), 1.51 (1H, dd, *J*=7.0, 9.7 Hz, S**H** *minor* regioisomer), 2.36 (1H, d, *J*=5.7 Hz, S**H** *major* regioisomer), 3.01-3.16 (2H, m), 3.18-3.32 (2H, m), 4.13-4.24 (1H, m, C**H**SH, *major* regioisomer), 4.26-4.38 (1H, m, C**H**SeH, *minor* regioisomer), 7.22-7.38 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.9 (CH2), 33.8 (CH2), 46.7 (CH), 49.0 (CH), 127.0 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.5 (CH), 128.8 (CH), 140.2 (C), 140.5 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -4.1 (*majo*r regioisomer), 188.8 (*minor* regioisomer) ppm.

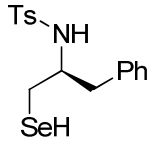
Synthesis of *N*-Tosyl β-aminooselenols 26. **General procedure**.

A solution of aziridine **6** (1 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1.6 mmol) in dry THF (3 mL) was cooled under inert atmosphere at 0°C, and treated with TBAF (0.32 mL of 1M THF solution, 0.32 mmol). The reaction was stirred for 3 min and then solid citric acid was added. The solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum affording a crude product pure enough so that it could be used without further purification.

Synthesis of *N*-Boc β-aminooselenols 27. **General procedure**.

A solution of aziridine **7** (1.00 mmol) and bis(trimethylsilyl)selenide (HMDSS) (1.60 mmol) in dry THF (3 mL) under inert atmosphere was treated with TBAF (1.60 mL of 1M THF solution, 1.60 mmol). The reaction was stirred for 1 h and then solid citric acid was added. The solution was diluted with diethyl ether, washed with water, and dried over Na_2SO_4. The solvent was evaporated under vacuum affording a crude product pure enough so that it could be used without further purification.

(*S*)-*N*-(1-Hydroseleno-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (26a)



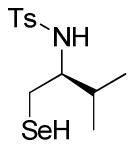
Following the general procedure, (*S*)-2-benzyl-1-tosylaziridine (100 mg, 0.35 mmol), bis(trimethylsilyl)selenide (135 mg, 0.60 mmol) and TBAF (120 uL, 1M THF solution) gave (*S*)-*N*-(1-hydroseleno-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (82%, 106 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.72 (1H, ap t, $^{3}J_{H\text{-}H}$=7.8 Hz; coupling with ^{77}Se: ap dt, $^{1}J_{Se\text{-}H}$=45.2 Hz, Se**H)**, 2.41 (3H, s). 2.60-2.69 (2H, m), 2.73-2.80 (2H, m), 3.48-3.79 (1H, m), 4.81 (1H, d, *J*=8.0 Hz, N**H**), 6.98-7.02 (2H, m), 7.15-7.24 (5H, m), 7.61 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4 (CH_3), 22.8 (CH_2), 39.9 (CH_2), 55.1 (CH), 126.7 (CH), 126.9 (CH), 128.6 (CH), 129.1 (CH),129.9 (CH), 136.5 (C), 137.3 (C), 143.3 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -94.0 ppm.

(*S*)-*N*-(1-Hydroseleno-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (26b)



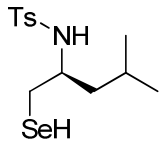
Following the general procedure, (*S*)-2-isopropyl-1-tosylaziridine (100 mg, 0.42 mmol), bis(trimethylsilyl)selenide (160 mg, 0.71mmol) and TBAF (142uL, 1M THF solution) gave (*S*)-*N*-(1-hydroseleno-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (84%, 112 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.88 (1H, dd, *J*=6.8, 8.0 Hz, Se**H**), 0.79 (6H, ap t, *J*=6.6 Hz, (C**H$_3$**)$_2$CH), 1.76-1.91 (1H, m, C**H**(CH_3)$_2$), 2.42 (3H, s), 2.45-2.65 (1H, m, C**H**$_2$Se), 2.70 (1H, ddd, *J*=4.0, 6.8, 11.0 Hz, C**H**$_2$Se), 2.99-3.16 (1H, m, C**H**NH), 5.02 (1H, d, *J*=8.8 Hz, N**H**), 7.30 (2H, ap d, ls=8.4 Hz), 7.77 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.0, 18.9, 21.4, 21.5, 30.4, 59.4, 127.0, 129.6, 137.8, 143.4 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -94.5 ppm.

(*S*)-*N*-(1-Hydroseleno-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (26c)



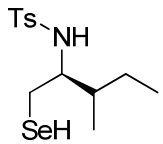
Following the general procedure, (*S*)-2-isobutyl-1-tosylaziridine (100 mg, 0.39 mmol), bis(trimethylsilyl)selenide (149 mg, 0.66 mmol) and TBAF (132 uL, 1M THF solution) gave (*S*)-*N*-(1-hydroseleno-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (77%, 100 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.88 (1H, ap t, $^{3}J_{H\text{-}H}$=8.0 Hz; coupling with ^{77}Se: ap dt, $^{1}J_{Se\text{-}H}$=45.2 Hz, Se**H**), 0.71 (3H, d, *J*=6.6 Hz), 0.81 (3H, d, *J*=6.6 Hz), 1.16-1.30 (2H, m), 1.39-1.53 (1H, m), 2.42 (3H, s), 2.55-2.62 (2H, m), 3.38-3.61 (1H, m), 4.78 (1H, d, *J*=8.8 Hz), 7.30 (2H, ap d, ls=8.0 Hz), 7.76 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5,21.7, 22.0, 23.0, 24.9, 43.7, 56.4, 127.6, 129.5, 137.7, 142.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -93.2 ppm.

***N*-((2*S*,3*S*)-1-Hydroseleno-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (26d)**



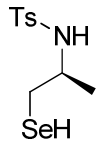
Following the general procedure, (*S*)-2-((*S*)-sec-butyl)-1-tosylaziridine (100 mg, 0.39 mmol), bis(trimethylsilyl)selenide (149 mg, 0.66 mmol) and TBAF (132 uL, 1M THF solution) gave *N*-((2*S*,3*S*)-1-Hydroseleno-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (78%, 102 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.92 (1H, dd, $^{3}J_{H\text{-}H}$=6.4, 8.4 Hz; coupling with ^{77}Se: ddd $^{1}J_{Se\text{-}H}$=40.0 Hz, Se**H**), 0.76 (3H, d, *J*=6.8 Hz), 0.81 (3H, t, J=7.2 Hz), 0.88-1.11 (1H, m), 1.40-1.90 (2H, m), 2.42 (3H, s), 2.47-2.71 (2H, m), 3.12-3.24 (1H, m), 5.1 (1H, d, *J*=8.8 Hz), 7.29 (2H, ap d, ls=7.2 Hz), 7.77 (2H, ap d, ls=7.2 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.2, 14.9, 21.0, 21.5, 24.6, 37.1, 58.1, 127.0, 129.6, 137.9, 143.4 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -95.6 ppm.

(*S*)-*N*-(1-Hydroselenopropan-2-yl)-4-methylbenzenesulfonamide (26e)



Following the general procedure, (*S*)-2-methyl-1-tosylaziridine (100 mg, 0.47mmol), bis(trimethylsilyl)selenide (180 mg, 0.80mmol) and TBAF (160uL, 1M THF solution) gave (*S*)-*N*-(1-hydroselenopropan-2-yl)-4-methylbenzenesulfonamide (80%, 110 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = -0.79 (1H, ap t, $^{3}J_{H\text{-}H}$=7.8 Hz; coupling with ^{77}Se: ap dt, $^{1}J_{Se\text{-}H}$=45.4 Hz, Se**H**), 1.08 (3H, d, *J*=6.6 Hz), 2.42 (3H, s), 2.61 (2H, dd, *J*=4.6, 7.8 Hz), 3.40-3.61 (1H, m), 5.10 (1H, bs), 7.30 (2H, ap d, ls=8.4 Hz), 7.76 (2H, ap d, ls=8.4 Hz) ppm.

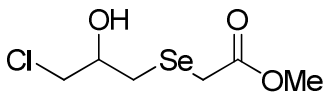
^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5 (CH_3), 21.5 (CH_3), 25.3 (CH_2), 49.9 (CH), 127.0 (CH), 129.7 (CH), 137.9 (C), 143.5 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = -90.8 ppm.

Alkylation of selenols. General procedure.

Cs_2CO_3 (1 mmol) and TBAI (1 mmol) were added to a solution of selenol **24-27** (1 mmol) in DMF (5 mL) at 0°C under inert atmosphere. Methyl 2-bromoacetate **31** - or other described electrophiles - (1.1 mmol) was slowly added and the solution stirred for 1 h. Afterwards the solution was diluted with diethyl ether (10 mL) and the organic phase was washed with brine (10 mL), then with H_2O (2 x 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude material was purified on silica gel.

Methyl 2-(3-chloro-2-hydroxypropylselanyl)acetate (32)

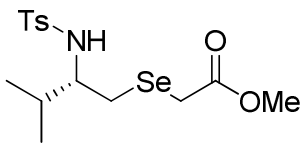


Following the general procedure, 1-chloro-3-hydroselenopropan-2-ol **24e** (87 mg, 0.5 mmol) and methyl 2-bromoacetate (77 mg, 0.5 mmol) gave methyl 2-(3-chloro-2-hydroxypropylselanyl)acetate (78%, 96 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.75 (1H, bs, OH), 2.91 (1H, dd, *J*=7.1, 13.3 Hz, C**H**$_a$H$_b$Se), 3.02 (1H, dd, *J*=4.7, 13.3 Hz, CH$_a$**H**$_b$Se), 3.27 (2H, s, CH_2Se), 3.65 (2H, ap d, *J*=5.3 Hz, CH_2Cl), 3.74 (3H, s, OCH_3), 3.99-4.11 (1H, m, C**H**OH) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.8, 29.9, 48.3, 52.5, 70.9, 172.2 ppm.

(*S*)-Methyl 2-(3-methyl-2-(4-methylphenylsulfonamido)butylselanyl)acetate (34a)

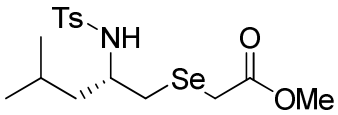


Following the general procedure, (*S*)-*N*-(1-hydroseleno-3-methylbutan-2-yl)-4-methylbenzenesulfonamide **26b** (96 mg, 0.3 mmol) and methyl 2-bromoacetate (46 mg, 0.3 mmol) gave (*S*)-methyl 2-(3-methyl-2-(4-methylphenylsulfonamido)butylselanyl)acetate (84%, 99 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (3H, d, *J*=6.8 Hz), 0.81 (3H, d, *J*=6.8 Hz), 1.78-1.98 (1H, m), 2.42 (3H, s), 2.68-2.87 (2H, m), 3.06 (2H, s, C**H**$_2$S), 3.15-3.36

(1H, m, C**H**NH), 3.72 (3H, s, OCH_3), 5.08 (1H, d, *J*=8.0 Hz, NH), 7.29 (2H, ap d, ls=8.4 Hz), 7.77 (2H, ap d, ls=8.4 Hz) ppm.

(*S*)-Methyl 2-(4-methyl-2-(4-methylphenylsulfonamido)pentylselanyl)acetate (34b)



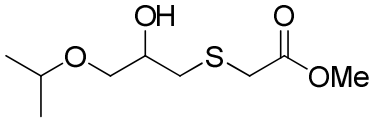
Following the general procedure, (*S*)-*N*-(1-hydroseleno-4-methylpentan-2-yl)-4-methylbenzenesulfonamide **26c** (100 mg, 0.3 mmol) and methyl 2-bromoacetate (46 mg, 0.3 mmol) gave (*S*)-methyl 2-(4-methyl-2-(4-methylphenylsulfonamido)pentylselanyl)acetate (81%, 99 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (3H, d, *J*=6.6 Hz), 0.79 (3H, d, *J*=6.6 Hz), 1.18-1.36 (2H, m), 1.39-1.59 (1H, m), 2.41 (3H, s), 2.78-2.90 (2H, m), 3.10 (2H, s), 3.42-3.61 (1H, m, C**H**NH), 3.71 (3H, s, OCH_3), 5.12 (1H, d, *J*=8.0 Hz, NH), 7.29 (2H, ap d, ls=8.4 Hz), 7.77 (2H, ap d, ls=8.4 Hz) ppm.

Alkylation of thiols. General procedure.

Cs_2CO_3 (1 mmol) and TBAI (1 mmol) were added to a solution of thiol **22** or **37** (1 mmol) in DMF (5 mL). After 10 min the solution was cooled at 0°C and methyl 2-bromoacetate **31** (1.1 mmol) was added. The reaction was stirred for 2 h. Afterwards the solution was diluted with diethyl ether (10 mL) and the organic phase was washed with brine (10 mL), then with H_2O (2 x 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude material was purified on silica gel.

Methyl 2-(2-hydroxy-3-isopropoxypropylthio)acetate (38a)

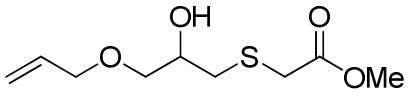


Following the general procedure, 1-isopropoxy-3-mercaptopropan-2-ol **37a** (105 mg, 0.7 mmol) and methyl 2-bromoacetate (107 mg, 0.7 mmol) gave methyl 2-(2-hydroxy-3-isopropoxypropylthio)acetate (83%, 129 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.13 (6H, d, *J*=6.4 Hz), 2.61-2.82 (3H, m overlapped with bs), 3.30 (2H, s), 3.35-3.52 (2H, m), 3.58-3.61 (1H, m), 3.72 (3H, s), 3.78-3.92 (1H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9, 34.1, 36.5, 52.3, 69.8, 70.6, 72.2, 171.0 ppm.

Methyl 2-(3-(allyloxy)-2-hydroxypropylthio)acetate (38b)

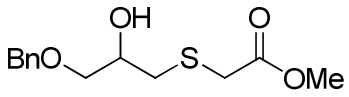


Following the general procedure, 1-(allyloxy)-3-mercaptopropan-2-ol (104 mg, 0.7 mmol) **37b** and methyl 2-bromoacetate (107 mg, 0.7 mmol) gave methyl 2-(3-(allyloxy)-2-hydroxypropylthio)acetate (88%, 136 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.44 (1H, bs, O**H**), 2.71 (1H, dd, *J*=7.4, 14.8 Hz, C**H**$_a$H$_b$S), 2.83 (1H, dd, *J*=4.9, 14.8 Hz, CH$_a$**H**$_b$S), 3.31 (2H, s, C**H**$_2$S), 3.43-3.56 (2H, m, C**H**$_2$O), 3.72 (3H, s, OC**H**$_3$), 3.88-3.96 (1H, m, C**H**OH), 3.98-4.05 (2H, m), 5.18-5.37 (2H, m), 5.78-5.99 (1H, m) ppm.

MS (EI) *m/z* (%): 220 ([$M^{+\cdot}$], 27), 205 (100), 177 (8), 145 (13), 105 (14), 57 (72), 41 (41).

Methyl 2-(3-(benzyloxy)-2-hydroxypropylthio)acetate (38c)

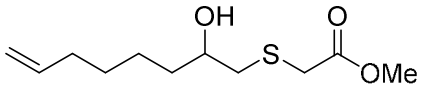


Following the general procedure, 1-(benzyloxy)-3-mercaptopropan-2-ol **37c** (158 mg, 0.8 mmol) and methyl 2-bromoacetate (122 mg, 0.8 mmol) gave methyl 2-(3-(benzyloxy)-2-hydroxypropylthio)acetate (68%, 147 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.68 (1H, bs, O**H**), 2.72 (1H, dd, *J*=7.4, 14.0 Hz, C**H**$_a$H$_b$S), 2.84 (1H, dd, *J*=5.2, 14.0 Hz, CH$_a$**H**$_b$S), 3.30 (2H, s, C**H**$_2$S), 3.51-3.55 (2H, m, C**H**$_2$O), 3.73 (3H, s, OC**H**$_3$), 3.89-4.01 (1H, m, C**H**OH), 4.55 (2H, ap s, C**H**$_2$Ph), 7.28-7.40 (5H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.1, 36.7, 52.3, 69.6, 72.9, 73.5, 127.7, 127.8, 128.4, 137.9, 171.1 ppm.

Methyl 2-(2-hydroxyhex-5-enylthio)acetate (38d)

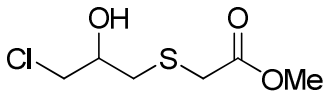


Following the general procedure, 1-mercaptooct-7-en-2-ol (80 mg, 0.5 mmol) **37d** and methyl 2-bromoacetate (77 mg, 0.5 mmol) gave methyl 2-(2-hydroxyoct-7-enylthio)acetate (91%, 106 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33-1.45 (6H, m), 1.99-2.10 (2H, m), 2.45 (1H, bs), 2.54 (1H, dd, *J*=8.8, 13.8 Hz, C**H$_a$**H$_b$S), 2.83 (1H, dd, *J*=3.4, 13.8 Hz, CH$_a$**H$_b$**S), 3.27 (2H, ap d, ls=2.2 Hz, C**H$_2$**S), 3.61-3.74 (1H, m, C**H**OH), 3.73 (3H, s, OC**H$_3$**), 4.90-4.96 (2H, m), 5.66-5.91 (1H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.1, 28.8, 33.5, 33.9, 36.1, 40.8, 52.4, 69.8, 114.4, 138.7, 171.2. ppm

Methyl 2-(3-chloro-2-hydroxypropylthio)acetate (38e)

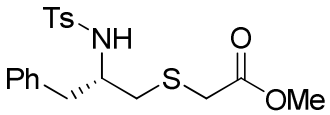


Following the general procedure, 1-chloro-3-mercaptopropan-2-ol **37e** (102 mg, 0.8 mmol) and methyl 2-bromoacetate (122 mg, 0.8 mmol) gave methyl 2-(3-chloro-2-hydroxypropylthio)acetate (89%, 142 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.71-2.98 (2H, m), 3.32 (3H, s), 3.61-3.63 (2H, m), 3.74 (3H, s), 3.91-4.03 (1H, m). ppm

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.1, 37.1, 47.7, 52.5, 70.4, 171.2 ppm.

(*S*)-Methyl 2-(2-(4-methylphenylsulfonamido)-3-phenylpropylthio)acetate (41a)



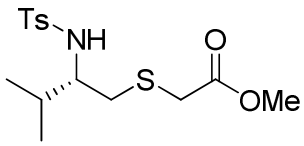
Following the general procedure, **22a** (80 mg, 0.25 mmol) and methyl 2-bromoacetate (38 mg, 0.25 mmol) gave (*S*)-methyl 2-(2-(4-methylphenylsulfonamido)-3-phenylpropylthio)acetate (78%, 77 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (3H, s), 2.74 (2H, ap d, *J*=5.5 Hz), 2.78 (1H, dd, *J*=6.7, 13.9 Hz), 2.85 (1H, dd, *J*=7.1, 13.9 Hz), 3.19 (2H, s, C**H**$_2$S), 3.57-3.65 (1H, m, C**H**NH), 3.72 (3H, s, OCH_3), 5.04 (1H, d, *J*=7.3 Hz, NH), 6.99-7.05 (2H, m), 7.17-7.22 (5H, m), 7.61 (2H, ap d, ls=8.3 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5, 34.4, 37.8, 39.8, 54.1, 126.8, 127.1, 128.6, 128.7, 129.3, 129.6, 136.5, 143.3, 171.1 ppm.

MS (EI) *m/z* (%): 362 ([$M^{+\cdot}$-MeO], 1), 302 ([$M^{+\cdot}$-Bn], 32), 274 (45), 155 (38), 147 (26), 91 (100, Bn^+), 65 (20), 45 (17).

(*S*)-Methyl 2-(3-methyl-2-(4-methylphenylsulfonamido)butylthio)acetate (41b)



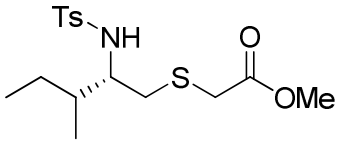
Following the general procedure, (*S*)-N-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide **22b** (82 mg, 0.3 mmol) and methyl 2-bromoacetate (46 mg, 0.3 mmol) gave (*S*)-methyl 2-(3-methyl-2-(4-methylphenylsulfonamido)butylthio)acetate (86%, 89 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (3H, d, *J*=6.8 Hz), 0.80 (3H, d, *J*=6.8 Hz), 1.88-1.98 (1H, m), 2.42 (3H, s), 2.65 (1H, dd, *J*=5.2, 13.6 Hz, C**H**$_a$H$_b$S), 2.76 (1H, dd, *J*=5.6, 13.6 Hz, CH$_a$**H**$_b$S), 3.09 (2H, s, C**H**$_2$S), 3.16-3.24 (1H, m, C**H**NH), 3.73 (3H, s, OCH_3), 4.93 (1H, d, *J*=8.4 Hz, NH), 7.29 (2H, ap d, ls=8.4 Hz), 7.76 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.9, 18.7, 21.5, 30.4, 34.1, 35.9, 52.6, 58.2, 127.2, 129.6, 137.8, 143.4, 170.9 ppm.

MS (EI) *m/z* (%): 314 (1), 226 (100), 155 (59), 91 (95), 65 (16), 45 (19).

Methyl 2-((2*S*,3*S*)-3-methyl-2-(4-methylphenylsulfonamido)pentylthio)acetate (41c)



Following the general procedure, **22c** (86 mg, 0.3 mmol) and methyl 2-bromoacetate (46 mg, 0.3 mmol) gave methyl 2-((2*S*,3*S*)-3-methyl-2-(4-methylphenylsulfonamido)pentylthio)acetate (81%, 87 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.81 (3H, t, *J*=7.2 Hz), 0.79 (3H, d, *J*=6.8 Hz), 0.89-1.11 (1H, m), 1.27-1.50 (1H, m), 1.60-1.86 (1H, m), 2.42 (3H, s), 2.68 (2H, ap d, *J*=5.7 Hz, CH_2S), 3.04 (2H, s, C**H**$_2$S), 3.20-3.34 (1H, m, C**H**NH), 3.72 (3H, s, OCH_3), 5.01 (1H, d, *J*=7.9 Hz, NH), 7.29 (2H, ap d, ls=7.9 Hz), 7.77 (2H, ap d, ls=7.9 Hz) ppm.

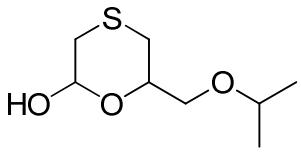
^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.4, 14.7, 21.5, 25.0, 34.0, 35.2, 37.5, 52.4, 57.0, 127.3, 129.5, 138.1, 143.2, 170.7 ppm.

MS (EI) *m/z* (%): 360 ([$M^{+\cdot}$], 1), 240 (42), 184 (11), 155 (35), 91 (45, Bn^+), 43 (100).

Sinthesis of 6-membered heterocycles from δ-functionalized α-thiol- or α-selenol- esters. General procedure.

A solution of δ-functionalized α-thiol- or α-selenol- ester (**32, 34, 38, 41** - 1 mmol) in dry toluene (10 mL) was cooled at -78°C and DIBAL-H (1.1 mL, 1 M solution in CH_2Cl_2, 1.1 mmol) was dropwise added. The reaction mixture was stirred at -78°C for 3 h, then mL of 7% *aq* HCl was added and the mixture stirred at r.t. for 3h. Afterwards the solution was diluted with diethyl ether (10 mL) and the organic phase was washed with brine (10 mL), then with H_2O (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude material was purified on silica gel.

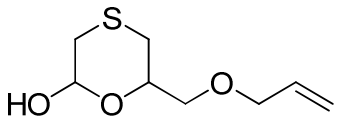
6-(Isopropoxymethyl)-1,4-oxathian-2-ol (40a)



Following the general procedure, methyl 2-(2-hydroxy-3-isopropoxypropylthio)acetate **38a** (66 mg, 0.30 mmol) gave, after silica gel chromatography purification (petroleum ether/ethyl acetate 4:1), 6-(isopropoxymethyl)-1,4-oxathian-2-ol (72%, 41 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (1H, d, *J*=6.1 Hz), 1.15 (1H, d, *J*=6.1 Hz), 2.31-2.74 (7H, m), 3.08 (1H, dd, *J*=2.1, 13.7 Hz), 3.29-3.68 (6H, m), 3.92-4.05 (1H, m, C**H**O), 4.21-4.33 (1H, m, CHO), 4.96 (1H, dd, *J*=4.0, 6.9 Hz, C**H**OH), 5.28 (1H, ap s, C**H**OH) ppm.

6-(Allyloxymethyl)-1,4-oxathian-2-ol (40b)



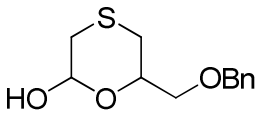
Following the general procedure, methyl methyl 2-(3-(allyloxy)-2-hydroxypropylthio)acetate **38b** (44 mg, 0.2 mmol) gave, after silica gel chromatography purification (petroleum ether/ethyl acetate 4:1), 6-(allyloxymethyl)-1,4-oxathian-2-ol (63%, 24 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27-2.40 (1H, m), 2.45-2.6 (2H, m), 2.72 (1H, dd, *J*=11.2, 13.4 Hz), 2.88-2.96 (1H, m), 3.0 (1H, dd, *J*=3.1, 12.5 Hz), 3.09 (1H, dd, *J*=2.1, 13.4 Hz), 3.23 (1H, ap d, ls=15.0 Hz), 3.37 (1H, dd, *J*=5.4, 10.0 Hz), 3.43 (1H, dd, *J*=4.2, 5.8 Hz), 3.46 (1H, dd, *J*=3.7, 5.8 Hz), 3.61 (1H, dd, *J*=5.4, 10.3 Hz), 3.71 (1H, dd, *J*=4.9, 10.3 Hz), 4.0-4.07 (4H, m), 4.29-4.35 (1H, m, CHO), 4.59-4.66 (1H, m, CHO), 4.97 (1H, dd, *J*=3.5, 7.6 Hz, C**H**OH), 5.18-5.32 (5H, m, C**H$_2$**=CH of two diastereoisomers overlapped with C**H**OH), 5.84-5.96 (2H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4, 28.5, 31.4, 32.5, 67.4, 70.7, 72.3, 72.5, 72.6, 78.0, 87.9, 95.8, 117.4, 117.6, 134.3, 134.4 ppm.

MS (EI) *m/z* (%): 190 ([$M^{+\cdot}$], 1), 188 ([$M^{+\cdot}$-2], 8), 147 (3), 119 (10), 89 (28), 73 (20), 61 (30), 41 (100).

6-(Benzyloxymethyl)-1,4-oxathian-2-ol (40c)

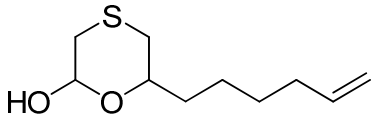


Following the general procedure, 2-(3-(benzyloxy)-2-hydroxypropylthio)acetate **38c** (67 mg, 0.25 mmol) gave, after silica gel chromatography purification (petroleum ether/ethyl acetate 5:1), 6-(benzyloxymethyl)-1,4-oxathian-2-ol (56%, 33 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27-2.39 (2H, m), 2.43-2.51 (3H, m), 2.56 (1H, dd, *J*=8.8, 13.1 Hz), 2.70 (1H, dd, *J*=11.1, 13.4 Hz), 3.05 (1H, dd, *J*=2.0, 13.4 Hz), 3.39 (1H, dd, *J*=5.4, 9.9 Hz), 3.43-3.49 (2H, m), 3.54 (1H, dd, *J*=5.8, 9.9 Hz), 4.01-4.07 (1H, m, C**H**O), 4.32-4.38 (1H, m, C**H**O), 4.45 (4H, ap s, C**H**$_2$Ph), 4.91 (1H, dd, *J*=2.2, 8.8 Hz, C**H**OH), 5.28 (1H, ap s, C**H**OH), 7.27-7.37 (10H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (CH_2), 28.6 (CH_2), 31.5 (CH_2), 32.5 (CH_2), 67.5 (CH), 72.5 (CH_2), 72.6 (CH_2), 73.5 (CH_2), 78.0 (CH), 87.9 (CH), 95.8 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 137.7 (C), 137.8 (C) ppm.

6-(Hex-5-enyl)-1,4-oxathian-2-ol (40d)

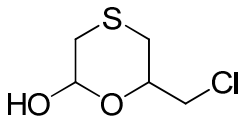


Following the general procedure, methyl 2-(2-hydroxyoct-7-enylthio)acetate **38d** (47 mg, 0.2 mmol) gave, after silica gel chromatography purification (petroleum ether/ethyl acetate 5:1), 6-(hex-5-enyl)-1,4-oxathian-2-ol (58%, 24 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28-1.63 (12H, m), 1.97-2.11 (4H, m), 2.22 (1H, dd, *J*=2.1, 13.4 Hz), 2.31-2.62 (6H, m), 3.05 (1H, dd, *J*=2.1, 13.4 Hz), 3.68-3.86 (1H, m), 3.98-4.15 (1H, m), 4.88-5.03 (5H, m, C**H**$_2$=CH overlapped with C**H**OH), 5.24 (1H, ap s, C**H**OH), 5.69-5.90 (2H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 24.7, 28.7, 30.0, 31.1, 31.5, 32.5, 33.5, 35.7, 35.8, 68.3, 79.3, 87.8, 95.9, 114.4, 138.6 ppm.

6-(Chloromethyl)-1,4-oxathian-2-ol (40e)

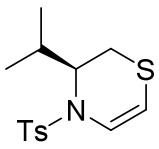


Following the general procedure, methyl 2-(3-chloro-2-hydroxypropylthio)acetate **38e** (40 mg, 0.2 mmol) gave, after silica gel chromatography purification (petroleum ether/ethyl acetate 6:1), 6-(chloromethyl)-1,4-oxathian-2-ol (82%, 28 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42-2.51 (4H, m), 2.54-2.57 (2H, m), 2.68 (1H, dd, *J*=10.8, 13.6 Hz), 3.05 (1H, dd, *J*=2.2, 13.6 Hz), 3.43 (1H, dd, *J*=6.1, 13.3 Hz), 3.46-3.53 (2H, m), 3.57 (1H, dd, *J*=5.6, 11.3 Hz), 4.00-4.07 (1H, m, CHO), 4.31-4.37 (1H, m, CHO), 4.98 (1H, dd, *J*=4.1, 6.8 Hz, C**H**OH), 5.30 (1H, ap s, C**H**OH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8, 28.7, 31.2, 32.2, 45.8, 46.4, 68.1, 78.3, 88.3, 96.0 ppm.

(*S*)-3-Isopropyl-4-tosyl-3,4-dihydro-2*H*-1,4-thiazine (44)



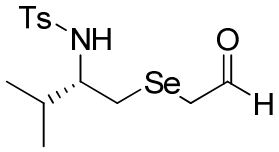
Following the general procedure, (*S*)-methyl 2-(3-methyl-2-(4-methylphenylsulfonamido)butylthio)acetate **41b** (35 mg, 0.1 mmol) gave after silica gel chromatography purification (petroleum ether/ethyl acetate 3:1), (*S*)-3-isopropyl-4-tosyl-3,4-dihydro-2*H*-1,4-thiazine (54%, 16 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (1H, d, *J*=6.6 Hz), 1.19 (1H, d, *J*=6.7 Hz), 1.86 (1H, dd, *J*=2.9, 13.3 Hz, C$\mathbf{H}_a$H$_b$S), 1.90-1.97 (1H, m), 2.42 (3H, s), 2.62 (1H, dt, *J*=2.7, 13.3 Hz, CH$_a$$\mathbf{H}_b$S), 3.74 (1H, dt, *J*=2.9, 10.2 Hz), 5.44 (1H, dd, $^{4}J_{H\text{-}H}$=2.7, $^{3}J_{H\text{-}H}$=8.4 Hz), 6.68 (1H, d, *J*=8.4 Hz), 7.30 (2H, ap d, ls=8.4 Hz), 7.62 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.6, 19.7, 21.5, 25.3, 28.5, 56.9, 104.1, 119.0, 127.2, 129.9, 135.8, 144.1 ppm.

MS (EI) *m/z* (%): 297 ([$M^{+\cdot}$], 34), 254 (24), 155 (32), 142 (68), 100 (100), 91 (92), 65 (38), 41 (68).

(*S*)-4-Methyl-*N*-(3-methyl-1-(2-oxoethylselanyl)butan-2-yl)benzenesulfonamide (47a)

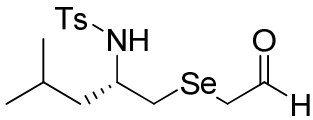


Following the general procedure, **34a** (70 mg, 0.18 mmol) gave, after silica gel chromatography purification (petroleum ether/ethyl acetate 3:1), **(*S*)-47a** (71%, 33 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (3H, d, *J*=6.6 Hz), 0.79 (3H, d, *J*=7.0 Hz), 1.72-1.97 (1H, m), 2.42 (3H, s), 2.44-2.61 (2H, m), 2.98-3.12 (2H, m), 3.12-3.25 (1H, m), 4.83 (1H, bd, *J*=7.8 Hz), 7.29 (2H, ap d, ls=8.4 Hz), 7.77 (2H, ap d, ls=8.4 Hz), 9.34 (1H, t, *J*=5.2 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.8, 18.7, 21.6, 27.7, 31.4, 32.8, 58.7, 127.1, 129.6, 138.1, 143.8, 191.6 ppm.

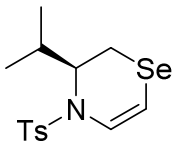
(*S*)-4-Methyl-*N*-(4-methyl-1-(2-oxoethylselanyl)pentan-2-yl)benzenesulfonamide (47b)



Following the general procedure, **34b** (50 mg, 0.12 mmol) gave, after silica gel chromatography purification (petroleum ether/ethyl acetate 3:1), (*S*)-4-methyl-*N*-(4-methyl-1-(2-oxoethylselanyl)pentan-2-yl)benzenesulfonamide (68%, 32 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.67 (3H, d, *J*=6.4 Hz), 0.80 (3H, d, *J*=6.4 Hz), 1.19-1.36 (2H, m), 1.38-1.59 (1H, m), 2.43 (3H, s), 2.60 (2H, ap d, *J*=4.6 Hz, C**H$_2$**SCHO), 3.03-3.21 (2H, m, C**H$_2$**S), 3.35-3.57 (1H, m), 4.65 (1H, d, *J*=8.4 Hz), 7.31 (2H, ap d, ls=8.2 Hz), 7.77 (2H, ap d, ls=8.2 Hz), 9.35 (1H, t, *J*=4.6 Hz) ppm.

(*S*)-3-Isopropyl-4-tosyl-3,4-dihydro-2*H*-1,4-selenazine (48a)



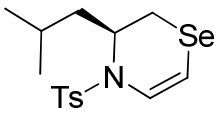
Spontaneous cyclization in $CHCl_3$ of compound **47a** afforded **48a** in quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (1H, d, *J*=6.6 Hz), 1.08 (1H, d, *J*=6.4 Hz), 1.90-2.05 (1H, m), 2.14 (1H, dd, *J*=3.4, 13.4 Hz, C**H$_a$**H$_b$Se), 2.42 (3H,

s), 2.55-2.62 (1H, m, $CH_a\mathbf{H_b}Se$), 3.67 (1H, dt, *J*=2.6, 10.1 Hz), 5.67 (1H, dd, $^4J_{H-H}$=1.4, $^3J_{H-H}$=8.4 Hz, coupling with ^{77}Se, ddd, $^2J_{Se-H}$=47.1 Hz, CHSe), 7.04 (1H, d, *J*=8.4 Hz, NC**H**CH), 7.30 (2H, ap d, ls=8.2 Hz), 7.64 (2H, ap d, ls=8.2 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5 (CH_3), 19.0 (CH_2), 19.7 (CH_3), 21.6 (CH_3), 29.3 (CH), 56.4 (CH), 98.4 (CH), 121.8 (CH), 126.8 (CH), 129.8 (CH), 135.8 (C), 143.7 (C) ppm.

(*S*)-3-Isobutyl-4-tosyl-3,4-dihydro-2*H*-1,4-selenazine (48b)



Spontaneous cyclization in $CHCl_3$ of compound **47b** afforded to (*S*)-3-isobutyl-4-tosyl-3,4-dihydro-2*H*-1,4-selenazine **48b** in quantitative yield.

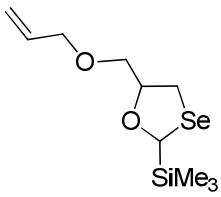
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (1H, d, *J*=6.8 Hz), 0.98 (1H, d, *J*=6.4 Hz), 1.32-1.41 (1H, m), 1.49-1.58 (1H, m), 1.68-1.92 (1H, m), 2.33 (1H, dd, *J*=3.6, 13.2 Hz, $C\mathbf{H_a}H_bSe$), 2.39-2.42 (1H, m, $CH_a\mathbf{H_b}Se$), 2.42 (3H, s), 4.36-4.22 (1H, m), 5.63 (1H, dd, $^4J_{H-H}$=1.8, $^3J_{H-H}$=8.4 Hz, coupling with ^{77}Se, ddd, $^2J_{Se-H}$=46.4 Hz, CHSe), 7.04 (1H, d, *J*=8.4 Hz, NC**H**CH), 7.31 (2H, ap d, ls=8.2 Hz), 7.66 (2H, ap d, ls=8.2 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.1 (CH_2), 21.6 (CH_3), 22.4 (CH_3), 22.9 (CH_3), 23.9 (CH), 42.2 (CH_2), 48.5 (CH), 96.9 (CH), 121.7 (CH), 126.9 (CH), 129.9 (CH), 136.0 (C), 143.8 (C) ppm.

Synthesis of 2-silyl-1,3-oxaselenolanes. General procedure.

Selenol **24** (1 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (1 mmol) **64** were dissolved in dry CH_2Cl_2 (3 mL) under inert atmosphere and then boron trifluoride diethyl etherate (0.4 mmol) was added dropwise. The mixture was stirred at r.t. for 1h, then the temperature was cooled at -18°C and the reaction stirred for 12 h. Afterwards the solution was diluted with diethyl ether and 0.1 N *aq* NaOH was added. The organic phase was washed with H_2O, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was purified by flash chromatography (Al_2O_3).

(5-((Allyloxy)methyl)-1,3-oxaselenolan-2-yl)trimethylsilane (62a)



Prepared from 1-(allyloxy)-3-hydroselenopropane-2-ol (53 mg, 0.27 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (57 mg, 0.27 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 10:1) to yield (5-((allyloxy)methyl)-1,3-oxaselenolan-2-yl)trimethylsilane (58%, 44 mg) as a 6:1 mixture of two diastereoisomers.

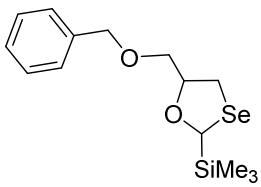
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.13 (18H, s, Si(C**H**$_3$)$_3$), 2.63 (1H, dd, *J*=9.0, 10.2 Hz, C**H**$_a$H$_b$Se, *major*), 3.97–3.09 (2H, m), 3.24 (1H, dd, *J*=4.8, 10.2 Hz, CH$_a$**H**$_b$Se, *major*), 3.35–3.54 (2H, m), 3.56–3.97 (2H, m), 3.83–3.98 (2H, m, CH$_2$C**H**O), 3.99–4.10 (4H, m), 5.01 (1H, s, OC**H**Se, *minor*), 5.04 (1H, s, OC**H**Se, *major*), 5.15–5.35 (4H, m), 5.79–6.01 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -3.2 (Si(CH_3)$_3$), 29.3 (CH_2Se), 29.7 (CH_2Se), 69.2 (OCHSe, *minor*), 71.1 (CH_2, *major*), 72.3 (CH_2), 72.4 (CH_2), 72.5 (CH_2), 74.9 (OCHSe, *major*), 83.6 (CH, *minor*), 87.7 (CH, *major*), 117.2 (CH_2), 134.5 (CH, *major*), 137.4 (CH, *minor*) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 220.8 (*minor*), 244.1 (*major*) ppm.

MS (EI) *m/z* (%):282 ([$M^{+\cdot}$+2], 1), 280 ([$M^{+\cdot}$], 1), 182 (7), 99 (11), 73 ([$SiMe_3^+$], 100).

(5-((Benzyloxy)methyl)-1,3-oxaselenolan-2-yl)trimethylsilane (62b)



Prepared from 1-(benzyloxy)-3-hydroselenopropan-2-ol (48 mg, 0.2 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (41 mg, 0.2 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 10:1) to yield (5-((benzyloxy)methyl)-1,3-oxaselenolan-2-yl)trimethylsilane (60%, 39 mg) as a mixture of two diastereoisomers in a 6:1 ratio.

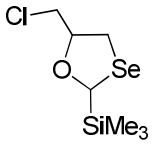
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.14 (18H, s, Si(C**H**$_3$)$_3$), 3.09-3.15 (1H, m, C**H**$_a$H$_b$Se, *minor*), 3.38-3.75 (5H, m), 3.68 (2H, ap t, *J*=5.0 Hz, C**H**$_2$O, *major*), 3.87-4.00 (1H, m, OC**H**CH$_2$, *major*), 4.03-4.11 (1H, m, OC**H**CH$_2$, *minor*), 4.54 (1H, s, OCHSe, *minor*), 4.57 (1H, s, OCHSe, *major*), 4.61 (4H, ap d, ls=1.0 Hz, C**H**$_2$Ph), 7.30–7.37 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -3.2 (Si(CH$_3$)$_3$), *major*), -3.1 (Si(**C**H$_3$)$_3$), *minor*), 29.3 (CH2Se, *minor*), 29.5 (CH2Se, *major*), 69.0 (CH2, *minor*), 70.9 (CH2, *major*), 72.2 (CH, *minor*), 72.9 (CH2, *minor*), 73.4 (CH2, *major*), 74.8 (CH, *major*), 83.6 (CH, *minor*), 87.6 (CH, *major*), 127.7 (CH), 128.4 (CH), 138.0 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 221.6, 245.1 ppm.

MS (EI) *m/z* (%): 254 (9), 239 ([M-Bn$^+$]$^-$, 3), 237 (12), 211 (5), 151 (5), 73 ([SiMe$_3^+$], 100).

(5-(Chloromethyl)-1,3-oxaselenolan-2-yl)trimethylsilane (62c)



Prepared from 1-chloro-3-hydroselenopropan-2-ol (130 mg, 0.76 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (158 mg, 0.76 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 6:1) to yield (5-(chloromethyl)-1,3-oxaselenolan-2-yl)trimethylsilane (47%, 92 mg) as a 3:1 mixture of two diastereoisomers.

Major diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 (9H, s, Si(C**H**$_3$)$_3$), 2.74 (1H, ap t, *J*=9.2 Hz, C**H**$_a$H$_b$Se), 3.31 (1H, dd, *J*=4.8, 9.2 Hz, CH$_a$**H**$_b$Se), 3.62 (1H, dd, *J*=6.0, 11.2 Hz, ClC**H**$_a$H$_b$), 3.72 (1H, dd, *J*=6.0, 11.2 Hz, ClCH$_a$**H**$_b$), 3.95 (1H, m, CH$_2$C**H**O), 5.05 (1H, s, OC**H**Se) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -3.3 (Si(CH$_3$)$_3$), 29.8 (CH_2Se), 44.5 (CH_2Cl), 74.5 (OCHSe), 87.1 (O**C**HCH$_2$) ppm.

MS (EI) *m/z* (%):258 ([$M^{+\cdot}$], 2), 182 (6), 167 (5), 74 (9), 59 (9), 73 ([$SiMe_3^+$], 100).

Minor diastereoisomer

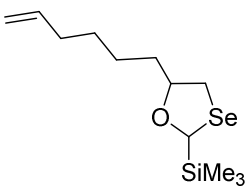
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.12 (9H, s, Si(C**H**$_3$)$_3$), 3.06 (1H, dd, *J*=6.0, 10.0 Hz, C**H**$_a$H$_b$Se), 3.17 (1H, dd, *J*=2.8, 10.0 Hz, CH$_a$**H**$_b$Se), 3.51 (1H, dd, *J*=6.8, 11.2 Hz, ClC**H**$_a$H$_b$), 3.55 (1H, dd, *J*=6.4, 11.2 Hz, ClCH$_a$**H**$_b$), 4.68 (1H, ap dq, *J*=2.8, 6.4 Hz, CH$_2$C**H**O), 4.98 (1H, s, OC**H**Se) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -3.3 (Si(CH$_3$)$_3$), 29.2 (CH_2Se), 43.3 (CH_2Cl), 71.9 (OCHSe), 84.4 (O**C**HCH$_2$) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 241.9, 253.9 (mixture of diastereoisomers) ppm.

MS (EI) *m/z* (%):258 ([$M^{+\cdot}$], 2), 182 (6), 167 (5), 74 (9), 59 (9), 73 ([$SiMe_3^+$], 100).

(5-(Hex-5-enyl)-1,3-oxaselenolan-2-yl)trimethylsilane (62d)



Prepared from 1-hydroselenooct-7-en-2-ol (40 mg, 0.2 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (41 mg, 0.2 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 10:1) to yield (5-(hex-5-enyl) -1,3-oxaselenolan-2-yl)trimethylsilane (63%, 37 mg) as a mixture of two diastereoisomers in a 8:1 ratio.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.12 (9H, s, Si(C**H**$_3$)$_3$, *major*), 0.13 (9H, s, Si(C**H**$_3$)$_3$, *minor*), 1.30-1.78 (12H, m), 2.01-2.14 (4H, m), 2.50 (1H, dd, *J*=9.1, 10.5

Hz, C**H**$_a$H$_b$Se, *major*), 3.23 (1H, dd, *J*=4.0, 9.1 Hz, CH$_a$**H$_b$**Se, *major*), 3.34-3.39 (2H, m, C**H**$_2$Se, *minor*), 3.54-3.73 (2H, m, OC**H**CH$_2$, *major* and *minor*), 4.90-5.01 (5H, m, C**H**$_2$=CH *major* and *minor* overlapped with s, OC**H**Se, *minor*), 4.97 (1H, s, OC**H**Se, *major)*, 5.70-5.91 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -3.3 (Si(CH$_3$)$_3$), 25.3 (CH$_2$, *minor*), 26.1 (CH$_2$, *major*), 28.8 (CH$_2$, *major*), 29.7 (CH$_2$, *minor*) 31.9 (CH, *minor*), 32.2 (CH$_2$, *major*), 33.6 (CH$_2$), 33.8 (CH$_2$), 74.3 (CH), 89.0 (CH), 114.4 (CH$_2$), 138.8 (CH) ppm.

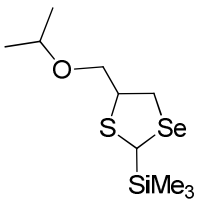
^{77}Se NMR (38 MHz, $CDCl_3$): δ = 245.5 (*major*) ppm.

MS (EI) *m/z* (%): 292 ([M$^{+\cdot}$], 1), 182 (13), 167 (9), 109 (5), 67 (16), 73 ([SiMe$_3^+$], 100).

Synthesis of 2-silyl-1,3-thiaselenolanes. General procedure.

Selenol **25** (1 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (1 mmol) **64** were dissolved in dry CH_2Cl_2 (3 mL) under inert atmosphere and then boron trifluoride diethyl etherate (0.4 mmol) was added dropwise. The mixture was stirred at r.t. for 1h, then the temperature was cooled at -18°C and the reaction stirred for 12 h. Afterwards the solution was diluted with diethyl ether and 0.1 N *aq* NaOH was added. The organic phase was washed with H_2O, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was purified by flash chromatography (Al_2O_3).

(5-(Isopropoxymethyl)-1,3-thiaselenolan-2-yl)trimethylsilane (61a)



Prepared from 1-hydroseleno-3-isopropoxypropane-2-thiol (210 mg, 0.98 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (207 mg, 0.98 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 10:1) and the two diastereoisomers of (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)trimethylsilane were isolated (67%, 200 mg).

Major diastereoisomer (128 mg, 64%)

^{1}H NMR(400 MHz, $CDCl_3$): δ = 0.17 (9H, s, Si(C**H**$_3$)$_3$), 1.16 (6H, d, *J*=6.0 Hz, (C**H**$_3$)$_2$), 3.24 (1H, bdd, *J*=4.8, 9.6 Hz, C**H**$_2$Se), 3.36 (1H, ap t, *J*=9.6 Hz, C**H**$_2$O), 3.44 (1H, dd, *J*=5.2, 9.6 Hz, C**H**$_2$O), 3.53–3.70 (2H, m, C**H**$_2$Se overlapped with OC**H**), 3.66 (1H, s, SC**H**Se), 3.96–4.21 (1H, m, CH_2C**H**S) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -1.9 (Si(CH_3)$_3$), 22.1 (CH_3), 22.2 (CH_3), 26.6 (SCHSe), 34.8 (CH_2Se), 56.2 (S**C**HCH_2) 69.0 (CH**C**H_2O), 72.0 (OCH) ppm.

MS (EI) *m/z* (%): 298 ([$M^{+\cdot}$], 2), 198 (37), 181 (6), 73 ([$SiMe_3^+$], 100).

Minor diastereoisomer (72 mg, 36%)

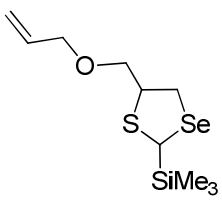
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.16 (9H, s, Si(C**H**$_3$)$_3$), 1.15 (3H, d, *J*=2.4 Hz, (C**H**$_3$)$_2$), 1.17 (3H, d, *J*=2.4 Hz, (C**H**$_3$)$_2$), 3.15–3.22 (1H, m, C**H**$_2$Se), 3.34 (1H, bdd, *J*=5.2, 10.4 Hz, C**H**$_2$Se), 3.46 (1H, dd, *J*=6.0, 9.6 Hz, C**H**$_2$O), 3.52–3.67 (2H, m, C**H**$_2$O overlapped OC**H**), 3.62–3.80 (1H, m, CH_2C**H**S), 3.78 (1H, s, SC**H**Se) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -1.8 (Si(CH_3)$_3$), 22.1 (CH_3), 22.2 (CH_3), 28.8 (SCHSe), 34.9 (CH_2Se), 58.3 (S**C**HCH_2) 70.0 (CH**C**H_2O), 72.1 (OCH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 322.2, 343.3 (mixture of diastereoisomers). ppm

MS (EI) *m/z* (%): 298 ([$M^{+\cdot}$], 2), 198 (37), 181 (6), 73 ([$SiMe_3^+$], 100).

(5-((Allyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (61b)



Prepared from 1-(allyloxy)-3-hydroselenopropane-2-thiol (230 mg, 1.09 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (230 mg, 1.09 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3column chromatography (petroleum ether/diethyl ether 10:1) to yield (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (63%, 203 mg) as a mixture of two diastereoisomers (ca. 5:1 ratio).

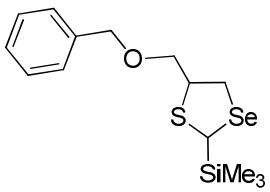
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.16 (18H, s, Si(C**H**$_3$)$_3$), 3.19 (2H, dd, *J*=6.6, 10.2 Hz), 3.29–3.52 (4H, m), 3.61 (2H, dd, *J*=7.4, 9.6 Hz), 3.73–3.88 (2H, m), 3.66 (1H, s, SC**H**Se, *minor*), 3.79 (1H, s, SC**H**Se, *major*), 4.01 (4H, ap dt, *J*=1.5, 5.4 Hz), 5.14–5.35 (4H, m), 5.69–6.01 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -1.9 (Si(CH_3)$_3$), 26.6 (SCHSe, *minor*), 28.8 (SCHSe, *major*), 34.7 (CH_2Se), 55.9 (S**C**HCH_2, *minor*), 57.9 (S**C**HCH_2, *major*), 70.8 (CH_2), 71.7 (CH_2), 72.2 (CH_2), 117.4 (CH_2), 134.3 (CH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 325.4 (*minor*), 345.3 (*major*) ppm.

MS (EI) *m/z* (%): 296 ([$M^{+\cdot}$], 1),198 (20), 196 (10), 73 ([$SiMe_3^+$], 100).

(5-((Benzyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (61c)



Prepared from 1-(benzyloxy)-3-hydroselenopropane-2-thiol (95 mg, 0.36 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (76 mg, 0.36 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 10:1) to yield (5-((benzyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (61%, 72 mg) as a mixture of two diastereoisomers in a 3:2 ratio.

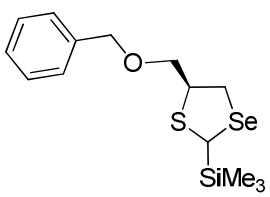
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.17 (18H, s, Si(C**H**$_3$)$_3$), 3.15-3.36 (3H, m), 3.47 (2H, ap d, *J*=7.8 Hz, *minor*), 3.52 (1H, dd, *J*=6.2, 9.4 Hz, C**H**$_2$O, *major*), 3.53-3.69 (2H, m, overlapped with s, SC**H**Se, *minor*), 3.64 (1H, s, SC**H**Se, *major*), 3.65 (1H, dd, *J*=7.8, 9.4 Hz, C**H**$_2$O, *major*), 3.72–3.87 (1H, m, CH_2C**H**S, *major*), 4.02–4.18 (1H, m, CH_2C**H**S, *minor*), 4.56 (4H, s, C**H**$_2$Ph), 7.28–7.41 (10H, m). ppm

^{13}C NMR (50 MHz, $CDCl_3$): δ = -1.9 (Si(CH_3)$_3$)), 26.6 (SCHSe, minor), 28.9 (SCHSe, major), 34.7 (CH_2), 55.9 (CH), 57.9 (CH), 70.8 (CH_2), 71.8 (CH_2), 73.2 (CH_2), 73.3 (CH_2), 127.7, 128.4, 137.8, 137 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 329.3, 348.9 ppm.

MS (EI) *m/z* (%): 346 ([$M^{+\cdot}$], 2),198 (24), 183 (7), 91 (60), 73 ([$SiMe_3^+$], 100).

((5*S*)-5-((Benzyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane ((*S*)-61c)



Prepared from **(*S*)-25c** (110 mg, 0.42 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (88 mg, 0.42 mmol) following the general procedure. The crude residue (ca. 2:1 mixture of two diastereoisomers) was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 10:1) to yield **((*S*)-61c)** (59%, 82 mg) as a mixture enriched in a *major* diastereoisomer and another one enriched in the *minor*.

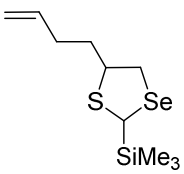
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.17 (18H, s, Si(C**H**$_3$)$_3$), 3.15-3.36 (3H, m), 3.47 (2H, ap d, *J*=7.8 Hz, *minor*), 3.52 (1H, dd, *J*=6.2, 9.4 Hz, C**H**$_2$O, *major*), 3.53-3.69 (2H, m, overlapped with s, SC**H**Se, *minor*), 3.64 (1H, s, SC**H**Se, *major*), 3.65 (1H, dd, *J*=7.8, 9.4 Hz, C**H**$_2$O, *major*), 3.72–3.87 (1H, m, CH_2C**H**S, *major*), 4.02–4.18 (1H, m, CH_2C**H**S, *minor*), 4.56 (4H, s, C**H**$_2$Ph), 7.28–7.41 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -1.9 (Si(CH_3)$_3$), 26.6 (SCHSe, *minor*), 28.9 (SCHSe, major), 34.7 (CH_2Se, *minor*), 34.8 (CH_2Se, *major*), 55.9 (S**C**HCH_2, *minor*), 57.9 (S**C**HCH_2, *major*), 70.8 (CH_2O, *minor*), 71.8 (CH_2O, *major*), 73.2 (CH_2), 73.3 (CH_2), 127.6, 127.7, 128.4, 137.8, 137.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 329.3, 348.9 ppm.

MS (EI) *m/z* (%): 346 ([$M^{+\cdot}$], 2),198 (24), 183 (7), 91 (60), 73 ([$SiMe_3^+$], 100).

(5-(But-3-enyl)-1,3-thiaselenolan-2-yl)trimethylsilane (61d)



Prepared from 1-hydroselenohex-5-en-2-thiol (95 mg, 0.50 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (102 mg, 0.50 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum

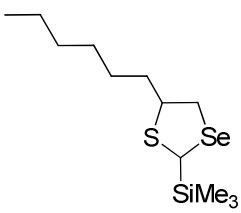
ether/diethyl ether 10:1) to yield **61d** (73%, 102 mg) as a mixture of two diastereoisomers (2:1 ratio).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.15 (18H, s, Si(C**H**$_3$)$_3$), 1.57-1.85 (4H, m), 1.89-1.97 (4H, m), 2.11-2.31 (4H, m), 2.73-2.88 (2H, m), 3.17-3.31 (2H, m), 3.37-3.51 (2H, m), 3.65 (1H, s, SCHSe, *minor*), 3.78 (1H, s, SCHSe, *major*), 4.91-5.09 (4H, m), 5.63-5.87 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -2.0 (Si(CH_3)$_3$), 26.0 (CH, *minor*), 28.7 (CH, *major*), 32.4 (CH_2), 32.7 (CH_2), 33.0 (CH_2), 33.6 (CH_2), 33.6 (CH_2), 37.0 (CH_2, *major*), 38.3 (CH_2, *minor*), 56.9 (CH, *minor*), 59.6 (CH, *major*), 115.3 (CH_2), 137.3 (CH, *major*), 137.5 (CH, *minor*) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 332.6 (*minor*), 361.9 (*major*) ppm.

(5-Hexyl-1,3-thiaselenolan-2-yl)trimethylsilane (61e)



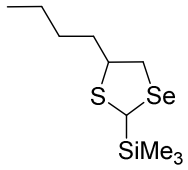
Prepared from 1-hydroselenooctan-2-thiol (280 mg, 1.24 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (261 mg, 1.24 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 10:1) to yield **61e** as a mixture of two diastereoisomers.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.16 (18H, s, Si(C**H**$_3$)$_3$), 0.88 (6H, ap t, ls=7.6 Hz) 1.19–1.83 (20H, m, (C**H**$_2$)$_5$), 3.16–3.32 (4H, m, C**H**$_2$Se), 3.33–3.57 (2H, m, OC**H**CH_2), 3.67 (1H, s, SC**H**Se), 3.78 (1H, s, SC**H**Se) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 332.7, 361.1 ppm.

MS (EI) *m/z* (%): 312 ([$M^{+\cdot}$+2], 6), 310 ([$M^{+\cdot}$], 24), 295 (7), 267 (5), 200 (53), 198 (25), 183 (6.5), 45 (12), 41 (13), 73 [$SiMe_3^+$], 100).

(5-Butyl-1,3-thiaselenolan-2-yl)trimethylsilane (61f)



Prepared from 1-hydroselenohexan-2-thiol (98 mg, 0.50 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (102 mg, 0.50 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 10:1) to yield (5-butyl-1,3-thiaselenolan-2-yl)trimethylsilane (68%, 96 mg) as a mixture of two diastereoisomers (7:5 ratio).

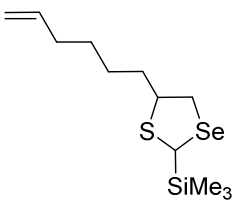
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.16 (9H, s, Si(C**H**$_3$)$_3$), 0.17 (9H, s, Si(C**H**$_3$)$_3$), 0.89 (6H, bt, *J*=6.9 Hz), 1.21-1.42 (8H, m), 1.48-1.61 (2H, m), 1.70-1.81 (2H, m), 2.74-2.85 (2H, m), 3.18-3.32 (1H, m), 3.35-3.49 (2H, m), 3.67 (1H, s, SC**H**Se, *minor*), 3.79 (1H, s, SC**H**Se, *major*) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -2.1 (Si(CH_3)$_3$, *major*), -1.9 (Si(CH_3)$_3$, *minor*), 13.8 (CH_3, *major*), 13.9 (CH_3, *minor*), 22.4 (CH_2), 22.6 (CH_2), 26.2 (CH, *minor*), 28.7 (CH, *major*), 30.7 (CH_2), 31.9 (CH_2), 33.4 (CH_2), 37.2 (CH_2, *major*), 38.2 (CH_2, *minor*), 57.7 (CH, *minor*), 60.4 (CH, *major*) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 332.3, 360.9 ppm.

MS (EI) *m/z* (%): 284 ([$M^{+\cdot}$+2], 1), 282 ([$M^{+\cdot}$], 3), 198 (18), 183 (8), 45 (12), 41 (9), 73 [$SiMe_3^+$], 100).

(5-(Hex-5-enyl)-1,3-thiaselenolan-2-yl)trimethylsilane (61h)



Prepared from 1-hydroselenooct-7-en-2-thiol (224 mg, 1.0 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (210 mg, 1.0 mmol) following the general procedure. The crude residue was purified by neutral Al_2O_3 column chromatography (petroleum ether/diethyl ether 10:1) to yield (5-(hex-5-enyl)-1,3-thiaselenolan-2-yl)trimethylsilane (67%, 205 mg) as a mixture of two diastereoisomers (7:5 ratio).

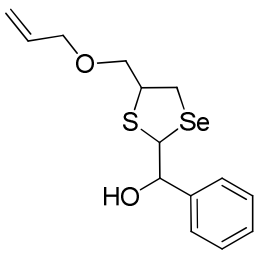
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.16 (9H, s, $Si(C\mathbf{H}_3)_3$, *major*), 0.17 (9H, s, $Si(C\mathbf{H}_3)_3$, *minor*), 1.36-1.55 (8H, m), 1.71-1.81 (4H, m), 1.98-2.10 (4H, m), 2.73-2.85 (1H, m), 3.21-3.28 (1H, m), 3.35-3.50 (4H, m), 3.66 (1H, s, SCHSe, *minor*), 3.78 (1H, s, SCHSe, *major*), 4.90-5.00 (4H, m), 5.69-5.90 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -2.0 ($Si(CH_3)_3$, *major*), -1.9 ($Si(CH_3)_3$, *minor*), 26.2 (CH, *minor*), 28.0 (CH_2), 28.6 (CH_2), 28.7 (CH, *major*), 28.8 (CH_2), 29.3 (CH_2), 33.4 (CH_2), 33.5 (CH_2), 33.6 (CH_2), 37.3 (CH_2, *major*), 38.3 (CH_2, *minor*), 57.6 (CH, *minor*), 60.4 (CH, *major*), 114.4 (CH_2, *minor*), 114.5 (CH_2, *major*), 138.6 (CH, *major*), 138.7 (CH, *minor*) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 332.5 (*minor*), 361.6 (*major*) ppm.

Functionalization of 2-silyl-thiaselenolanes with aldehydes. General procedure.
A solution of 2-silyl-1,3-thiaselenolane **61** (1 mmol) and aldehyde (1 mmol) in dry DMF (5 mL) was treated under inert atmosphere with 0.1 mmol of CsF (dried by Kugelrohr at 250°C for 3 h). and stirred at r.t. for 4-6 h. Afterwards the solution was diluted with diethyl ether (10 mL) and the organic phase was washed with brine (7 mL), then with H_2O (2 x 7 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude material was purified on silica gel.

(5-((Allyloxy)methyl)-1,3-thiaselenolan-2-yl)(phenyl)methanol (66a)



Prepared from (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (48 mg, 0.16 mmol) and freshly distilled benzaldehyde (17 mg, 0.16 mmol) following the general procedure. The crude residue (2:2:1:1 mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 8:1) to yield (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)(phenyl)methanol (42%, 22 mg). Purification allowed to isolate one diastereoisomer (A) and a fraction containing a mixture 2:1:1 of the other three diastereoisomers.

Diastereoisomer (A)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.34 (1H, dd, *J*=6.4, 10.8 Hz, C**H**$_a$H$_b$Se), 3.41 (1H, dd, *J*=4.8, 10.8 Hz, CH$_a$**H**$_b$Se), 3.54 (1H, dd, *J*=5.6, 9.6 Hz, C**H**$_a$H$_b$CHS), 3.66 (1H, dd, *J*=8.4, 9.6 Hz, CH$_a$**H**$_b$CHS), 3.96-4.01 (1H, m, CH$_2$C**H**S), 4.02 (2H, ap dt, *J*=1.6, 5.6 Hz), 4.72 (1H, d, *J*=6.8 Hz, C**H**OH), 5.01 (1H, d, *J*=6.8 Hz, SC**H**Se), 5.17-5.34 (2H, m), 5.82-5.97 (1H, m), 7.27-7.45 (5H, m) ppm.

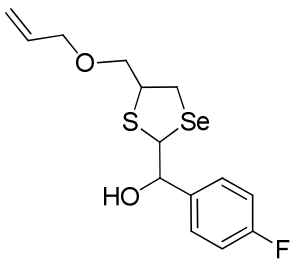
^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.9 (CH_2Se), 54.1, 57.3, 71.9, 72.2, 77.6, 117.5, 126.4, 128.3, 128.4, 134.3 ppm.

MS (ESI, positive) *m/z*: 353 $[M+Na]^{+\cdot}$.

Mixture of other three diastereoisomers (2:1:1 ratio)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24-3.70 (12H, m), 3.95-4.08 (3H, m, $CH_2C\mathbf{H}S$), 4.04 (6H, ap d, ls=6.0 Hz), 4.64-4.73 (3H, m, C**H**OH), 4.89 (1H, d, *J*=8.0 Hz, SC**H**Se), 4.93 (1H, d, *J*=6.8 Hz, SC**H**Se), 4.96 (1H, d, *J*=8.0 Hz, SC**H**Se), 5.17-5.34 (6H, m), 5.82-5.97 (3H, m), 7.28-7.43 (15H, m) ppm.

(5-((Allyloxy)methyl)-1,3-thiaselenolan-2-yl)(4-fluorophenyl)methanol (66b)



Prepared from (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (50 mg, 0.17 mmol) and 4-fluorobenzaldehyde (21 mg, 0.17 mmol) following the general procedure. The crude residue (mixture of four diastereoisomers in a ca. equimolar ratio) was purified by silica gel chromatography (petroleum ether/ethyl acetate 6:1) to yield (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)(4-fluorophenyl)methanol (54%, 30 mg). Purification allowed to isolate one diastereoisomer (A) and a fraction containing an equimolar mixture of the other three diastereoisomers.

Diastereoisomer (A)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.88 (1H, d, *J*=3.2 Hz, O**H**), 3.32 (1H, dd, *J*=6.4, 10.8 Hz, C$\mathbf{H_a}H_b$Se), 3.41 (1H, dd, *J*=5.2, 10.8 Hz, $CH_a\mathbf{H_b}$Se), 3.54 (1H, dd, *J*=5.6, 9.6 Hz, C$\mathbf{H_a}H_b$CHS), 3.65 (1H, dd, *J*=8.0, 9.6 Hz, $CH_a\mathbf{H_b}$CHS), 3.98-4.01 (1H, m, $CH_2C\mathbf{H}S$), 4.02 (2H, ap d, ls=6.0 Hz), 4.70 (1H, bdd, *J*=3.2, 6.8 Hz, OHC**H**), 4.94 (1H, d, *J*=6.8 Hz, SC**H**Se), 5.19-5.33 (2H, m), 5.82-6.01 (1H, m), 7.04 (2H, t, *J*=8.4 Hz), 7.38 (2H, dd, *J*=5.6, 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.9 (**C**H_2Se), 54.1, 57.4, 71.8, 72.2, 77.2, 115.3 (d, $^2J_{C\text{-}F}$=21.3 Hz), 117.6, 128.1 (d, $^3J_{C\text{-}F}$=8.5 Hz), 134.3, 138.1, 165.1 (d, $^1J_{C\text{-}F}$=245.6 Hz) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 333.5 ppm.

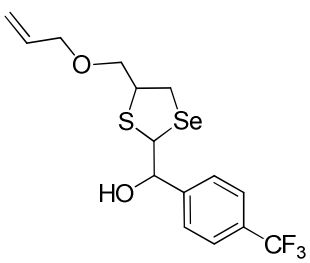
MS (ESI, positive) *m/z*: 370 $[M+Na]^{+\cdot}$.

Mixture of other three diastereoisomers (2:1:1 ratio)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23-3.72 (12H, m, C**H**$_2$Se overlapped with C**H**$_2$CHS), 3.90-4.09 (9H, m, CH$_2$C**H**S overlapped with C**H**$_2$CH=CH$_2$), 4.61-4.74 (3H, m, C**H**OH), 4.48 (1H, d, *J*=8.0 Hz, SC**H**Se), 4.96 (1H, d, *J*=7.8 Hz, SC**H**Se), 5.01 (1H, d, *J*=6.8 Hz, SC**H**Se), 5.17-5.36 (6H, m), 5.80-6.01 (3H, m). 7.03 (6H, ap t, ls=8.8 Hz), 7.32-7.43 (6H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.6, 34.7, 35.2, 52.7, 53.5, 54.0, 71.2, 71.4, 71.9, 72.1, 72.2, 78.6, 115.1-115.4 (C(3)Ar of three diastereoisomers), 117.4, 117.6, 128.1-128.8 (C(2)Ar of three diastereoisomers), 134.3, 136.9, 137.0, 162.7 (d, $^1J_{C\text{-}F}$=245.0 Hz), 162.7 (d, $^1J_{C\text{-}F}$=245.0 Hz), 162.8 (d, $^1J_{C\text{-}F}$=245.0 Hz) ppm.

((5-((Allyloxy)methyl)-1,3-thiaselenolan-2-yl)(4-(trifluoromethyl)phenyl)methanol (66c)



Prepared from (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (37 mg, 0.12 mmol) and 4-(trifluoromethyl)benzaldehyde (22 mg, 0.12 mmol) following the general procedure. The crude residue (5:2:1:1 mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 8:1) to yield (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)(4-(trifluoromethyl)phenyl)methanol (38%, 18 mg). Purification allowed to isolate the major diastereoisomer (A) and a fraction containing a mixture 2:1:1 of the other three diastereoisomers.

Diastereoisomer (A)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.05 (1H, d, *J*=3.2 Hz, O**H**), 3.34 (1H, dd, *J*=6.8, 10.8 Hz, C**H$_a$**H$_b$Se), 3.42 (1H, dd, *J*=4.8, 10.8 Hz, CH$_a$**H$_b$**Se), 3.57 (1H, dd, *J*=5.6, 9.6 Hz, C**H$_a$**H$_b$CHS), 3.66 (1H, dd, *J*=7.6, 9.6 Hz, CH$_a$**H$_b$**CHS), 3.99-4.07 (1H, m, CH$_2$C**H**S), 4.03 (2H, ap d, ls=5.6 Hz), 4.77 (1H, bdd, *J*=3.2, 6.4 Hz, OHC**H**), 4.95 (1H, d, *J*=6.4 Hz, SC**H**Se), 5.20-5.33 (2H, m), 5.84-5.24 (1H, m), 7.54 (2H, d, *J*=8.0 Hz), 7.61 (2H, d, *J*=8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.9 (CH_2Se), 53.9, 57.6, 71.8, 72.2, 76.8, 117.4, 125.3, 125.4, 126.9, 138.4, 134.3, 145.3 ppm.

MS (ESI, positive) *m/z*: 421 $[M+Na]^{+\cdot}$.

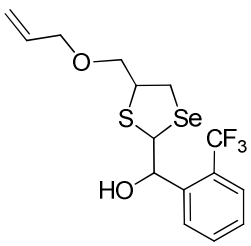
Mixture of other three diastereoisomers (2:1:1 ratio)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.30-3.74 (12H, m), 3.96-4.09 (9H, m, CH_2C**H**S overlapped with C**H**$_2$CH=CH_2), 4.70-4.76 (3H, m, C**H**OH), 4.84 (1H, d, *J*=7.2 Hz, SC**H**Se), 4.87 (1H, d, *J*=6.0 Hz, SC**H**Se), 4.91 (1H, d, *J*=7.2 Hz, SC**H**Se), 5.18-5.27 (6H, m), 5.83-5.97 (3H, m), 7.50-7.64 (12H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.8, 34.8, 35.3, 52.4, 53.2, 53.9, 55.7, 56.3, 56.7, 71.2, 71.4, 71.9, 72.8, 78.2, 117.6, 125.2, 126.9, 127.0, 127.3, 134.1 ppm.

MS (ESI, positive) *m/z*: 421 $[M+Na]^{+\cdot}$.

(5-((Allyloxy)methyl)-1,3-thiaselenolan-2-yl)(2-(trifluoromethyl)phenyl)methanol (66d)



Prepared from (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (30 mg, 0.10 mmol) and 2-(trifluoromethyl)benzaldehyde (18 mg, 0.10 mmol) following the general procedure. The crude residue (mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 9:1) to yield (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)(2-(trifluoromethyl)phenyl)methanol (30%, 12 mg). Purification allowed to isolate the major diastereoisomer (A) and a fraction containing a mixture of the other three diastereoisomers.

Diastereoisomer (A)

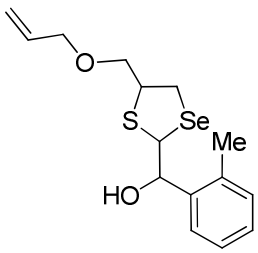
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.16 (1H, bs, O**H**), 3.38-3.52 (2H, m), 3.54 (1H, dd, *J*=5.2, 9.6 Hz), 3.69 (1H, dd, *J*=8.4, 9.6 Hz), 3.96-4.12 (3H, m, CH_2C**H**S overlapped with C**H**$_2$CH=CH_2), 5.11 (1H, d, *J*=5.6 Hz, OHC**H**), 4.20 (1H, d, *J*=5.6

Hz, SC**H**Se), 5.20-5.32 (2H, m), 5.84-5.96 (1H, m), 7.42 (1H, ap t, ls=7.6 Hz), 7.64 (1H, ap d, ls=7.6 Hz), 7.82 (1H, ap d, ls=7.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.2 (CH_2Se), 51.7, 56.9, 71.8, 72.3, 77.2, 117.6, 125.8, 125.9, 127.7, 128.3, 132.3, 134.2 ppm.

MS (ESI, positive) *m/z*: 421 $[M+Na]^{+\cdot}$.

(5-((Allyloxy)methyl)-1,3-thiaselenolan-2-yl)(o-tolyl)methanol (66e)



Prepared from (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (30 mg, 0.10 mmol) and 2-methylbenzaldehyde (16 mg, 0.10 mmol) following the general procedure. The crude residue (2:2:1:1 mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 7:1) to yield (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)(o-tolyl)methanol (46%, 16 mg). Purification allowed to isolate two diastereoisomers (A and B) and a fraction containing a mixture 1:1 of the other two diastereoisomers.

Diastereoisomer (A)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (3H, s), 2.80 (1H, d, *J*=4.4 Hz, O**H**), 3.38-3.63 (4H, m), 3.99 (2H, ap d, ls=5.4 Hz), 4.0-4.14 (1H, m, CH_2C**H**S), 4.91 (1H, dd, *J*=4.4, 6.6 Hz, C**H**OH), 4.97 (1H, d, *J*=6.6 Hz, SC**H**Se), 5.17-5.31 (2H, m), 5.84-5.96 (1H, m), 7.11-7.30 (3H, m), 7.43-7.49 (1H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.6, 33.8 (CH_2Se), 53.2, 56.1, 71.4, 72.1, 73.5, 117.4, 125.6, 126.2, 127.9, 130.4, 134.2 ppm.

MS (ESI, positive) *m/z*: 367 $[M+Na]^{+\cdot}$.

Diastereoisomer (B)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (3H, s), 2.78 (1H, d, *J*=4.0 Hz, O**H**), 3.34-3.52 (2H, m), 3.55 (1H, dd, *J*=5.2, 9.6 Hz), 3.70 (1H, ap t, ls=9.2 Hz), 3.95-4.01

(1H, m, CH_2C**H**S), 4.02 (2H, ap d, ls=5.6 Hz), 4.96 (1H, dd, *J*=4.0, 6.8 Hz, C**H**OH), 5.09 (1H, d, *J*=6.8 Hz, SC**H**Se), 5.18-5.34 (2H, m), 5.84-5.97 (1H, m), 7.10-7.25 (3H, m), 7.48 (1H, ap d, ls=7.8 Hz) ppm.

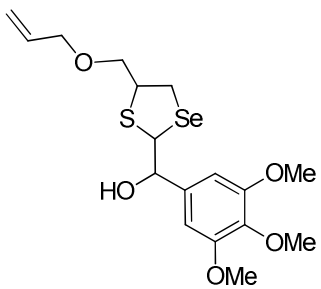
^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 34.0 (CH_2Se), 53.1, 57.2, 71.9, 72.2, 73.8, 117.5, 125.6, 126.3, 128.0, 130.5, 134.2 ppm.

MS (ESI, positive) *m/z*: 367 $[M+Na]^{+\cdot}$.

Mixture of other two diastereoisomers (1:1 ratio)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (3H, s), 2.44 (3H, s), 2.85 (1H, bd, *J*=3.6 Hz, O**H**), 2.89 (1H, bd, *J*=2.4 Hz, O**H**), 3.32 (1H, dd, *J*=6.4, 10.4 Hz), 3.41-3.58 (5H, m), 3.62 (1H, dd, *J*=8.0, 9.6 Hz), 3.71 (1H, ap t, ls=9.2 Hz), 3.98-4.07 (6H, m, CH_2C**H**S overlapped with C**H**$_2$CH=CH_2), 4.94 (1H, bdd, *J*=3.6, 8.0 Hz, C**H**OH), 4.96-5.01 (2H, m), 5.08 (1H, d, *J*=8.0 Hz, SC**H**Se), 5.19-5.25 (2H, m), 5.26-5.34 (2H, m), 5.84-5.96 (2H, m), 7.11-7.28 (6H, m), 7.41-7.44 (2H, m) ppm.

(5-((Allyloxy)methyl)-1,3-thiaselenolan-2-yl)(3,4,5-trimethoxyphenyl)methanol (66f)

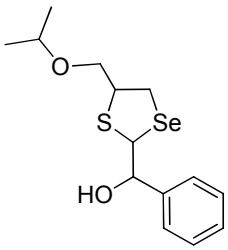


Prepared from (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (30 mg, 0.10 mmol) and 3,4,5-trimethoxybenzaldehyde (20 mg, 0.10 mmol) following the general procedure. The crude residue (mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 7:1) to yield (5-((allyloxy)methyl)-1,3-thiaselenolan-2-yl)(3,4,5-trimethoxyphenyl)methanol (26%, 11 mg) as a 3:3:1:1 mixture of diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31-3.37 (6H, m), 3.45-3.73 (10H, m), 3.84 (12H, s, OC**H**$_3$), 3.87 (24H, s, OC**H**$_3$), 3.92-4.10 (12H, m), 4.59 (1H, d, *J*=8.0 Hz), 4.59-4.63 (2H, m), 4.66 (1H, d, *J*=6.4 Hz), 4.85 (1H, d, *J*=7.6 Hz), 4.90 (1H, d, *J*=6.0 Hz), 4.92 (1H, d, *J*=8.0 Hz), 4.99 (1H, d, *J*=6.4 Hz), 5.10-5.29 (8H, m), 5.77-5.91 (4H, m), 6.61-6.67 (8H, m) ppm.

MS (ESI, positive) *m/z*: 419 $[M+H]^{+\cdot}$.

(5-(Isopropoxymethyl)-1,3-thiaselenolan-2-yl)(phenyl)methanol (67a)



Prepared from (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)trimethylsilane (44 mg, 0.15 mmol) and freshly distilled benzaldehyde (16 mg, 0.15 mmol) following the general procedure. The crude residue (2:2:1:1 mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 7:1) to yield (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)(phenyl)methanol (38%, 19 mg). Purification allowed to isolate one diastereoisomer (A) and a fraction containing a mixture 2:1:1 of the other three diastereoisomers.

Diastereoisomer(A)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (6H, d, *J*=6.4 Hz, $CH(C\mathbf{H}_3)_2$), 2.90 (1H, bs, O**H**) 3.28-3.46 (2H, m), 3.47-3.62 (3H, m), 3.91-4.01 (1H, m, $CH_2C\mathbf{H}S$), 4.73 (1H, bd, *J*=6.4 Hz, C**H**OH), 5.00 (1H, d, *J*=6.4 Hz, SC**H**Se), 7.27-7.44 (5H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 34.1 (CH_2Se), 54.2, 57.7, 70.0, 72.3, 126.3, 128.2, 128.4 ppm.

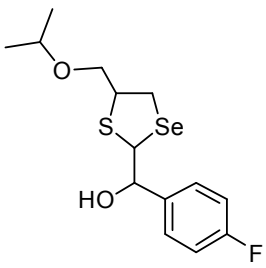
MS (ESI, positive) *m/z*: 355 $[M+Na]^{+\cdot}$.

Mixture of other three diastereoisomers (2:1:1 ratio)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12-1.20 (18H, m), 3.11-3.68 (15H, m), 3.83-4.03 (3H, m, $CH_2C\mathbf{H}S$), 4.64-4.79 (3H, m, C**H**OH), 4.88 (1H, d, *J*=7.6 Hz, SC**H**Se), 4.92 (1H, d, *J*=6.4 Hz, SC**H**Se), 4.95 (1H, d, *J*=8.0 Hz, SC**H**Se), 7.27-7.44 (15H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 22.2, 33.8, 34.8, 35.3, 52.7, 53.4, 54.1, 56.0, 56.5, 57.0, 69.4, 70.0, 72.2, 77.2, 78.0, 79.3, 126.4, 126.6, 126.9, 128.2, 128.3 ppm.

(4-Fluorophenyl)(5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)methanol (67b)



Prepared from (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)trimethylsilane (47 mg, 0.16 mmol) and 4-fluorobenzaldehyde (20 mg, 0.16 mmol) following the general procedure. The crude residue (3:3:2:2 mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 7:1) to yield (4-fluorophenyl)(5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)methanol (54%, 30 mg). Purification allowed to isolate one diastereoisomer (A) and a fraction containing a mixture 3:2:2 of the other three diastereoisomers.

Diastereoisomer (A)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (6H, d, *J*=6.0 Hz, CH(C**H**$_3$)$_2$), 3.33 (1H, bdd, *J*=6.8, 10.8 Hz), 3.40 (1H, dd, *J*=4.8, 10.8 Hz), 3.53 (1H, dd, *J*=5.2, 9.2 Hz), 3.57-3.66 (2H, m), 3.94-4.00 (1H, m, CH_2C**H**S), 4.71 (1H, d, *J*=6.6 Hz, C**H**OH), 4.93 (1H, d, *J*=6.6 Hz, SC**H**Se), 7.04 (2H, ap t, ls=8.8 Hz), 7.39 (2H, dd, *J*=5.2, 8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 22.1, 33.9 (CH_2Se), 54.2, 57.9, 70.0, 72.3, 77.2, 115.2 (d, $^{2}J_{C\text{-}F}$=21.3 Hz), 128.2 (d, $^{3}J_{C\text{-}F}$=8.4 Hz), 138, 164.2 (d, $^{1}J_{C\text{-}F}$=248.0 Hz) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 332.4 ppm.

MS (ESI, negative) *m/z*: 349 $[M\text{-}H]^-$.

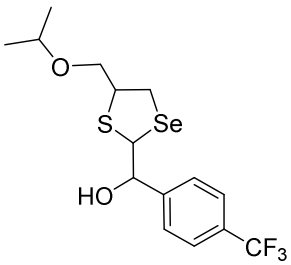
Mixture of other three diastereoisomers (3:2:2 ratio)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (6H, d, *J*=6.0 Hz, CH(C**H**$_3$)$_2$), 1.17 (6H, d, *J*=6.0 Hz, CH(C**H**$_3$)$_2$), 1.18 (6H, d, *J*=6.0 Hz, CH(C**H**$_3$)$_2$), 3.12-3.68 (15H, m), 3.84-4.19 (3H, m, CH_2C**H**S), 4.61-4.69 (3H, m, C**H**OH), 4.81 (1H, d, *J*=7.6 Hz, SC**H**Se), 4.85 (1H, d, *J*=6.8 Hz, SC**H**Se), 4.89 (1H, d, *J*=7.6 Hz, SC**H**Se), 7.03 (6H, ap t, ls=8.8 Hz), 7.35-7.42 (6H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 22.2, 33.7 (CH_2Se one diastereoisomer), 34.8 (CH_2Se one diastereoisomer), 35.3 (CH_2Se one diastereoisomer), 52.7, 53.6, 54.1, 56.0, 56.5, 57.1, 69.4, 70.0, 72.1, 76.7, 77.3, 78.7, 114.9 (C(3)Ar one diastereoisomer, d, $^2J_{C\text{-}F}$=21.5 Hz), 114.9 (C(3)Ar one diastereoisomer, d, $^2J_{C\text{-}F}$=21.5 Hz), 114.8 (C(3)Ar one diastereoisomer, d, $^2J_{C\text{-}F}$=21.5 Hz),127.7-128.4 (C(2)Ar, three diastereoisomers), 137.7 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 303.0, 336.8, 338.3 ppm.

(5-(Isopropoxymethyl)-1,3-thiaselenolan-2-yl)(4-(trifluoromethyl)phenyl)methanol (67c)



Prepared from the *major* diastereoisomer of (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)trimethylsilane (33 mg, 0.11 mmol) and 4-(trifluoromethyl)benzaldehyde (19 mg, 0.11 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 7:1) to yield (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)(4-(trifluoromethyl)phenyl)methanol (60%, 27 mg) as a 1:1 mixture of two diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13-1.17 (12H, m, $CH(C\mathbf{H}_3)_2$), 3.03 (1H, bs, O**H**), 3.18 (1H, bs, O**H**), 3.32 (1H, dd, *J*=6.0, 10.4 Hz), 3.34-3.65 (9H, m), 3.91-3.97 (1H, m, $CH_2C\mathbf{H}S$), 3.98-4.05 (1H, m, $CH_2C\mathbf{H}S$), 4.71 (1H, bd, *J*=6.4 Hz, C**H**OH), 4.75 (1H, bd, *J*=7.2 Hz, C**H**OH), 4.82 (1H, d, *J*=7.2 Hz, SC**H**Se), 4.86 (1H, d, *J*=6.4Hz, SC**H**Se), 7.52-7.56 (4H, m), 7.59-7.62 (4H, m) ppm.

MS (ESI, negative) *m/z*: 398 $[M\text{-}H]^-$.

Reacting a 1:1 diastereomeric mixture of (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)trimethylsilane with 4-(trifluoromethyl)benzaldehyde a 3:3:1:1 mixture of the four possible diastereoisomers of 67c has been achieved. Purification by silica gel

chromatography gave a diastereoenriched fraction (>20:1 dr) and a mixture of the other three diastereoisomers (3:1:1 ratio).

Diastereoenriched fraction (>20:1 dr)

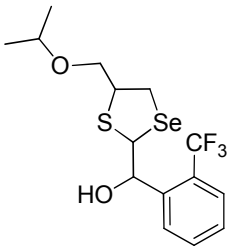
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (6H, d, *J*=6.0 Hz, $CH(C\mathbf{H}_3)_2$), 3.30-3.51 (2H, m), 3.55 (1H, dd, *J*=5.2, 9.6 Hz), 3.59-3.68 (2H, m), 4.01 (1H, m, $CH_2C\mathbf{H}S$), 4.79 (1H, d, *J*=6.4 Hz), 4.94 (1H, bd, *J*=6.4 Hz), 7.54 (2H, ap d, ls=8.0 Hz), 7.61 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 22.1, 30.9, 34.0, 53.9, 58.1, 69.9, 72.3, 125.3, 126.9 ppm.

Mixture of three diastereoisomers (3:1:1 ratio)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13-1.17 (18H, m, $CH(C\mathbf{H}_3)_2$), 3.03 (1H, bs, O**H**), 3.18 (1H, bs, O**H**), 3.19-3.67 (15H, m), 3.91-3.98 (2H, m, $CH_2C\mathbf{H}S$), 3.98-4.05 (1H, m, $CH_2C\mathbf{H}S$), 4.71 (1H, bd, *J*=6.4 Hz, C**H**OH), 4.74 (1H, d, *J*=7.6 Hz, C**H**OH, *major*), 4.75 (1H, bd, *J*=7.2 Hz, C**H**OH), 4.82 (1H, d, *J*=7.2 Hz, SC**H**Se), 4.86 (1H, d, *J*=6.4Hz, SC**H**Se), 4.90 (1H, d, *J*=7.6 Hz, SC**H**Se, *major*), 7.52-7.56 (6H, m), 7.59-7.62 (6H, m) ppm.

(5-(Isopropoxymethyl)-1,3-thiaselenolan-2-yl)(2-(trifluoromethyl)phenyl)methanol (67d)



Prepared from (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)trimethylsilane (45 mg, 0.15 mmol) and 2-(trifluoromethyl)benzaldehyde (26 mg, 0.15 mmol) following the general procedure. The crude residue (mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 7:1) to yield two fractions of (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)(2-(trifluoromethyl)phenyl)methanol (38%, 23 mg) each containing two diastereoisomers.

Mixture of two diastereoisomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (3H, d, *J*=6.0 Hz), 1.14 (3H, d, *J*=6.0 Hz), 1.17 (3H, d, *J*=6.0 Hz, CH(C**H**$_3$)$_2$), 1.17 (3H, d, *J*=6.0 Hz, CH(C**H**$_3$)$_2$), 3.01 (2H, bs, O**H**), 3.22-3.69 (10H, m), 3.92-4.07 (2H, m), 4.83 (1H, bd, *J*=5.2 Hz, C**H**OH), 5.09 (1H, d, *J*=6.8 Hz, C**H**OH), 5.16 (1H, d, *J*=6.8 Hz, SC**H**Se), 5.21 (1H, bd, *J*=5.2 Hz, SC**H**Se), 7.41 (2H, ap t, ls=7.6 Hz), 7.60 (2H, ap t, ls=7.6 Hz), 7.64 (2H, ap d, ls=8.0 Hz), 7.80 (1H, ap d, ls=7.6 Hz), 7.84 (1H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 22.2, 34.1 (CH_2Se), 53.0, 53.2, 56.4, 57.9, 69.4, 69.8, 72.1, 72.3, 72.5, 125.7, 125.8, 127.6, 127.8, 128.4, 132.1 ppm.

MS (ESI, negative) *m/z*: 398 $[M-H]^-$.

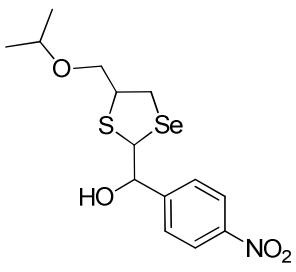
Mixture of the other two diastereoisomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11-1.23 (12H, m), 3.22-3.70 (10H, m), 3.88-4.08 (2H, m), 5.00 (2H, ap t, ls=6.4, 6.8 Hz, C**H**OH), 5.10 (1H, d, *J*=5.6 Hz, SC**H**Se), 5.19 (1H, bd, *J*=6.0 Hz, SC**H**Se), 7.31-7.48 (2H, m), 7.56-7.67 (4H, m), 7.73-7.81 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1, 22.2, 34.9 (CH_2Se), 35.3 (CH_2Se), 51.2, 51.7, 56.5, 57.3, 69.5, 69.8, 72.3, 72.6, 73.5, 125.7, 125.9, 127.7, 127.8, 128.2, 132.2 ppm.

MS (ESI, negative) *m/z*: 398 $[M-H]^-$.

(5-(Isopropoxymethyl)-1,3-thiaselenolan-2-yl)(4-nitrophenyl)methanol (67e)



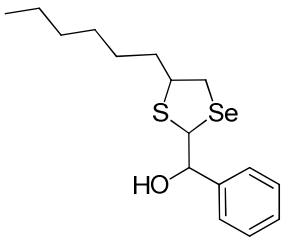
Prepared from the *major* diastereoisomer of **61a** (24 mg, 0.08 mmol) and 4-nitrobenzaldehyde (12 mg, 0.08 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 8:1) to yield **67e** (43%, 14 mg) as a equimolar mixture of two diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13-1.21 (12H, m, CH(CH_3)$_2$), 3.33 (1H, dd, *J*=6.0, 10.1 Hz), 3.36-3.67 (9H, m), 3.92-3.99 (1H, m, CH_2C**H**S), 4.00-4.07 (1H, m, CH_2C**H**S), 4.75 (1H, d, *J*=6.4 Hz), 4.77-4.81 (2H, m), 4.83 (1H, d, *J*=6.4 Hz), 7.59-7.63 (4H, m), 8.18-8.23 (4H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 22.1, 34.0 (CH_2Se), 35.0 (CH_2Se), 52.3, 53.6, 56.2, 56.8, 69.3, 69.4, 72.2, 72.3, 76.2, 77.2, 123.4, 123.5, 127.4, 127.6, 128.0, 147.7, 148.2 ppm.

MS (ESI, negative) *m/z*: 377 $[M-H]^-$.

(5-Hexyl-1,3-thiaselenolan-2-yl)(phenyl)methanol (68a)



Prepared from (5-hexyl-1,3-thiaselenolan-2-yl)trimethylsilane (47 mg, 0.15 mmol) and freshly distilled benzaldehyde (16 mg, 0.15 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 10:1) to yield two fractions of (5-hexyl-1,3-thiaselenolan-2-yl)(phenyl)methanol (38%, 20 mg) each containing a mixture of two diastereoisomers.

Mixture of diastereoisomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (6H, t, *J*=6.2 Hz, C**H**$_3$), 1.18-1.55 (16H, m), 1.62-1.82 (4H, m), 2.95-3.04 (2H, m), 3.34 (1H, dd, *J*=4.4, 10.4 Hz), 3.45 (1H, dd, *J*=4.4, 10.0 Hz), 3.67-3.79 (2H, m, CH_2C**H**S), 4.68-4.74 (2H, m, C**H**OH), 4.93 (1H, d, *J*=6.4 Hz, SC**H**Se), 5.00 (1H, d, *J*=6.4 Hz, SC**H**Se), 7.27-7.43 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.6, 29.1, 29.2, 29.3, 31.6, 34.4, 34.9, 36.3, 37.8, 53.8, 54.1, 57.7, 59.7, 77.2, 77.5, 126.2, 126.3, 126.5, 128.1, 128.2, 128.3, 128.4, 141.5, 141.6 ppm.

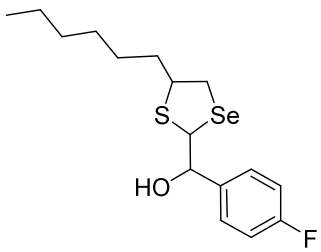
MS (ESI, positive) *m/z*: 343 $[M+H]^{+\cdot}$.

Mixture of the other two diastereoisomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85-0.94 (6H, m), 1.25-1.55 (16H, m), 1.59-1.82 (4H, m), 2.96 (1H, ap t, *J*=10.4 Hz), 3.08 (1H, dd, *J*=8.4, 10.0 Hz), 3.38 (1H, dd, *J*=4.4, 10.4 Hz), 3.45 (1H, dd, *J*=4.4, 10.0 Hz), 3.61-3.70 (1H, m, $CH_2C\mathbf{H}S$), 3.71-3.79 (1H, m, $CH_2C\mathbf{H}S$), 4.64 (1H, d, *J*=8.4 Hz, C**H**OH), 4.79 (1H, d, *J*=7.2 Hz, C**H**OH), 4.83 (1H, d, *J*=8.4 Hz, SC**H**Se), 4.99 (1H, d, *J*=7.2 Hz, SC**H**Se), 7.27-7.44 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1 (**C**H_3), 22.6 (**C**H_2CH_3), 29.1, 29.2, 29.4, 31.6, 33.8, 35.3, 37.6, 38.4, 52.2, 53.3, 56.4, 59.2, 77.3, 78.1, 126.5, 127.2, 128.2, 128.3, 141.3 ppm.

(4-Fluorophenyl)(5-hexyl-1,3-thiaselenolan-2-yl)methanol (68b)



Prepared from (5-hexyl-1,3-thiaselenolan-2-yl)trimethylsilane (80 mg, 0.26 mmol) and 4-fluorobenzaldehyde (32 mg, 0.26 mmol) following the general procedure. The crude residue (3:3:2:2 mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 10:1) to yield two fractions of (4-fluorophenyl)(5-hexyl-1,3-thiaselenolan-2-yl)methanol (61%, 57 mg) each containing a mixture of two diastereoisomers.

Mixture of diastereoisomers

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (6H, t, *J*=6.4 Hz), C$\mathbf{H}_3$), 1.19-1.49 (16H, m), 1.61-1.82 (4H, m), 2.82-3.08 (4H, m), 3.34 (1H, dd, *J*=4.0, 10.2 Hz), 3.46 (1H, dd, *J*=4.0, 10.2 Hz), 3.63-3.84 (2H, m, $CH_2C\mathbf{H}S$), 4.63-4.75 (2H, m, C**H**OH), 4.86 (1H, d, *J*=6.6 Hz, SC**H**Se), 4.93 (1H, d, *J*=5.6 Hz, SC**H**Se), 7.04 (4H, ap t, *J*=7.6 Hz), 7.28-7.49 (4H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.5, 29.0, 29.1, 29.2, 31.6, 34.4, 34.9, 36.2, 37.7, 53.8, 54.0, 57.7, 59.9, 76.9, 115.2 (d, $^2J_{C\text{-}F}$=21.3 Hz), 115.3 (d, $^2J_{C\text{-}F}$=21.3 Hz),

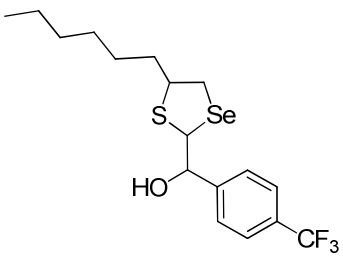
128.1 (d, $^{3}J_{C\text{-}F}$=7.6 Hz), 128.2 (d, $^{3}J_{C\text{-}F}$=7.6 Hz), 137.2, 137.3 162.6 (d, $^{1}J_{C\text{-}F}$=244.9 Hz) ppm.

MS (ESI, positive) *m/z*: 384 $[M+Na]^{+\cdot}$.

Mixture of the other two diastereoisomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (6H, t, *J*=6.4 Hz, C**H**$_3$), 1.21-1.48 (16H, m), 1.59-1.80 (4H, m), 2.85-3.18 (4H, m), 3.38 (1H, dd, *J*=4.4, 10.6 Hz), 3.42-3.52 (1H, m), 3.54-3.83 (2H, m, CH_2C**H**S), 4.56-4.80 (1H, m, C**H**OH), 4.62 (1H, dd, *J*= 2.2, 8.4 Hz, C**H**OH), 4.76 (1H, d, *J*=8.4 Hz, SC**H**Se), 4.92 (1H, d, *J*=7.2 Hz, SC**H**Se), 7.03 (4H, ap t, *J*=7.6 Hz), 7.28-7.47 (4H, m) ppm.

(5-Hexyl-1,3-thiaselenolan-2-yl)(4-(trifluoromethyl)phenyl)methanol (68c)



Prepared from (5-hexyl-1,3-thiaselenolan-2-yl)trimethylsilane (40 mg, 0.13 mmol) and 4-(trifluoromethyl)benzaldehyde (23 mg, 0.13 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 10:1) to yield (5-hexyl-1,3-thiaselenolan-2-yl)(4-(trifluoromethyl)phenyl)methanol (40%, 21 mg) asa mixture of four diastereoisomers.

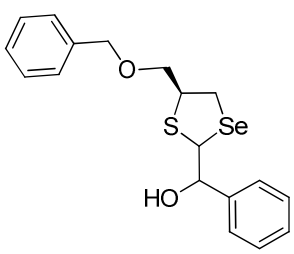
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84-0.94 (12H, m), 1.21-1.48 (32H, m), 1.62-1.78 (8H, m), 2.89-3.17 (4H, m), 3.33 (1H, dd, *J*=4.4, 10.4 Hz, C**H$_2$**Se), 3.39 (1H, dd, *J*=4.8, 10.8 Hz, C**H$_2$**Se), 3.42-3.49 (2H, m), 3.59-3.79 (4H, m, CH_2C**H**S), 4.67-4.79 (2H, m), 4.77 (1H, d, *J*=6.4 Hz), 4.83 (1H, d, *J*=6.8 Hz) 4.88 (1H, d, *J*=6.4 Hz, SC**H**Se), 4.94 (1H, d, *J*=6.8 Hz, SC**H**Se), 5.05 (1H, d, *J*=9.6 Hz), 5.18 (1H, d, *J*=9.6 Hz), 7.48-7.63 (16H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.5, 29.1, 29.2, 29.4, 31.6, 33.8, 34.4, 35.3, 37.7, 37.9, 38.5, 52.1, 53.1, 56.6, 57.8, 59.4, 77.2, 125.3, 126.7, 126.8, 126.9, 127.6 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 312.0, 327.2, 341.0, 352.0 ppm.

MS (ESI, positive) *m/z*: 411 $[M+H]^{+\cdot}$.

((5*S*)-5-((Benzyloxy)methyl)-1,3-thiaselenolan-2-yl)(phenyl)methanol ((5*S*)-69a)



Prepared from ((5*S*)-5-((benzyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (35 mg, 0.10 mmol) and freshly distilled benzaldehyde (11 mg, 0.10 mmol) following the general procedure. The crude residue (4:2:1:1 mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 8:1) to yield ((5*S*)-5-((benzyloxy)methyl)-1,3-thiaselenolan-2-yl)(phenyl)methanol (41%, 16 mg). Purification gave a diastereoenriched fraction (>20:1 dr) and a mixture of all the four diastereoisomers.

Mixture of four diastereoisomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.82 (1H, bs, O**H**), 2.85 (1H, bs, O**H**), 2.94 (1H, bs, O**H**), 3.00 (1H, bs, O**H**), 3.11-3.73 (16H, m), 3.89-4.11 (4H, m, CH_2C**H**S), 4.53 (2H, ap s, C**H**$_2$Bn), 4.55 (2H, ap s, C**H**$_2$Bn), 4.56 (2H, ap s, C**H**$_2$Bn), 4.57 (2H, ap s, C**H**$_2$Bn), 4.59-4.69 (4H, m, C**H**OH), 4.88 (1H, d, *J*=7.6 Hz, SC**H**Se), 4.92 (1H, d, *J*=6.4 Hz, SC**H**Se), 4.95 (1H, d, *J*=7.6 Hz, SC**H**Se), 5.01 (1H, d, *J*=6.8 Hz, SC**H**Se), 7.27-7.38 (40H, m) ppm.

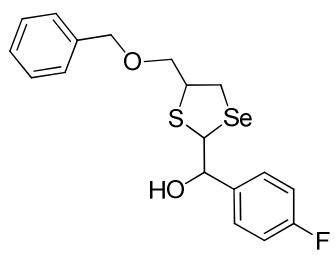
Diastereoenriched fraction (>20:1 dr)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.81 (1H, bd, *J*=3.6 Hz, O**H**), 3.33 (1H, dd, *J*=6.4, 10.8 Hz, C**H$_a$**H$_b$Se), 3.41 (1H, dd, *J*=5.2, 10.8 Hz, CH$_a$**H$_b$**Se), 3.58 (1H, dd, *J*=5.6, 10.0 Hz, C**H$_a$**H$_b$CHS), 3.70 (1H, dd, *J*=8.0 Hz, 10.0 Hz, CH$_a$**H$_b$**CHS), 3.97-4.08 (1H, m, CH_2C**H**S), 4.56 (2H, ap s, OC**H**$_2$Ph), 4.70 (1H, bdd, *J*=3.6, 6.8 Hz, C**H**OH), 5.01 (1H, d, *J*=6.8 Hz, SC**H**Se), 7.27-7.41 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.9 (CH_2Se), 54.1, 57.3, 72.0, 73.3, 77.5, 126.4, 127.7, 127.8, 128.3, 128.4, 128.5, 137.7, 141.5 ppm.

MS (ESI, positive) *m/z*: 379 $[M+H]^{+\cdot}$.

(5-((Benzyloxy)methyl)-1,3-thiaselenolan-2-yl)(4-fluorophenyl)methanol (69b)



Prepared from (5-((benzyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (53 mg, 0.15 mmol) and 4-fluorobenzaldehyde (19 mg, 0.15 mmol) following the general procedure.The crude residue (2:2:1:1 mixture of four diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 5:1) to yield (5-((benzyloxy)methyl)-1,3-thiaselenolan-2-yl)(4-fluorophenyl)methanol (32%, 19 mg) as a diastereoenriched fraction (>20:1 dr) and a mixture of all the four diastereoisomers.

Mixture of four diastereoisomers

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.09-3.71 (16H, m), 3.89-4.09 (4H, m, $CH_2C\mathbf{H}S$), 4.53 (2H, ap s, $PhC\mathbf{H}_2O$), 4.55 (2H, ap s, $PhC\mathbf{H}_2O$), 4.56 (2H, ap s, $PhC\mathbf{H}_2O$), 4.57 (2H, ap s, $PhC\mathbf{H}_2O$), 4.58-4.72 (4H, m, C**H**OH), 4.81 (1H, d, *J*=7.6 Hz, SC**H**Se), 4.85 (1H, d, *J*=6.4 Hz, SC**H**Se), 4.88 (1H, d, *J*=8.0 Hz, SC**H**Se), 4.94 (1H, d, *J*=6.8 Hz, SC**H**Se), 6.96-7.08 (8H, m), 7.28-7.43 (28H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.7, 33.9, 34.7, 35.3, 52.7, 53.5, 54.0, 54.1, 55.6, 56.1, 56.6, 57.4, 71.2, 71.4, 71.8, 71.9, 73.2, 73.3, 76.7, 77.3, 78.6, 114.9 (d, $^{2}J_{C\text{-}F}$=21.3 Hz), 127.3-128.5 (of C(2)Ar of *p*F-C_6H_4 groups overlapped with C of Ph groups of four diastereoisomers), 137.4, 137.6 ppm.

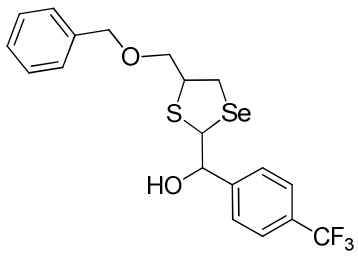
Diastereoenriched fraction (>20:1 dr)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.85 (1H, bs, O**H**), 3.28-3.54 (2H, m), 3.57 (1H, dd, *J*=5.6, 9.6 Hz, $C\mathbf{H}_aH_bCHS$), 3.68 (1H, dd, *J*=8.0, 9.6 Hz, $CH_a\mathbf{H}_bCHS$), 4.50-4.62 (1H, m, $CH_2C\mathbf{H}S$), 4.56 (2H, ap s, $OC\mathbf{H}_2Ph$), 4.69 (1H, bd, *J*=6.8 Hz, C**H**OH), 4.94 (1H, d, *J*=6.8 Hz, SC**H**Se), 7.03 (2H, ap t, *J*=7.6 Hz), 7.28-7.44 (7H, m).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.9 (CH_2Se), 54.1, 57.4, 71.9, 73.3, 78.2, 115.3 (d, $^2J_{C\text{-}F}$=21.3 Hz), 127.7, 127.9, 128.2 (d, $^3J_{C\text{-}F}$=8.4 Hz), 128.5, 137.4, 165.1 (d, $^1J_{C\text{-}F}$=249.4 Hz) ppm.

MS (ESI, positive) *m/z*: 421 $[M+Na]^{+\cdot}$.

(5-((Benzyloxy)methyl)-1,3-thiaselenolan-2-yl)(4-(trifluoromethyl)phenyl)methanol (69c)



Prepared from (5-((benzyloxy)methyl)-1,3-thiaselenolan-2-yl)trimethylsilane (38 mg, 0.11 mmol) and 4-(trifluoromethyl)benzaldehyde (19 mg, 0.11 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 7:1) to yield **69c** (35%, 22 mg) as a mixture of four diastereoisomers.

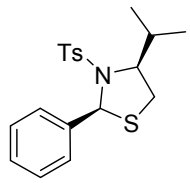
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (1H, dd, *J*=1.5, 5.5 Hz), 3.30-3.37 (3H, m), 3.37-3.49 (4H, m), 3.52-374 (8H, m), 3.91-4.15 (4H, m), 4.53 (2H, s), 4.55 (2H, ap d, ls=1.9 Hz), 4.56 (2H, ap d, ls=1.4 Hz), 4.57 (2H, ap d, ls=2.0 Hz), 4.67 (1H, d, *J*=7.4 Hz, C**H**OH), 4.71 (1H, d, *J*=6.5 Hz, C**H**OH), 4.75 (1H, d, *J*=7.5 Hz, C**H**OH), 4.76 (1H, d, *J*=6.3 Hz, C**H**OH), 4.82 (1H, d, *J*=7.4 Hz, SC**H**Se), 4.86 (1H, d, *J*=6.3 Hz, SC**H**Se), 4.89 (1H, d, *J*=7.5 Hz, SC**H**Se), 4.95 (1H, d, *J*=6.5 Hz, SC**H**Se), 7.28-7.38 (20H, m), 7.47-7.57 (8H, m), 7.60-7.62 (8H, m) ppm.

MS (ESI, positive) *m/z*: 470 $[M+Na]^{+\cdot}$.

Synthesis of 2,4-disubstituted 1,3-thiazolidines. General procedure.

β-aminothiol **22-23** (1 mmol) and aldehyde (1 mmol) were dissolved in dry CH_2Cl_2 (3 mL) under inert atmosphere and then boron trifluoride diethyl etherate (1 mmol) was added dropwise. The mixture was stirred at r.t. for 1h, then the temperature was cooled at -18°C and the reaction stirred for 12 h. Afterwards the solution was diluted with diethyl ether and 0.1 N *aq* NaOH was added. The organic phase was washed with H_2O, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was purified on silica gel.

(2*S*,4*S*)-4-Isopropyl-2-phenyl-3-tosyl-1,3-thiazolidine (70a)



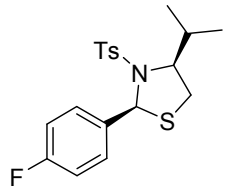
Prepared from **22b** (60 mg, 0.22 mmol) and benzaldehyde (25 mg, 0.22 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 15:1) to yield **70a** (88%, 70 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (3H, d, *J*=6.6 Hz, (C**H**$_3$)$_3$CH), 0.94 (3H, d, *J*=6.9 Hz, (C**H**$_3$)$_3$CH), 1.74-1.83 (1H, m), 2.45 (3H, s), 2.49 (1H, dd, *J*=6.6, 11.7 Hz, C**H**$_a$H$_b$S), 2.79 (1H, dd, *J*=3.0, 11.7 Hz, CH$_a$**H**$_b$S), 3.88-3.93 (1H, m), 6.16 (1H, s, NC**H**S), 7.27-7.35 (5H, m), 7.67 (2H, ap d, ls=8.1 Hz), 7.78 (2H, ap d, ls=8.1 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3 (CH_3), 20.1 (CH_3), 21.6 (CH_3), 31.0 (CH), 34.2 (CH_2), 68.1 (CH), 71.5 (CH), 127.1 (CH), 127.8 (CH), 128.1 (CH), 129.8 (CH), 134.9 (C), 140.0 (C), 144.1 (C) ppm.

MS (ESI, positive) *m/z* (%): 384 $[M+Na]^+$.

(2*S*,4*S*)-2-(4-Fluorophenyl)-4-isopropyl-3-tosylthiazolidine (70b)



Prepared from (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (27 mg, 0.1 mmol) and 4-fluorobenzaldehyde (12 mg, 0.1 mmol) following the general procedure. The crude residue was purified by silica gel

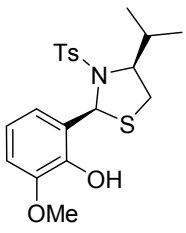
chromatography (petroleum ether/ethyl acetate 15:1) to yield (2*S*,4*S*)-2-(4-fluorophenyl)-4-isopropyl-3-tosylthiazolidine (78%, 30 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (3H, d, *J*=6.8 Hz, $(CH_3)_2CH$), 0.94 (3H, d, *J*=6.8 Hz, $(CH_3)_3CH$), 1.71-1.82 (1H, m), 2.46 (3H, s), 2.49 (1H, dd, *J*=3.4, 5.8 Hz, CH_aH_bS), 2.80 (1H, dd, *J*=2.8, 5.8 Hz, CH_aH_bS), 3.88-3.92 (1H, m), 6.12 (1H, s, NCHSe), 7.01 (2H, ap t, ls=8.8 Hz), 7.34 (2H, ap d, ls=8.4 Hz), 7.62-7.65 (2H, m), 7.76 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.4, 20.2, 21.7, 31.2, 34.4, 67.6, 71.5, 115.0 (d, $^2J_{C\text{-}F}$= 21.9 Hz), 127.8, 129.1 (d, $^3J_{C\text{-}F}$= 8.2 Hz), 129.9, 135.7(d, $^4J_{C\text{-}F}$=2.8 Hz), 144.2, 162.2, (d, $^1J_{C\text{-}F}$= 250.0 Hz) ppm.

MS (EI) *m/z* (%): 336 [$M^{+\cdot}$-$CH(CH_3)_2$,(14)], 224 (19), 189 (100), 155 (28), 91 [Bn^+, (68)].

2-((2*S*,4*S*)-4-Isopropyl-3-tosylthiazolidin-2-yl)-6-methoxyphenol (70c)



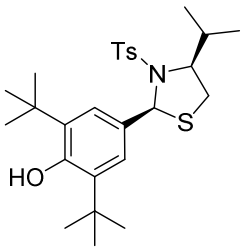
Prepared from (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (54 mg, 0.2 mmol) and 2-hydroxy-3-methoxybenzaldehyde (30 mg, 0.2 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 1:1) to yield 2-((2*S*,4*S*)-4-isopropyl-3-tosylthiazolidin-2-yl)-6-methoxyphenol (72%, 58 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (3H, d, *J*=6.4 Hz), 1.27 (3H, d, *J*=6.8 Hz), 2.11-2.23 (1H, m), 2.37 (1H, dd, *J*=5.6, 11.6 Hz, CH_aH_bS), 2.44 (3H, s), 2.79 (1H, dd, *J*=1.6, 11.6 Hz, CH_aH_bS), 3.88 (3H, s), 3.94 (1H, ddd, *J*=1.6, 5.6, 7.6 Hz), 6.02 (1H, s), 6.26 (1H, s), 6.79 (1H, dd, *J*=1.6, 8.0 Hz), 6.87 (1H, ap t, ls= 8.0 Hz), 7.22 (1H, dd, *J*=1.6, 8.0 Hz), 7.34 (2H, ap d, ls=8.0 Hz), 7.79 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.6, 20.6, 21.5, 31.1, 33.5, 56.2, 62.8, 71.9, 110.4, 119.6, 127.0, 128.1, 128.7, 129.9, 135.0, 142.9, 144.0, 146.4 ppm.

MS (EI) *m/z* (%): 364 [$M^{+\cdot}$-$CH(CH_3)_2$,(50)], 251 (46), 209 (67), 193 (12), 167 (90), 135 (44), 91 [Bn^+, (100)].

2,6-Di-tert-butyl-4-((2*S*,4*S*)-4-isopropyl-3-tosylthiazolidin-2-yl)phenol (70d)



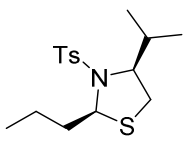
Prepared from (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (54 mg, 0.2 mmol) and 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (47 mg, 0.2 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 15:1) to yield 2,6-di-tert-butyl-4-((2*S*,4*S*)-4-isopropyl-3-tosylthiazolidin-2-yl)phenol (67%, 66 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0,87 (3H, d, *J*=6.8 Hz), 1.04 (3H, d, *J*=6.8 Hz), 1.42 (18H, s), 1.88-1.98 (1H, m), 2.42 (3H, s), 2.57 (1H, dd, *J*=6.4, 11.6 Hz, C**H$_a$**H$_b$S), 2.80 (1H, dd, *J*=2.8, 11.6 Hz, CH$_a$**H$_b$**S), 3.96-4.00 (1H, m), 5.18 (1H, s), 6.08 (1H, s), 7.29 (2H, ap d, ls=8.4 Hz), 7.33 (2H, s), 7.49 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.7 (CH3), 20.5 (CH_3), 21.6 (CH3), 30.3 (CH_3), 31.3 (CH), 34.4 (CH), 34.6 (CH2), 68.7 (CH), 71.4 (CH), 124.0 (CH), 127.9 (CH), 129.7 (CH), 131.3 (C), 130.2 (C), 135.3 (C), 143.8 (C), 153.3 (C) ppm.

MS (ESI, positive) *m/z* (%): 491 $[M+H]^{+\cdot}$.

(2*S*,4*S*)-4-Isopropyl-2-propyl-3-tosylthiazolidine (70e)



22b (54 mg, 0.2 mmol) and butyraldehyde (14 mg, 0.2 mmol) following the general procedure gave (2*S*,4*S*)-4-isopropyl-2-propyl-3-tosylthiazolidine (77%, 50 mg).

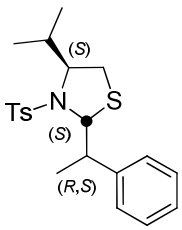
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95 (3H, t, *J*=7.2 Hz), 0.94 (3H, d, *J*=6.4 Hz), 1.07 (3H, d, *J*=6.8 Hz), 1.36-1.44 (2H, m), 1.57-1.64 (1H, m), 1.98-2.10 (2H, m), 2.30 (1H, dd, *J*=6.4, 11.2 Hz, C**H$_a$**H$_b$S), 2.43 (3H, s), 2.74 (1H, dd, *J*=3.2, 11.2 Hz,

CH_aH_bS), 3.76-3.81 (1H, m), 4.93 (1H, dd, *J*=5.6, 8.8 Hz, NC**H**S), 7.31 (2H, ap d, ls= 8.4 Hz), 7.71 (2H, ap d, ls= 8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 19.7, 20.1, 20.6, 21.6, 31.1, 33.1, 42.8, 66.5, 70.8, 127.5, 129.8, 135.1, 143.8. ppm

MS (ESI, positive) *m/z* (%): 350 $[M+Na]^+$.

(2*S*,4*S*)-4-Isopropyl-2-1-phenylethyl)-3-tosylthiazolidine (70f)



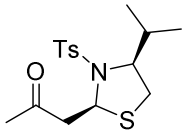
Prepared from (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (54 mg, 0.2 mmol) and 2-phenylpropanal (27 mg, 0.2 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to yield (2*S*,4*S*)-4-isopropyl-2-1-phenylethyl)-3-tosylthiazolidine (58%, 45 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96-0.99 (9H, m), 1.15 (3H, d, *J*=6.4 Hz), 1.43 (3H, d, *J*=7.2 Hz), 1.62 (3H, d, *J*=7.2 Hz), 2.01-2.07 (1H, m), 2.08-2.14 (2H, m), 2.42 (1H, dd, *J*=6.4, 11.6 Hz), 2.43 (3H, s), 2.46 (3H, s), 2.67 (1H, dd, *J*=2.4, 11.6 Hz), 2.79 (1H, dd, *J*=2.0, 11.6 Hz), 2.92-3.00 (1H, m), 3.44-3.54 (1H, m), 3.75 (1H, ddd, *J*=2.0, 6.0, 8.4 Hz), 3.78-3.83 (1H, m), 5.30 (1H, d, *J*=10.4 Hz), 5.32 (1H, d, *J*=6.8 Hz), 7.28-7.31 (6H, m), 7.33-7.38 (8H, m), 7.53 (2H, ap d, ls=8.4 Hz), 7.80 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.6, 20.0, 20.2, 20.2, 20.3, 21.2, 21.5, 21.6, 30.8, 31.1, 33.1, 46.6, 49.4, 71.8, 71.9, 72.6, 73.1, 126.8, 127.0, 127.8, 128.0, 128.1, 128.1, 128.4, 128.4, 129.7, 129.9, 134.8, 135.0, 135.4, 143.3, 143.4, 143.8, 144.1.

MS (EI) *m/z* (%): 284 [$M^{+\cdot}$-$PhCHCH_3$, (100)], 155 (40), 105 (26), 101 (29), 91 [Bn^+, (84)] ppm.

1-((2*S*,4*S*)-4-Isopropyl-3-tosylthiazolidin-2-yl)propan-2-one (70g)



Prepared from (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (54 mg, 0.2 mmol) and 3-oxobutanal (26 mg, 0.2 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 15:1) to yield 1-((2*S*,4*S*)-4-isopropyl-3-tosylthiazolidin-2-yl)propan-2-one (87%, 59 mg).

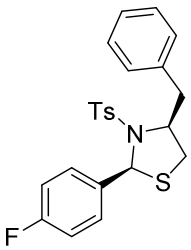
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (3H, d, *J*=6.6 Hz), 1.11 (3H, d, *J*=6.8 Hz), 2.16 (3H, s), 2.27 (1H, dd, *J*=6.3, 11.6 Hz), 2.43 (3H, s), 2.68 (1H, dd, *J*=2.4, 11.6 Hz), 2.90 (1H, dd, *J*=10.5, 18.1 Hz), 3.43 (1H, dd, *J*=3.3, 18.1 Hz), 3.74-3.86 (1H, m), 5.23 (1H, dd, *J*=3.2, 10.5 Hz), 7.32 (2H, ap d, ls=8.0 Hz), 7.71 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3, 19.9, 21.6, 30.0, 30.9, 32.7, 54.0, 60.7, 70.6, 127.3, 130.0, 134.7, 144.1, 205.5 ppm.

MS (ESI, positive) *m/z* (%): 364 $[M+Na]^+$.

α_D^{25}= -61.0° (c=2.0, CH_2Cl_2).

(2*S*,4*S*)-4-Benzyl-2-(4-fluorophenyl)-3-tosylthiazolidine (73a)



Prepared from (*S*)-*N*-(1-mercapto-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (64 mg, 0.2mmol) and 4-fluorobenzaldehyde (25 mg, 0.2mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 15:1) to yield (2*S*,4*S*)-4-benzyl-2-(4-fluorophenyl)-3-tosylthiazolidine (81%, 69 mg).

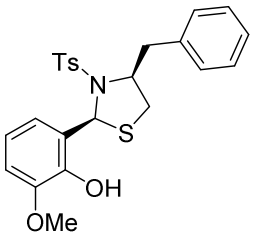
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (3H, s), 2.58 (1H, dd, *J*=6.4, 12.0 Hz), 2.66 (1H, dd, *J*=4.0, 12.0 Hz), 2.86 (1H, dd, *J*=10.8, 13.2 Hz), 3.34 (1H, dd, *J*=3.6, 13.2 Hz), 4.35-4.42 (1H, m), 6.06 (1H, s), 7.04 (2H, ap t, ls=8.4 Hz), 7.16 (2H, ap d,

ls=7.6 Hz), 7.22-7.33 (5H, m), 7.57 (2H, dd, *J*=5.2, 8.4 Hz), 7.74 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (CH_3), 35.6 (CH_2), 42.3 (CH_2), 67.1 (CH), 68.1 (CH), 115.2 (d, $^2J_{C\text{-}F}$=22.0 Hz), 126.8 (CH), 127.7 (CH), 128.6 (d, $^3J_{C\text{-}F}$=8.2 Hz), 128.7 (CH), 129.2 (CH), 129.9 (CH), 136.0 (d, $^4J_{C\text{-}F}$=2.7 Hz), 137.7 (C), 144.2 (C), 162.2 (d, $^1J_{C\text{-}F}$= 245.9 Hz) ppm.

MS (ESI, positive) *m/z* (%): 428 $[M+H]^+$.

2-((2*S*,4*S*)-4-Benzyl-3-tosylthiazolidin-2-yl)-6-methoxyphenol (73b)



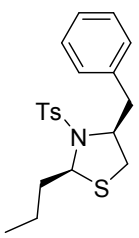
Prepared from (*S*)-*N*-(1-mercapto-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (40 mg, 0.12 mmol) and 2-hydroxy-3-methoxybenzaldehyde (18 mg, 0.12 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 8:1) to yield 2-((2*S*,4*S*)-4-benzyl-3-tosylthiazolidin-2-yl)-6-methoxyphenol (78%, 42 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (3H, s), 2.45 (1H, dd, *J*=6.0, 11.6 Hz), 2.65 (1H, dd, *J*=3.6, 11.6 Hz), 3.16 (1H, dd, *J*=11.2, 13.2 Hz), 3.51 (1H, dd, *J*=3.2, 13.2 Hz), 3.90 (3H, s), 4.36-4.41 (1H, m), 5.94 (1H, s), 6.31 (1H, s), 6.82 (1H, dd, *J*=1.2, 8.0 Hz), 6.90 (1H, ap t, ls=8.0 Hz), 7.23-7.27 (4H, ap d, m), 7.30-7.34 (4H, m), 7.81 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6, 34.2, 42.1, 56.1, 63.1, 67.4, 110.1, 118.9, 119.6, 126.7, 128.6, 129.6, 129.9, 134.9, 144.0, 188.9 ppm.

MS (ESI, positive) *m/z* (%): 478 $[M+Na]^+$.

(2*S*,4*S*)-4-Benzyl-2-propyl-3-tosylthiazolidine (73c)



Prepared from (*S*)-*N*-(1-mercapto-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (40 mg, 0.12 mmol) and butyraldehyde (9 mg, 0.12 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 10:1) to yield (2*S*,4*S*)-4-benzyl-2-propyl-3-tosylthiazolidine (84%, 38 mg).

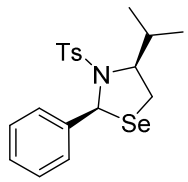
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (3H, t, *J*=7.2 Hz), 1.37-1.47 (1H, m), 1.52-1.69 (2H, m), 1.97-2.05 (1H, m), 2.40 (1H, dd, *J*=5.6, 11.6 Hz, C**H$_a$**H$_b$Ph), 2.42 (3H, s), 2.70 (1H, dd, *J*=4.4, 11.6 Hz, CH$_a$**H$_b$**Ph), 2.99 (1H, dd, *J*=10.4, 13.2 Hz, C**H$_a$**H$_b$S), 3.23 (1H, dd, *J*=4.0, 13.2 Hz, CH$_a$**H$_b$**S), 4.20-4.25 (1H, m, NCHS), 4.93 (1H, dd, *J*=5.2, 9.2 Hz), 7.22-7.32 (7H, m), 7.73 (2H, ap d, ls=8.4 Hz) ppm.

MS (ESI, positive) *m/z* (%): 398 $[M+Na]^+$.

Synthesis of 2,4-disubstituted 1,3-selenazolidines. General procedure.

β-aminoselenol **26** (1 mmol) and aldehyde (1 mmol) were dissolved in dry CH_2Cl_2 (3 mL) under inert atmosphere and then boron trifluoride diethyl etherate (1 mmol) was added dropwise. The mixture was stirred at r.t. for 1h, then the temperature was cooled at -18°C and the reaction stirred for 12 h. Afterwards the solution was diluted with diethyl ether and 0.1 N *aq* NaOH was added. The organic phase was washed with H_2O, dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was purified on silica gel.

(2*S*,4*S*)-4-Isopropyl-2-phenyl-3-tosyl-1,3-selenazolidine (76a)



Prepared from (*S*)-*N*-(1-hydroseleno-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.32 mmol) and benzaldehyde (33 mg, 0.32 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to yield (2*S*,4*S*)-4-isopropyl-2-phenyl-3-tosyl-1,3-selenazolidine (71%, 90 mg).

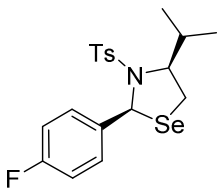
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.82 (3H, d, *J*=6.6 Hz, (C**H**$_3$)$_3$CH), 0.91 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_3$CH), 1.61-1.80 (1H, m), 2.44 (1H, dd, *J*=1.8, 10.6 Hz, C**H**$_a$H$_b$Se), 2.45 (3H, s), 2.98 (1H, dd, *J*=1.4, 10.6 Hz, CH$_a$**H**$_b$Se), 4.18 (1H, ddd, *J*=1.4, 1.8, 6.2 Hz), 6.60 (1H, s, NC**H**Se), 7.27-7.36 (5H, m), 7.63 (2H, ap d, ls=8.2 Hz), 7.80 (2H, ap d, ls=8.2 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.0, 20.2, 21.7, 28.9, 30.5, 61.1, 73.3, 127.4, 127.6, 128.1, 129.9, 135.4, 141.0, 144.1 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 301.0 ppm.

MS *m/z* (%): 366 (7), 69 (100), 91 (82), 41 (66), 155 (48), 260 (41), 150 (28), 104 (21), 77 (14).

(2*S*,4*S*)-2-(4-Fluorophenyl)-4-isopropyl-3-tosyl-1,3-selenazolidine (76b)



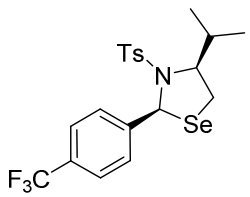
Prepared from **26b** (105 mg, 0.33 mmol) and 4-fluorobenzaldehyde (41 mg, 0.33 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 15:1) to yield (2*S*,4*S*)-2-(4-fluorophenyl)-4-isopropyl-3-tosyl-1,3-selenazolidine (73%, 102 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_3$CH), 0.87 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_3$CH), 1.60-1.71 (1H, m), 2.45 (1H, dd, *J*=7.6, 10.8 Hz, C**H**$_a$H$_b$Se), 2.46 (3H, s), 2.98 (1H, dd, *J*=1.6, 10.8 Hz, CH$_a$**H**$_b$Se), 4.15 (1H, ddd, *J*=1.6, 6.4, 7.6 Hz), 6.55 (1H, s, NC**H**Se), 7.00 (2H, ap t, ls=8.8 Hz), 7.34 (2H, ap d, ls=8.0 Hz), 7.61-7.68 (2H, m) 7.79 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.9, 20.0, 21.6, 29.1, 30.5, 60.4, 73.2, 114.9 (d, $^{2}J_{C\text{-}F}$=21.3 Hz), 127.7, 129.4 (d, $^{3}J_{C\text{-}F}$=8.4 Hz), 129.9, 135.4, 136.7 (d, $^{4}J_{C\text{-}F}$=3.2 Hz), 144.3, 162.3, (d, $^{1}J_{C\text{-}F}$=250.0 Hz) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 301.2 ppm.

(2*S*,4*S*)-4-Isopropyl-3-tosyl-2-(4-(trifluoromethyl)phenyl)-1,3-selenazolidine (76c)



Prepared from (*S*)-*N*-(1-hydroseleno-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.31 mmol) and 4-(trifluoromethyl)benzaldehyde (54 mg, 0.31 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to yield (2*S*,4*S*)-4-isopropyl-3-tosyl-2-(4-(trifluoromethyl)phenyl)-1,3-selenazolidine (62%, 92 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_2$CH), 0.94 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_2$CH), 1.60-1.70 (1H, m), 2.46 (3H, s), 2,49 (1H, dd, *J*=6.4, 10.8 Hz, C**H**$_a$H$_b$Se) 3.00 (1H, dd, *J*=1.6, 10.8 Hz, CH$_a$**H**$_b$Se), 4.15 (1H, ddd, *J*=1.6, 6.4, 8.0

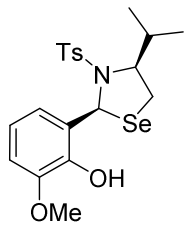
Hz), 6.57 (1H, s, NC**H**Se), 7.35 (2H, ap d, ls=8.0 Hz), 7.58 (2H, ap d, ls=8.4 Hz), 7.74 (2H, ap d, ls=8.0 Hz), 7.79 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.9, 20.2, 21.7, 29.2, 30.5, 60.3, 73.4, 125.1, 127.7, 130.0, 135.2, 137.4, 144.0, 145.0 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 312.5 ppm.

MS *m/z* (%): 477 (1), 434 (12), 328 (7), 278 (11), 150 (28), 91 (53), 69 (100), 41 (36).

2-((2*S*,4*S*)-4-Isopropyl-3-tosyl-1,3-selenazolidin-2-yl)-6-methoxyphenol (76d)



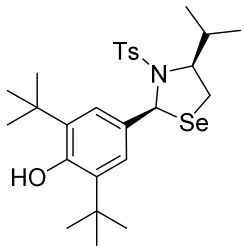
Prepared from (*S*)-*N*-(1-hydroseleno-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.31 mmol) and2-hydroxy-3-methoxybenzaldehyde (47 mg, 0.31 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 1:1) to yield 2-((2*S*,4*S*)-4-isopropyl-3-tosyl-1,3-selenazolidin-2-yl)-6-methoxyphenol (72%, 102 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (3H, d, *J*=6.8 Hz, $(CH_3)_2CH$), 1.29 (3H, d, *J*=6.8 Hz, $(CH_3)_2CH$), 2.03-2.10 (1H, m), 2.35 (1H, dd, *J*=6.0, 10.8 Hz, CH_aH_bSe), 2.44 (3H, s), 2.85 (1H, ap d, *J*=10.8 Hz, CH_aH_bSe), 3.87 (3H, s), 4.27 (1H, ap dd, *J*=6.0, 9.6 Hz), 6.00 (1H, bs, O**H**), 6.58 (1H, s, NC**H**Se), 6.78 (1H, ap d, ls=8.0 Hz), 6.85 (1H, ap t, ls=8.0 Hz), 7.26 (1H, ap d, ls=8.0 Hz), 7.34 (2H, ap d, ls=8.4 Hz), 7.80 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.4 (CH_3), 20.9 (CH_3), 21.6 (CH_3), 26.3 (CH_2), 30.5 (CH), 54.6 (CH), 56.1 (CH_3), 73.7 (CH), 109.8 (CH), 118.3 (CH), 119.4 (CH), 127.6 (CH), 128.8 (C), 129.9 (CH), 135.3 (C), 141.8 (C), 144.0 (C), 146.0 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 358.3 ppm.

2,6-Di-*tert*-butyl-4-((2*S*,4*S*)-4-isopropyl-3-tosyl-1,3-selenazolidin-2-yl)phenol (76e)

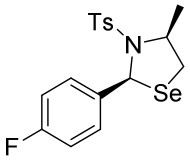


Prepared from **26b** (30 mg, 0.09 mmol) and 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (16 mg, 0.09 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 3:1) to yield 2,6-di-*tert*-butyl-4-((2*S*,4*S*)-4-isopropyl-3-tosyl-1,3-selenazolidin-2-yl)phenol (77%, 37 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0,87 (3H, d, *J*=6.6 Hz), 0.97 (3H, d, *J*=6.6 Hz), 1.43 (18H, s), 2.44 (3H, s), 2.54 (1H, dd, *J*=6.2, 10.6 Hz, C**H$_a$**H$_b$Se), 2.98 (1H, ap d, *J*=10.6 Hz, CH$_a$**H$_b$**Se), 4.15-4.27 (1H, m), 5.18 (1H, s), 6.54 (1H, s), 7.31 (2H, ap d, ls=8.4 Hz), 7.36 (2H, s), 7.77 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.0 (CH_3), 20.4 (CH_3), 21.7 (CH_3), 29.1 (CH_2), 30.1 (CH), 30.3 (CH_3), 30.8 (CH), 34.5 (C), 61.6 (CH), 73.2 (CH), 124.1 (CH), 127.6 (CH), 129.7 (CH), 131.3 (C), 135.2 (C), 135.7 (C), 143.8 (C), 156.2 (C) ppm.

(2*S*,4*S*)-2-(4-Fluorophenyl)-4-methyl-3-tosyl-1,3-selenazolidine (77a)



Prepared from **26e** (100 mg, 0.34mmol) and 4-fluorobenzaldehyde (42 mg, 0.3 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 1:1) to yield (2*S*,4*S*)-2-(4-fluorophenyl)-4-methyl-3-tosyl-1,3-selenazolidine (81%, 134 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (3H, d, *J*=6.8 Hz), 2.45 (3H, s), 2.72 (1H, dd, *J*=3.2, 10.4 Hz, C**H$_a$**H$_b$Se), 2.81 (1H, dd, *J*=6.0, 10.4 Hz, CH$_a$**H$_b$**Se), 4.65-4.78 (1H, m), 6.51 (1H, s, NC**H**Se), 7.00 (2H, ap t, ls=8.8 Hz), 7.33 (2H, ap d, ls=8.4 Hz), 7.45-7.54 (2H, m), 7.76 (2H, ap d, ls=8.4 Hz) ppm.

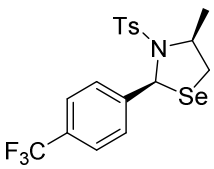
^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (CH_3), 22.9 (CH_3), 33.2 (CH_2), 60.3 (CH), 62.5 (CH), 114.9 (CH, d, $^2J_{C\text{-}F}$=21.0 Hz), 127.5 (CH), 128.3 (CH, d, $^3J_{C\text{-}F}$=8.2 Hz),

129.8 (CH), 135.2 (C), 138.0 (C, d, $^{4}J_{C\text{-}F}$=2.8 Hz), 144.1 (C), 162.1 (C, d, $^{1}J_{C\text{-}F}$=244.9Hz). ppm

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 356.6 ppm.

MS *m/z* (%): 335 (5), 122 (100), 41 (94), 91 (88), 65 (29), 139 (25), 155 (24), 77 (5).

(2*S*,4*S*)-4-Methyl-3-tosyl-2-(4-(trifluoromethyl)phenyl)-1,3-selenazolidine (77b)



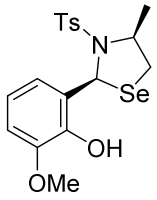
Prepared from (*S*)-*N*-(1-hydroselenopropan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.34mmol) and 4-(trifluoromethyl)benzaldehyde (59 mg, 0.34 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to yield (2*S*,4*S*)-4-methyl-3-tosyl-2-(4-(trifluoromethyl)phenyl)-1,3-selenazolidine (76%, 115 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (3H, d, *J*=6.8 Hz), 2.45 (3H, s), 2.73 (1H, dd, *J*=3.2, 10.4 Hz, C**H$_a$**H$_b$Se), 2.83 (1H, dd, *J*=6.0, 10.4, CH$_a$**H$_b$**Se), 4.72-4.79 (1H, m), 6.55 (1H, s, NC**H**Se), 7.34 (2H, ap d, ls=8.4 Hz), 7.56-7.62 (4H, m), 7.76 (2H, ap d, ls=8.0) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (CH_3), 22.8 (CH_3), 33.2 (CH_2), 60.1 (CH), 62.5 (CH), 125.2 (CH), 126.7 (CH), 127.5 (CH), 127.6 (C), 129.9 (CH), 135.1 (C), 144.3 (C), 145.4 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 364.3 ppm.

2-Methoxy-6-((2*S*,4*S*)-4-methyl-3-tosyl-1,3-selenazolidin-2-yl)phenol (77c)



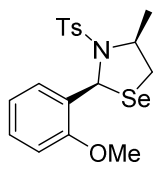
Prepared from (*S*)-*N*-(1-hydroselenopropan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.34 mmol) and 2-hydroxy-3-methoxybenzaldehyde (52 mg, 0.34 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 1:1) to yield 2-methoxy-6-((2*S*,4*S*)-4-methyl-3-tosyl-1,3-selenazolidin-2-yl)phenol (71%, 103 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (3H, d, *J*=6.4 Hz), 2.45 (3H, s), 2.62 (1H, dd, *J*=2.8, 10.4 Hz, C**H**$_a$H$_b$Se), 2.67 (1H, dd, *J*=6.0, 10.4 Hz, CH$_a$**H**$_b$Se), 3.88 (3H, s), 4.75-4.81 (1H, m), 5.87 (1H, s), 6.61 (1H, s), 6.78 (1H, ap d, ls=8.0 Hz), 6.85 (1H, ap t, ls=8.0 Hz), 7.18 (1H, ap d, ls=8.0 Hz), 7.34 (2H, ap d, ls=8.0 Hz), 7.80 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 22.8, 30.5, 54.7, 56.1, 62.8, 109.7, 118.1, 119.3, 127.4, 128.4, 129.9, 129.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 379.7 ppm.

(2*S*,4*S*)-2-(2-Methoxyphenyl)-4-methyl-3-tosyl-1,3-selenazolidine (77d)



Prepared from (*S*)-*N*-(1-hydroselenopropan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.34 mmol) and 2-methoxybenzaldehyde (46 mg, 0.34 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 3:1) to yield (2*S*,4*S*)-2-(2-methoxyphenyl)-4-methyl-3-tosyl-1,3-selenazolidine (91%, 127 mg).

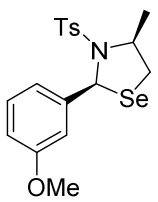
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (3H, d, *J*=6.4 Hz), 2.45 (3H, s), 2.53 (1H, dd, *J*=2.8, 10.4 Hz, C**H**$_a$H$_b$Se), 2.60 (1H, dd, *J*=6.0, 10.4 Hz, CH$_a$**H**$_b$Se), 3.88 (3H, s), 4.80-4.86 (1H, m), 6.56 (1H, s, NC**H**Se), 6.84 (1H, ap d, ls=8.0 Hz), 6.96 (1H, ap t, ls=7.2 Hz), 7.21-7.24 (1H, m), 7.35 (2H, ap d, ls=8.4 Hz), 7.55-7.59 (1H, m), 7.80 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 22.7, 30.0, 55.1, 55.2, 62.6, 109.8, 120.2, 125.5, 127.3, 128.2, 129.9, 131.8, 135.7, 143.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 380.5 ppm.

MS *m/z* (%): 347 (7), 91 (100), 83 (73), 55 (49), 41 (48), 155 (41), 260 (31), 43 (25), 65 (22), 77 (16).

(2*S*,4*S*)-2-(3-Methoxyphenyl)-4-methyl-3-tosyl-1,3-selenazolidine (77e)

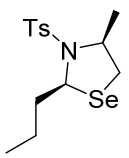


Prepared from (*S*)-*N*-(1-hydroselenopropan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.34 mmol) and 2-methoxybenzaldehyde (46 mg, 0.34 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 3:1) to yield (2*S*,4*S*)-2-(3-methoxyphenyl)-4-methyl-3-tosyl-1,3-selenazolidine (86%, 120 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37 (3H, d, *J*=6.8 Hz), 2.44 (3H, s), 2.63-2.82 (2H, m, C**H$_2$**Se), 3.79 (3H, s), 5.63-5.82 (1H, m), 6.53 (1H, s), 6.76-7.82 (1H, m), 7.00-7.55 (5H, m), 7.76 (2H, ap d, ls=8.0 Hz) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 358.5 ppm.

(2*S*,4*S*)-4-Methyl-2-propyl-3-tosyl-1,3-selenazolidine (77f).



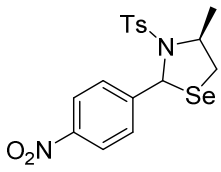
Prepared from (*S*)-*N*-(1-hydroselenopropan-2-yl)-4-methylbenzenesulfonamide (50 mg, 0.17 mmol) and butyraldehyde (12 mg, 0.17 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 4:1) to yield (2*S*,4*S*)-4-methyl-2-propyl-3-tosyl-1,3-selenazolidine (86%, 120 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95 (3H, t, *J*=7.4 Hz), 1.44 (3H, d, *J*=6.6 Hz), 1.57-1.95 (2H, m), 2.05-2.31 (2H, m), 2.43 (3H, s), 2.43 (1H, ap d, *J*=10.2 Hz, C**H$_a$**H$_b$Se), 2.64 (1H, ap d, *J*=10.2 Hz, CH$_a$**H$_b$**Se), 4.51-4.62 (1H, m), 5.29 (1H, dd, *J*=5.8, 9.6 Hz, NC**H**Se), 7.31 (2H, ap d, ls=8.4 Hz), 7.72 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.5 (CH_3), 21.4 (CH_2), 21.6 (CH_3), 23.2 (CH_3), 31.5 (CH_2), 44.5 (CH_2), 60.5 (CH), 61.3 (CH), 127.3 (CH), 129.8 (CH), 135.9 (C), 143.8 (CH) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 300.5 ppm.

(4*S*)-4-Methyl-2-(4-nitrophenyl)-3-tosyl-1,3-selenazolidine (77g)



Prepared from (*S*)-*N*-(1-hydroselenopropan-2-yl)-4-methylbenzenesulfonamide(100 mg, 0.34mmol) and 4-nitrobenzaldehyde (60 mg, 0.34 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 4:1) to yield (4*S*)-4-methyl-2-(4-nitrophenyl)-3-tosyl-1,3-selenazolidine (81%, 117 mg) as equimolar mixture of diastereoisomers.

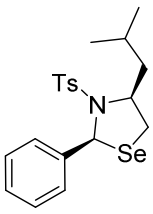
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (3H, d, *J*=6.4 Hz), 1.60 (3H, d, *J*=5.2 Hz), 2.37 (3H, s), 2.47 (3H, s), 2.76 (1H, dd, *J*=3.0, 10.8 Hz), 2.82-3.87 (2H, m), 3.59 (1H, dd, *J*=5.8, 10.2 Hz), 4.73-4,79 (1H, m), 4.87-4.90 (1H, m), 6.19 (1H, s), 6.56 (1H, s), 7.09-7.12 (2H, m), 7.33-7.35 (2H, m), 7.36-7.38 (2H, m), 7.43-7.45 (2H, m), 7.65-7.68 (2H, m), 7.77-7.79 (2H, m) 7.94-7.96 (2H, m), 8.18-8.20 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.7, 21.5, 21.9, 22.8, 32.0, 33.5, 56.4, 59.7, 62.6, 63.4, 123.2, 123.5, 127.2, 123.5, 127.2, 127.5, 127.8, 129.3, 130.0 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 370.0. 437.2 ppm.

MS *m/z* (%): 246 (66), 123 (100), 45 (51), 79 (25), 77 (25), 39 (19), 124 (17), 91 (16).

(2*S*,4*S*)-4-Isobutyl-2-phenyl-3-tosyl-1,3-selenazolidine (78a)



Prepared from **26c** (100 mg, 0.30 mmol) and benzaldehyde (32 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to give (2*S*,4*S*)-4-isobutyl-2-phenyl-3-tosyl-1,3-selenazolidine (87%, 106 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (3H, d, *J*=6.8 Hz), 0.92 (3H, d, *J*=6.8 Hz), 1.10-1.22 (1H, m), 1.48-1.69 (2H, m), 2.46 (3H, s), 2.63-2.75 (2H, m, C**H$_2$**Se), 4.59-

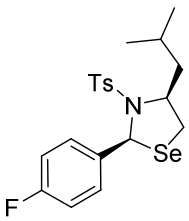
4.71 (1H, m), 6.65 (1H, s, NC**H**Se), 7.23-7.40 (5H, m), 7.55-7.57 (2H, m), 7.78-7.80 (2H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 22.3, 24.8, 32.1, 44.3, 61.0, 64.8, 126.8, 127.5, 127.6, 128.1, 129.8, 135.5, 141.8, 144.1 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 327.1. ppm

MS *m/z* (%):275 (12), 91 (100), 83 (73), 55 (49), 41 (48), 155 (41), 260 (31), 43 (25), 65 (22), 77 (16).

(2*S*,4*S*)-2-(4-Fluorophenyl)-4-isobutyl-3-tosyl-1,3-selenazolidine (78b)



Prepared from (*S*)-*N*-(1-hydroseleno-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.30 mmol) and 4-fluorobenzaldehyde (37 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to yield (2*S*,4*S*)-2-(4-fluorophenyl)-4-isobutyl-3-tosyl-1,3-selenazolidine (63%, 84 mg).

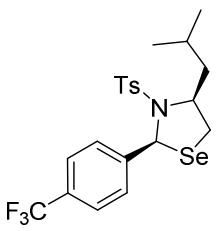
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_2$CH), 0.92 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_2$CH), 1.11-1.24 (1H, m), 1.45-1,61 (2H, m), 2.46 (3H, s), 2.60-2.80 (2H, m), 4.61-4,73 (1H, m), 6.60 (1H, s, NC**H**Se), 7.00 (2H, ap t, ls=8.8 Hz), 7.34 (2H, ap d, ls=8.0 Hz), 7.53-7.62 (2H, m), 7.79 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 22.3, 24.8, 32.3, 44.3, 60.3, 64.8, 114.8 (d, $^{2}J_{C\text{-}F}$=21.5 Hz), 127.6, 128.7 (d, $^{3}J_{C\text{-}F}$=8.5 Hz), 129.9, 135.4, 137.5 (d, $^{4}J_{C\text{-}F}$=2.8 Hz), 144.2, 162.0 (d, $^{1}J_{C\text{-}F}$ =245 Hz), 128.3, 129.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 328.1 ppm.

MS *m/z* (%): 346 (3), 83 (100), 91 (90), 55 (61), 155 (37), 43 (30), 148 (23), 65 (22), 122 (22), 278 (21), 77 (3).

(2*S*,4*S*)-4-Isobutyl-3-tosyl-2-(4-(trifluoromethyl)phenyl)-1,3-selenazolidine (78c)



Prepared from (*S*)-*N*-(1-hydroseleno-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.30 mmol) and 4-(trifluoromethyl)benzaldehyde (52 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to yield (2*S*,4*S*)-4-isobutyl-3-tosyl-2-(4-(trifluoromethyl)phenyl)-1,3-selenazolidine (74%, 108 mg).

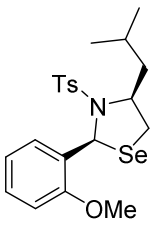
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_2$CH), 0.93 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_2$CH), 1.17-1.24 (1H, m), 1.48-1.67 (2H, m), 2.46 (3H, s), 2.71 (1H, dd, *J*=5.8, 10.4 Hz, C**H**$_a$H$_b$Se), 2.75 (1H, dd, *J*=3.0, 10.4 Hz, CH$_a$**H**$_b$Se), 4.65-4.70 (1H, m), 6,61 (1H, s, NC**H**Se), 7.35 (2H, ap d, ls=8.0 Hz), 7.58 (2H, ap d, ls=8.4 Hz), 7.67 (2H ap d, ls=8.0 Hz), 7.79 (2H, ap d, ls=8.4Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7 (CH_3), 22.2 (CH_3), 22.4 (CH_3), 24.9 (CH), 32.2 (CH_2), 44.3 (CH_2), 60.1 (CH), 64.9 (CH), 125.1 (CH), 127.1 (CH), 127.5 (CH), 130.0 (CH), 135.0 (C), 144.2 (C), 146.0 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 338.8 ppm.

MS *m/z* (%): 172 (6), 83 (100), 91 (87), 55 (59), 41 (46), 164 (35), 65 (26), 79 (3).

(2*S*,4*S*)-4-Isobutyl-2-(2-methoxyphenyl)-3-tosyl-1,3-selenazolidine (78d)



Prepared from (*S*)-*N*-(1-hydroseleno-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.30 mmol) and 2-methoxybenzaldehyde (41 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 3:1) to yield (2*S*,4*S*)-4-isobutyl-2-(2-methoxyphenyl)-3-tosyl-1,3-selenazolidine (68%, 92 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_2$CH), 1.00 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_2$CH), 1.31-1.42 (1H, m), 1.74-1.93 (2H, m), 2.46 (3H, s), 2.40-2.61

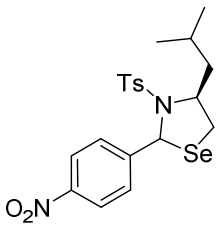
(2H, m), 3.87 (3H, s), 4.71-4.75 (1H, m), 6.55 (1H, s, NC**H**Se), 6.83 (1H, ap d, ls=8.0 Hz), 6.96 (1H, ap t, ls=7.8 Hz), 7.19-7.24 (1H, ap d, ls=7.8 Hz), 7.35 (2H, ap d, ls=8.4 Hz), 7.59 (1H, ap d, ls=7.8 Hz), 7.81 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 22.1, 22.8, 25.3, 28.3, 44.3, 55.0, 55.2, 65.2, 109.8, 120.2, 124.7, 125.3, 127.3, 128.3, 129.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 379.6 ppm.

MS *m/z* (%): 305 (7), 91 (100), 41 (44), 55 (43), 83 (43), 43 (29), 155 (24), 290 (23), 65 (22), 107 (21), 119 (20), 77 (14).

(4*S*)-4-Isobutyl-2-(4-nitrophenyl)-3-tosyl-1,3-selenazolidine (78e)



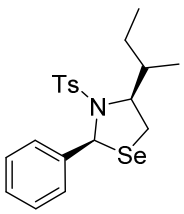
Prepared from (*S*)-*N*-(1-hydroseleno-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.30 mmol) and 4-nitrobenzaldehyde (45 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 1:1) to yield (4*S*)-4-isobutyl-2-(4-nitrophenyl)-3-tosyl-1,3-selenazolidine (47%, 66 mg) as a mixture ca. 2:1 of two diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_2$CH, *major* dia), 0.94 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_2$CH, *major* dia), 0.97 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_2$CH, *minor* dia), 1.00 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_2$CH, *minor* dia), 1.10-1.32 (4H, m), 1.80-2.05 (2H, m), 2.37 (3H, s, *minor* dia), 2.47 (3H, s, *major* dia), 2.65-2.81 (3H, m), 2.95 (1H, dd, *J*=4, 10.2 Hz, *minor* dia), 4.60-4.80 (2H, m), 6.20 (1H, s, NC**H**Se, *minor* dia), 6.61 (1H, s, NC**H**Se, *major* dia), 7.09 (2H, ap d, ls=8.8 Hz, *minor* dia), 7.33 (2H, ap d, ls=8.8 Hz, *minor* dia), 7.37 (2H, ap d, ls=8.8 Hz, *major* dia), 7.40 (2H, ap d, ls=8.4 Hz, *minor* dia), 7.72 (2H, ap d, ls=8.8 Hz, *major* dia), 7.80 (2H, ap d, ls=8.4 Hz, *major* dia), 7.92 (2H, ap d, ls=8.8 Hz, *minor* dia), 8.19 (2H, ap d, ls=8.8 Hz, *major* dia) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 21.7, 22.2, 22.4, 24.9, 26.5, 29.5, 29.7, 32.4, 41.1, 44.4, 56.7, 59.7, 65.0, 123.2., 123.4, 127.3, 127.6, 127.7, 128.2, 129.2, 130.1, 135.1, 144.6, 149.6 ppm.

MS (ESI, positive) *m/z* (%): 490 $[M+Na]^+$.

(2*S*,4*S*)-4-((*S*)-Sec-butyl)-2-phenyl-3-tosyl-1,3-selenazolidine (79a).



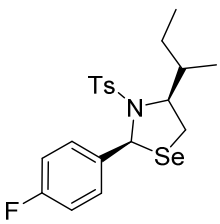
Prepared from **26d** (100 mg, 0.30 mmol) and benzaldehyde (32 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to yield **79a** (75%, 95 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.60 (3H, t, *J*=7.4 Hz), 0.76 (3H, d, *J*=6.8 Hz), 0.91-1.06 (1H, m), 1.31-1.41(1H, m), 1.62-1.84 (1H, m), 2.42 (1H, dd, *J*=6.3, 10.6 Hz, C**H$_a$**H$_b$Se), 2.46 (3H, s), 2.98 (1H, dd, *J*=1.4, 10.6 Hz, CH$_a$**H$_b$**Se), 4.23 (1H, ddd, *J*=1.6, 6.2, 10.1 Hz), 6.64 (1H, s), 7.32-7.36 (5H, m), 7.63 (2H, ap d, ls=8.4 Hz), 7.75 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.1, 15.8, 21.6, 25.8, 28.8, 36.4, 61.0, 71.8, 127.3, 127.7, 128.1, 129.9, 135.5, 141.2, 144.2 ppm.

MS *m/z* (%): 366 (9), 91 (100), 55 (62), 260 (52), 83 (51), 155 (51), 41 (47), 164 (21), 65 (21), 77 (15).

(2*S*,4*S*)-4-((*S*)-Sec-butyl)-2-(4-fluorophenyl)-3-tosyl-1,3-selenazolidine (79b)



Prepared from *N*-((2*S*,3*S*)-1-hydroseleno-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.30 mmol) and 4-fluorobenzaldehyde (37 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 1:1) to yield (2*S*,4*S*)-4-((*S*)-sec-butyl)-2-(4-fluorophenyl)-3-tosyl-1,3-selenazolidine (79%, 104 mg).

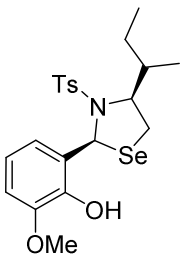
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 (3H, t, *J*=7.6 Hz), 0.76 (3H, d, *J*=6.4 Hz), 0.91-1.03 (1H, m), 1.27-1.42 (1H, m), 1.65-1.81 (1H, m), 2.38-2.45 (1H, m), 2.46 (3H, s), 3.0 (1H, ap d, *J*=10.6 Hz), 4.22 (1H, ddd, *J*=1.6, 6.4, 8.0 Hz), 6.58 (1H, s, NC**H**Se), 7.00 (2H, ap t, ls=8.8 Hz), 7.35 (2H, ap d, ls=8.4 Hz), 7.63 (2H, ap dd, *J*=5.2, 8.8 Hz), 7.79 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.1 (CH_3), 15.9 (CH_3), 21.7 (CH_3), 25.8 (CH_2), 29.0 (CH_2), 36.5 (CH), 60.4 (CH), 71.8 (CH), 114.8 (d, $^{2}J_{C\text{-}F}$=21.9 Hz), 127.6, 129.2 (d, $^{3}J_{C\text{-}F}$=8.2 Hz), 129.9, 135.3 136.8, 144.2, 162.2 (d, $^{1}J_{C\text{-}F}$=245.8 Hz) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 297.7 ppm.

MS *m/z* (%): 384 (7), 91 (100), 55 (75), 83 (72), 41 (54), 155 (54), 278 (29), 65 (24), 122 (24), 77 (2).

2-((2*S*,4*S*)-4-((*S*)-Sec-butyl)-3-tosyl-1,3-selenazolidin-2-yl)-6-methoxyphenol (79c)



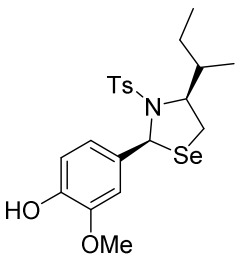
Prepared from *N*-((2*S*,3*S*)-1-hydroseleno-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.30 mmol) and 2-hydroxy-3-methoxybenzaldehyde (46 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 1:1) to yield **79c** (81%, 114 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (3H, d, *J*=6.6 Hz), 0.96 (3H, t, *J*=6.4 Hz), 1.61-1.99 (3H, m), 2.28 (1H, dd, *J*=5.2, 10.0 Hz), 2.45 (3H, s), 2.84 (1H, ap d, *J*=10.0 Hz), 3.87 (3H, s), 4.32 (1H, ap dd, *J*=5.2, 10.4 Hz), 6.57 (1H, s), 6.78-6.90 (2H, m), 7.19-7.25 (1H, m), 7.33 (2H, ap d, ls=8.4 Hz), 7.79 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.3, 15.1, 21.6, 26.0, 26.3, 36.5, 54.5, 56.1, 72.1, 109.9, 118.2, 119.4, 127.5, 129.6, 130.0, 135.4, 141.9, 144.0, 146.1 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 357.8 ppm.

4-((2*S*,4*S*)-4-((*S*)-Sec-butyl)-3-tosyl-1,3-selenazolidin-2-yl)-2-methoxyphenol (79d)



Prepared from *N*-((2*S*,3*S*)-1-hydroseleno-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.30 mmol) and 4-hydroxy-3-methoxybenzaldehyde (46 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 1:1) to yield 4-((2*S*,4*S*)-4-((*S*)-sec-butyl)-3-tosyl-1,3-selenazolidin-2-yl)-2-methoxyphenol (73%, 103 mg).

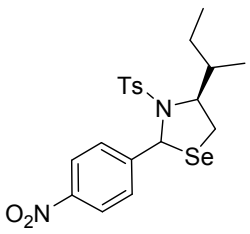
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (3H, t, *J*=7.5 Hz), 0.77 (3H, d, *J*=6.6 Hz), 0.94-1.09 (1H, m), 1.40-1.58 (1H, m), 1.77-1.87 (1H, m), 2,45 (3H, s), 2.41 (1H, dd, *J*=6.1, 10.8 Hz, C**H**$_a$H$_b$Se), 2,97 (1H, dd, *J*=1.6, 10.8 Hz, CH$_a$**H**$_b$Se), 3.87 (3H, s), 4.21 (1H, ddd, *J*=1.6, 6.3, 10.8 Hz), 5.59 (1H, bs, O**H**), 6.53 (1H, s), 6.77 (1H, ap d, ls=8.4 Hz), 7.10-7.20 (2H, m), 7.33 (2H, ap d, ls=8.1 Hz), 7.79 (2H, ap d, ls=8.1 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.2, 15.9, 21.7, 25.9, 28.9, 36.6, 56.0, 60.8, 71.8, 110.1, 113.9, 119.1, 127.8, 129.9, 134.3, 135.2, 144.1, 145.2, 145.9 ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 303.2 ppm.

MS *m/z* (%): 338 (20), 155 (100), 91 (83), 65 (19), 41 (10), 156 (9), 77 (4).

(2*S*,4*S*)-4-((*S*)-Sec-butyl)-2-(4-nitrophenyl)-3-tosyl-1,3-selenazolidine (79e)



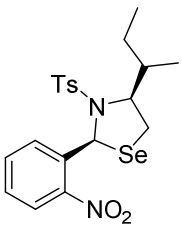
Prepared from *N*-((2*S*,3*S*)-1-hydroseleno-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.30 mmol) and 4-nitrobenzaldehyde (45 mg, 0.30 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to yield (4*S*)-4-((*S*)-Sec-butyl)-2-(4-nitrophenyl)-3-tosyl-1,3-selenazolidine as a 2:1 mixture of two diastereoisomers (62%, 86 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90-0.94 (6H, m), 1.10-1.20 (2H, m), 1.78-1.90 (1H, m) 2.43 (3H, s), 2.76 (1H, dd, *J*=7.6, 10.0 Hz, C**H$_a$**H$_b$Se), 3.33 (1H, dd, *J*=5.6, 10.0 Hz, CH$_a$**H$_b$**Se), 3.80-3.87 (1H, m), 6.63 (1H, s, NC**H**Se), 7.23 (2H, ap d, ls=8.4 Hz), 7.49 (2H, ap d, ls=8.8 Hz), 7,64 (2H, ap d, ls=8.4 Hz), 8.07 (2H, ap d, ls=8.8 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.4, 16.4, 21.6, 28.2, 29.7, 36.8, 59.8, 72.9, 123.4, 127.6, 128.0, 129.5, 132.9, 138.0, 144.2, 149.0 ppm.

MS (ESI, positive) *m/z* (%): 490 $[M+Na]^+$.

(2*S*,4*S*)-4-((*S*)-Sec-butyl)-2-(2-nitrophenyl)-3-tosyl-1,3-selenazolidine (79f)

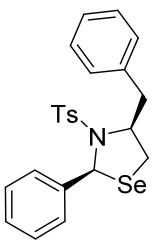


Prepared from **26d** (25 mg, 0.075mmol) and 2-nitrobenzaldehyde (11 mg, 0.075mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 3:1) to yield **79f** (51%, 18 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (3H, d, *J*=6.4 Hz), 1.02 (3H, t, *J*=7.6 Hz), 1.28-1.37 (1H, m), 1.91-1.98 (1H, m), 2.05-2.19 (1H, m), 2.47 (3H, s), 2,52 (1H, dd, *J*=6.0, 11.2 Hz, C**H$_a$**H$_b$Se), 2.93 (1H, dd, *J*=3.2, 11.2 Hz, CH$_a$**H$_b$**Se), 4.21-4.26 (1H, m), 7.02 (1H, s, NC**H**Se), 7.39 (2H, ap d, ls=8.4 Hz), 7.43 (1H, ap d, ls=7.2 Hz), 7.61-7.65 (1H, m), 7.77 (2H, ap d, ls=8.4 Hz), 7.99-8.03 (2H, m) ppm.

MS (ESI, positive) *m/z* (%): 468 $[M+H]^+$.

(2*S*,4*S*)-4-Benzyl-2-phenyl-3-tosyl-1,3-selenazolidine (80a)



Prepared from (*S*)-*N*-(1-hydroseleno-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.27 mmol) and benzaldehyde (29 mg, 0.27 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 3:1) to give (2*S*,4*S*)-4-benzyl-2-phenyl-3-tosyl-1,3-selenazolidine (84%, 103 mg).

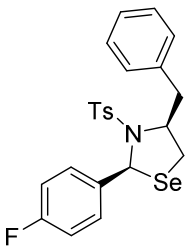
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (3H, s), 2.58 (1H, dd, *J*=6.0, 10.8 Hz), 2.79 (1H, dd, *J*=2.4, 13.2 Hz), 2.84 (1H, dd, *J*=10.8, 13.2 Hz), 3.12 (1H, dd, *J*=4.2, 13.2 Hz), 4.75-4,81 (1H, m), 6.60 (1H, s), 7.13-7.15 (2H, m), 7.26-7.35 (8H, m), 7.54-7.55 (2H, m), 7.77 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3), 29.8 (CH_2), 42.1 (CH_2), 60.9 (CH), 68.4 (CH), 126.6 (CH), 126.8 (CH), 127.6 (CH), 127.7 (CH), 128.3 (CH), 128.7 (CH), 129.2 (CH), 129.9 (CH), 135.4 (C), 138.1 (C), 142.0 (C), 144.2 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 345.2 ppm.

MS (ESI, positive) *m/z* (%): 479 $[M+Na]^+$.

(2*S*,4*S*)-4-Benzyl-2-(4-fluorophenyl)-3-tosyl-1,3-selenazolidine (80b)



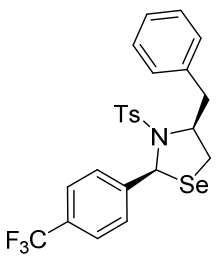
Prepared from (*S*)-*N*-(1-hydroseleno-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (100 mg, 0.27 mmol) and 4-fluorobenzaldehyde (34 mg, 0.27 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 15:1) to yield (2*S*,4*S*)-4-benzyl-2-(4-fluorophenyl)-3-tosyl-1,3-selenazolidine (91%, 116 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (3H, s), 2.58 (1H, dd, *J*=6.2, 11.0 Hz), 2.76-2.87 (2H, m), 3.10 (1H, dd, *J*=4.8, 12.6 Hz), 4.66-4.84 (1H, m), 6.54 (1H, s), 7.02(2H, ap t, ls=8.6 Hz), 7.14-7.33 (7H, m), 7.53-7.58 (2H, m), 7.76 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7 (CH_3), 30.1 (CH_2), 42.2 (CH_2), 60.4 (CH), 68.4 (CH), 115.1 (d, $^{2}J_{C\text{-}F}$=22.0 Hz), 126.8 (CH), 127.5 (CH), 128.4 (d, $^{3}J_{C\text{-}F}$=8.2 Hz), 128.7 (CH), 129.2 (CH), 129.9 (CH), 135.2 (C), 137.4 (C), 137.8 (C), 144.3 (C), 162.2 (d, $^{1}J_{C\text{-}F}$=245.9 Hz) ppm.

MS (ESI, positive) *m/z* (%): 475 $[M+H]^+$.

(2*S*,4*S*)-4-Benzyl-3-tosyl-2-(4-(trifluoromethyl)phenyl)-1,3-selenazolidine (80c)



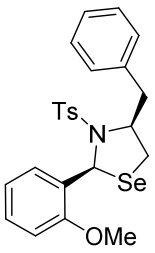
Prepared from (*S*)-*N*-(1-hydroseleno-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (37 mg, 0.1 mmol) and 4-(trifluoromethyl)benzaldehyde (18 mg, 0.1mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 15:1) to yield (2*S*,4*S*)-4-benzyl-3-tosyl-2-(4-(trifluoromethyl)phenyl)-1,3-selenazolidine (77%, 40 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (3H, s), 2.61 (1H, dd, *J*=6.0, 10.0 Hz), 2.79-2,86 (2H, m), 3.12 (1H, dd, *J*=4.4, 13.2 Hz), 4.77-4.83 (1H, m), 6.57 (1H, s), 7.13-7.15 (2H, m), 7.21-7.30 (3H, m), 7.33 (2H, ap s, ls=8.4 Hz), 7.59 (2H, ap d, ls=8.4 Hz), 7.64 (2H, ap s, ls=8.4 Hz), 7.77 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 30.0, 42.1, 60.0, 68.4, 125.3, 125.4, 126.9, 126.9, 127.6, 128.8, 129.2, 130.1, 135.2, 137.7, 144.8 ppm.

MS (ESI, positive) *m/z* (%): 547 $[M+Na]^+$.

(2*S*,4*S*)-4-Benzyl-2-(2-methoxyphenyl)-3-tosyl-1,3-selenazolidine (80d)



Prepared from (*S*)-*N*-(1-hydroseleno-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (37 mg, 0.1 mmol) and 2-methoxybenzaldehyde (14 mg, 0.1 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 3:1) to give (2*S*,4*S*)-4-benzyl-2-(2-methoxyphenyl)-3-tosyl-1,3-selenazolidine (83%, 42 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (1H, dd, *J*=5.2, 10.8 Hz), 2.43 (3H, s), 2.56 (1H, dd, *J*=1.6, 10.8 Hz), 2.97 (1H, dd, *J*=11.2, 13.2 Hz), 3.27 (1H, dd, *J*=3.6, 13.2 Hz), 4.82-4.88 (1H, m), 6.58 (1H, s), 6.87 (1H, dd, *J*=0.8, 8.0 Hz), 6.98 (1H , td,

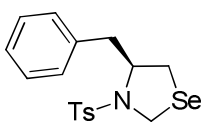
J=0.8, 7.6 Hz), 7.19-7.34 (8H, m), 7.68 (1H, dt, *J*=1.2, 7.6 Hz), 7.81 (2H, ap d, ls=8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3), 26.2 (CH_2), 41.8 (CH_2), 55.1 (CH), 55.3 (CH_3), 68.4 (CH), 110.0 (CH), 120.3 (CH), 125.6 (CH), 126.8 (CH), 127.4 (CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 130.0 (CH), 131.5 (C), 135.8 (C), 138.3 (C), 144.0 (C) ppm.

^{77}Se NMR (38 MHz, $CDCl_3$): δ = 372.7 ppm.

MS (EI) *m/z* (%): 398 (8), 396 (30), 241 (19), 198 (9), 161 (11), 155 (13), 117 (80), 104 (29), 91 (100), 65 (20).

(*S*)-4-Benzyl-3-tosyl-1,3-selenazolidine (80e)



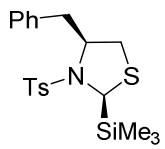
Prepared from (*S*)-*N*-(1-hydroseleno-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (55 mg, 0.15 mmol) and dimethoxymethane (23 mg, 0.30 mmol, 2 equiv) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 5:1) to yield (*S*)-4-benzyl-3-tosyl-1,3-selenazolidine (46%, 26 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (3H, s), 2.48 (1H, dd, *J*=6.4, 10.8 Hz), 2.77-2.89 (3H, m), 4.38 (1H, d, *J*=9.6 Hz, NC**H**$_a$H$_b$Se), 4.75-4.82 (1H, m, NC**H**CH_2), 5.10 (1H, d, *J*=9.6 Hz, NCH$_a$**H**$_b$Se), 7.15-7.30 (7H, m), 7.64 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5, 28.7, 39.4, 39.7, 65.4, 126.8, 127.5, 128.7, 129.3, 129.7 ppm.

MS (ESI, positive) *m/z* (%): 381 $[M+H]^+$.

(2*R*,4*S*)-4-Benzyl-3-tosyl-2-(trimethylsilyl)thiazolidine (84a).

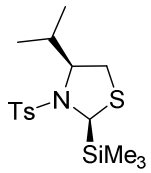


Prepared from (*S*)-*N*-(1-mercapto-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (32 mg, 0.1 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (21 mg, 0.1 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 3:1) to yield (2*R*,4*S*)-4-benzyl-3-tosyl-2-(trimethylsilyl)thiazolidine (59%, 24 mg, d.r.> 96:4 ca.).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.23 (9H, s), 2.19 (1H, dd, *J*=6.3, 11.4 Hz, C**H**$_a$H$_b$S), 2.42 (3H, s), 2.53 (1H, dd, *J*=3.3, 11.4 Hz, CH$_a$**H**$_b$S), 2.86 (1H, ap t, *J*=12.6 Hz, C**H**$_a$H$_b$Ph), 3.26 (1H, dd, *J*=2.4, 12.6 Hz, CH$_a$**H**$_b$Ph), 4.12-4.23 (1H, m, NC**H**CH$_2$), 4.28 (1H, s, NC**H**S), 7.20-7.33 (7H, m), 7.72 (2H, ap d, ls=7.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -2.0, 21.6, 34.7, 42.2, 55.9, 67.3, 126.7, 127.9, 128.7, 129.3, 129.8, 138.1, 143.8 ppm.

(2*R*,4*S*)-4-Isopropyl-3-tosyl-2-(trimethylsilyl)thiazolidine (84a).



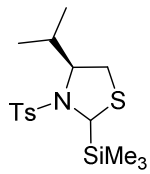
Prepared from (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (60 mg, 0.22 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (46 mg, 0.22 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 3:1) to yield (2*R*,4*S*)-4-isopropyl-3-tosyl-2-(trimethylsilyl)thiazolidine (43%, 34 mg, d.r.>96:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (9H, s), 0.91 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_3$CH), 0.91 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_3$CH), 1.82-1.91 (1H, m), 2.06 (1H, dd, *J*=6.0, 11.6 Hz, C**H**$_a$H$_b$S), 2.43 (3H, s), 2.59 (1H, dd, *J*=2.4, 11.6 Hz, CH$_a$**H**$_b$S), 3.74-3.80 (1H, m, NC**H**CH$_2$), 4.33 (1H, s, NC**H**S), 7.33 (2H, ap d, ls=8.0 Hz), 7.70 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -2.2 (CH_3), 19.6 (CH_3), 20.3 (CH_3), 21.6 (CH_3), 30.5 (CH), 32.7 (CH_2), 54.8 (NCHS), 71.8 (N**C**HCH_2), 128.0 (CH), 129.8 (CH), 134.3 (C), 143.8 (C) ppm.

MS (EI) *m/z* (%): 342 ([M-CH_3]$^+$, 2), 284 (14), 228 (11), 180 (23), 149 (26), 119 (48), 91 (41), 73 ([$SiMe_3^+$], 100) ppm.

(4*S*)-4-Isopropyl-3-tosyl-2-(trimethylsilyl)thiazolidine (84b) Mixture of *cis* and *trans* isomer.



Prepared from (*S*)-*N*-(1-mercapto-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (34 mg, 0.12 mmol) and (bromo(methoxy)methyl)trimethylsilane (24 mg, 0.12 mmol) following the general procedure. The crude residue (2:1 mixture of two diastereoisomers) was purified by silica gel chromatography (petroleum ether/diethyl ether 10:1) affording to the two diastereoisomers of (4*S*)-4-isopropyl-3-tosyl-2-(trimethylsilyl)thiazolidine (41%, 22 mg).

Major diastereoisomer (*cis*)

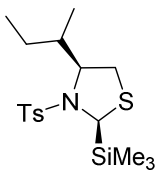
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (9H, s), 0.91 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_3$CH), 0.91 (3H, d, *J*=6.8 Hz, (C**H**$_3$)$_3$CH), 1.82-1.91 (1H, m), 2.06 (1H, dd, *J*=6.0, 11.6 Hz, C**H**$_a$H$_b$S), 2.43 (3H, s), 2.59 (1H, dd, *J*=2.4, 11.6 Hz, CH$_a$**H**$_b$S), 3.74-3.80 (1H, m, NC**H**CH$_2$), 4.33 (1H, s, NC**H**S), 7.33 (2H, ap d, ls=8.0 Hz), 7.70 (2H, ap d, ls=8.0 Hz) ppm.

Minor diastereoisomer (*trans*)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.35 (9H, s), 0.77 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_3$CH), 0.89 (3H, d, *J*=6.4 Hz, (C**H**$_3$)$_3$CH), 1.65-1.73 (1H, m), 2.42 (3H, s), 2.50 (1H, dd, *J*=6.8, 10.4 Hz, C**H**$_a$H$_b$S), 2.75 (1H, dd, *J*=2.4, 10.4 Hz, CH$_a$**H**$_b$S), 3.60-3.64 (1H, m, NC**H**CH$_2$), 3.95 (1H, s, NC**H**S), 7.27 (2H, ap d, ls=8.4 Hz), 7.79 (2H, ap d, ls=8.4 Hz) ppm.

MS (EI) *m/z* (%): 342 ([M-CH_3]$^+$, 2), 284 (14), 228 (11), 180 (23), 149 (26), 119 (48), 91 (41), 73 ([$SiMe_3^+$], 100).

(2*R*,4*S*)-4-((*S*)-Sec-butyl)-3-tosyl-2-(trimethylsilyl)thiazolidine (84c).

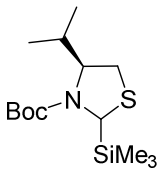


Prepared from *N*-((2*S*,3*S*)-1-mercapto-3-methylpentan-2-yl)-4-methylbenzenesulfonamide (29 mg, 0.1 mmol) and (methoxy(phenoxy)methyl)trimethylsilane (21 mg, 0.1 mmol) following the general procedure. The crude residue was purified by silica gel chromatography (petroleum ether/diethyl ether 3:1) to yield (2*R*,4*S*)-4-((*S*)-sec-butyl)-3-tosyl-2-(trimethylsilyl)thiazolidine (39%, 15 mg, d.r. 10:1 ca.).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (9H, s), 0.86-0.97 (6H, m), 1.01-1.24 (2H, m), 1.73-1.96 (1H, m), 1.82-1.91 (1H, m), 2.09 (1H, dd, *J*=6.3, 11.7 Hz, C**H$_a$**H$_b$S), 2.43 (3H, s), 2.62 (1H, dd, *J*=3.3, 11.7 Hz, CH$_a$**H$_b$**S), 3.77-3.83 (1H, m, NC**H**CH$_2$), 4.33 (1H, s, NC**H**S), 7.33 (2H, ap d, ls=8.4 Hz), 7.70 (2H, ap d, ls=8.4 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -2.2, 11.4, 15.4, 21.6, 26.2, 32.6, 36.8, 55.2, 70.6, 128.1, 129.8, 133.8, 143.9 ppm.

***Tert*-butyl (4*S*)-4-isopropyl-2-(trimethylsilyl)thiazolidine-3-carboxylate (85a).**



Prepared from (*S*)-*tert*-butyl (1-mercapto-3-methylbutan-2-yl)carbamate (70 mg, 0.32 mmol) and (bromo(methoxy)methyl)trimethylsilane (63 mg, 0.32 mmol) following the general procedure. The crude residue (ca. 2:1 mixture of two diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 15:1) affording to the two diastereoisomers of *tert*-butyl (4*S*)-4-isopropyl-2-(trimethylsilyl)thiazolidine-3-carboxylate (40%, 38 mg).

Minor diastereoisomer (*cis*)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.17 (9H, s), 0.88 (3H, d, *J*=6.2 Hz, $(CH_3)_3CH$), 0.92 (3H, d, *J*=6.2 Hz, $(CH_3)_3CH$), 1.43 (9H, s), 1.80-2.06 (1H, m), 2.81 (1H, dd, *J*=4.0, 12.0 Hz, CH_aH_bS), 2.95 (1H, dd, *J*=7.0, 12.0 Hz, CH_aH_bS), 3.83 (1H, s, NCHS), 4.08-4.17 (1H, m, $NCHCH_2$) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -0.1, 19.0, 19.3, 28.4, 30.3, 33.5, 53.3, 66.8, 83.0, 153.7 ppm.

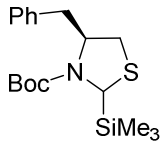
Major diastereoisomer (*trans*)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.12 (9H, s), 0.90 (3H, d, *J*=6.6 Hz, $(CH_3)_3CH$), 0.96 (3H, d, *J*=6.6 Hz, $(CH_3)_3CH$), 1.45 (9H, s), 1.77-1.95 (1H, m), 2.73-2.93 (2H, m, CH_2S), 4.02-4.11 (1H, m, $NCHCH_2$), 4.54 (1H, s, NCHS) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -1.8, 17.6, 18.8, 28.3, 31.1, 33.5, 53.3, 63.0, 79.8, 153.7 ppm.

MS (EI) *m/z* (%): 304 ([M^++1], 1), 246 (51), 230 (3), 202 (53), 188 (1), 118 (5), 100 (9), 86 (12), 73 ([$SiMe_3^+$], 100), 57 (79).

***Tert*-butyl (4*S*)-4-benzyl-2-(trimethylsilyl)thiazolidine-3-carboxylate (85b).**



Prepared from (*S*)-*tert*-butyl (1-mercapto-3-phenylpropan-2-yl)carbamate (150 mg, 0.50 mmol) and (bromo(methoxy)methyl)trimethylsilane (100 mg, 0.50 mmol) following the general procedure. The crude residue (1:1 mixture of two diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 5:1) affording to the two diastereoisomers of *tert*-butyl (4*S*)-4-benzyl-2-(trimethylsilyl)thiazolidine-3-carboxylate (43%, 76 mg).

Cis diastereoisomer

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.14 (9H, s), 1.48 (9H, s), 2.63-2.93 (3H, m, C**H$_a$**H$_b$S overlapped with CH_2Ph), 3.03-3.23 (1H, m, C**H$_a$**H$_b$S), 4.30 (1H, s, NC**H**S), 4.28-4.43 (1H, m, NC**H**CH_2), 7.18-7.40 (5H, m) ppm.

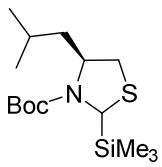
^{13}C NMR (50 MHz, $CDCl_3$): δ = -0.9, 28.4, 34.7, 40.5, 52.7, 62.7, 80.0, 128.3, 129.2, 129.4, 138.7, 156.0 ppm.

Trans diastereoisomer

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.17 (9H, s), 1.53 (9H, s), 2.57-2.89 (3H, m, C**H$_a$**H$_b$S overlapped with CH_2Ph), 3.10-3.35 (1H, m, C**H$_a$**H$_b$S), 4.30-4.44 (1H, m, NC**H**CH_2), 4.45 (1H, s, NC**H**S), 7.18-7.33 (5H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -1.7, 28.6, 34.8, 40.5, 53.0, 63.6, 80.2, 126.4, 128.5, 129.1, 136.6, 156.0 ppm.

***Tert*-butyl (4*S*)-4-isobutyl-2-(trimethylsilyl)thiazolidine-3-carboxylate (85c).**



Prepared from *tert*-butyl (*S*)-(1-mercapto-4-methylpentan-2-yl)carbamate (117 mg, 0.50 mmol) and (bromo(methoxy)methyl)trimethylsilane (100 mg, 0.50 mmol) following the general procedure. The crude residue (1:1 mixture of two diastereoisomers) was purified by silica gel chromatography (petroleum ether/ethyl acetate 6:1) affording to the two diastereoisomers of *tert*-butyl (4*S*)-4-isobutyl-2-(trimethylsilyl)thiazolidine-3-carboxylate (40%, 64 mg).

Cis diastereoisomer

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.15 (9H, s), 0.94 (6H, d, *J*=5.8 Hz), 1.35-1.44 (2H, m), 1.45 (9H, s), 1.53-1.60 (1H, m), 2.65 (1H, dd, *J*=2.0, 11.2 Hz, C**H$_a$**H$_b$S), 3.03 (1H, dd, *J*=6.8, 11.2 Hz, CH$_a$**H$_b$**S), 4.09 (1H, s, NC**H**S), 4.28-4.36 (1H, m, NC**H**CH_2) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -0.6, 22.0, 23.5, 25.7, 28.4, 36.0, 42.4, 52.1, 59.5, 80.0, 156.0 ppm.

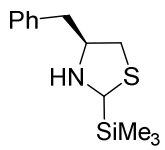
Trans diastereoisomer

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.12 (9H, s), 0.94 (6H, d, *J*=5.8 Hz), 1.20-1.45 (2H, m), 1.46 (9H, s), 1.50-1.60 (1H, m), 2.63 (1H, dd, *J*=3.8, 11.6 Hz, C**H$_a$**H$_b$S), 3.02 (1H, dd, *J*=6.4, 11.6 Hz, CH$_a$**H$_b$**S), 4.09 (1H, s, NC**H**S), 4.28-4.36 (1H, m, NC**H**CH$_2$) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -1.8, 21.8, 23.8, 25.7, 28.5, 36.1, 43.8, 52.3, 60.0, 80.0, 156.0 ppm.

MS (EI) *m/z* (%): 260 (7), 216 (8), 188 (5), 144 (7), 118 (1), 86 (4), 73 ([$SiMe_3^+$], 56), 57 (100).

(4*S*)-4-Benzyl-2-(trimethylsilyl)thiazolidine (88a).



(4*S*)-4-Benzyl-2-(trimethylsilyl)thiazolidine (30 mg, 0.08 mmol, 1 eq) was dissolved in dry DCM (1 mL) and the solution cooled down to 0°C. Then trifluoroacetic acid (96 mg, 0.80 mmol, 10 eq) was slowly added and the temperature was allowed to warm at r.t. After 12 h the mixture was diluted with DCM and washed with water (x3). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure to yield (4*S*)-4-benzyl-2-(trimethylsilyl)thiazolidine (87%, 18 mg) pure enough to be used without a further purification.

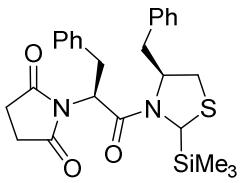
Mixture of *cis* and *trans* diastereoisomers (ratio 1:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.26 (9H, s), 0.27 (9H, s), 2.88-3.02 (6H, m), 3.34 (1H, dd, *J*=4.0, 13.2 Hz), 3.46 (1H, dd, *J*=4.0, 8.8 Hz), 3.86-3.94 (1H, m, NC**H**CH$_2$), 3.98 (1H, s, NC**H**S), 4.09 (1H, s, NC**H**S), 4.08-4.14 (1H, m, NC**H**CH$_2$), 7.12-7.31 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -3.4, -3.3, 33.7, 34.7, 36.1, 36.9, 51.5, 53.1, 65.9, 67.4, 127.3, 127.4, 128.7, 128.9, 129.0, 135.7, 136.0 ppm.

MS (EI) *m/z* (%): 236 ($[M\text{-}CH_3]^{+\cdot}$, 5), 178 (100), 160 ($[M\text{-}Bn]^{+\cdot}$, 32), 134 (28), 117 (52), 91 ($[Bn^+]$, 35), 73 ($[SiMe_3^+]$, 50).

1-((2*S*)-1-((4*S*)-4-Benzyl-2-(trimethylsilyl)thiazolidin-3-yl)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2,5-dione (90a).



(4*S*)-4-benzyl-2-(trimethylsilyl)thiazolidine (50 mg, 0.2 mmol, 1 eq) was dissolved in dry $CHCl_3$ (1 mL) and Et_3N (24 mg, 0.24 mmol, 1.2 eq) was added under inert atmosphere. Then (*S*)-2-(2,5-dioxopyrrolidin-1-yl)-3-phenylpropanoyl chloride (64 mg, 0.24 mmol, 1.2 eq) was added dropwise and the reaction was stirred for 2 h. Afterwards the solution is diluted with $CHCl_3$, the organic layer is washed with water, brine and dried over Na_2SO_4. The solvent is evaporated under reduced pressure and the crude was purified by flash column chromatography (petroleum ether/ethyl acetate 2:1) to yield **90a** (48%, 46 mg).

Mixture of *cis* and *trans* diastereoisomers (ratio 1:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (9H, s), 2.57 (4H, s, $(CH_2)_2$), 2.65-2.78 (3H, m), 3.01-3.07 (1H, m), 3.37 (1H, dd, *J*=7.2, 14.0 Hz), 3.80 (1H, dd, *J*=9.6, 14.0 Hz), 4.63 (1H, s, NCHS), 4.77-4.80 (1H, m), 5.27 (1H, dd, *J*=6.4, 9.6 Hz, COCHN), 7.11-7.37 (10H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = -1.39, 27.9, 29.7, 34.4, 40.3, 53.6, 55.7, 62.2, 127.0, 127.1, 128.7, 128.7, 128.9, 129.2, 129.3, 136.6, 137.2, 165.9, 176.7 ppm.

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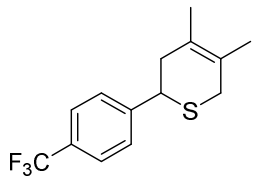
Synthesis of thio- and seleno- carbonyl compounds in ILs. General procedure

A mixture of 0.5 mL of ionic liquid (maintained under high vacuum prior to use), aldehyde (0.28 mmol) and the diene (0.56 mmol) was treated under inert atmosphere at room temperature with HMDST (0.56 mmol) and $CoCl_2 \cdot 6H_2O$ (0.056 mmol) (or TfOTMS, 0.056 mmol). The progress of the reaction was monitored by TLC (petroleum ether/diethyl ether). After completion of the reaction (2-3 h), the mixture was diluted with diethyl ether. The organic phase was then washed with NH_4Cl (3 x 1 mL) and extracted with diethyl ether (3 x 2 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under vacuum. TLC purification (petroleum ether/diethyl ether) afforded the substituted 3,6-dihydro-2*H*-thiopyrans **92**. Compounds **92** characterization is reported (see Ref. 11c, chapter 8).
Synthesis of substituted 3,6-dihydro-2*H*-selenopiranes **95** in ILs has been achieved following the same procedure, using 0.56 mmol of HMDSS. Compounds **95** characterization is reported (see Ref. 25c, chapter 8).
When ring opening reactions (paragraph 8.4) were carried out, ILs have been maintained at high vacuum prior to use. Apart from that, the procedure is like the one reported to perform reactions in traditional solvents.

4,5-dimethyl-2-(4-(trifluoromethyl)-phenyl)-3,6-dihydro-2H-thiopyran 92b.

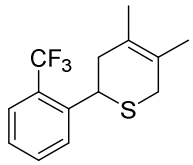


Following the general procedure, 4-trifluoromethylbenzaldehyde and 2,3-dimethyl-1,3-butadiene gave, after purification, **92b** (63%).

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.73 (3H, s), 1.77 (3H, s), 2.45-2.55 (2H, m), 2.91 (1H, bd, *J*=16.8 Hz), 3.42 (1H, bd, *J* = 16.8 Hz), 4.02 (1H, dd, *J*=4.5, 8.4 Hz), 7.45 (2H, ap d, *J*=8.3 Hz), 7.61 (2H, ap d, *J*=8.3 Hz) ppm.

MS (EI), *m/z* (%): 272 (26) [$M^{+\cdot}$], 239 (16), 190 (59), 82 (100).

4,5-dimethyl-2-(2-(trifluoromethyl)phenyl)-3,6-dihydro-2H-thiopyran (**92c**).



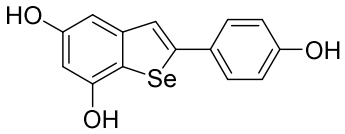
Following the general procedure, 2-trifluoromethylbenzaldehyde and 2,3-dimethyl-1,3-butadiene gave, after purification, **92c** (68%).

^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 1.72 (3H, s), 1.74 (3H, s), 2.33-2.51 (2H, m), 2.93 (1H, bd, *J*=17.0 Hz), 3.44 (1H, d, *J*=17.0 Hz), 4.16 (1H, dd, *J*=4.5, 10.0 Hz), 7.30-7.38 (1H, m), 7.50-7.56 (1H, m), 7.79-7.83 (1H, m), 7.95-8.01 (1H, m) ppm.

MS (EI), *m/z* (%): 272 (24) [M^+], 239 (12), 190 (62), 82 (100).

General procedure for preparation of the benzoselenophene derivatives. All the reactions were carried out in a oven-dried glassware under inert atmosphere (N_2). Fresh distilled SO_2Cl_2 (0.8 mmol, 1 mmol or 2 mmol to obtain **108**, **109** or **110** as major product, in that order) was added dropwise to selenium powder (79 mg, 1 mmol) and stirred at rt for 10 min, then 2.5 mL of distilled THF was added. After 1 h resveratrol (94 mg, 0.4 mmol) dissolved in 0.8 mL of dry DMF was added. The mixture was stirred for 24 h at rt. The brownish red product was filtered over celite before extraction with ethyl acetate (3 × 15 mL), and the organic layer washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to afford the crude product, which was purified by flash column chromatography (chloroform/methanol 9:1, 1% acetic acid).

2-(4-Hydroxyphenyl)benzo[*b*]selenophene-5,7-diol (108).



Following the general procedure, from 200 mg of resveratrol, compound **108** was obtained together with **109** (70:30) (ratio determined by NMR), and purified by flash column chromatography to give 128 mg of **108** as hygroscopic brownish red powder, yield: 48%.

^{1}H-NMR (400 MHz, CD_3OD): δ = 6.25 (1H, d, *J*=2.2 Hz), 6.72 (1H, d, *J*=2.2 Hz), 6.81 (2H, ap d, ls=8.0 Hz), 7.44 (1H, s), 7.48 (2H, ap d, ls=8.0 Hz) ppm.

^{13}C-NMR (50 MHz, CD_3OD): δ = 99.6, 103.1, 116.6, 122.4, 128.7, 129.0, 129.4, 146.7, 149.1, 155.2, 157.7, 158.9 ppm.

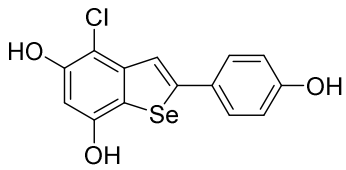
^{77}Se-NMR (76 MHz, CD_3OD): δ = 462.5 ppm.

MS (ESI, *negative*): *m/z* 304 ($[M-H]^-$).

$C_{14}H_{10}O_3Se$ (305.19): calcd. C 55.10, H 3.30; found C 54.72, H 3.64.

Compound **108** was exposed to Se/SO_2Cl_2 in THF under the standard reaction conditions, and products formed were analyzed by TLC (eluant chloroform/methanol 9:1, 1% acetic acid).

4-Chloro-2-(4-hydroxyphenyl)benzo[b]selenophene-5,7-diol (109).



Following the general procedure, starting from 200 mg of resveratrol, compound **109** was obtained as a mixture 85:15 (ratio determined by NMR) with **110**. After flash chromatography purification 211 mg of **109** were isolated as hygroscopic dark brownish green compound. Yield: 71%.

^{1}H-NMR (300 MHz, CD_3OD): δ = 6.41 (1H, s), 6.85 (2H, ap d, ls=9.0 Hz), 7.47 (2H, ap d, ls=9.0 Hz), 7.66 (1H, s) ppm.

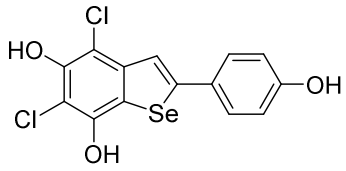
^{13}C-NMR (50 MHz, CD_3OD): δ = 101.2, 107.7, 117.7, 120.8, 121.2, 129.8, 129.9, 144.6, 151.7, 153.6, 154.7, 160.2 ppm.

^{77}Se-NMR (76 MHz, CD_3OD): δ = 498.6 ppm.

MS (ESI, *negative*) *m/z* 339 ($[M-H]^-$).

$C_{14}H_9ClO_3Se$ (339.63): calcd. C 49.51, H 2.67; found C 49.84, H 2.36.

4,6-Dichloro-2-(4-hydroxyphenyl)benzo[b]selenophene-5,7-diol (110).



Following the general procedure, starting from 200 mg of resveratrol, after flash column chromatography purification 269 mg of **110** were obtained as hygroscopic dark brownish compound. Yield: 82%.

^{1}H-NMR (400 MHz, CD_3OD): δ = 6.83 (2H, ap d, ls=8.8 Hz), 7.50 (2H, ap d, ls=8.8 Hz), 7.65 (1H, s) ppm.

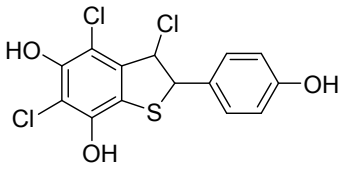
^{13}C-NMR (50 MHz, CD_3OD): δ = 108.2, 109.3, 117.7, 120.9, 129.9, 133.0, 124.2, 149.7, 150.4, 152.1, 160.4, 174.3 ppm.

^{77}Se-NMR (76 MHz, CD_3OD): δ = 510.9 ppm.

MS (ESI, negative): *m/z* 373 ($[M-H]^-$).

$C_{14}H_8Cl_2O_3Se$ (374.08): calcd. C 44.95, H 2.16; found C 44.68, H 2.40.

3,4,6-Trichloro-2-(4-hydroxyphenyl)-2,3-dihydrobenzo[*b*]thiophene-5,7-diol (111)

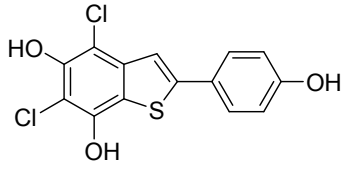


Freshly distilled SO_2Cl_2 (297 mg, 2.20 mmol, 2.0 eq) was added to S(0) (35 mg, 1.10 mmol, 1 eq) and stirred at r.t. for 10 min. Dry THF (7.5 mL) was added and the mixture was maintained under stirring for 1 h. Then, resveratrol (100 mg, 0.44 mmol, 0.4 eq) solubilised in DMF (2 mL) was added and the reaction was stirred at r.t. for 24 h. Afterwards, the crude mixture is filtered on celite, extracted with EtOAc and washed with H_2O (3x10 mL). The organic layer was dried over Na_2SO_4 and the solvent eliminated under reduced pressure. The crude material was purified by flash chromatography ($CHCl_3$/MeOH 9:1, 1% acetic acid) to afford 3,4,6-trichloro-2-(4-hydroxyphenyl)-2,3-dihydrobenzo[*b*]thiophene-5,7-diol (**111**) as a brownish solid (9%, 45 mg).

^{1}H NMR (200 MHz, CD_3OD): δ = 4.92 (3H, s), 5.22 (1H, d, *J*=9.6 Hz), 5.85 (1H, d, *J*=9.6 Hz), 6.59 (2H, d, *J*=8.8 Hz), 7.08 (2H, d, *J*=8.8 Hz) ppm.

MS (ESI, negative) *m/z* (%): 362 $[M-H]^-$.

4,6-Dichloro-2-(4-hydroxyphenyl)benzo[*b*]thiophene-5,7-diol (112)



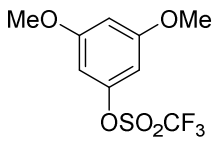
Product **112** was obtained from **111** by HCl elimination occurred on SiO_2.

^{1}H NMR (400 MHz, CD_3OD): δ = 4.85 (3H, bs), 6.86 (2H, d, *J*=8.8 Hz), 7.42 (1H, s), 7.58 (2H, d, *J*=8.8 Hz) ppm.

^{13}C NMR (100 MHz, CD_3OD): δ = 106.3, 107.4, 116.8, 120.9, 126.6, 128.7, 128.8, 139.4, 147.8, 147.9, 148.5, 159.5 ppm.

MS (EI) *m/z* (%): 325 ($M^{+\bullet}$, 100), 305 (60).

3,5-Dimethoxyphenyl trifluoromethanesulfonate (114)



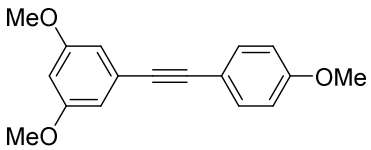
Triethylamine (1314 mg, 13 mmol) was added to a stirred solution of 3,5-dimethoxyphenol (500 mg, 3.25 mmol) in dry CH_2Cl_2 (30 mL) under inert atmosphere (N_2). The solution is then cooled at 0°C and trifluoromethanesulfonic anhydride was added dropwise and the mixture was stirred for 5 h. Afterwards, the organic layer was extracted with CH_2Cl_2, washed with H_2O (2x150 mL) and with saturated *aq* NaCl (150 mL). The organic phase was dried over Na_2SO_4. and the solvent was eliminated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/ethyl acetate 4:1) to afford **114** as a yellowish oil (62%, 949 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80 (3H, s), 6.41 (2H, d, *J*=2.2 Hz), 6.45 (1H, t, *J*=2.2 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.5, 100.2, 101.1, 121.9 (q, $^1J_{C\text{-}F}$=318.6 Hz), 121.9, 150.6, 161.5 ppm.

IR [$CDCl_3$] υ (cm^{-1}): 2944, 1625, 1422, 1217, 1158.

1,3-Dimethoxy-5-((4-methoxyphenyl)ethynyl)benzene (113)



General procedure for the Sonogashira *cross coupling*. A solution of the bromide or of the triflate (1.05 mmol) in the solvents was prepared in a schlenk tube and CuI (0.07 mmol),

$Pd(PPh_3)_2Cl_2$ and the base (3.15 mmol) were added under inert atmosphere (N_2). The solution was deoxigenated by *freezing pump* (x3). Then a solution of the alkine (1.60 mmol) in dry THF was added in the schlenk tube and the reation was stirred under inert atmosphere at room temperature for 20 h. Afterwards the reaction was diluted with CH_2Cl_2, washed with saturated *aq*. NH_4Cl (1x60 mL) and with H_2O (2x60 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Purification by flash coloumn chromatography (Hexane/CH_2Cl_2 2:1) afforded **113** as a yellowish oil.

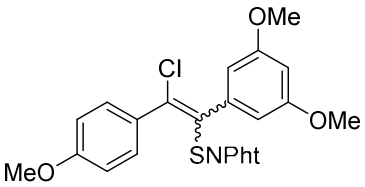
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80 (6H, s), 3.83 (3H, s), 6.45 (1H, t, *J*=2.4 Hz), 6.68 (2H, d, *J*=2.4 Hz), 6.88 (2H, d, *J*=8.8 Hz), 7.47 (2H, d, *J*=8.8 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 54.2, 55.6, 88.3, 90.5, 100.1, 111.2, 114.5, 115.1, 124.5, 133.5, 159.6, 160.7 ppm.

IR [$CDCl_3$] υ (cm^{-1}): 3018, 2926, 1210.

MS (EI) *m/z* (%): 268 ($M^{+\bullet}$, 100), 253 (30).

(*E,Z*)-2-((2-Chloro-1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)vinyl)thio)isoindoline-1,3-dione. (*E*-115) and (*Z*-115) - Mixture 2:1 of isomers.



1,3-dioxoisoindolin-2-yl hypochlorothioite (PhtNSCl) (44 mg, 0.19 mmol) in dry CH_2Cl_2 (2.0 mL) was added dropwise to a stirred solution of alkine **113** (41 mg, 0.15 mmol) in CH_2Cl_2 (1.5 mL) under inert atmosphere (N_2) at -10°C. The reaction was allowed to warm up and stirred at r.t. for 22 h. Afterwards, the mixture was diluted with CH_2Cl_2, washed with H_2O (3x10 mL) and the organic phase was dried over Na_2SO_4. The solvent was eliminated under reduced pressure and the crude material was purified by flash chromatography (CH_2Cl_2/petroleum ether 5:1) to afford **115** in a 2:1 mixture of diastereoisomers as a pale yellow oil (58%, 42 mg).

Major diastereoisomer

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.58 (6H, s), 3.70 (3H, s), 5.89 (1H, t, *J*=2.2 Hz), 6.21 (2H, d, *J*=2.2 Hz), 6.62 (2H, d, *J*=8.8 Hz), 7.14 (2H, d, *J*=8.8 Hz), 7.68 (4H, m) ppm.

Minor diastereoisomer

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.64 (6H, s), 3.75 (3H, s), 6.11 (1H, t, *J*=2.2 Hz), 6.45 (2H, d, *J*=2.2 Hz), 6.96 (2H, d, *J*=8.8 Hz), 7.63 (2H, d, *J*=8.8 Hz), 7.68 (4H, m) ppm.

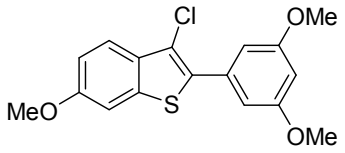
Mixture of diastereoisomers

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.1, 55.2, 55.3, 101.6, 101.7, 107.5, 108.3, 113.3, 113.9, 123.4, 124.2, 127.0, 129.9, 130.1, 130.7, 131.6, 134.4, 135.9, 137.0, 159.4, 160.0, 160.2, 160.4, 176.5, 177.8 ppm.

IR [$CDCl_3$] υ (cm^{-1}): 3018, 1745, 1214.

MS (EI) *m/z* (%): 481 ($M^{+\bullet}$, 100), 300 (95), 268 (78), 76 (98).

3-Chloro-2-(3,5-dimethoxyphenyl)-6-methoxybenzo[*b*]thiophene (118)



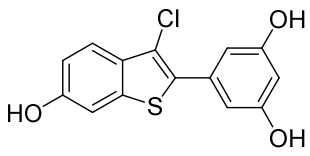
A solution of **(*E*,*Z*)-115** (170 mg, 0.35 mmol) in dry CH_2Cl_2 (3.5 mL) was added dropwise to a stirred suspension of $AlCl_3$ (94 mg, 0.71 mmol) in dry CH_2Cl_2 (7.0 mL) at r.t. The colour changed from yellow to red and the reaction was stirred for 3 h. Afterwards, the organic phase was extracted with CH_2Cl_2 (20 mL), washed with saturated *aq* $NaHCO_3$ (1x20 mL), 1M NaOH (2x20 mL), H_2O (1x20 mL), dried over Na_2SO_4, filtered and the solvent was evaporated. The crude material was purified by flash chromatography (CH_2Cl_2/hexane 5:1) to afford benzo[*b*]thiofene **118** as a yellowish oil (61%, 70 mg).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75 (3H, s), 3.81 (6H, s), 6.54 (1H, t, *J*=2.2 Hz), 6.88 (2H, d, *J*=2.2 Hz), 7.10 (1H, dd, J_{meta}=2.2, J_{orto}=8.8 Hz), 7.42 (1H, d, *J*=2.2 Hz), 7.71 (1H, d, *J*=8.8 Hz) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.5, 55.7, 100.7, 104.9, 107.3, 115.1, 123.0, 131.9, 133.4, 134.2, 138.1, 154.1, 158.5, 160.8 ppm.

MS (EI) *m/z* (%): 334 ($M^{+\bullet}$, 100), 319 (55), 167 (20).

5-(3-Chloro-6-hydroxybenzo[*b*]thiophen-2-yl)benzene-1,3-diol (119)



To a dry CH_2Cl_2 stirred solution of **118** (20 mg, 0.06 mmol) maintained at 0°C in inert atmosphere (N_2), 0.27 mL of a 1M solution of BBr_3 in CH_2Cl_2 were added. The colour of the mixture changed from yellow to dark red and the reaction was stirred for 3 h. The mixture was added wit crushed ice, the organic phase was extracted with EtOAc (20 mL), washed with H_2O (3x20 mL) and dried over Na_2SO_4. The solvent was eliminated under reduced pressure and the crude material was purified by flash chromatography (chloroform/methanol 9:1 with 1% acetic acid) to afford **119** as a yellow solid (48%, 8.5 mg).

^{1}H NMR (400 MHz, CD_3OD): δ = 4.91 (3H, s), 6.30 (1H, t, *J*=2.2 Hz), 6.70 (2H, d, *J*=2.2 Hz), 6.98 (1H, dd, J_{meta}=2.2, J_{orto}=8.8 Hz), 7.20 (1H, d, *J*=2.2 Hz), 7.63 (1H, d, *J*=8.8 Hz) ppm.

^{13}C NMR (50 MHz, CD_3OD): δ = 103.8 (C_a), 108.3 (C_e), 108.6 (C_b), 116.3 (C_d), 116.6, 123.7 (C_c), 132.3, 134.2, 135.4, 139.4, 157.6, 159.8 ppm.

MS (ESI, negative) *m/z* (%): 291 $[M-H]^-$.

2,2,-Diphenyl-1-picrylhydrazyl (DPPH) assay. The assay was performed as described.[2] Briefly, to 1.98 mL of 200 μM DPPH in methanol 20 μL of 5 mM methanolic solution of compounds **108**, **109**, **110** or resveratrol were added. The

reaction was followed by spectrophotometric analysis measuring the absorbance at 515 nm every 30 s for 10 min. Trolox was used as standard.

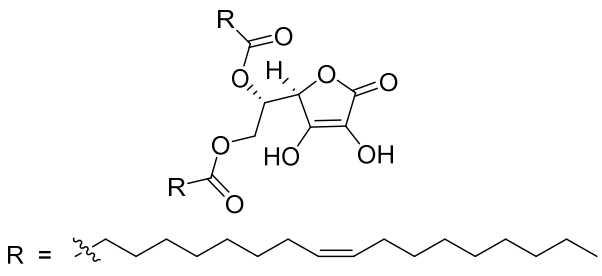
Ferric reducing/antioxidant power (FRAP) assay. The assay was performed as described.[3] To 3.6 mL solution of FRAP reagent, 10-30 μL of 5 mM methanolic solution of compounds **108**, **109**, **110** or resveratrol (10-70 μM final concentration) were added. After 10 minutes the absorbance at 593 nm was measured. Trolox was used as standard. The FRAP reagent was prepared freshly by mixing 0.3 M acetate buffer (pH 3.6), 10 mM 2,4,6-tris(2-pyridyl)-*s*-triazine in 40 mM HCl, and 20 mM ferric chloride in water, in the ratio 10:1:1, in that order.

Kinetics with peroxyl radicals. The chain-breaking antioxidant activity of the title compounds was evaluated by studying the inhibition of the thermally initiated autoxidation of styrene in chlorobenzene or acetonitrile. Autoxidation experiments were followed by measuring the O_2 consumption by a gas-uptake recording apparatus. In a typical experiment, an air-saturated mixture of styrene in acetonitrile or chlorobenzene (50% v/v) containing AIBN (5×10^{-2} M) was equilibrated with the reference solution containing also an excess of α-TOH in the same solvent at 30 °C. After equilibration, a concentrated solution of the antioxidant was injected into the sample flask (final concentration from 5×10^{-6} to 5×10^{-5} M), and the oxygen consumption in the sample was measured. From the slope of the oxygen consumption during the inhibited period, k_{inh} values were obtained as previously reported,[4] while the *n* coefficient was determined from the length of the inhibited period using α-TOH (*n*=2) as a reference.

Calculations. DFT calculations were carried out using the Gaussian03 system of programs.[5] Gas phase geometries were optimized at the B3LYP/LANL2DZ level,[6-8] with added diffuse and polarization basis function, i.e B3LYP/LANL2DZdp level.[9] The nature of the located stationary points was determined by computation of harmonic vibrational frequencies (zero imaginary frequency). Enthalpies at 298 K were computed at the stationary points from frequency calculations, after scaling the results by a factor of 0.9809.[10]

Preliminary evaluation of the GPx-like activity. **108** (30- 150 μM final concentration) was incubated with 5 mM GSH in the presence of 2 mM H_2O_2 in 0.1 M phosphate buffer (pH 7.4). At 0, 5, 15 and 30 min aliquots of the reaction mixture were checked for the amount of GSH according to the Ellman's method.[11] In other experiments the reaction was run:i) in the absence of **108**; ii) in the presence of 150 μM diphenyldiselenide or selenocystine instead of **108**.

(*S*)-1-((*R*)-3,4-Dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl dioleate (122)



To a stirred solution of L-ascorbic acid (1 g, 25.6 mmol) in MeCN (10 mL) under inert atmosphere Et_3N (0.94 mL, 6.75 mmol) was added. After 10 min oleoyl chloride (2.27 mL, 6.85 mmol) was dropwise added and the reaction mixture was stirred for 3 h. Then, the organic phase was extracted with Et_2O, washed with H_2O, brine, dried over Na_2SO_4. The solvent was eliminated under reduced pressure and the crude material purified on silica gel (Et_2O/EtOAc 1:1) yielding **122** (32%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84-0.91 (6H, m), 1.21-1.40 (40H, m), 1.53-1.79 (4H, m), 1.92-2.11 (8H, m), 2.37 (2H, t, *J*=7.0 Hz), 2.60 (2H, t, *J*=7.6 Hz), 4.20-4.43 (3H, m), 4.82 (1H, d, *J*=2.2 Hz), 5.31-5.37 (4H, ap. t) ppm.

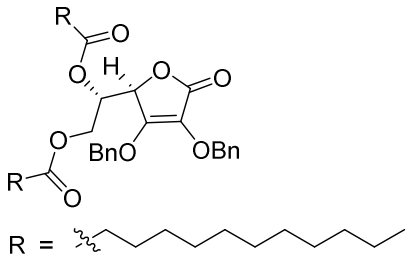
^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.6, 24.8, 27.1, 27.2, 28.7, 28.8, 28.9, 29.0, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.8, 32.4, 33.7, 34.0, 64.6, 68.1, 75.3, 115.3, 129.7, 130.0, 130.1, 155.3, 166.1, 173.9, 174.2 ppm.

MS (ESI, positive) *m/z*: 702 [M-H$^-$]

Synthesis of ascorbyl 5-O-,6-O-dialkanoates protected as 2,3-dibenzylethers. General procedure.

4-DMAP (12 mmol, 3 eq.) and DCC (12 mmol, 3 eq.) were added to a stirred solution of (*R*)-3,4-bis(benzyloxy)-5-((*S*)-1,2-dihydroxyethyl)furan-2(5*H*)-one **123** (4 mmol, 1 eq.) in MeCN (40 mL) under inert atmosphere. alkanoyl chloride (9.2 mmol, 2.3 eq.) was slowly added and the mixture was stirred for 12 h. Afterwards the solvent was removed under reduced pressure and the crude material purified by flash chromatography (petroleum ether/EtOAc 8:1).

(*S*)-1-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl didodecanoate (125a)



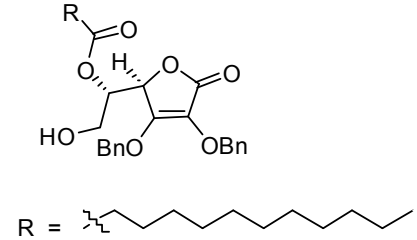
Following the general procedure, **123** (1.41 g, 3.95 mmol) and dodecanoyl chloride (1.981 g, 9.1 mmol) gave after flash chromatography, **125a** (2.59 g, 91%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84-0.90 (6H, m), 1.24 (32H, m), 1.48-1.53 (4H, m), 2.14-2.26 (4H, m), 3.83 (2H, ap d, ls=6.2 Hz, CH_2O), 4.90 (1H, d, *J*=1.8 Hz, CHO), 5.10 (2H, ap s, C**H**$_2$Ph), 5.17 (2H, m, C**H**$_2$Ph), 5.18-5.23 (1H, m, C**H**CH_2), 7.17-7.28 (2H, m), 7.33-7.41 (8H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.7, 24.8, 25.0, 29.1, 29.3, 29.4, 29.6, 31.9, 34.0, 61.9, 67.5, 73.8, 121.6, 128.0, 128.7, 128.8, 128.9, 135.2, 136.0, 155.1, 168.5, 172.2, 173.0 ppm.

MS (ESI positive) *m/z* (%): 744 $[M+Na]^+$

(*S*)-1-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl didecanoate (125b)



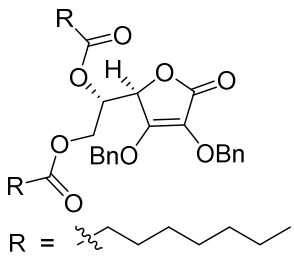
Following the general procedure, **123** (1.0 g, 2.80 mmol) and decanoyl chloride (1.22 g, 6.44 mmol) gave after flash chromatography, **125b** (1.64 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84-0.90 (6H, m), 1.25 (24H, m), 1.52-1.66 (4H, m), 2.13-2.22 (2H, m), 2.22-2.33 (2H, m), 4.22 (1H, dd, *J*=7.0, 11.7 Hz, CH_2O), 4.32 (1H, dd, *J*=5.9, 11.7Hz, CH_2O), 4.80 (1H, d, *J*=2.0 Hz, CHO), 5.10 (2H, ap s, C**H**$_2$Ph), 5.15 (2H, ap d, ls=1.6 Hz , C**H**$_2$Ph), 5.35-5.39 (1H, m, C**H**CH_2), 7.21-7.23 (2H, m), 7.33-7.39 (8H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 22.3, 24.3, 24.5, 24.7, 25.2, 28.8, 28.9, 29.1, 31.6, 33.6, 34.6, 55.3, 61.6, 67.2, 73.3, 73.5, 121.2, 127.7, 128.3, 128.4, 134.9, 135.7, 154.7, 168.1, 171.7, 172.5 ppm.

MS (ESI positive) *m/z* (%): 687 $[M+Na]^+$

(*S*)-1-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl dioctanoate (125c)



Following the general procedure, **123** (1.0 g, 2.80 mmol) and decanoyl chloride (1043 g, 6.44 mmol) gave after flash chromatography, **125c** (1.53 g, 90%).

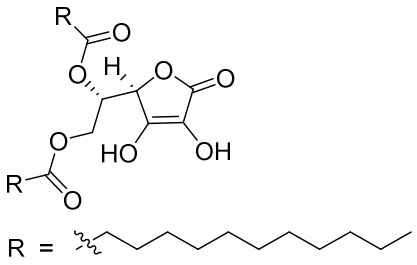
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.82-0.89 (6H, m), 1.18-1.27 (16H, m), 1.43-1.54 (4H, m), 2.16-2.37 (4H, m), 4.22 (1H, dd, *J*=7.4, 11.6 Hz, C**H**$_a$H$_b$O), 4.33 (1H, dd, *J*=5.6, 11.6 Hz, CH$_a$**H**$_b$O) 4.80 (1H, d, *J*=2.2 Hz, CHO), 5.10 (2H, ap. s, C**H**$_2$Ph), 5.15 (2H, ap. s, C**H**$_2$Ph), 5.34-5.42 (1H, m), 7.19-7.25 (4H, m), 7.27-7.42 (6H, m) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.6, 24.7, 24.8, 28.7, 28.8, 28.9, 31.5, 33.8, 61.8, 67.3, 73.6, 121.2,135.0, 135.9, 154.9, 168.3, 172.1, 172.8 ppm.

Cleavage of benzyl ether of 125. General procedure.

To a solution of ascorbyl 5-O-,6-O-dialkanoate-2,3-dibenzyl ether **125** (3.0 mmol) in ethyl acetate (30 mL), Pd/C (10%) was added. Then H_2 was added by placing a balloon on the flask and the reaction was stirred for 2 h. Afterwards, the mixture was filtered through celite and the solvent was removed under reduced pressure. Crystallization from diethyl ether/petroleum ether gave ascorbyl 5-O-,6-O-dialkanoate **126** in quantitative yield.

(*S*)-1-((*R*)-3,4-Dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl didodecanoate (126a)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (6H, t, *J*=6.8 Hz), 1.26 (32H, m), 1.54-1.65 (4H, m), 2.29-2.34 (4H, m), 4.31 (1H, dd, *J*=6.6, 11.7 Hz, C**H**$_a$H$_b$O), 4.41 (1H, dd, *J*=4.8, 11.7 Hz, CH$_a$**H**$_b$O), 4.90 (1H, d, *J*=3.1 Hz, CHO), 5.38-5.43 (1H, m, C**H**CH$_2$) ppm.

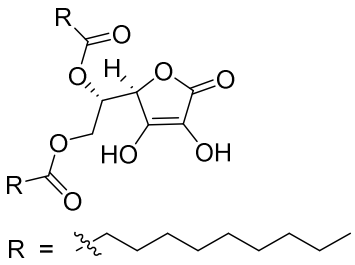
^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.6, 24.7, 28.9, 29.0, 29.2, 29.4, 29.5, 31.8, 33.8, 33.9, 62.1, 68.1, 74.7, 118.8, 151.4, 171.5, 173.0, 173.8 ppm.

MS (ESI negative) *m/z* (%): 539 $[M-H]^-$.

IR [$CDCl_3$] υ (cm^{-1}): 3300-3500, 2800-2950, 1770, 1690, 1100-1190.

Elemental Analysis: $C_{30}H_{52}O_8$ C 64,64%, H 9.69%. Found C 64.32%, H 9.59%.

(*S*)-1-((*R*)-3,4-Dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl didecanoate (126b)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (6H, t, *J*= 6.6 Hz), 1.26 (24H, m), 1.51-1.68 (4H, m), 2.29-2.38 (4H, m), 4.30 (1H, dd, *J*= 6.8, 11.6 Hz, C**H**$_a$H$_b$O), 4.42 (1H, dd, *J*=4.8, 11.6 Hz, CH$_a$**H**$_b$O), 4.92 (1H, d, *J*=3.6 Hz, CHO), 5.41-5.45 (1H, m, C**H**CH$_2$) ppm.

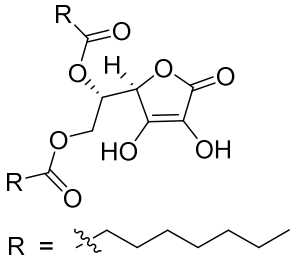
^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.6, 24.7, 28.9, 29.0, 29.1, 29.3, 31.7, 33.9, 34.0, 62.1, 68.1, 74.8, 119.1, 150.9, 171.5, 173.1, 173.9 ppm.

MS (ESI negative) *m/z* (%): 483 $[M-H]^-$

IR [$CDCl_3$] υ (cm^{-1}): 3350-3400, 3100-3200, 2800-2950, 1550, 1690, 1620, 1100-1200.

Elemental Analysis: $C_{26}H_{44}O_8$ C 64,44%, H 9.15%. Found: C 64.09%, H 9.25%.

(*S*)-1-((*R*)-3,4-Dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl dioctanoate (126c)



^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84-0.90 (6H, m), 1.22-1.29 (16H, m), 1.51-1.67 (4H, m), 2.28-2.36 (4H, m), 4.29 (1H, dd, *J*=6.6, 11.8 Hz, C**H$_a$**H$_b$O), 4.42 (1H, dd, *J*=4.8, 12.0 Hz, CH$_a$**H$_b$**O), 4.91 (1H, d, *J*=3.4 Hz, CHO), 5.38-5.46 (1H, m, CHO) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.7, 24.8, 28.8, 28.9, 29.0, 31.5, 34.0, 62.0, 68.2, 74.6, 119.5, 148.9, 170.1, 172.9, 173.7 ppm.

Elemental Analysis: $C_{22}H_{36}O_8$ C 61,66%, H 8.47%. Found: C 61,59%, H 8.50%.

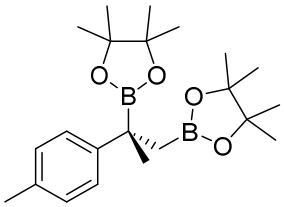
GP1 - General procedures for lithiation/borylation of secondary benzylic and allylic carbamates

To a vigorously stirred solution of secondary carbamate **141** (1.5 equiv) and TMEDA (1.5 equiv) in anhydrous diethyl ether (0.33 M) at −78 °C under a nitrogen atmosphere, was added sBuLi (1.3 M in hexane, 1.45 equiv) dropwise. After 15 min, a solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane **140a** (1.0 equiv) in diethyl ether (0.5 M) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h and then a 1.0 M solution of $MgBr_2$ in anhydrous MeOH (1.7 equiv) was added slowly at −78 °C. After 5 min, the cooling bath was removed and stirring was continued at room temperature overnight (16 h). Afterwards the reaction was diluted with water and extracted with Et_2O (3 ×). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the crude material purified by flash chromatography.

GP2 - General procedures for lithiation/borylation of primary carbamates and 2,4,6-Triisopropylbenzoates

A solution of a primary carbamate **141** or 2,4,6-Triisopropylbenzoate **143** (1.0 equiv) and TMEDA, (+)-sparteine or (-)-sparteine (1.1 equiv) in anhydrous diethyl ether (0.33 M) was cooled to −78 °C. sBuLi (1.1 equiv) was added dropwise and the reaction mixture was stirred at this temperature for 5 h. A solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane **140a** (1.3 equiv) in anhydrous diethyl ether (0.75 M) was added dropwise and the mixture was stirred for 1 h at −78 °C. Afterwards, the cooling bath was removed and the reaction mixture was heated at 40^0C overnight (16 h). The reaction mixture was cooled to room temperature, diluted with water and extracted with Et_2O (3 ×). The combined organic phases were washed with 1 M HCl solution, brine and dried over $MgSO_4$. The solvent was removed in vacuo and the crude material purified by flash chromatography.

(*S*)-2,2'-(2-(p-tolyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (142c)



Following **GP1** with **(*S*)-141c** (0.63 mmol, 166 mg, 99:1 er) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.42 mmol, 112 mg) gave **(*S*)-142c** as a white solid (68%, 110 mg, 98:2 er). R_f = 0.2 (Pentane/Diethyl ether 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (1H, d, *J*=15.6 Hz), 1.19 (6H, s), 1.21 (7H, s), 1.23 (11H, s), 1.48 (1H, d, *J*=15.6 Hz), 2.30 (3H, s), 7.07 (2H, d, *J*=8.2 Hz), 7.28 (2H, d, *J*=8.2 Hz) ppm.

^{13}C NMR (76 MHz, $CDCl_3$): δ = 20.9 (CH_3), 22.0, 24.5 (CH_3), 24.6 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 25.2 (CH_3), 26.8, 83.0 (C), 83.3 (C), 126.4 (CH), 128.7 (CH), 134.1 (C), 146.3 (C) ppm.

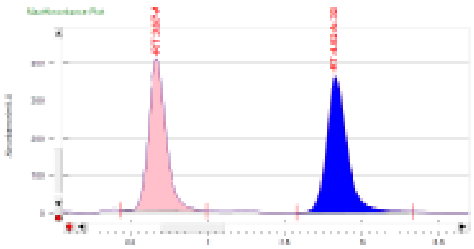
^{11}B NMR (96 MHz; $CDCl_3$): δ = 33.1 ppm.

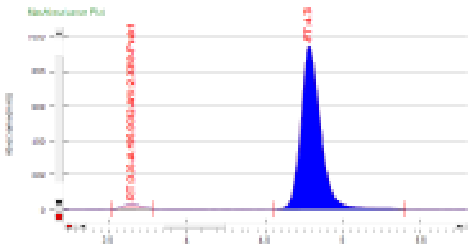
IR (film): υ (cm^{-1}) 2977, 2927, 1511, 1462, 1348, 1308, 1142, 969, 845, 672.

HRMS (CI): calcd. for $C_{22}H_{36}B_2NaO_4$ $[M+Na]^+$ 409.2700, found 409.2713.

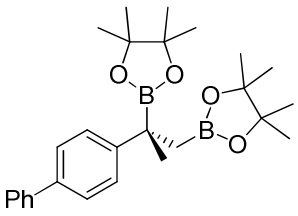
$[\alpha]_D^{24} = -13$ (*c* 1, $CHCl_3$).

Chiral SFC: Whelk-01, 125 bar, 42°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 3.65 min (minor), 4.78 min (major), er 98:2.





(*S*)-2,2'-(2-((1,1'-biphenyl)-4-yl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2 dioxaborolane) (142d)



Following **GP1** (modified using MTBE as solvent, without TMEDA and performing the reaction at -96^{0}C) with **(*S*)-141d** (0.63 mmol, 205 mg, 98:2 er) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.42 mmol, 112 mg) gave **(*S*)-142d** as a white solid (67%, 126 mg, 95:5 er). R_f = 0.38 (Pentane/Diethyl ether 6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18-1.23 (25H, m), 1.46 (3H, s), 1.53 (1H, d, *J*=15.7 Hz), 7.31 (1, ap t, *J*=7.6 Hz), 7.42 (2H, ap t, *J*=7.6 Hz), 7.46-7.48 (2H, m), 7.51-7.53 (2H, m), 7.60 (2H, ap d, *J*=8.3Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (CH_3), 24.6 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 25.1 (CH_3), 83.0 (C), 83.3 (C), 126.5 (CH), 126.7 (CH), 126.8 (CH), 126.9 (CH), 137.5 (C), 141.2 (C), 148.4 (C) ppm, *carbons attached to boron not observed*.

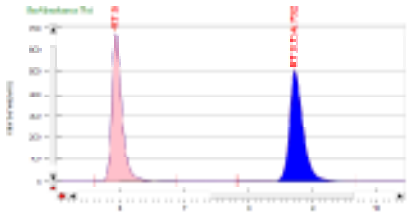
^{11}B NMR (128 MHz; $CDCl_3$): δ = 34.8 ppm.

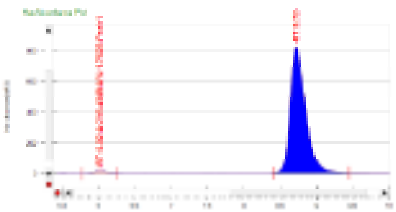
IR (film): υ (cm^{-1}) 2977, 2928, 1487, 1466, 1358, 1347, 1311, 1143.

HRMS (ESI) calcd. for $C_{27}H_{38}B_2NaO_4$ $[M+Na]^+$ 471.2858, found 471.2846.

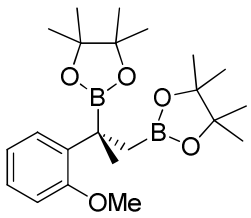
$[\alpha]_D^{25}$ = −22 (*c* 1, $CHCl_3$).

Chiral SFC: Whelk-01, 125 bar, 40°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 11.87 min (minor), 17.54 min (major), er 95:5.





(*S*)-2,2'-(2-(2-methoxyphenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (142f)



Following **GP1** with **(*S*)-141f** (0.63 mmol, 176 mg, >99:1 er) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.42 mmol, 112 mg) gave **(*S*)-142f** as a white solid (45%, 76 mg, >99:1 er). R_f = 0.49 (Pentane/diethyl ether 3:2 1% Et_3N).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (6H, s), 1.16 (6H, s),. 1.23 (13H, s), 1.29 (1H, d, *J*=14.7 Hz), 1.41 (3H, s), 3.79 (3H, s), 6.77 (2H, dd, *J*=1.2, 8.1 Hz), 6.87-6.91 (1H, m), 7.08-7.13 (1H, m), 7.29 (1H, dd, *J*=1.6, 7.7 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 54.8 (CH_3), 82.5 (C), 82.8 (C), 109.6 (CH), 120.5 (CH), 125.9 (CH), 126.1 (CH), 138.0 (C), 156.6 (C) ppm, *carbons attached to boron not observed*.

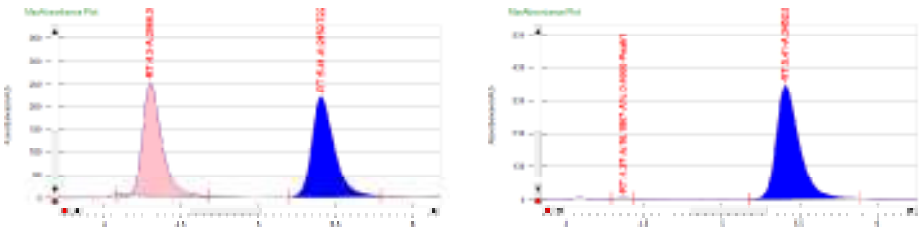
^{11}B NMR (128 MHz; $CDCl_3$): δ = 35.0 ppm.

IR (film): υ (cm^{-1}) 2976, 2931, 1607, 1615, 1488, 1463, 1347, 1323, 1239, 1144.

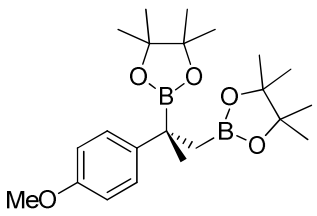
HRMS (ESI) calcd. for $C_{22}H_{37}B_2O_5$ $[M+H]^+$ 403.2830, found 403.2844.

$[\alpha]_D^{26} = -27$ (*c* 1, $CHCl_3$).

Chiral SFC: Whelk-01, 125 bar, 40°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 4.37 min (minor), 5.41 min (major), er >99:1.



(*S*)-2,2'-(2-(4-methoxyphenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (142a)



Following **GP1** with **141a** (0.63 mmol, 176 mg, >99:1 er) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.42 mmol, 112 mg) gave **(*S*)-142a** as a white solid (81%, 137 mg, 98:2 er). R_f = 0.39 (Pentane/Diethyl ether 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (1H, d, *J*=15.7 Hz), 1.18 (6H, s), 1.19 (6H, s), 1.21 (12H, s), 1.37 (3H, s), 1.45 (1H, d, *J*=15.5 Hz), 3.77 (3H, s), 6.81 (2H, ap d, *J*=8.8 Hz), 7.30 (2H, ap d, *J*=8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4 (CH_3), 24.5 (CH_3), 24.7 (CH_3), 24.9 (CH_3), 25.1 (CH_3), 55.1 (CH_3), 82.9 (C), 83.2 (C), 113.2 (CH), 127.3 (CH), 141.3 (C), 156.9 (C) ppm, *carbons attached to boron not observed*.

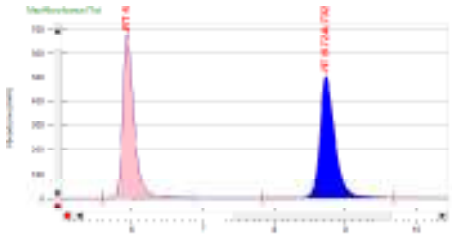
^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.3 ppm.

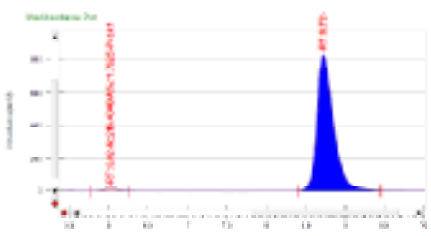
IR (film): υ (cm^{-1}) 2977, 2931, 1614, 1510, 1378, 1349, 1308, 1247, 1142.

HRMS (ESI) calcd. for $C_{22}H_{36}B_2NaO_5$ $[M+Na]^+$ 425.2649, found 425.2646.

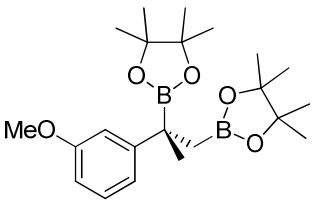
$[\alpha]_D^{26} = -9$ (*c* 1, $CHCl_3$).

Chiral SFC: Whelk-01, 125 bar, 42°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 6.02 min (minor), 8.72 min (major), er 98:2.





(*S*)-2,2'-(2-(3-methoxyphenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (142f)



Following **GP1** with **(*S*)-141f** (0.63 mmol, 176 mg, 87:13 er) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.42 mmol, 112 mg) gave **(*S*)-142f** as a white solid (62%, 105 mg, 87:13 er). R_f = 0.44 (Pentane/Diethyl ether 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (1H, d, *J*=15.6 Hz), 1.19 (6H, s), 1.21 (6H, s), 1.21 (6H, s), 1.22 (6H, s), 1.39 (3H, s), 1.47 (1H, d, *J*=15.6 Hz), 3.78 (3H, s), 6.66 (1H, dd, *J*=2.3, 8.0 Hz), 6.95-6.99 (2H, m), 7.17 (1H, t, *J*=8.0 Hz) ppm.

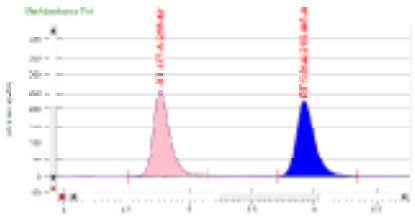
^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 24.4 (CH_3), 24.5 (CH_3), 24.7 (CH_3), 24.9 (CH_3), 25.1 (CH_3), 27.4, 55.0 (CH_3), 82.9 (C), 83.2 (C), 110.3 (CH), 112.1 (CH), 119.0 (CH), 128.7 (CH), 151.0 (C), 159.3 (C) ppm.

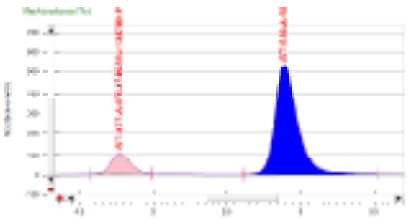
^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.6 ppm.

IR (film): υ (cm^{-1}) 2977, 1607, 1586, 1465, 1346, 1215, 1144, 969, 848.

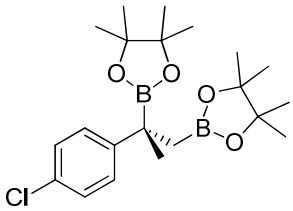
$[\alpha]_D^{22}$ = -6 (*c* 1, $CHCl_3$).

Chiral SFC: Whelk-01, 125 bar, 42°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 4.77 min (minor), 5.89 min (major), er 87:13.





(*S*)-2,2'-(2-(4-chlorophenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (142g)



Following **GP1** (modified without using TMEDA) with **(*S*)-141g** (0.63 mmol, 179 mg, 99:1 er) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.42 mmol, 112 mg) gave **(*S*)-142g** as a white solid (73%, 125 mg, 98:2 er). R_f = 0.45 (Pentane/Diethyl ether 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (1H, d, *J*=15.6 Hz), 1.17-1.24 (24H, m), 1.37 (3H, s), 1.42 (1H, d, *J*=15.6 Hz), 1.45 (1H, d, *J*=15.6 Hz), 7.21 (2H, ap d, *J*=8.6 Hz), 7.31 (2H, ap d, *J*=8.6 Hz). ppm

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 24.4 (CH_3), 24.5 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 25.0 (CH_3), 27.0, 83.0 (C), 83.4 (C), 127.8 (CH), 127.9 (CH), 130.5 (C), 147.7 (C) ppm.

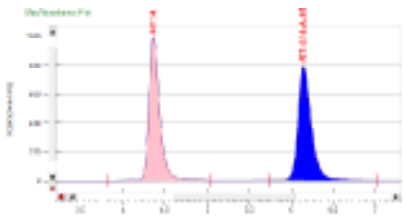
^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.1 ppm.

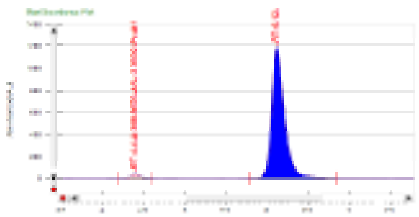
IR (film): υ (cm^{-1}) 2978, 2928, 1490, 1471, 1379, 1342, 1313, 1136, 1008, 968, 838, 713.

HRMS (ESI) calcd. for C21H34B2ClO4 $[M+H]^+$, 407.2334, found 407.2329.

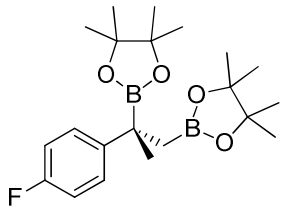
$[\alpha]_D^{26}$ = -6 (*c* 1, $CHCl_3$).

Chiral SFC: Whelk-01, 125 bar, 40°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 4.40 min (minor), 6.12 min (major), er 98:2.





(*S*)-2,2'-(2-(4-fluorophenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (142h)



Following **GP1** (modified without using TMEDA) with **(*S*)-141h** (0.63 mmol, 168 mg, 99:1 er) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.42 mmol, 112 mg) gave **(*S*)-142h** as a white solid (75%, 123 mg, 99:1 er). R_f = 0.38 (Pentane/Diethyl ether 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (1H, d, *J*=15.6 Hz), 1.17 (6H, s), 1.19 (18H, bs), 1.38 (3H, s), 1.45 (1H, d, *J*=15.6 Hz), 6.93 (2H, ap t, *J*=8.8 Hz), 7.33 (2H, ap dd, *J*=5.6, 8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (CH_3), 23.5 (CH_3), 23.7 (CH_3), 23.8 (CH_3), 24.0 (CH_3), 82.0 (C), 82.3 (C), 113.4 (CH, d, $^{2}J_{C\text{-}F}$=20.7 Hz), 126.9 (CH, d, $^{3}J_{C\text{-}F}$ 7.6), 143.7 (C), 159.6 (C, d, $^{1}J_{C\text{-}F}$ 242.4) ppm, *carbons attached to boron not detected.*

^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.8 ppm.

^{19}F NMR (376 MHz; $CDCl_3$): δ = 119.4-119.5 (m) ppm.

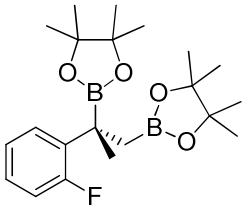
IR (film): υ (cm^{-1}) 2978, 2931, 1605, 1508, 1371, 1314, 1143, 968, 846.

HRMS (ESI) calcd. for $C_{21}H_{34}B_2FO_4$ $[M+H]^+$ 391.2629, found 391.2632.

$[\alpha]_D^{26}$ = -6 (*c* 1, $CHCl_3$).

Chiral SFC: Whelk-01, 125 bar, 40°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 3.02 min (major), 3.68 min (minor), er > 99:1

(*S*)-2,2'-(2-(2-fluorophenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (142i)



Following **GP1** (modified without using TMEDA) with **(*S*)-142i** (0.63 mmol, 168 mg, 99:1 er) and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.42 mmol, 112 mg) gave **(*S*)-141i** as a white solid (46%, 75 mg, 99:1 er). R_f = 0.49 (Pentane/Diethyl ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (6H, s), 1.17 (6H, bs), 1.24 (12H, s), 1.28 (2H, ap s), 1.42 (3H, s), 6.94 (1H, ap ddd, *J*=1.4, 7.9, 11.4 Hz), 7.03-7.13 (2H, m), 7.34 (1H, ap td, *J*=1.9, 7.9 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 23.2 (CH_3), 23.7 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 24.7 (CH_3), 24.9, 82.8 (C), 83.4 (C), 114.8 (CH, d, $J_{C\text{-}F}$= 23.1 Hz), 123.8 (CH, d, $J_{C\text{-}F}$= 3.2 Hz), 126.6 (CH, d, $J_{C\text{-}F}$= 8.6 Hz), 127.1 (CH, d, $J_{C\text{-}F}$= 5.4 Hz), 136.6 (C, d, $^{2}J_{C\text{-}F}$= 14.1 Hz), 161.1 (C, d, $^{1}J_{C\text{-}F}$= 243.9 Hz) ppm.

^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.7 ppm.

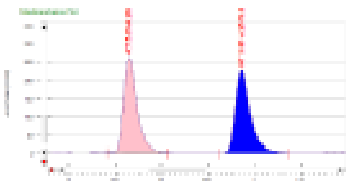
^{19}F NMR (376 MHz; $CDCl_3$): δ = 112.0 (dt, *J*=5.6, 11.4 Hz) ppm.

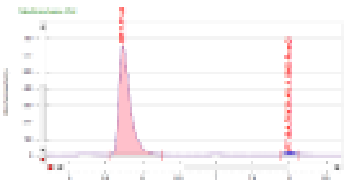
IR (film): υ (cm^{-1}) 2977, 2931, 1449, 1371, 1352, 1144, 968, 845, 754.

HRMS (ESI) calcd. for $C_{21}H_{33}B_2FNaO_4$ $[M+Na]^+$ 413.2449, found 413.2451.

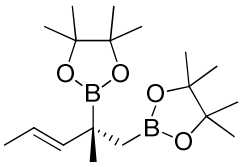
$[\alpha]_D^{26}$ = -11 (*c* 1, $CHCl_3$).

Chiral SFC: Chiralcel IA , 125 bar, 42°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 5.73 min (major), 8.00 min (minor), er 99:1.





(*S*,*E*)-2,2'-(2-methylpent-3-ene-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (142l)



Following **GP2** with **(*S*,*E*)-141l** (0.63 mmol, 134 mg, >99:1 er), TMEDA (0.69 mmol, 162 mg), and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane gave **(*S*,*E*)-142l** (0.82 mmol, 219 mg) as a colourless oil (73%, 200 mg, 99:1 er). R_f = 0.25 (Pentane/Diethyl ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (1H, d, *J* = 15.6 Hz). 1.04 (1H, d, *J*=15.6 Hz), 1.07 (3H, s), 1.21 (12H, s), 1.23 (12H, s), 1.64 (3H, dd, *J*=1.6, 6.3 Hz), 5.31 (1H, dq, *J*=6.3, 15.4 Hz), 5.54 (1H, dq, *J*=1.6, 15.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3 (CH_3), 21.4, 23.8 (CH_3), 24.5 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 25.0 (CH_3), 82.8 (C), 83.0 (C), 120.3 (CH), 140.0 (CH) ppm.

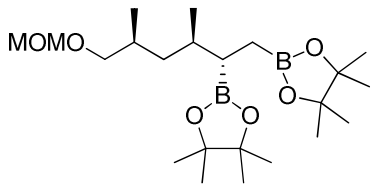
^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.4 ppm.

IR (film): υ (cm^{-1}) 2978, 2930, 2869, 1734, 1457, 1356, 1308, 1140, 969, 848, 674.

HRMS (ESI) calcd. for $C_{18}H_{34}B_2NaO_4$ $[M+Na]^+$359.2542, found 359.2539.

$[\alpha]_D^{26}$ = +6 (*c* 1, $CHCl_3$).

2,2'-((2*S*,3*R*,5*S*)-6-(methoxymethoxy)-3,5-dimethylhexane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ((2*S*)-142m)



Following **GP2** with **(2*R*,4*S*)-141m** (0.33 mmol, 100 mg), (+)-sparteine (0.36 mmol, 85 mg), and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.43 mmol, 115 mg) gave **(2*S*)-142m** as a colourless oil (69%, 126 mg, >20:1 dr). R_f = 0.55 (Pentane/Diethyl ether 5:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70 (1H, dd, *J*=9.4, 15.7 Hz), 0.89 (3H, d, *J*=6.8 Hz), 0.93 (3H, d, *J*=6.7 Hz), 0.96-1.06 (1H, m), 1.15 (1H, dt, *J*=5.1, 9.9 Hz), 1.25 (24H, bs, overlapped with 1H, m), 1.34-1.42 (1H, m), 1.58-1.65 (1H, m), 1.78-1.86 (1H, m), 3.19 (1H, dd, *J*=7.5, 9.3 Hz), 3.34 (3H, s), 3.44 (1H, dd, *J*=4.6, 9.3 Hz), 4.59 (2H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.2, 18.2 (CH_3), 18.6 (CH_3), 24.1, 24.7 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 30.9 (CH), 33.9 (CH), 34.4 (CH_2), 40.5 (CH_2), 55.0 (CH_3), 73.2 (CH_2), 82.7 (C), 82.7 (C), 96.4 (CH_2) ppm.

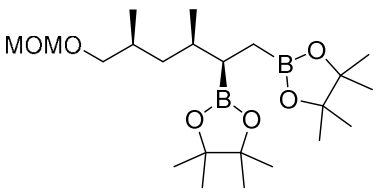
^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.5 ppm.

IR (film): υ (cm^{-1}) 2977, 2928, 2878, 1370, 1309, 1141, 1047, 968, 846.

HRMS (ESI) calcd. for $C_{22}H_{44}B_2NaO_6$ $[M+Na]^+$449.3224, found 449.3231.

$[\alpha]_D^{26}$ = +3 (*c* 1, $CHCl_3$).

2,2'-((2*R*,3*R*,5*S*)-6-(methoxymethoxy)-3,5-dimethylhexane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ((2*R*)-142m)



Following **GP2** with **(2*R*,4*S*)-141m** (0.33 mmol, 100 mg), (-)-sparteine (0.36 mmol, 85 mg), and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.43 mmol, 115 mg) gave **(2*R*)-142m** as a colourless oil (31%, 57 mg, >20:1 dr). R_f = 0.55 (Pentane/Diethyl ether 5:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (1H, dd, *J*=4.6, 16.0 Hz), 0.78-0.83 (1H, m), 0.86 (3H, d, *J*=6.8 Hz), 0.94 (3H, d, *J*=6.6 Hz, overlapped with 1H, m), 1.13 (1H, dt, *J*=4.4, 11.9 Hz), 1.22 (12H, s), 1.23 (12H, s), 1.35-1.40 (1H, m), 1.71-1.78 (2H, m), 3.21 (1H, dd, *J*=7.4, 9.3 Hz), 3.34 (3H, s), 3.44 (1H, *J*=4.7, 9.3 Hz), 4.60 (2H, s) ppm.

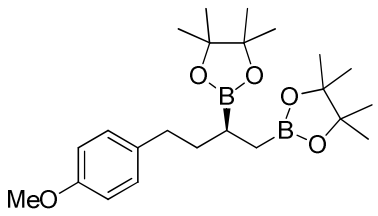
^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4 (CH_3), 18.6 (CH_3), 24.7 (CH_3), 24.7 (CH_3), 24.9 (CH_3), 25.0 (CH_3), 31.1 (CH), 32.5 (CH), 39.3 (CH_2), 55.0 (CH_3), 73.2 (CH_2), 82.7 (C), 82.8 (C), 96.5 (CH_2) ppm, *carbons attached to boron not observed*.

^{11}B NMR (128 MHz; $CDCl_3$): δ = 34.0 ppm.

IR (film): υ (cm^{-1}) 2975, 2901, 1406, 1379, 1310, 1142, 1066, 1050, 892.

$[\alpha]_D^{23}$ = +12 (*c* 1, $CHCl_3$).

(*S*)-2,2'-(4-(4-methoxyphenyl)butane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (142o)



Following **GP2** with **143a** (0.63 mmol, 250 mg), (+)-sparteine (0.69 mmol, 162 mg), and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.82 mmol, 219 mg) gave **(*S*)-142o** as a colourless oil (71%, 242 mg, 97:3 er). R_f = 0.54 (Pentane/Diethyl ether 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (1H, dd, *J*=5.9, 15.7 Hz), 0.93 (1H, dd, *J*=9.4, 15.7 Hz), 1.15-1.21 (1H, m), 1.23 (12H, s), 1.25 (12H, s), 1.53-1.67 (1H, m), 1.68-1.81 (1H, m), 2.55 (2H, t, *J*=8.2 Hz), 3.77 (3H, s), 6.80 (2H, ap d, *J*=8.8 Hz), 7.09 (2H, ap d, *J*=8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 18.3, 24.8 (CH_3), 24.9 (CH_3), 24.9 (CH_3), 34.4 (CH_2), 36.2 (CH_2), 55.2 (CH_3), 82.8 (C), 113.6 (CH), 129.2 (CH), 135.4 (C), 157.5 (C) ppm.

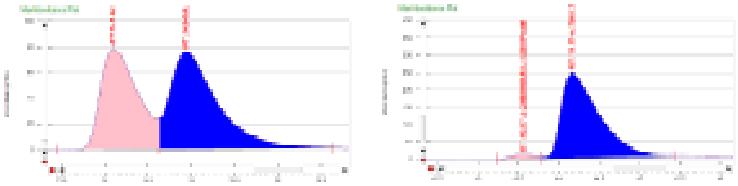
^{11}B NMR (128 MHz; $CDCl_3$): δ = 34.4 ppm.

IR (film): υ (cm^{-1}) 2977, 2929, 1614, 1512, 1370, 1311, 1244, 1140, 967, 845, 824, 671.

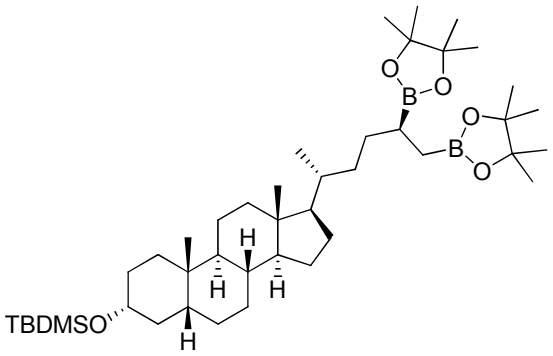
HRMS (ESI) calcd. for $C_{23}H_{38}B_2NaO_5$ $[M+Na]^+$439.2806, found 439.2802.

$[\alpha]_D^{26}$ = -7 (*c* 1, $CHCl_3$).

Chiral SFC: Chiralcel IB , 125 bar, 42°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 13.57 min (minor), 14.17 min (major), er 97:3.



((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-17-((2*R*,5*S*)-5,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)(tert-butyl)dimethylsilane (142p)



Following **GP2** with **143b** (0.33 mmol, 233 mg), (+)-sparteine (0.36 mmol, 85 mg), and bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (0.43 mmol, 115 mg) gave **142p** as a colourless oil (73%, 228 mg, >20:1 dr). R_f = 0.39 (Pentane/Diethyl ether 5:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (6H, s), 0.61 (3H, s), 0.80 (1H, dd, *J*=6.1, 15.7 Hz), 0.89 (16H, ap s), 1.01-1.15 (8H, m), 1.23 (24H, s), 1.29-1.43 (12H, m), 1.52-1.57 (3H, m), 1.73-1.86 (5H, m), 1.94 (1H, ap d, *J*=12.0 Hz), 3.55-3.62 (1H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.6, 12.0, 12.6, 18.3, 18.7, 18.8, 20.8, 23.4, 24.2, 24.7, 24.8, 24.9, 25.0, 26.0, 26.4, 27.3, 28.2, 30.2, 31.0, 34.6, 35.1, 35.6, 35.9, 36.0, 36.9, 40.1, 40.2, 42.3, 42.6, 56.1, 56.4, 72.8, 82.7, 82.7 ppm.

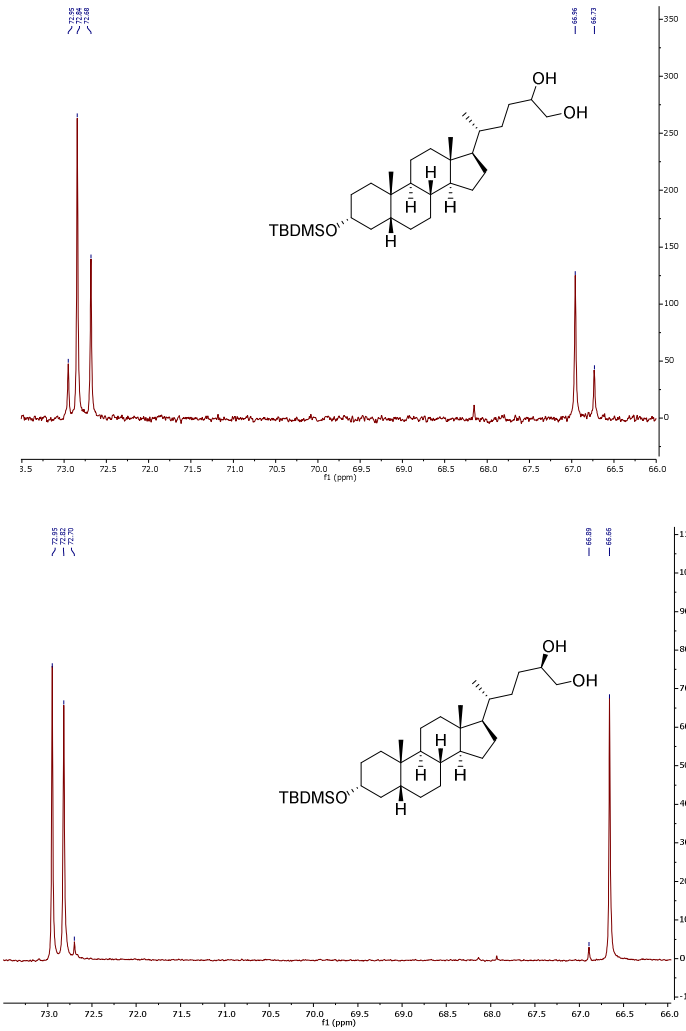
^{11}B NMR (128 MHz; $CDCl_3$): δ = 35.7 ppm.

IR (film): υ (cm^{-1}) 2975, 2927, 2863, 1463, 1449, 1370, 1311, 1250, 1142, 1094, 1079, 968, 870, 835, 774, 758, 668.

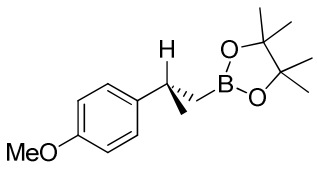
HRMS (ESI) calcd. for $C_{43}H_{84}B_2NO_5Si$ $[M+NH_4]^+$ 744.6314, found 744.6330.

$[\alpha]_D^{26}$ = -15 (*c* 1, $CHCl_3$).

dr determined by observing the CHOH, CHOTBDMS and CH_2OH of the ^{13}C NMR spectra of the diastereoenriched and of the mixture of diastereoisomers synthetized respectively using (+)-sparteine and TMEDA.



(*S*)-2-(2-(4-methoxyphenyl)propyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((*S*)-147)



The boronic ester **(*S*)-142a** (80 mg, 0.2 mmol, 1 equiv, 98:2 er) and tetra-n-butylammonium fluoride trihydrate (189 mg, 0.6 mmol, 3 equiv) were stirred in toluene at 90^{0}C for 2h. Afterwards the mixture was filtered on a short silica column, concentrated in vacuo and the residue subjected to flash chromatography to afford **(*S*)-147** (72%, 40 mg, 90:10 er). R_f = 0.28 (Pentane/diethyl ether 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (2H, ap t, *J*=6.8 Hz), 1.16 (12H, s), 1.24 (3H, d, *J*=6.9 Hz), 2.94-3.03 (1H, m), 3.78 (3H, s), 6.81 (2H, ap d, *J*=8.5 Hz), 7.15 (2H, ap d, *J*=8.5 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7 (CH_3), 24.8 (CH_3), 25.1 (CH_3), 35.0 (CH), 55.3 (CH_3), 83.0 (C), 113.5 (CH), 127.4 (CH), 141.5 (C), 157.6 (C) ppm, *carbons attached to boron not observed*.

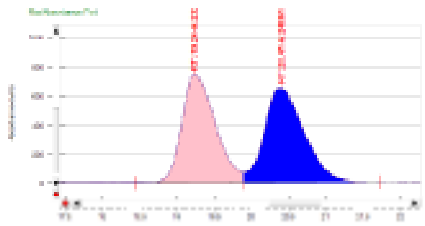
^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.0 ppm.

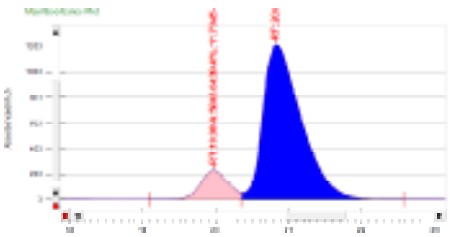
IR (film): υ (cm^{-1}) 2977, 2956, 2926, 2835, 1735, 1612, 1513, 1367, 1322, 1246, 1144, 1038, 969, 829.

HRMS (ESI) calcd. for $C_{16}H_{25}BNaO_3$ $[M+Na]^+$ 299.1792, found 299.1780.

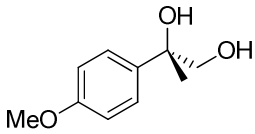
$[\alpha]_D^{26}$ = +18 (*c* 1, $CHCl_3$).

Chiral SFC: Whelk-01, 125 bar, 42°C, 2 mL/min, 10% co-solvent (10% IPA/Hexane); t_R: 19.98 min (minor), 20.82 min (major), er 88:12.





(*S*)-2-(4-methoxyphenyl)propane-1,2-diol ((*S*)-146)



A premixed solution of NaOH (2 M)/H_2O_2 (30% aq.) (2:1, 3 mL) was added dropwise to a solution of boronic ester **(*S*)-142a** (80 mg, 0.2 mmol, 98:2 er) in THF (2 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred at this temperature for 4 h. The reaction mixture was diluted with H_2O (2 mL) and Et_2O (2 mL). The phases were separated and the aqueous phase washed with Et_2O (3 × 2 mL). The combined organic phases were washed with H_2O (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography gave (*S*)-2-(4-methoxyphenyl)propane-1,2-diol (98%, 36 mg, 98:2 er). R_f = 0.29 (Ethyl acetate/Pentane 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (3H, s), 2.10 (2H, bs), 3.59 (1H, d, *J*=11.1 Hz), 3.75 (1H, d, *J*=11.1 Hz), 3.80 (3H, s), 6.89 (2H, ap d, *J*=8.8 Hz), 7.37 (2H, ap d, *J*=8.8 Hz) ppm.

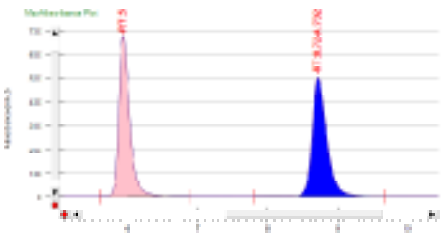
^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0 (CH_3), 55.3 (CH_3), 71.1 (CH_2), 74.5 (C), 113.7 (CH), 126.3 (CH), 137.0 (C), 158.7 (C) ppm.

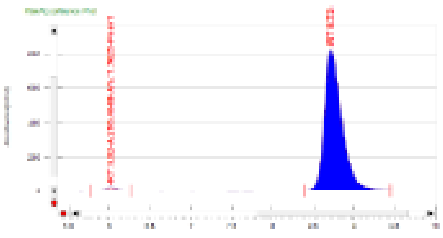
IR (film): υ (cm^{-1}) 3392, 2933, 1611, 1512, 1301, 1247, 1179, 1031, 831.

HRMS (ESI) calcd. for $C_{10}H_{14}NaO_3$ $[M+Na]^+$ 205.0835, found 205.0835.

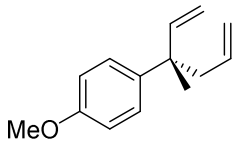
$[\alpha]_D^{26}$ = +6 (*c* 1, $CHCl_3$).

Chiral SFC: Whelk-01, 125 bar, 42°C, 4 mL/min, 10% co-solvent (50% IPA/Hexane); t_R: 6.02 min (minor), 8.72 min (major), er 98:2.





_(S)_-1-methoxy-4-(3-methylhexa-1,5-dien-3-yl)benzene ((_S_)-148)



To stirred neat tetravinyltin (36 µl, 0.2 mmol) under an atmosphere of nitrogen at ambient temperature, was added *n*butyl lithium (1.6 M in hexane, 0.5 ml, 0.8 mmol) dropwise and stirred for 30 min. Then the precipitate was washed with anhydrous hexane (~0.5 ml x3). Anhydrous THF (0.5 mL) was added to dissolve the precipitate and the resulting homogenous solution was taken up into a syringe and was added dropwise to a stirred solution of boronic ester (*S*)-2,2'-(2-(4-methoxyphenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (80 mg, 0.2 mmol) in anhydrous Et_2O (1 ml) under an atmosphere of nitrogen at −78 °C. The reaction mixture was stirred for 45 min at -78°C, then was warmed at ambient temperature and stirred for 20 min. The reaction mixture was cooled to −78 °C and a solution of iodine (203 mg, 0.8 mmol) in anhydrous THF (0.8 ml) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min and then a suspension of NaOMe (86 mg, 1.6 mmol) in MeOH (2 ml) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C and then allowed to reach ambient temperature and stirred for approximately 2 h. Sat. $Na_2S_2O_3$(aq) (5 ml) and water (2 ml) was added and the mixture stirred until the brown colour dissipated. The mixture was extracted with diethyl ether (3 × 10 ml), washed with NaOH (5 mL, 1M solution), KF (5 mL) and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo* to give *(S)*-1-methoxy-4-(3-methylhexa-1,5-dien-3-yl)benzene (77%, 32 mg) as a colourless oil. $\boldsymbol{R_f}$ = 0.6 (Pentane/diethyl ether 20:1).

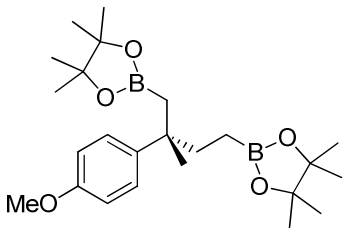
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (3H, s), 2.45-2.56 (2H, m), 3.80 (3H, s), 4.97-5.04 (2H, m), 5.03 (1H, dd, *J*=1.3, 17.5 Hz), 5.09 (1H, dd, *J*=1.3, 10.7 Hz), 5.61 (1H, ddt, *J*=7.4, 10.2, 17.3 Hz), 6.02 (1H, dd, *J*=10.7, 17.5 Hz), 6.85 (2H, ap d, *J*=8.5 Hz), 7.24 (2H, ap d, *J*=8.5 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (CH_3), 43.4 (C), 45.6 (CH_2), 55.2 (CH_3), 111.7 (CH_2), 113.4 (CH), 117.1 (CH_2), 127.7 (CH), 135.2 (CH), 139.0 (C), 146.8 (CH), 157.6 (C) ppm.

IR (film): υ (cm^{-1}) 2972, 2901, 1625, 1597, 1512, 1410, 1249, 1183, 1066, 1038, 913, 828.

$[\alpha]_D^{23}$ = +15 (*c* 1, $CHCl_3$).

(*R*)-2,2'-(2-(4-methoxyphenyl)-2-methylbutane-1,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ((*S*)-149)



A solution of boronic ester (*S*)-2,2'-(2-(4-methoxyphenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (80 mg, 0.2 mmol, 1.0 equiv) and bromochloromethane (155 mg, 78 µL, 1.2 mmol, 6.0 equiv) was dissolved in anhydrous Et_2O (0.2 M) under an atmosphere of nitrogen. The reaction mixture was cooled to –78 °C. nBuLi (1.6 M in hexanes, 5 equiv) was added dropwise to the reaction mixture at –78 °C. The reaction mixture was stirred for 20 min at –78 °C. The reaction mixture was removed from the cooling bath and stirred at room temperature for 1 h. Afterwards the reaction was diluted with water and extracted with Et_2O (3 ×). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the crude material purified by flash chromatography to afford (*R*)-2,2'-(2-(4-methoxyphenyl)-2-methylbutane-1,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (83%, 71 mg). $\boldsymbol{R_f}$ = 0.16 (Pentane/diethyl ether 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.45 (1H, ddd, *J*=5.3, 12.0, 15.7 Hz), 0.55 (1H, ddd, *J*=5.4, 12.0, 15.7 Hz), 1.04 (6H, s), 1.06 (6H, s), 1.19 (12H, s), 1.38 (3H, s), 1.67 (1H, ddd, *J*=5.4, 12.0, 13.8 Hz), 1.75 (1H, ddd, *J*=5.3, 12.0, 13.8 Hz), 3.76 (3H, s), 6.78 (2H, ap d, *J*=8.8 Hz,), 7.22 (2H, ap d, *J*=8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 26.0 (CH_3), 39.5, 40.1, 55.2 (CH_3), 82.6 (C), 82.7 (C), 113.0 (CH), 127.4 (CH), 141.4 (C), 157.1 (C) ppm, *carbons attached to boron not observed*.

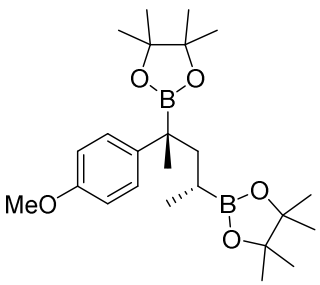
^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.1 ppm.

IR (film): υ (cm^{-1}) 2977, 2930, 1610, 1513, 1356, 1318, 1249, 1145, 1037, 969, 848, 830.

HRMS (ESI) calcd. for $C_{24}H_{40}B_2NaO_5$ $[M+Na]^+$ 453.2963, found 453.2963.

$[\alpha]_D^{26}$ = +15 (*c* 1, $CHCl_3$).

2,2'-((2*S*,4*R*)-2-(4-methoxyphenyl)pentane-2,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ((2*S*,4*R*)-150)



A solution of stannane ((*S*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate, 79 mg, 0.18 mmol, 0.9 equiv) was dissolved in anhydrous Et_2O (0.2 M) under an atmosphere of nitrogen. The reaction mixture was cooled to –78 °C. nBuLi (1.6 M in hexanes, 2.1 equiv) was added dropwise to the reaction mixture at –78 °C. The reaction mixture was stirred for 1 h at –78 °C. Then was slowly added to a solution of boronic ester (*S*)-2,2'-(2-(4-methoxyphenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (80 mg, 0.2 mmol, 98:2 er, 0.5 M in anhydrous Et_2O, 1.0 eq) and the reaction mixture was stirred at – 78 °C for 30 min. The reaction mixture was then removed from the cooling bath and stirred at room temperature for 4h. Afterwards the reaction was diluted with water and extracted with Et_2O (3 ×). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the crude material purified by flash chromatography to afford 2,2'-((2*S*,4*R*)-2-(4-methoxyphenyl)pentane-2,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (59%, 46 mg, >20:1 dr) as a white solid. $\boldsymbol{R_f}$ = 0.18 (dichloromethane/pentane 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73-0.80 (1H, m), 0.85 (3H, d, *J*=7.2 Hz), 1.16 (6H, s), 1.17 (6H, s), 1.19 (12H, s), 1.30 (3H, s), 1.79 (1H, dd, *J*=3.6, 13.8 Hz), 2.01 (1H, dd, *J*=8.0, 13.8 Hz), 3.76 (3H, s), 6.79 (2H, ap d, *J*=8.8 Hz), 7.22 (2H, ap d, *J*=8.8 Hz) ppm.

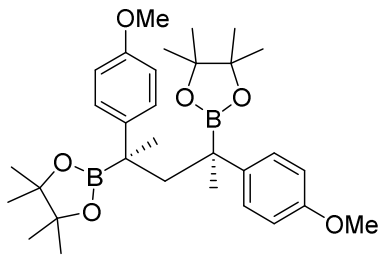
^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (CH_3), 21.4 (CH_3), 24.5 (CH_3), 24.6 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 42.0 (CH_2), 55.1 (CH_3), 82.6 (C), 83.0 (C), 113.3 (CH), 128.1 (CH), 138.3 (C), 156.9 (C) ppm, *carbons attached to boron not observed*.

^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.9 ppm.

IR (film): υ (cm^{-1}) 2976, 2901, 1510, 1406, 1380, 1308, 1249, 1145, 1066, 1057.

$[\alpha]_D^{26}$ = -12 (*c* 1, $CHCl_3$).

2,2'-((2*S*,4*S*)-2,4-bis(4-methoxyphenyl)pentane-2,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ((2*S*,4*S*)-152)



To a vigorously stirred solution of (*S*)-1-(4-methoxyphenyl)ethyl diisopropylcarbamate (112 mg, 0.4 mmol, 1.0 equiv, >99:1 er) and TMEDA (1.0 equiv) in anhydrous diethyl ether (0.33 M) at −78 °C under a nitrogen atmosphere, was added sBuLi (1.3 M in hexane, 1.1 equiv) dropwise. After 15 min, a solution of (*S*)-2,2'-(2-(4-methoxyphenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (80 mg, 0.2 mmol, 0.5 equiv, 98:2 er) in diethyl ether (0.5 M) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h and then the cooling bath was removed and stirring was continued at room temperature overnight (16 h). Afterwards the reaction was diluted with water and extracted with Et_2O (3 ×). The combined organic phases were washed with brine and dried over MgSO4. The solvent was removed in vacuo and the crude material purified by flash chromatography affording to 2,2'-((2*S*,4*S*)-2,4-bis(4-methoxyphenyl)pentane-2,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (32%, 34 mg, >20:1 dr) as a white solid. $\boldsymbol{R_f}$ = 0.25 (pentane/diethyl ether 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (12H, s), 1.10 (12H, s), 1.43 (3H, s), 2.34 (2H, s), 3.77 (3H, s), 6.80 (2H, ap d, *J*=8.7 Hz), 7.36 (2H, ap d, *J*=8.7 Hz) ppm.

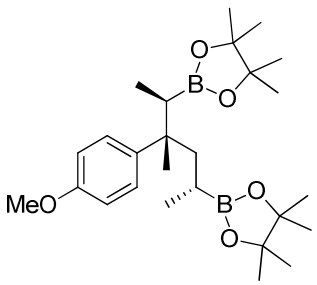
^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (CH_3), 24.3 (CH_3), 24.7 (CH_3), 47.9 (CH_2), 55.2 (CH_3), 83.3 (C), 113.2 (CH), 127.8 (CH), 140.0 (C), 157.0 (C) ppm, *carbons attached to boron not observed*.

^{11}B NMR (128 MHz; $CDCl_3$): δ = 34.6 ppm.

IR (film): υ (cm^{-1}) 2973, 2903, 1509, 1467, 1379, 1307, 1248, 1186, 1129, 1057, 840.

$[\alpha]_D^{23}$ = -2 (*c* 1, $CHCl_3$).

2,2'-((2*R*,3*S*,5*R*)-3-(4-methoxyphenyl)-3-methylhexane-2,5-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ((2*R*,3*S*,5*R*)-151)



A solution of stannane ((*S*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate, 194 mg, 0.44 mmol, 2.2 equiv) in a Schlenk reaction vessel was dissolved in anhydrous Et_2O (0.2 M) under an atmosphere of nitrogen. The reaction mixture was cooled to –78 °C. nBuLi (1.6 M in hexanes, 2.1 equiv) was added dropwise to the reaction mixture at –78 °C. The reaction mixture was stirred for 1 h at –78 °C. Boronic ester (*S*)-2,2'-(2-(4-methoxyphenyl)propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (80 mg, 0.2 mmol, 98:2 er, 0.5 M in anhydrous Et_2O, 1.0 eq) was then added dropwise to the reaction mixture at –78 °C. The reaction mixture was stirred at – 78 °C for 30 min, then was removed from the cooling bath and stirred at room temperature for 4h. Afterwards the reaction was diluted with water and extracted with Et_2O (3 ×). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the crude material purified by flash chromatography to afford 2,2'-((2*R*,3*S*,5*R*)-3-(4-methoxyphenyl)-3-methylhexane-2,5-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (52%, 48 mg, >20:1 dr) as a white solid. $\boldsymbol{R_f}$ = 0.42 (Pentane/diethyl ether 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.58 (3H, d, *J*=7.4 Hz), 0.71 (3H, d, *J*=7.5 Hz), 1.18 (6H, s), 1.19 (6H, s), 1.26 (3H, s, partially overlapped with 1H, q), 1.28 (6H, s), 1.28 (6H, s), 1.42 (1H, q, *J*=7.4 Hz), 1.67 (1H, dd, *J*=2.6, 13.5 Hz), 2.02 (1H, dd, *J*=8.8, 13.5 Hz), 3.77 (3H, s), 6.98 (2H, ap d, *J*=8.8 Hz), 7.18 (2H, ap d, *J*=8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0 (CH_3), 17.8 (CH_3), 19.9 (CH_3), 24.4 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 43.2 (C), 47.4 (CH_2), 55.1 (CH_3), 82.6 (C), 82.8 (C), 112.9 (CH), 127.7 (CH), 139.9 (C), 157.0 (C) ppm, *carbons attached to boron not observed*.

^{11}B NMR (128 MHz; $CDCl_3$): δ = 33.3 ppm.

IR (film): υ (cm^{-1}) 2976, 2930, 1512, 1379, 1313, 1249, 1146, 1042.

HRMS (ESI) calcd. for $C_{26}H_{44}B_2NaO_5$ $[M+Na]^+$ 481.3276, found 481.3295.

$[\alpha]_D^{23}$ = -16 (*c* 1, $CHCl_3$).

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