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Novel Enantioselective Methodologies for the Synthesis of Chiral Compounds. Catalytic and Stoichiometric Processes

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Part I

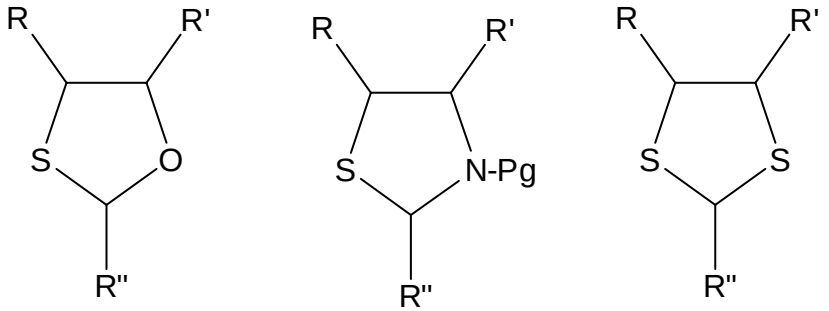
Organosilane reactivity for the synthesis of sulfur containing chiral molecules.

Chapter 1

Sulfur containing silylated heterocycles as useful building blocks in organic chemistry: synthesis and functionalization under different conditions

1.1. Introduction

In the last years, sulfur containing heterocyclic rings have attracted considerable attention, because they are very interesting molecules having applications in synthetic organic chemistry and for their properties as biologically and pharmaceutically active compounds. Among them, five-membered heterocyclic derivatives containing one or more sulfur atoms are important intermediates in organic chemistry, firstly as protecting group for carbonyl compounds and as building blocks for
the synthesis of more complex structures.
1,3-Oxathiolanes, 1,3-thiazolidines and 1,3-dithiolanes (Figure 1) have found wide application, due to the presence of this kind of heteroatomic skeletons in a number of molecules with biological activity.



1,3-oxathiolane 1,3-thiazolidine 1,3-dithiolane

Figure 1

1,3-Oxathiolanes with suitable substituting groups, for example, showed pharmaceutical activities as anti-Alzheimer agents (Figure 2, left),[1] anti-HIV agents[2] (Figure 2, middle) and muscarinic agonists (R, R_1=H, CH_3) or antagonist

(R, R_1=Ph, Cy; Figure 2, right), depending on different substituting groups at position 2[3].

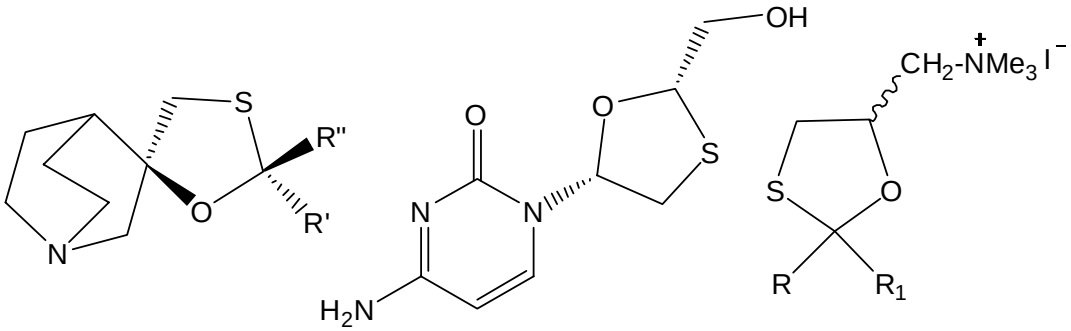


Figure 2

Likewise, the 1,3-thiazolidinic system is present in a large number of molecules with activities as radio-protective agents[4] (Figure 3, left), glycosidase inhibitors[5] (Figure 3, right) and antitussive agents.

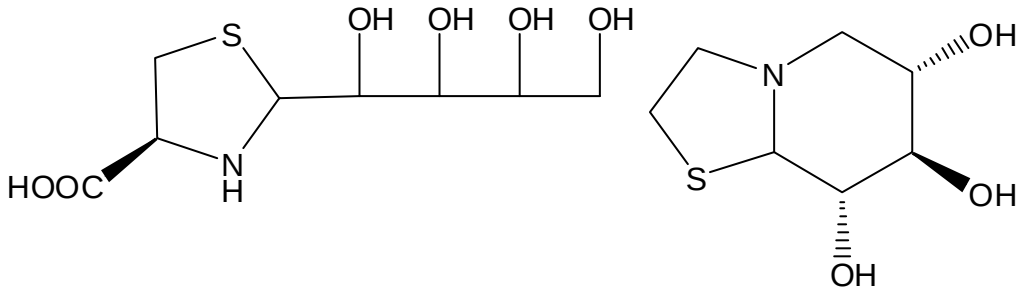


Figure 3

Very recently a paper dealing with the potent antitumor activity of *cis*-2-carbonylethyl-4,5-di(*L*-aminoacyloxymethyl)-1,3-dithiolanes has been reported in the literature[6] (Figure 4, left); moreover, differently substituted α-, β- and γ-semicarbazone- and thiosemicarbazone-1,3-dithiolanes are known as radio-protectors,[7] thus confirming the high versatility of such structures in the pharmaceutical field (Figure 4, right).

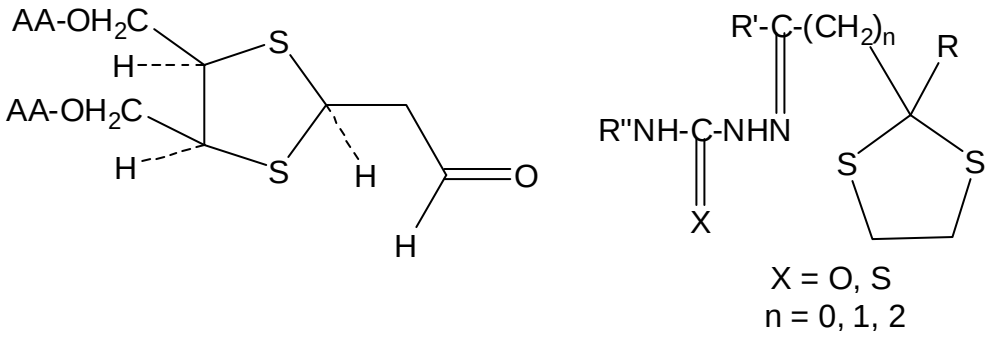


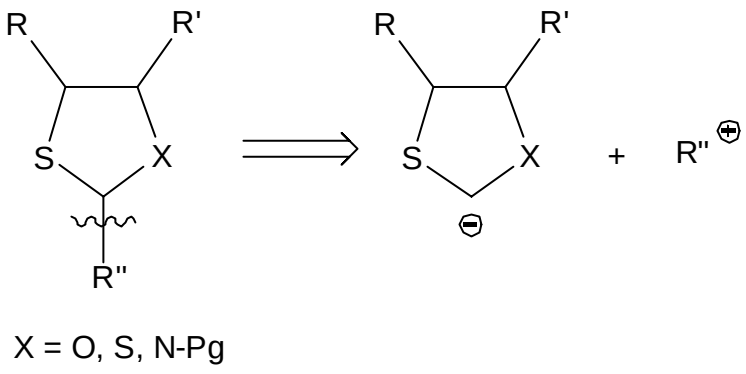
Figure 4

Moreover, chiral 1,3-dithiolanes can find possible applications as chiral auxiliaries in asymmetric synthesis.

As a consequence of the importance and versatility of five-membered heterocyclic intermediates, the development of a general strategy to transfer the cyclic unit onto electrophiles, in order to obtain differently substituted compounds, attracted a great deal of interest in organic synthesis.

1.2.1. Stereoselective functionalization of silylated heterocycles, as a class of formyl anion equivalents, induced by fluoride-ion

The retrosynthetic approach to the synthesis of functionalized heterocycles would foresee the nucleophilc attack of heterocyclic anions, arising from the corresponding synthetic equivalents by treatment under basic conditions, onto electrophiles (Scheme 1).



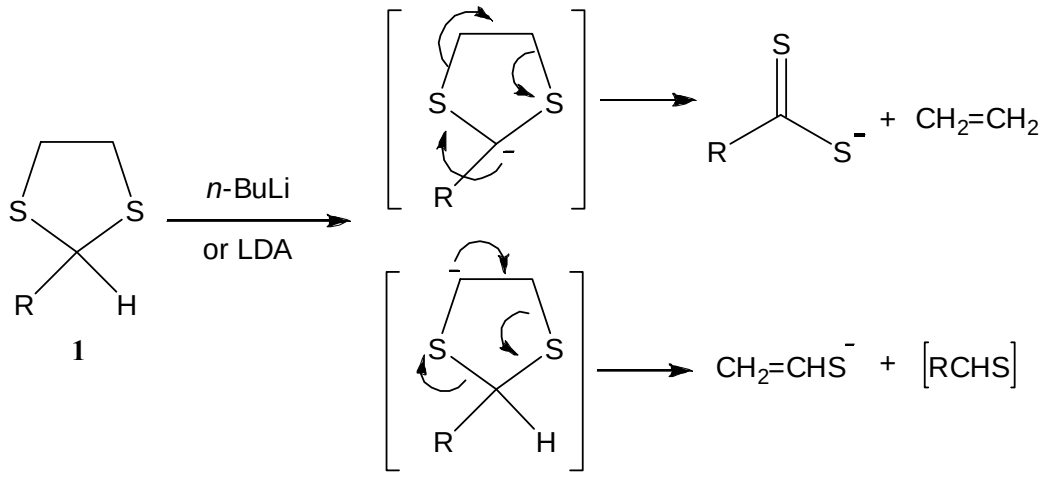
Scheme 1

In this context, umpolung reactivity is a remarkable strategy, providing the formation of C-C bonds *via* the inversion of normal reactivity.[8] As a consequence, the development of synthetic equivalents of acyl anions has in the recent years grown due to the potentiality of this approach, and suitable protected carbonyl derivatives are a very interesting class of molecules acting as equivalents of acyl anions.

Acyclic derivatives, such as α-silyl sulfides,[9] α -metalated derivatives[10] have been employed as masked formyl and acyl anion synthons, but, among them thioacetals represent certainly the most versatile class of synthetic equivalents . In particular, hetorocyclic thioacetals showed a valuable versatility for the development of such reactivity. The most common classes of cyclic thioacetals are 1,3-dithianes and 1,3-dithiolanes, which are interesting protecting groups of carbonyl compounds and can also react as masked acyl anions.[11] The use of these compounds, when compared with their oxygen analogues, presents some advantages, for example thioacetals are easier to obtain and they are more stable to hydrolytic cleavage under basic and acidic conditions.

1,3-Dithianes undergo easy metalation with BuLi and react with a large range of electrophiles, showing their versatility as umpoled reagents.[11,12]

On the other hand, deprotonation of the corresponding 1,3-dithiolanes **1** invariably gives unstable anions and consequent cleavage of the rings is always observed, so limiting their use as masked acyl carbanions and preventing the possibility of further functionalizations of the dithiolane moiety.[13] In fact, 1,3-dithiolane anions, upon treatment with bases, have been reported to undergo either deprotonation at C-2, with subsequent cycloelimination to the corresponding alkenes and dithiocarboxylate anions,[13c] or at C-4, affording products derived from thiocarbonyl derivatives and vinyl thiolate anion (Scheme 2).[13a,b]



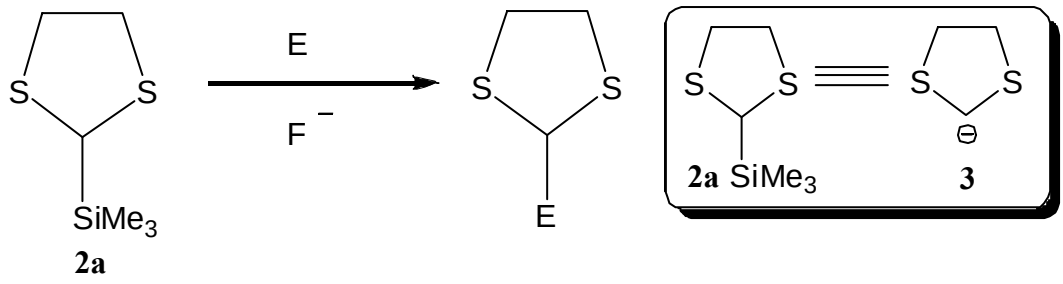
Scheme 2

Although, in fact, two examples of fuctionalization under basic conditions of dithiolanes bearing electron-withdrawing groups have been reported in the literature,[14] there is not a general protocol for the dithiolane-moiety transfer.

In recent years, organosilicon compound chemistry has grown, due to the critical role that silylated molecules play in organic synthesis and to their versatility and tolerance of other functional groups. The functionalization of carbon-silicon bond represents an interesting methodology for the formation of novel carbon-carbon bonds. Thus, synthetic methods based on silicon chemistry are an important and always increasing area of organic synthesis. The application of heterocyclic silanes to organic synthesis offers a fundamental opportunity for new methodologies, since these cycles can react effectively as precursors of heterocyclic carbanions.

The interest in the reactivity of organosilanes showed the possibility to consider the 2-trimethylsilyl-1,3-dithiolane **2a** as a possible masked dithiolane anion **3** equivalent.

Previous works published by Degl'Innocenti, Capperucci *et al.*[15] revealed that the fluoride ion-induced carbodesilylation reaction of silyl dithiolanes **2a** in the presence of electrophiles, occurred with success forming new C-C bonds (Scheme 3).



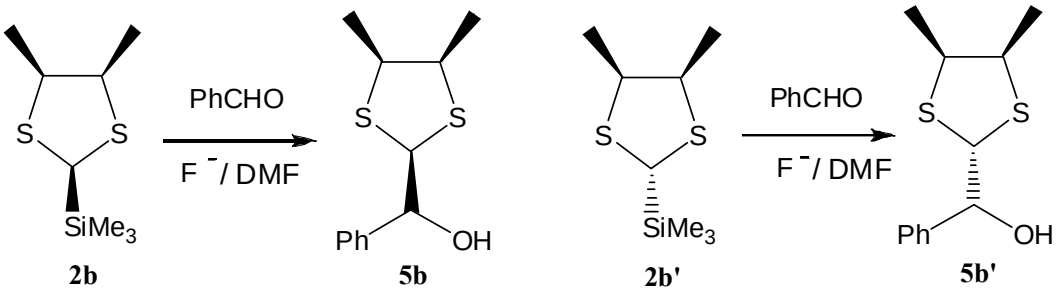
Scheme 3

These results suggested that the carbodesilylation reaction proceeded through a pentacoordinated silicon intermediate, due to the tendence of silicon to extend its coordination sphere to five or even six,[16] rather than through a free carbanion, which we expected to decompose.

Due to the mildness of such basic conditions, it was possible to observe an effective transfer of a dithiolane unit onto electrophiles, without decomposition of the ring, as observed in the presence of stronger bases, such as BuLi or LDA (Scheme 2).

Thus, when 2-trimethylsilyl-1,3-dithiolane was treated with aldehydes in the presence of different sources of fluoride ion, the functionalization of C-Si bond occurred, leading to the corresponding functionalized α-hydroxy dithiolane **5**, with a small amount of protodesilylation product (around 20%). This was the first example of silyl mediated dithiolane transfer reported in the literature.[15a]

In this context, several fluoride ion sources were evaluated, ranging from CsF, TASF, TBAT and TBAF, and TBAF was found to be the best choice. Interestingly this reactivity was extended to aromatic, heteroaromatic, aliphatic and α,β-unsaturated aldehydes, as electrophiles, affording in all cases protected α-hydroxy aldehydes **5** in good yields. It is interesting to underline that in the presence of α,β-unsaturated aldehydes, only 1,2-adducts have been obtained. In the same context,[15b,c,d] the stereochemical fate of the reaction was also considered. When both c*is* and *trans*-4,5-dimethyl-2-trimethylsilyl-1,3-dithiolanes (**2b, 2b'**) were employed in the presence of aldehydes **4** (such as benzaldehyde), a stereoconservative carbodesilylation reaction occurred at C-2, affording **5b** and **5b'**, and no traces of epimerization were detected (Scheme 4).



Scheme 4

Nevertheless it was not possible to obtain asymmetric induction on the newly formed stereogenic center. As a consequence, the crude products were isolated as a mixture of the two enantiopure diasteroisomers, which could be chromatographically separated to give chiral funtionalized 1,3-dithiolanes in good yields.

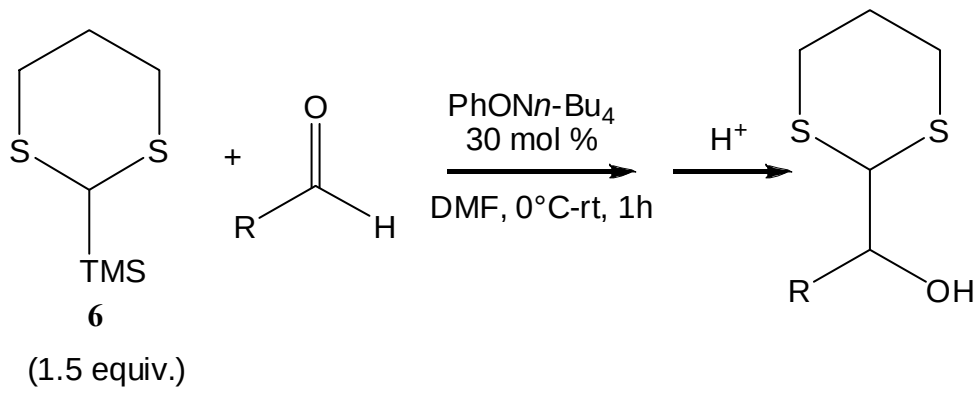
Such results then outlined the peculiarity of the silicon moiety in promoting these reactions, and evidenced the fluoride ion induced functionalization of the C-Si bond as a possible general tool for the functionalization of otherwise not easily functionalizable heterocycles.

1.2.2. Recent results:

tetrabutylammonium phenoxide induced functionalization of silylated dithiolanes

Several drawbacks are nevertheless linked to the use of TBAF, such as the difficulties in having an anhydrous solution, and its stability along with time.[17] In the past, Majetich *et al.*[17c] reported a long procedure to dry tetra-*n*-butylammonium fluoride, by treatment of commercially available TBAF $\cdot 3H_2O$ under vacuum, in the presence of activated molecular sieves and dry DMF; stock solution of DMF/TBAF stored at room temperature were found effective for only one day. This is why we began to look for different catalytic systems in the activation of C-Si bond.

A recent investigation by Mukaiyama and coworkers[18] reported that Lewis base catalysts, such as phenoxide ion based catalysts, can promote C-Si bond activation of trimethylsilylacetylenes and of 2-trimethylsilyl-1,3-dithianes **6**. Mukaiyama found that the use of PhON*n*-Bu_4 as catalyst in DMF gave the best results, in the fuctionalization of silyl dithianes with aromatic having electron-donating or -withdrawing groups, heteroaromatic and α,β-unsaturated aldehydes (80-97% yiels). When aliphatic aldehydes were used, the reaction proceeded smoothly, giving the adducts in moderate to good yiels (60-83%). Since dithiane adducts were recovered as a mixture of their TMS-ethers and desilylated alcohols, hydrolysis by treating the crudes with 1 M HCl was necessary, affording the corresponding alcohols (Scheme 5).

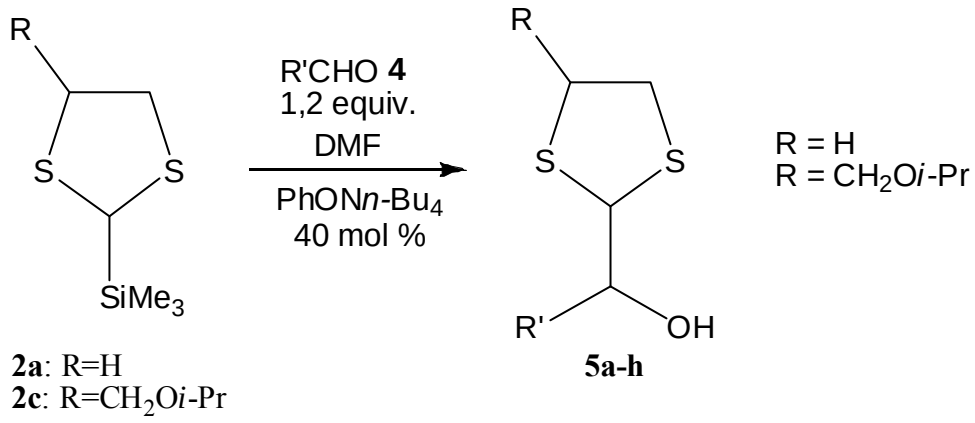


Scheme 5

Prompted by these results, our attention was turned to the possibility to use phenoxide ion catalysts in replacement of TBAF in promoting the reactions of silyl dithiolanes, thus overcoming the aforementioned drawbacks connected with the use of TBAF.[17]

Our hope was that the reaction conditions in using phenoxide ion catalysis could have been mild enough to allow the functionalization of silyl dithiolanes without decomposition of the heterocyclic system.

In this context, both PhONa and PhON*n*-Bu_4 were used as catalysts in the reactions of silyl dithiolanes **2a**, **2c** with aldehydes **4** and different solvents taken into consideration, and we also found the best choice being PhON*n*-Bu_4 in polar solvents such as DMF (Scheme 6).[19]



2a: R=H
2c: R=CH_2O*i*-Pr

5a-h

Scheme 6

The use of PhONa generally led to the formation of variable amounts of desilylation products, and solvents like THF to low yields of the expected products. Moreover, reactions in DMF were faster than in THF, being the starting dithiolane reacted in 2-4 h in DMF with respect 12-24 h in THF.

Results of this investigation are summarized in Table 1.

Reactivity proveded general, occurring smoothly with aromatic, heteroaromatic and aliphatic aldehydes. In all reactions no trace of decomposition of the dithiolane ring was observed, thus showing that also under the influence of phenoxide ion a real carbanion **3** was not generated in the present conditions. The substituted 2-silyl-4-(isopropoxymethyl)-1,3-dithiolane **2c** was reacted as well with benzaldehyde, leading to the formation of the 4-substituted-α-hydroxy-dithiolane **5c** as a mixure of *cis*/*trans* isomers (Table 1, entry 4), that could be separated on silica gel. It should be

mentioned that when reacting substituted dithiolanes a greater amount of protodesilylation was observed.

Table 1 Carbodesilylation of silyldithiolanes

entry	dithiolane	R'CHO	catalyst	solvent	product	yield (%) [a]
1	**2a**	PhCHO	PhONa	DMF	**5a**	42
2	**2a**	PhCHO	$PhONBu_4$	THF	**5a**	10
3	**2a**	PhCHO	$PhONBu_4$	DMF	**5a**	87
4	**2c**	PhCHO	$PhONBu_4$	DMF	**5c**	49 [b]
5	**2a**	Thienyl-CHO	$PhONBu_4$	DMF	**5d**	88
6	**2a**	*p*-Br-C_6H_4-CHO	$PhONBu_4$	DMF	**5e**	70
7	**2a**	*E*-PhCH=CHCHO	$PhONBu_4$	DMF	**5f**	78
8	**2a**	$C_6H_{11}CHO$	$PhONBu_4$	DMF	**5g**	60
9	**2a**	$(CH_3)_2CHCH_2CHO$	$PhONBu_4$	DMF	**5h**	30

[a] Based on isolated yield.
[b] Mixture of *cis* and *trans* isomers.

Similarly to Mukaiyama findings,[18] usually dithiolane adducts were obtained as a mixture of hydroxy compounds and trimethylsilyl ethers. The use of saturated aqueous NH_4Cl solution during the work-up led to the exclusive formation of the corresponding alcohols **5a-h**.

1.2.3. Conclusions

In conclusion, the phenoxide ion-induced activation of the C-Si bond of silyl 1,3-dithiolanes has led to the development of a simple and mild protocol for their not obvious functionalization. This methodology was completely general, as shown in Table 1, and could be interestingly extended to 4-substituted-heterocyclic rings **2c**, thus leading to polyfunctionalized systems which are important building blocks for the synthesis of more complex molecules.

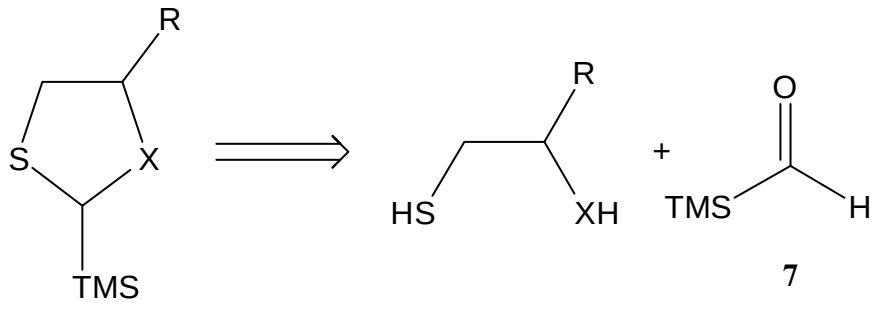
In the presence of stereochemically defined substrates, it was possible to tranfer the dithiolane moiety with retention of configuration, in analogy with the corresponding reaction induced by fluoride-ion. In this case, also without asymmetric induction onto the new stereogenic center at carbon 2, it was possible to isolate enantiopure diastereoisomers, which could be separated on silica gel,

giving chiral cycles. The importance of chiral polyfunctionalized heterocyclic skeletons, present in a variety of biologically active compounds, was discussed before underlining the versatility of the methodology here reported.

1.3.1. Five-membered silylated heterocycle synthesis

Taking advantage of the previously outlined results[15,19] for the reactivity of 1,3-dithiolanes **2**, which seems to proceed *via* pentacoordinated silicon species and not *via* a free carbanion, we envisaged that functionalization of the C-Si bond under the mild catalytic activity of phenoxide ion, as well as under catalysis of fluoride ion, could lead to a solution to the functionalization problem for such labile heterocycles. In this context, it appeared obvious the importance to find a general and effective methodology leading to the synthesis of these key-intermediate silylated heterocycles.

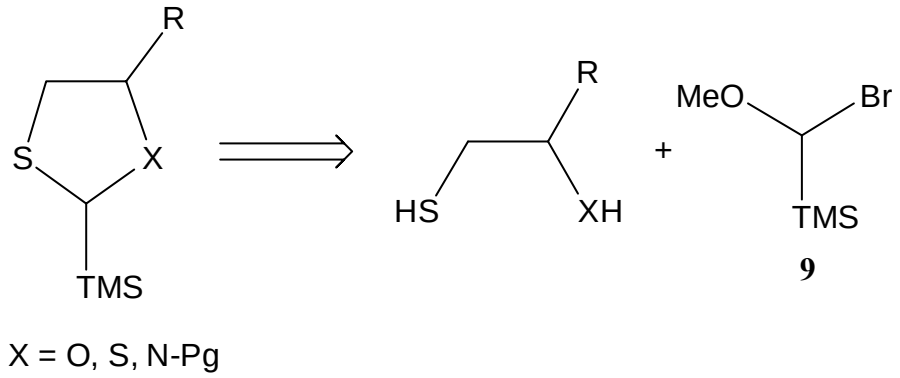
Since direct access to silyl heterocycles is difficult, an alternative route to such molecules had to be devised. A possible route to silyl dithiolanes and, in general, to five-membered ring silylated heterocycles could be envisaged through the reaction of bifunctional molecules, such as 1,2-dithiols, 1,2-mercaptoalcohols and 1,2-aminothiols with formyl trimethylsilane **7** (Scheme 7).



X = O, S, N-Pg

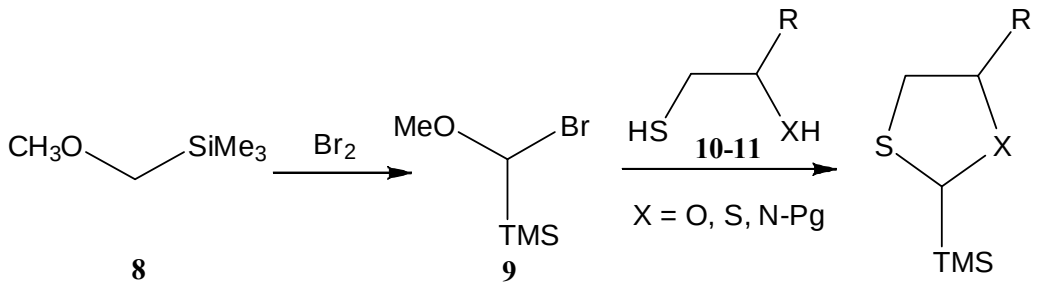
Scheme 7

Nevertheless, formyl trimethylsilane **7** presents some difficulties in its generation[20] due to its lability , and as a consequence, the research for a possible synthetic equivalent of such a compound is required. In our group, we previously envisaged bromo(methoxy)methyl trimethylsilane **9** to be the right reagent for the cyclization process of bifunctional molecules (Scheme 8).[15c,21]



Scheme 8

In fact, bromo(methoxy)methyl trimethylsilane was synthesized in quantitative yield (80%) by the radical reaction of commercially available methoxymethyl trimethylsilane **8** with bromine, and a subsequent one-pot cyclization with the required mercaptan **10**, aminothiol or mercaptoalcohol **11** led to desired silylated heterocyclic systems (Scheme 9).[15c,21]



Scheme 9

The formation of the bromo(methoxy)methyl trimethylsilane **9** intermediate could be checked by ^{1}H-NMR analysis, before the addition of bifunctional compound.

The one-pot procedure was general and occurred under mild conditions, affording the corresponding heterocycles in good yield and allowing to extend the protocol to bifunctionalized mercapto-derivatives bearing substituting group of different nature. Such a reaction then evidenced the ability of bromo(methoxy)methyl trimethylsilane **9** to act as a real synthetic equivalent of formyl silane **7** and opened the way to a possible general route to access a wide variety of silyl heterocycles. Nonetheless, it is clear that the generality of this procedure is strictly related to the availability of the required starting bifunctionalized molecules, namely 1,2-dithiols **10**, 1,2-mercapto alcohols **11** and 1,2-amino thiols.

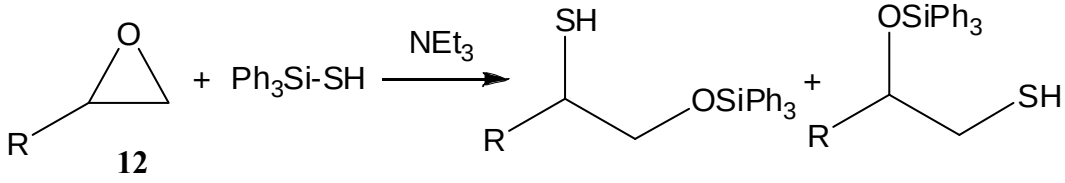
1.3.2. Synthesis of β-mercapto alcohols: a recently reported versatile method using HMDST

Probably due to their ease of oxidation, it is not easy to obtain and to store β-mercapto alcohols **11** and 1,2-dithiols **10**, so limiting the generality of the already mentioned synthetic route to five-membered heterocyclic rings.

Despite these difficulties, bifunctionalized molecules of this kind play a fundamental role in organic chemistry as crucial building blocks for the synthesis of polyfunctionalized molecules and, if chiral, as possible ligands in asymmetric synthesis. As a consequence, the development of general methodology for their synthesis has attracted a great deal of attention during the years.

It is well know that ring opening of epoxides **12** with nucleophiles represent a very versatile chemical transformation to access a wide range of functionalized molecules.[22] In particular, reactions with thio nucleophiles offer the opportunity to access different interesting sulfurated molecules,[23] and among them there are a few methods which allow a direct access to β-mercapto alcohols. Some protocols involve reactions of H_2S,[24] and thiourea.[25]

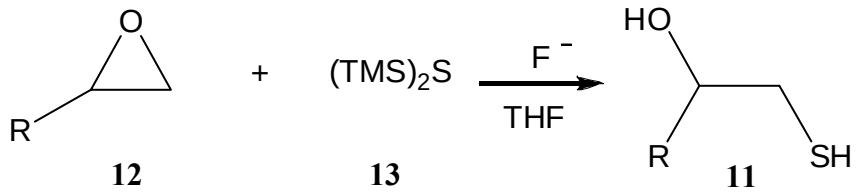
Moreover, in the course of time, thiosilanes[26] and silane thiols such as Ph_3SiSH[27] (Scheme 10) and *i*-Pr_3SiSH[28], which behave as mono-protected H_2S but are easier to use, have been used as nucleophiles in the opening of oxiranes affording the desired β-hydroxy thiols, even if not always a regiocontrolled reaction was achieved.



Scheme 10

An interesting route to these structures was found by our group in the use of a versatile thionating agent, bis(trimethylsilyl)sulfide (hexamethyldisilathiane, HMDST) $(TMS)_2S$ **13**, which proved a very versatile reagent in the delivery of sulfurated moieties with ring-strained heterocycles, such as oxiranes, thiiranes, aziridines. HMDST **13** can be considered as a synthetic equivalent of H_2S, affording hydroxythio-, dithio-, aminothio- derivatives owing to the ring opening reactions of ring-strained cycles, but it is easier to handle and to measure than H_2S.[15,29]

Previous results in our group [15c,d, 29] showed that reaction of differently substituted epoxides **12** with HMDST **13** and TBAF as catalyst in the activation of the S-Si bond, afforded a mild ring opening of heterocyclic ring, leading to the formation of various β-mercaptoalcohols **11** in good yields (40-95%), arising from a regioselective attack of the silyl sulfide on the less hindered side of the oxirane (Scheme 11).

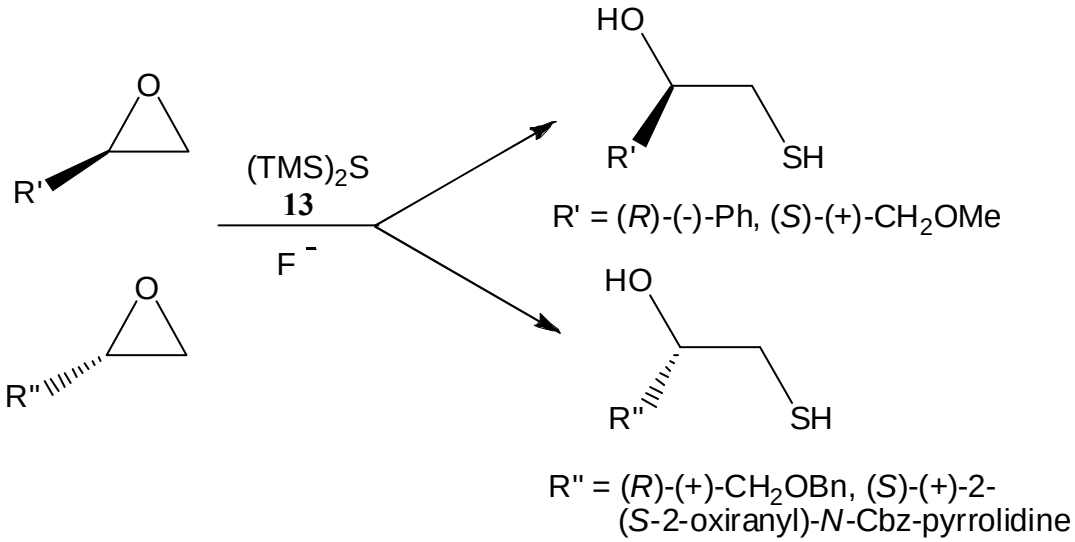


R = Me, Ph, CH_2O*i*-Pr, CH_2Cl, CH_2OAll, $CH{=}CH_2$

Scheme 11

Due to the mild reaction conditions, this methodology was applied also to useful but very labile compounds, such as glycidol derivatives and epichlorohydrin (Scheme 11), which represent important versatile structures in the biological and pharmaceutical fields, without removing of the protective moieties.

Moreover, the mild conditions allowed to apply such procedure as well to enantiopure epoxides, thus affording a regioselective and totally enantioconservative access to chiral β-mercaptoalcohols (65-95% yields) (Scheme 12). Only in the case of styrene oxide was the corresponding regioisomer detected in little amount (regioisomeric ratio 10 : 0.5).

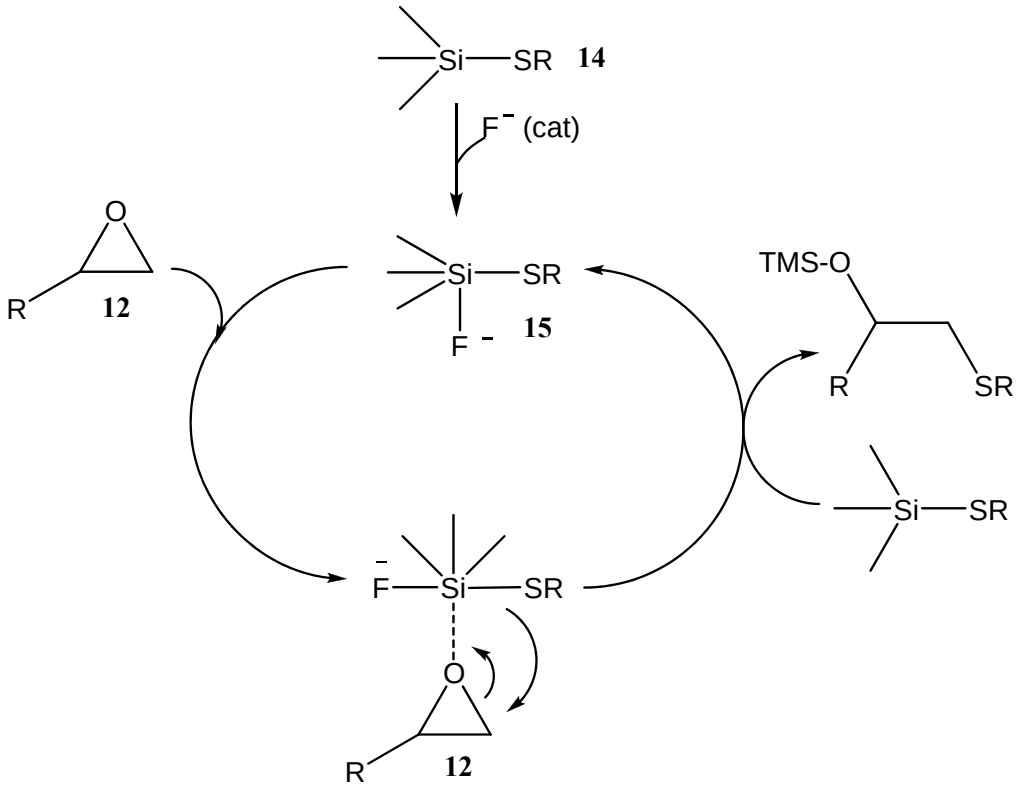


Scheme 12

A plausible reaction mechanism for the activation of the Si-S bond was proposed by Tanabe, for the ring opening of epoxides with thio nucleophiles, such as PhS-TMS, in DMF (Scheme 13).[26a]

Thus, activation of the silicon-heteroatom bond by fluoride ion contributes to ring-opening reaction *via* hypervalent silicate intermediates, as shown in Scheme 16 . In the catalytic cycle, the TBAF catalyst firstly attacks the thiosilane **14** to give the reactive pentavalent thiosilicate **15**, which coordinates to the oxygen of the epoxide **12** and forces the thiol group towards the carbon centre of the substrate. After the ring opening process, the fluoride anion is immediately

transferred from the alkoxy(fluoro)silicate to another molecule of thiosilane **15** with the release of the silyl ether product and regeneration of the thiosilicate.



Scheme 13

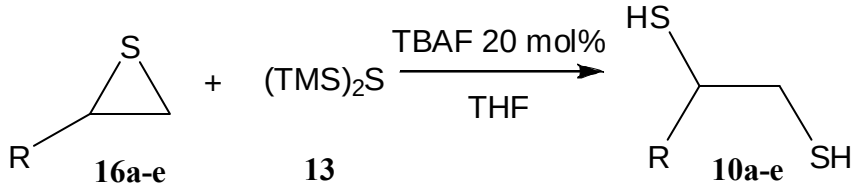
1.3.3. Stereoselective synthesis of 1,2-dithiols under fluoride ion catalysis

The reactivity of HMDST **13** towards epoxides was conveniently extended to other ring strained compounds, such as thiiranes **16**, affording an easy access to a variety of building blocks for use in the synthesis of five-membered ring silylated heterocycles.[15, 29]

Unlike the case of epoxides, to the best of our knowledge, only few examples have been described on the ring opening of thiiranes,[30] probably due to their easy polymerization and tendency to be desulfurized. Generally such reactions are reported under Lewis acid catalysis, and represent a very useful method to obtain sulfurated systems, even if they often show poor regio- and stereoselectivity.

Thus, the approach using HMDST afforded an easy access to a variety of functionalized mercaptans **10**, useful precursors for the synthesis of five-membered silylated heterocycles.

With our delight, in fact, episulfides **16** upon treatment with bis(trimethylsilyl)sulfide **13** and TBAF as catalyst, were converted smoothly to the corresponding 1,2-dithiols **10a-e** in good yields. The reaction occurred regioselectively in this case too, with the nucleophilic attack on the less hindered position of the substrate (Scheme 14).[15c,d]



Scheme 14

The isolation of 1,2-dithiols, which are extremely labile substrates due to the presence of easily oxidizable thiol-groups, was possible by a simple work-up in the presence of anti-oxidant agents, such as citric acid solution (50% aqueous solution). In these conditions it was possible to isolate 1,2-dithiols, which were pure enough to be used without further purification.

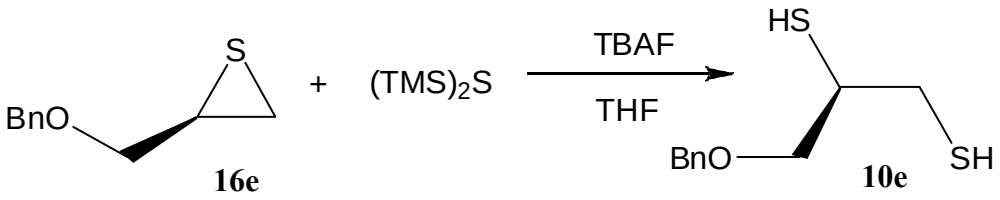
The reactivity proved general, leading to the synthesis of substituted 1,2-dithiols **10a-e** bearing aromatic and aliphatic moieties, as reported in the Table 2.

Table2 Direct synthesis of 1,2-dithiols

entry	R	product	yield (%)[a,b]
1	CH_2OAll (**16a**)	**10a**	54
2	Ph (**16b**)	**10b**	75
3	*i*-$PrOCH_2$ (**16c**)	**10c**	74
4	(±)-CH_2OBn (**16d**)	**10d**	80
5	(*R*)-CH_2OBn (**16e**)	**10e**	77

[a] Based on isolated yield.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy.

Interestingly, as already reported in the case of epoxides, the reactivity was successfully extended to enantiopure thiiranes, leading to the isolation of optically active 1,2-dithiols, with retention of the stereochemistry (Table 2, entry 5; Scheme 15).



Scheme 15

1.3.4. Stereoselective synthesis of β-mercaptoalcohols and 1,2-dithiols under phenoxide ion catalysis

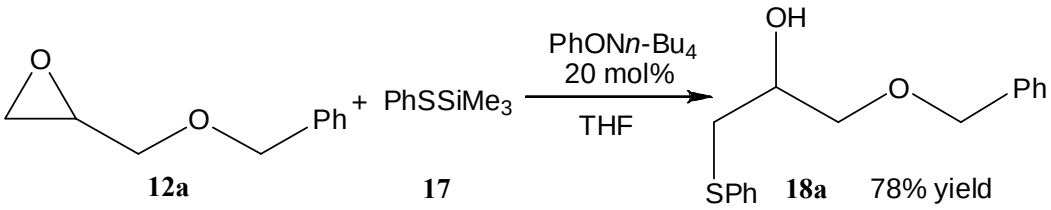
In a previous section, we established the efficiency of phenoxide ion in promoting the functionalization of the C-Si bond in silylated dithiolanes;[19] here we turned our attention to different organosilanes, namely those containing an heteroatom-silicon bond, such as S-Si.

As previously reported, we have been interested in the activation of the S-Si bond of nucleophiles for regio- and stereoselective ring opening reactions of ring strained molecules with HMDST, under mild catalysis of fluoride ion.[15c,d, 29]

As a further step, our aim was to study the reactivity of HMDST **13** in the ring opening reactions of oxiranes **12** and episulfides **16**, in the presence of phenoxide ion as catalyst for the activation of the S-Si bond. This extension of the reactivity of thiosilanes was very interesting, due to the aforementioned advantages in the use of phenoxide ion based catalysts, with respect to the fluoride ion catalysts.

A preliminary research concerning the role of phenoxide ion in the functionalization of S-Si bond, was directed to the evaluation of the reactivity of the less labile silylated nucleophile PhS-TMS **17**, towards epoxides and thiiranes.

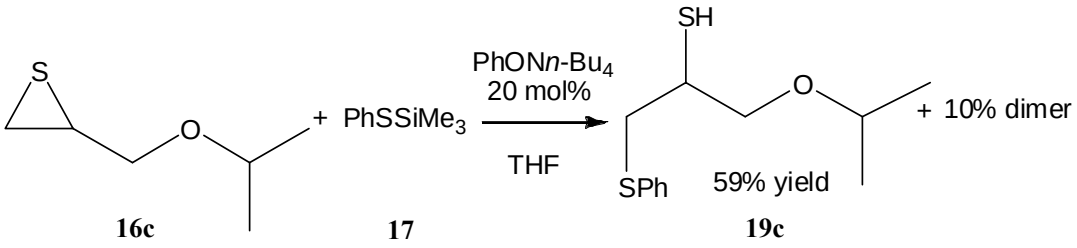
Thus, when phenylthiotrimethylsilane **17** was reacted with benzylglycidol **12a** and a catalytic amount of PhON*n*-Bu_4 (20%), a clean reaction occurred, leading to the isolation in good yield of compound **18a**, arising from a regioselective attack of the nucleophile on the less hindered side of the oxirane ring (Scheme 16).[19] Then, the above described procedure may represent a simple and efficient approach to access β-hydroxy sulfides, that behave as useful intermediates in different synthetic transformations.



Scheme 16

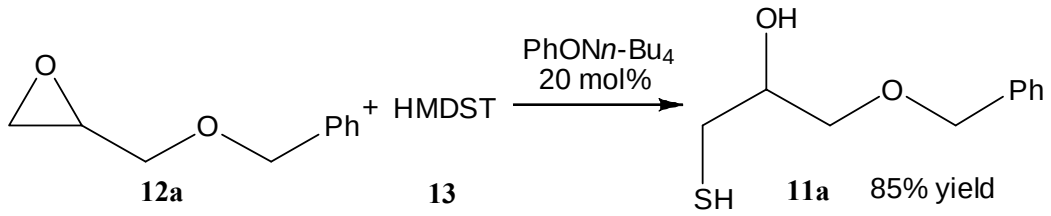
Likewise, the reaction of **17** with 2-(isopropoxymethyl)thiirane **16c** and PhON*n*-Bu_4 (20 mol%), led to the isolation of compound **19c**, with total regioselectivity. The isolation of labile β-mercapto-sulfide was possible by treating the reaction mixture with citric acid (50% aqueous solution), as anti-oxidant agent, to avoid the total dimerization of the -SH group; nevertheless, a little amount of dimerization product was detected in the crude (Scheme 17).

Interestingly, epoxide and thiirane ring opening reactions in the presence of thio nucleophiles under phenoxide ion catalysis, was conveniently performed in THF instead of DMF, as for the activation of C-Si bond under catalysis of PhON*n*-Bu_4; moreover it was possible to reduce the amount of the catalyst to 20 mol%, instead of 40 mol% employed in the carbodesilylation reactions.[19]



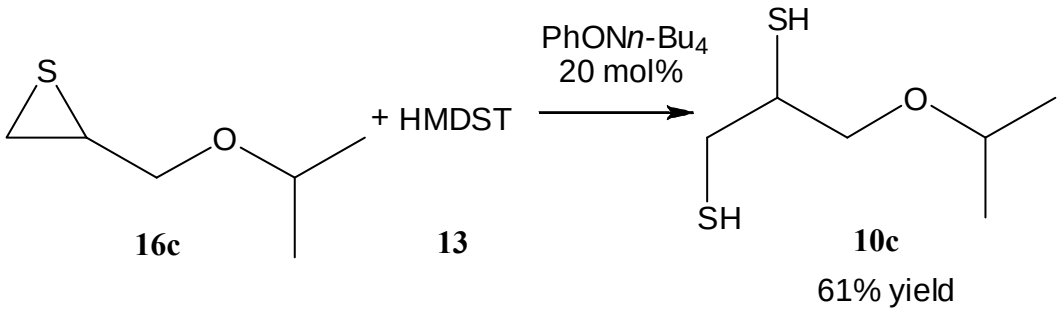
Scheme 17

The efficiency of the methodology was further demonstrated by the use in such reactions of the much more labile chalcogen derivative HMDST **13** as nucleophile, which in turn reacted smoothly with oxirane **12a**, affording the β-hydroxythiol **11a** in comparable yields with those already reported under fluoride ion conditions (Scheme 18).[19] In some cases, products were isolated as their trimethylsilyl ethers.



Scheme 18

The extension of the reactivity to ring opening of **16c**, showed a behavior completely comparable in terms of selectivity with that already observed under fluoride catalysis, allowing the isolatation of the 1,2-dithiol **10c** in good yield. In this case the treatment with citric acid (50% aqueous solution), led to the isolation of **10c** in 61% of yield (Scheme 19).

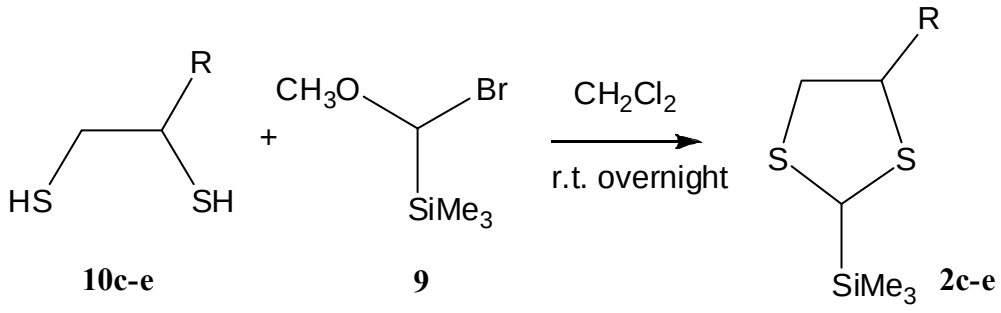


Scheme 19

It is remarkable to underline that, as well as in the case of TBAF, the phenoxide ion catalysis assured mildness of the reaction conditions so that they was applied to labile compounds, such as glycidol derivatives, without decomposition.

1.4. Synthesis of 4-functionalized-2-trimethylsilyl 1,3-dithiolanes by cyclization of 1,2-dithiols

The obtained bifunctionalized derivatives are versatile building blocks for the synthesis of silylated heterocyclic rings, such as 4-functionalized-2-trimethylsilyl 1,3-dithiolanes **2c-e**. In this context, as already reported,[15] a one-pot procedure with the *in situ* preformed trapping agent, bromo(methoxy)methyl trimethylsilane **9**, and 1,2-dithiols **10c-e** led to silylated heterocyclic rings in moderate to good yields (Scheme 20, Table 3).



10c-e **9** **2c-e**

Scheme 20

Table 3 Synthesis of 4-functionalized-2-trimethylsilyl 1,3-dithiolanes

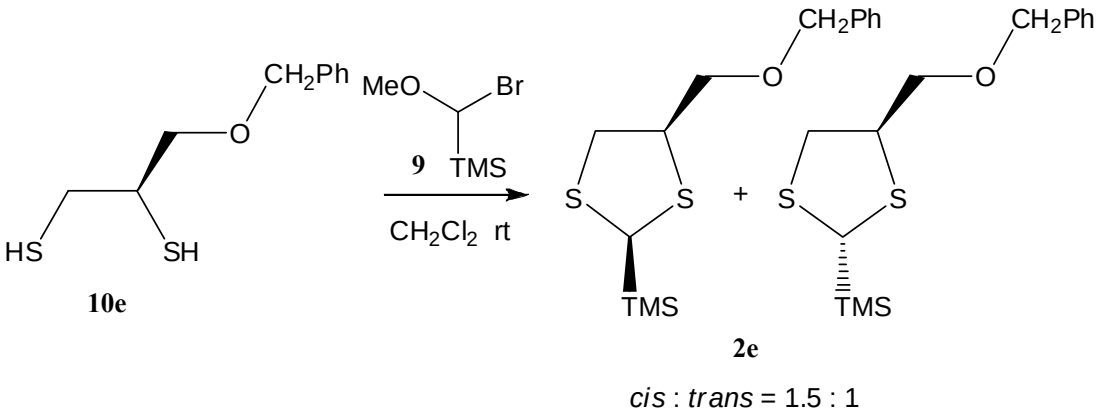
entry	R	product	yield (%)[a]	d.r. (*cis : trans*)[b]
1	CH_2O*i*-Pr	**2c**	44	2.5 : 1
2	(±)-CH_2OBn	**2d**	37	1.5 :1
3	(*R*)-CH_2OBn	**2e**	40	1.5 :1

[a] Based on isolated yield, after purification.
[b] Determined by correlation spectroscopy.

The reaction was performed with glycidol derivatives without appreciable decomposition of the protective moieties, and only a little amount of 4-(bromomethyl)-2-trimethylsilyl 1,3-dithiolane, arising from the nucleophilic

substitution of bromide on the isopropyl or benzyl groups was detected in the crude.

With our delight, such one-pot protocol could be successfully extended to chiral 1,2-dithiols (Table 3 , entry 3), no racemization being ever detected in the cyclization step.



Scheme 21

In this case the methodology afforded enantiopure diastereoisomers, which was chromatographically separated to give chiral 4-functionalized-2-trimethylsilyl 1,3-dithiolanes (Scheme 21). This result was not obvious, and represented an important potentiality for the synthesis of chiral polyfunctionalized silylated heterocycles of different nature, which can be further reacted by activation of the C-Si bond, so opening the doors to a general protocol to obtain complex molecules with applicability in different fields.

1.5. Conclusions

In this chapter we reported the synthesis of 2-trimethylsilyl 1,3-dithiolanes **2** by cyclization reaction of bifunctionalized intermediates, such as β-mercaptoalcohols **11** and 1,2-dithiols **12**. Such molecules, which are important building blocks in organic synthesis as well as possible chiral ligands in asymmetric synthesis, could be easily obtained by a general approach consisting of the regio- and enantioselective fluoride induced ring opening reaction of epoxides and episulfides with HMDST **13**. The methodology was extended to the use of different catalytic systems, such as phenoxide ion,[19] in order to overcome the drawbacks connected with the use of fluoride ion catalysts.

Finally we examined the activation of the C-Si bond of 2-trimethylsilyl 1,3-dithiolanes **2**, induced by phenoxide ion catalysis, in the transfer of the dithiolane moiety onto electrophiles.[19]

These results underlined the high versatility of phenoxide ion in promoting the activation of C-Si and heteroatom-Si bond under mild reaction conditions.

Chapter 2

Investigation of organothiosilane reactivity in ionic liquids

2.1. Ionic Liquids in organic synthesis, an alternative to traditional organic media

Once established the role of fluoride and phenoxide ions in promoting the activation of the C-Si and heteroatom-Si bonds in traditional organic solvents, we turned our attention to study the reactivity of organosilanes in alternative reaction media, such as ionic liquids. In fact in the last decades, the use of ionic liquids (ILs) as media for organic reactions has grown constantly, due to their peculiar properties that have highlighted their wide applicability. Moreover, the growing attention and sensitivity to environmental problems, prompted us to investigate the possibility to use greener solvents for our reactions.

In this context, new chemicals are constantly being designed to meet the needs of industry and society, for example to reduce the toxicity, to enhance the biodegradability, all of which are fundamental principles of green chemistry.

Ionic liquids (ILs) are defined as pure compounds, consisting only of large organic cations and inorganic anions, which melt at or below 100°C. Among them, many are liquid at room temperature, and for this reason there are sometimes called 'Room Temperature Ionic Liquids' (RTILs). The cation is generally a bulky organic structure with a low degree of symmetry, in order to decrease the melting point, while the anion is generally a polyatomic species such as BF_4^-, PF_6^-, CF_3COO^-, $CF_3SO_3^-$, NTf_2^-, $N(CN)_2^-$.

Despite a lot of cations have been reported in the literature, such as ammonium, sulfonium, phosphonium, imidazolium, pyridinium, most of the data are focused on N,N-dialkylimidazolium salts (Figure 5).[31]

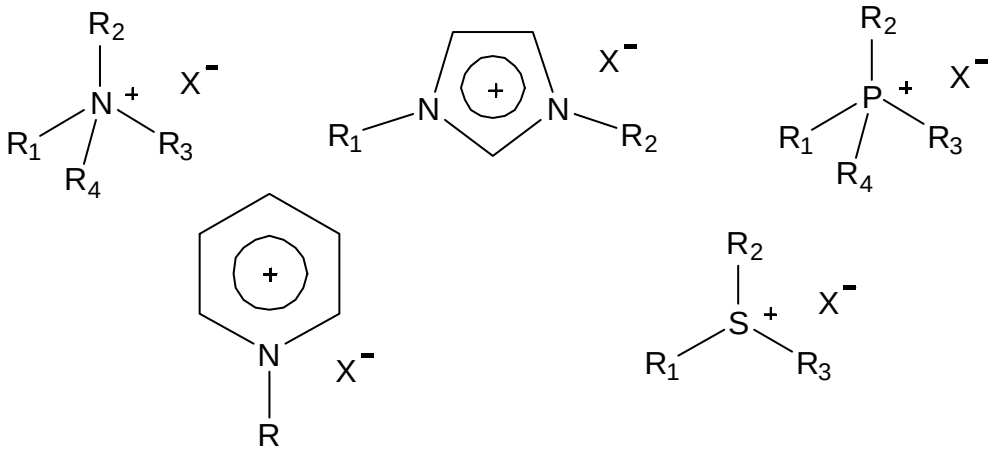


Figure 5

The first examples of ILs based on dialkylimidazolium cations were reported around 1980 years by Wilkes *et al.*,[32] and they contained chloroaluminate anions ($AlCl_4^-$ or $Al_2Cl_7^-$); however problem in using these ILs was the high reactivity of the chloroaluminate anion towards water.

The first examples of ILs of new generation, ethylmethylimidazolium tetrafluoroborate [emim][BF_4] and the corresponding hexafluorophosphate [emim][PF_6] were reported in the literature by Wilkes in 1992,[33, 34] and they showed to be stable towards hydrolysis.

Ionic liquids have been widely considered greener solvents, suitable for a range of organic reactions and providing possibilities such as enhanced rate and reactivity, ease of product recovery, catalyst immobilization and recycling.

They have many fascinating properties which make them of fundamental interest to all chemists as potentially attractive media for organic synthesis, since both the thermodynamics and kinetics of reactions carried out in ILs are different to those in conventional organic solvents. [35]

RTILs have essentially no vapour pressure, so they don't evaporate with consequent ease to be contained; they present high thermal stability and their high polarity allows to dissolve a wide range of organic, inorganic and organometallic compounds. Their ability to dissolve organic and inorganic compounds and their high polarity sort out in a general increase of the rate and the selectivity of plenty of chemical processes, when compared with traditional synthetic media.

Furthermore the polarity and hydrophilicity/lipophilicity can be modified by a suitable choice of cation and anion, and for this reason ILs have been denoted as 'designer solvents'. For example, butylmethylimidazolium tetrafluoroborate [bmim][BF_4] is completely miscible with water, while the analogous [bmim][PF_6] salt is largely immiscible with water.

The polarity and the absence of vapour pressure allow an easy recovering of the reaction products. Precisely, volatile products can be recovered by distillation, while non-volatile compounds by solvent extraction.

ILs are immiscible with some organic solvents and hence they can be employed in two-phase systems instead of water; similarly, lipophilic ILs can be used in aqueous biphasic systems.[34]

There is also significant interest in the development of 'task specific' ionic liquids, where the anion and cation are designed to affect the chemical and physical properties for a specific use as solvents and/or catalysts and reagents in chemical processes. In the literature are described several anions and cations having distinct Lewis/Brønsted acidity or basicity and how these properties can influence the choice and application of the ILs. The most common ILs, butylmethylimidazolium tetrafluoroborate [bmim][BF_4] and butylmethylimidazolium hexafluorophosphate [bmim][PF_6] are classified as neutral ionic liquid (Figure 6).[36]

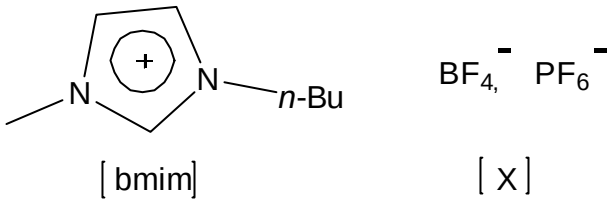


Figure 6

RTILs are described as 'green solvents', and due to their low vapour pressure and limited miscibility with water and organic solvents they are completely recyclable, with consequent benign effect on pollution. Nevertheless, about their biodegradability and toxicity, relatively little is known; in the last years the

studies in this direction grew up, highlighting strictly connection between the biodegradability of ILs and the structure of the anions.[37]
The peculiar properties, some of which have been here described, can highlight why ILs are considered valid and always growing alternative to traditional organic systems.

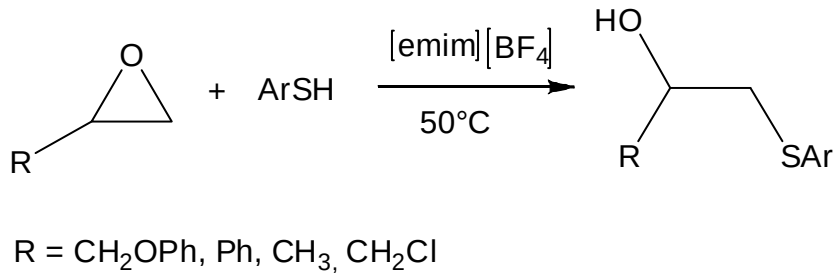
2.2. Synthesis of bifunctionalized compounds in ionic liquids under fluoride ion catalysis

The brief introduction about the IL use in organic chemistry could explain the interest to report our research-line in this direction, that showed how ILs can be efficiently used in replacement of the traditional molecular solvents for the reaction of silylated species towards electrophiles.
In fact, as a consequence of the interesting properties of ILs and of the social demand to investigate greener alternatives to the conventional organic solvents as important step towards sustainable chemistry, we focused our attention on the possibility to extend the methodologies for the synthesis of bifunctionalized molecules with silylated thio nucleophiles in ILs as reaction media.

2.2.1. Ring opening of epoxides and thiiranes with PhSTMS, under catalysis of fluoride ion

ILs used in this first investigation were dialkylimidazolium based neutral ILs, such as butylmethylimidazolium tetrafluoroborate [bmim][BF_4] and butylmethylimidazolium hexafluorophosphate [bmim][PF_6].
Firstly, we considered the possibility of obtaining β-mercapto-derivatives by ring opening reactions of ring strained heterocycles with different thiosilanes in ionic liquids, under the catalysis of fluoride ion. In this context, not so many examples have been described in the literature concerning the ring opening of epoxides with nucleophiles of different nature in ILs,[38] and among them only few papers reported the ring opening of oxiranes in presence of thio nucleophiles, [39] such as thiophenols and aryl disulfides, to give β-hydroxy sulfides.

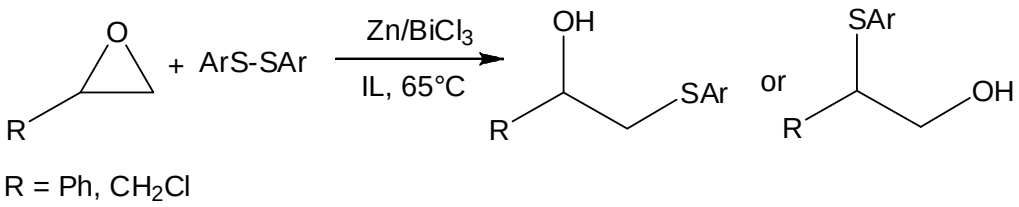
The reaction in Scheme 22, for example, generated β-hydroxy sulfides in excellent yield with high regioselectivity and chemoselectivity, without the use of any catalyst. In this context, among several



Scheme 22

ILs, ethylmethylimidazolium tetrafluoroborate, [emim][BF_4], gave the best results in term of yields, promoting the nucleophilic attack of thiophenols on the less substituted α-carbon.[39c]

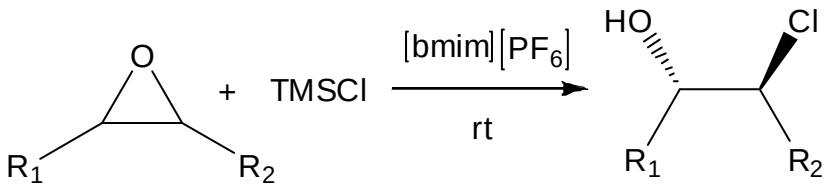
Another interesting example in this direction foresaw the synthesis of β-hydroxysulfides arising from the ring opening reaction of 1,2-epoxides with diaryl disulfides in the presence of zinc powder, catalyzed by $BiCl_3$ immobilized on IL (tetrabutylphosphonium bromide) (Scheme 23).[39b]



Scheme 23

The products were obtained by the attack of nucleophiles on the less hindered carbon of substrates, however in the case of styrene oxide, a reverse regioselectivity was reported.

Moreover, there is only one report on the reactivity of silylated nucleophiles in ILs. Precisely in this paper, was reported the ring opening reaction of epoxides with TMSCl, affording chlorohydrins in good yields (Scheme 24).[40]

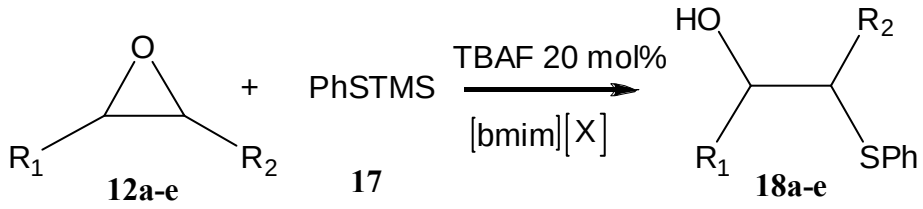


Scheme 24

The IL, due to its high polarity, promoted the activation of TMSCl, facilitating the attack on the less substituted carbon of the epoxide, with the exception of styrene oxide.

Our interest was then turned to evaluate the possibility to activate S-Si bond of thio nucleophiles by catalysis of fluoride ion in ILs, with the intention to extend the scope of our already reported methodologies.

In this direction, firstly we reacted oxiranes **12a-e** with PhSTMS **17**, in the presence of TBAF as fluoride ion source, using [bmim][BF_4] or [bmim][PF_6] as solvents (Scheme 25, Table 4).



Scheme 25

Table 4. Synthesis of β-hydroxysulfides in ILs

entry	R_1, R_2	[X]	product	yield (%)[a]
1	CH_2OBn, H (**12a**)	$[BF_4]$	**18a**	73
2	CH_2O*i*-Pr, H (**12b**)	$[BF_4]$	**18b**	81
3	Ph, H (**12c**)	$[BF_4]$	**18c**	67[b]
4	CH_2OBn, H (**12a**)	$[PF_6]$	**18a**	75
5	cyclohexyl (**12d**)	$[PF_6]$	**18d**	59[c]
6	CH_2Cl, H (**12e**)	$[PF_6]$	**18e**	47

[a] Based on isolated yield.
[b] Mixture of two regioisomers, in ratio 6 : 1.
[c] Amount of cyclohexene-oxide recovered: 15 %.

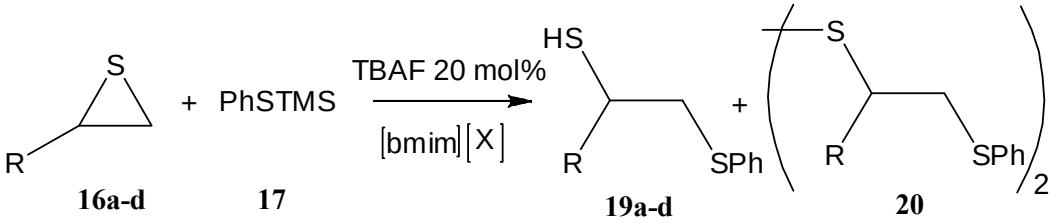
It is interesting to underline that the process was generally highly regioselective, only one product **18a-e** being observed in the crude arising from clean regioselective attack of the thio nucleophile on the less hindered side of the substrate, in accord to the results previously obtained in THF.

Only in the case of styrene oxide **12c** (Table 4, entry 3), was the corresponding regioisomer detected, and this particularity was observed also in traditional organic solvent, due probably to the activation of the benzylic position.

Due to the mildness of the experimental conditions, this methodology in ionic liquids could be applied to useful but labile molecules, such as glycidol derivatives and the protective moieties were not removed. This result was not obvious, due to the high polarity and in general the different properties of ionic liquids, when compared with traditional organic solvents.

We performed such reactions using both [bmim][BF_4] and [bmim][PF_6] with excellent results, but due to the less hygroscopicity of [bmim][PF_6], we used this one to react the highly sensitive epichlorohydrin (Table 4, entry 6). In these conditions it was possible to obtain the corresponding compound **18e** in satisfactory yield; the oxirane was again regioselectively opened at the less hindered carbon, and nucleophilic attack occurred exclusively on the epoxide, the halide being preserved on the side chain.

The scope of the reaction was extended successfully to the ring opening of episulfides **16a-c** in the same conditions, leading to the isolation of β-mercaptosulfides **19a-d** with total regioselectivity for the substrates examined (Scheme 26, Table 5).



Scheme 26

Table 5. Synthesis of β-mercaptosulfides in ILs

entry	R	IL	product	yield (**19**) (%)[a]
1	CH_2O*i*-Pr (**16c**)	[bmim][BF_4]	**19c**	43[b]
2	CH_2OBn (**16d**)	[bmim][BF_4]	**19d**	66[c]
3	CH_2O*i*-Pr (**16c**)	[bmim][PF_6]	**19c**	71
4	CH_2OBn (**16d**)	[bmim][PF_6]	**19d**	69
5	CH_2OAll (**16a**)	[bmim][PF_6]	**19a**	65

[a] Refers to crude products, determined by ^{1}H-NMR analysis.

[b] Yield of the corresponding disulfide **20c**: 23%.

[c] Yield of the corresponding disulfide **20d**: 10%.

It is particularly important the possibility to extend with success the methodology to thiiranes, considering also that no example relative to the reactivity in ILs of such substrates has been reported in the literature.

Nevertheless, due to the ease of polymerization of the thiol-group, when using [bmim][BF_4] as reaction medium, the products were obtained as a mixture of β-mercapto thiols **19c**,**d** and the corresponding dimerization products **20c**,**d** (Table

5, entries 1-2). Such trend was observed also when carrying the work-up in the presence of an anti-oxidant citric acid solution.

In order to avoid, or anyway to reduce the dimerization process, we tried to substitute [bmim][BF_4] with [bmim][PF_6]. With our delight it was possible, in these conditions, to isolate thiols **19** in excellent yield (Table 5, entries 3-5). The products were recovered from the reaction medium by extraction with diethyl ether, and subsequent treatment with citric acid solution gave the crude mixtures. Unluckily after purification on silica gel (the purification was required to remove PhS-SPh, always present in the crude), variable amounts of dimerization products were recovered in all cases, due to the instability of the -SH group.

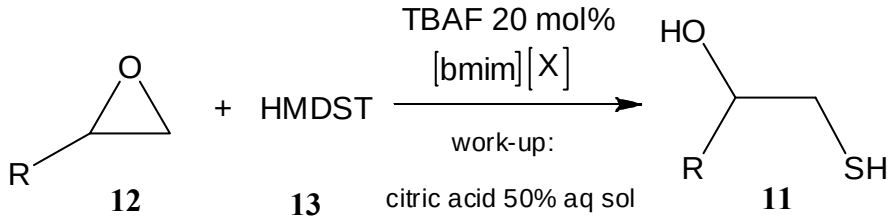
The advantages of the reported methodology in ILs included high regioselectivity and chemoselectivity, comparable to those already observed in traditional organic solvents,[15c,d, 29] good yields, fast reactions, simple operations and recyclability of the reaction media.

Experiments about the recyclability of ILs were performed, and ILs were reused for three runs, without any appreciable loss of activity.

2.2.2. Ring opening of epoxides and thiiranes with HMDST under catalysis of fluoride ion

To the best of our knowledge, no example has been described in the literature of epoxide and episulfide reactions with thio nucleophiles to give directly β-mercaptoalcohols **11** and 1,2-dithiols **10**, probably due to the lability of such molecules.

In this context, the versatility of our methodology was further demonstrated by the use, for the ring opening reactions of three-membered heterocycles in ILs, of the much more labile HMDST **13**. HMDST reacted smoothly with oxiranes **12** under the catalysis of fluoride ion, to give **11** in comparable yields with those reported under traditional conditions (Scheme 27, Table 6).



Scheme 27

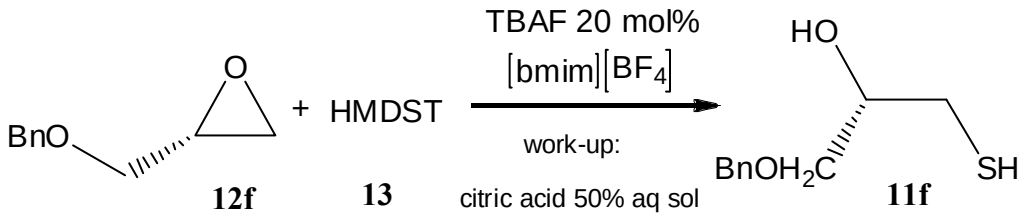
The compounds were recovered from the reaction medium by simple extraction with diethyl ether and subsequent treatment with anti-oxidant citric acid solution, which gave **11** pure enough to be used without further purification. The possibility to avoid the purification step was fundamental for this kind of molecules, due to their tendency to polymerize during the treatment on silica gel.

Table 6. Synthesis of 1,2-mercaptoalcohols in ILs

entry	R	[X]	product	yield (%)[a]
1	(±)-CH_2OBn (**12a**)	[PF_6]	**11a**	69
2	(*R*)-CH_2OBn (**12f**)	[BF_4]	**11f**	60
3	CH_2O*i*-Pr (**12b**)	[BF_4]	**11b**	57
4	CH_2O*i*-Pr (**12b**)	[PF_6]	**11b**	73
5	CH_3 (**12g**)	[BF_4]	**11g**	35 [b]

[a] Refers to isolated products whose spectroscopic data are consistent with the assigned structure.
[b] The lower yield depends on the volatility of **11g**.

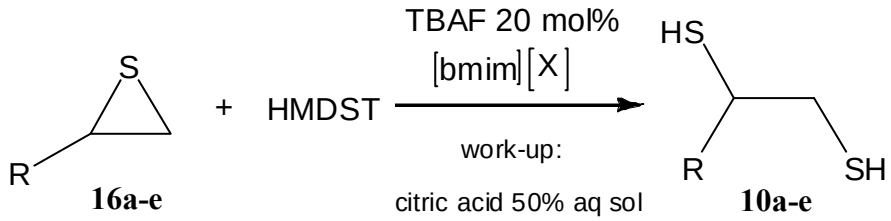
Interestingly, the reactivity in IL showed the same regioselectivity than in THF, giving the products arising from regioselective attack of nucleophile on the less hindered side of the epoxide. When the enantiopure substrate **12f** was reacted under such mild conditions, enantioconservation was observed with the formation of the optically active **11f** (Scheme 28).



Scheme 28

Table 6 underlines how the reactivity of **13** is completely comparable using both ionic liquids, [bmim][BF_4] and [bmim][PF_6], but in the presence of [bmim][PF_6] yields were just higher (entries 1, 4).

As a further step, we decided to evaluate the possible extension of the reactivity of HMST to the ring opening reactions of thiiranes (Scheme 29).



Scheme 29

The regio- and enantioconservative methodology afforded compounds **10** in good yields, which

were pure enough to be used without further purification. The reactivity proved general, occurring smoothly with differently substituted episulfides (Table 7).

Table 7. Synthesis of 1,2-dithiols in ILs

entry	R	[X]	product	yield (%)[a]
1	CH_2OAll (**16a**)	$[PF_6]$	**10a**	64
2	CH_2O*i*-Pr (**16c**)	$[BF_4]$	**10c**	64
3	CH_2OBn (**16d**)	$[BF_4]$	**10d**	75
4	(*R*)-CH_2OBn (**16e**)	$[PF_6]$	**10e**	77

[a] Refers to isolated products whose spectroscopic data are consistent with the assigned structure.

The reported results were, in a first moment, completely unexpected due to the instability of 1,2-dithiols and to the difficulties in obtaining them also in anhydrous THF. Nevertheless it was possible to disclose an efficient procedure for the obtainment of such molecules in high yields, using both [bmim][BF_4] and [bmim][PF_6] as solvents.

In conclusion, the reactivity of thiosilanes as nucleophiles in the ring opening reactions of strained heterocyclic rings could be applied successfully to the use of ionic liquids, under catalysis of fluoride ion, affording bifunctionalized molecules in good yields. The methodology revealed to be highly regioselective and, with enantiopure substrates, enantioconservative, according with the behaviour previously observed in traditional organic solvents.[15c,d, 29]

The use of different ILs as well as different ring strained heterocycles as substrates are now under investigation.

2.3. Synthesis of bifunctionalized compounds in ionic liquids under phenoxide ion catalysis

Despite the efficiency of TBAF in promoting the activation of the S-Si bond in the ring opening reactions of three-membered heterocycles, several drawbacks, as reported in the previous chapter, are linked to the use of this catalyst.

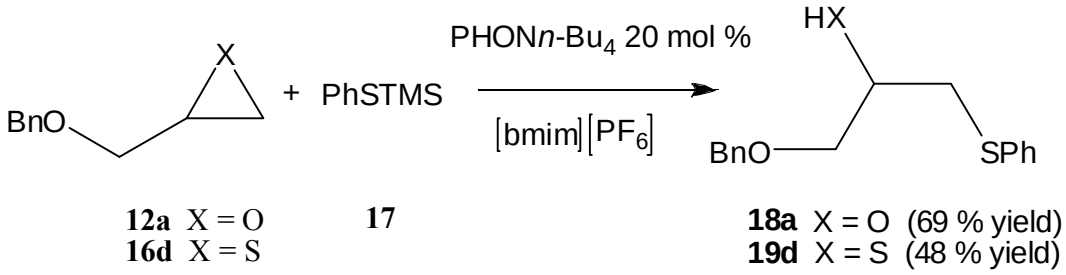
For this reason, in Chapter 1 we highlighted the possibility of using different catalytic systems in order to overcome such drawbacks, and in this direction we found that PhON*n*-Bu_4 was a suitable catalyst in activating organosilanes under traditional conditions.[19]

In this section we report our results concerning the reactivity of silylated nucleophiles in ILs, induced by PhON*n*-Bu_4.

2.3.1. Ring opening of epoxides and thiiranes with PhSTMS under catalysis of phenoxide ion in ILs

In this context, we started to check the reactivity of phenylthiotrimethylsilane **17** with benzyl glycidol **12a** in [bmim][PF_6], under catalysis of PhON*n*-Bu_4. The reaction proved quite efficient, leading to the isolation of the β-hydroxy phenylthio-derivative **18a** in good yield, thus confirming the versatility of this new catalytic system in S-Si bond activation also in ILs. The regioselectivity was the same that for the analogous reaction in the presence of TBAF, with the attack of the thio nucleophile on the less hindered carbon of the substrate, no trace of the other regioisomer being detected (Scheme 30).

Similarly, the reaction of the corresponding glycidol thiirane **16d** showed total regioselectivity, allowing to obtain the β-mercapto phenylthio-derivative **19d** in quite good yield after purification on silica gel (Scheme 30).



12a X = O
16d X = S

17

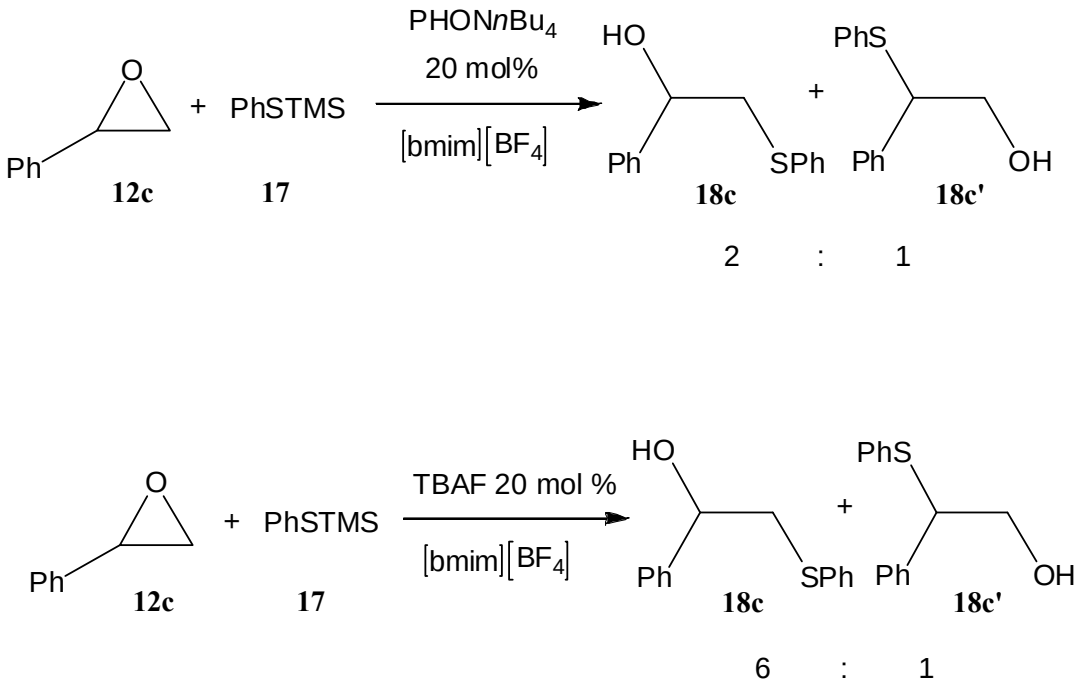
18a X = O (69 % yield)
19d X = S (48 % yield)

Scheme 30

When enantiopure substrates were used, the regioselective attack of PhSTMS allowed to obtain chiral phenylthio-derivatives with complete enantioconservation.

An interesting study concerning the influence of different catalysts, TBAF and PhON*n*-Bu_4, on the reactivity and stereoselectivity of organosilanes in ILs, was carried out with PhSTMS **17** and styrene oxide **12c** in [bmim][BF_4] (Scheme 31). The peculiarity of this substrate is that, due to the presence of phenyl group which activates the benzylic position, nucleophiles usually afford products as mixture of both regiosomers arising from attack on the less as well as on the more hindered side of the substrate. Only in this case both regioisomers were isolated in the ring opening reaction with our thio nucleophiles, and the same behaviour was also observed in THF.[15c,d, 29]

The results reported in Scheme 31 showed that, as expected, the two regioisomers **18c** and **18c'** were obtained either under catalysis of both fluoride ion (in 67 % of total yield) or phenoxide ion (in 51 % of total yield), but with different regioisomeric ratios.



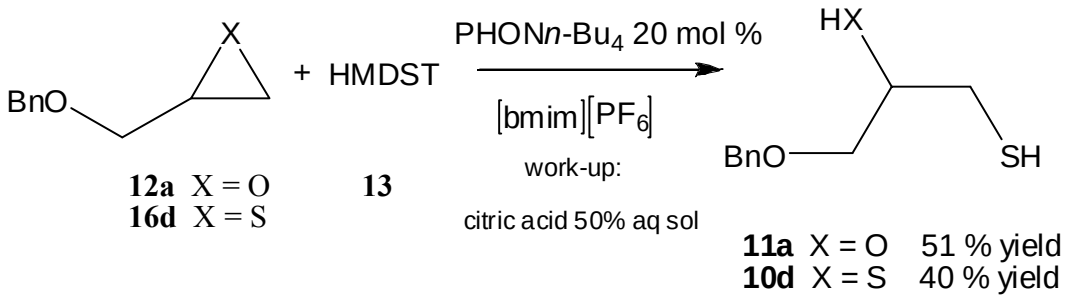
Scheme 31

2.3.2. Ring opening of epoxides and episulfides with HMDST under catalysis of phenoxide ion in ILs

Finally, we tried to extended the protocol under phenoxide ion catalysis to the use of labile HMDST, with the aim to obtain β-mercaptoalcohols **11** and 1,2-dithiols **10**.

When we reacted benzylglycidol **12a** with HMDST **13** and a catalytic amount of PhON*n*-Bu$_4$, a clean reaction occurred, leading to the isolation of the mercaptoalcohol **11a** with total regioselectivity, in moderate yield after purification on silica gel (Scheme 32).

In the same way, the ring opening of **16d** in such reaction conditions afforded regioselectively the corresponding 1,2-dithiol **10d** in moderate yield after purification, due to the oxidation of the -SH group.



Scheme 32

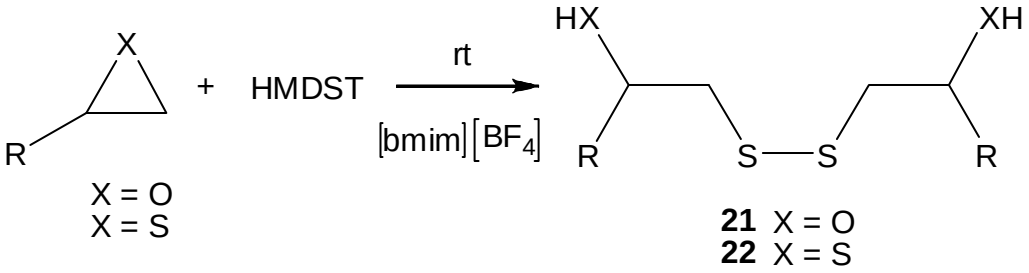
Performing the reactions in ILs, no trimethylsilyl ether formation was detected, as observed for the corresponding reaction in THF, but only hydroxy compounds were isolated.

Experiments about the recyclability of ILs were performed, and ILs were reused without any appreciable loss of activity.

2.4. Spontaneous reactivity of organosilanes in ionic liquids

It is worthwhile mentioning that in ILs, reactions of organosilanes occurred also spontaneously without the use of any catalyst, even if with a noticeable slowering of the rate.

In fact, due to the high polarity of ionic liquids with consequent polarization of the S-Si bond, uncatalysed ring opening reactions of epoxides and episulfides occurred with HMDST, leading to the formation of β-hydroxy and β-mercapto disulfides, **21** and **22** respectively (Scheme 33).



Scheme 33

Results of this investigation are summarized in Table 8.

Table 8. Synthesis of β-thio-derivatives

entry	X	R	product	yield (%)[a]
1	O	(±)-CH_2OBn (**12a**)	**21a**	27
2	O	(*R*)-CH_2OBn (**12f**)	**21f**	31
3	O	CH_3 (**12g**)	**21g**	21
4	O	CH_2O*i*-Pr (**12b**)	**21b**	25
5	S	CH_2O*i*-Pr (**16c**)	**22c**	19

[a] Based on isolated yield.

In some cases, ring opening products were isolated as mixtures of hydroxy compounds and their trimethylsilyl ethers, but simple treatment with 0.2 equivalents of TBAF afforded the desired β-hydroxy derivatives.

Due to the longer reaction times and to the easy polymerization of thiol-groups, the ring opening products were obtained as dimers, also performing the work-up in the presence of anti-oxidant citric acid.

Chiral compounds of this kind find possible applications as ligands in asymmetric synthesis.

The S-S bond, moreover, can be reduced with $NaBH_4$, to give the corresponding β-mercapto alcohols and 1,2-dithiols, which can be *in situ* used for further transformations.

The conversion degree of the process is not high, even when carrying out the reaction for several days and trying to heat the system, and starting materials were recovered after purification on silica gel, together with the dimerization products in moderate yields. The reaction proceeded with total regioselectivity for the substrates examined, and no trace of the regioisomer arising from the nucleophilc attack on the more hindered side of the cycle, was detected.

2.5. Conclusions

In conclusion, the results reported in this section showed as the S-Si bond activation of nucleophiles could be extended to the use of alternative and greener reaction media, such as ionic liquids, for the synthesis of bifuctionalized molecules, such as β-mercaptoalcohols, 1,2-dithiols, and β-phenyl thio-derivatives, useful intermediates in the synthesis of more complex molecules and possible ligands for asymmetric synthesis.

The organosilane reactivity in ILs, in terms of yields and stereoselectivity, was completely comparable with that already observed under traditional reaction conditions. These considerations highlighted the total generality and versatility of our synthetic methodologies also in the perspective of more environmental sustainable processes.

The use of different ILs is now under investigation.

Part I

Selenosilane reactivity for the synthesis of selenium containing chiral molecules.

Chapter 3

Synthesis of selenium containing polyfunctionalized molecules in traditional organic solvents

3.1. Introduction

Selenium was discovered by the chemist Jöns Jacob Berzelius in 1818 and during the last decades the chemistry of organoselenium compounds has attracted great interest, from both the synthetic and biologic point of view.[41] Selenated reagents are in fact used either as useful intermediates in the synthesis of selenium containing complex molecules, or heterocyclic compounds.[42]

Selenium is an essential nutrient of fundamental importance to human biology.[43] Selenocysteine, the 21st aminoacid, is a component of selenoproteins, some of which have fundamental enzymatic functions. Selenium functions as a redox centre in enzymes involved in reduction processes. An example of this redox function is the reduction of hydrogen peroxide and damaging lipid and phospholipid hydroperoxides to harmless products, such as water and alcohols, by the family of selenium-dependent glutathione peroxidases. This function helps to maintain membrane integrity and to reduce the propagation of oxidative damage to biomolecules such as lipids, lipoproteins and DNA, with consequent decreasing of cancer risks. Due to the important role of selenoproteins in metabolism, selenium deficiency has adverse consequences in human health. Selenium deficiency is accompanied with loss of immunocompetence and progression of some viral infections, such as Keshan disease, atherosclerosis, HIV-virus, as well as cardiovascular diseases.[43]

Selenium enters the food chain mostly through plants, which take it up from the soil. Food sources of selenium are cereals, fish, liver. Inorganic selenium salts, such as sodium selenite, represent common supplements, but organic forms appear to possess superior properties from both a safety and efficacy standpoint.[43a]

Interest in the use of organoselenium compounds in biochemistry grew with the findings that organoselenium compounds are much less toxic, compared with the inorganic selenium species. During the past decade, the attention has been

directed toward the synthesis of stable organoselenium compounds that could be used as antioxidants, enzyme inhibitors, antitumor and anti-infective agents.[44] In this context, selenated aminoacids such as selenocysteine (Figure 7, left) and selenotyrosine (Figure 7, right), useful intermediates for the synthesis of selenoproteins and heterocyclic compounds, showed themselves activity as antitumor agents.[45]

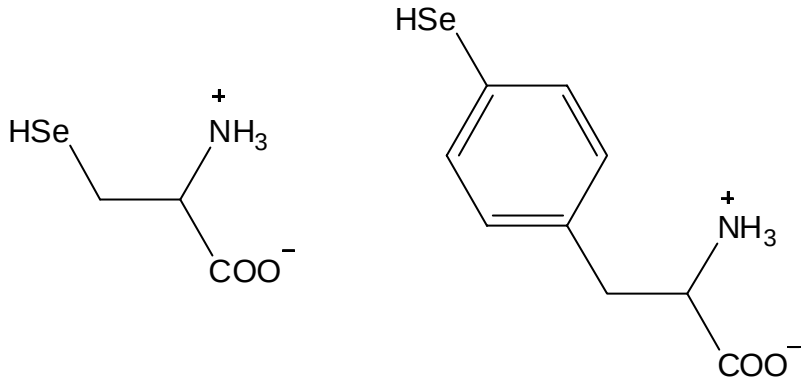


Figure 7

The isosteric replacement of sulfur by selenium showed increasing activity toward biological targets, for example some selenium containing anti-cancer molecules present pharmaceutical activity 50-140 times higher than that of their sulfur analogues.[44] The interchanging of selenium for sulfur can be considered as an important approach that has been extensively used in medicinal chemistry. The unique redox properties of selenium are crucial in the biological activity oh these compounds.

Sometimes the toxicity of selenium compounds becomes the limiting factor of their use in pharmacology; recent investigations highlighted that the toxicity could be lowered by suitable substitutions in the molecular skeleton.

The application of organoselenium compounds in cancer prevention and treatment represents now an important field for selenium research, and nucleoside like the selenium analogues of 6-thioguanosine (Figure 8, left) and 6-mercaptopurine (Figure 8, right) have been studied for their antitumor activities.[44]

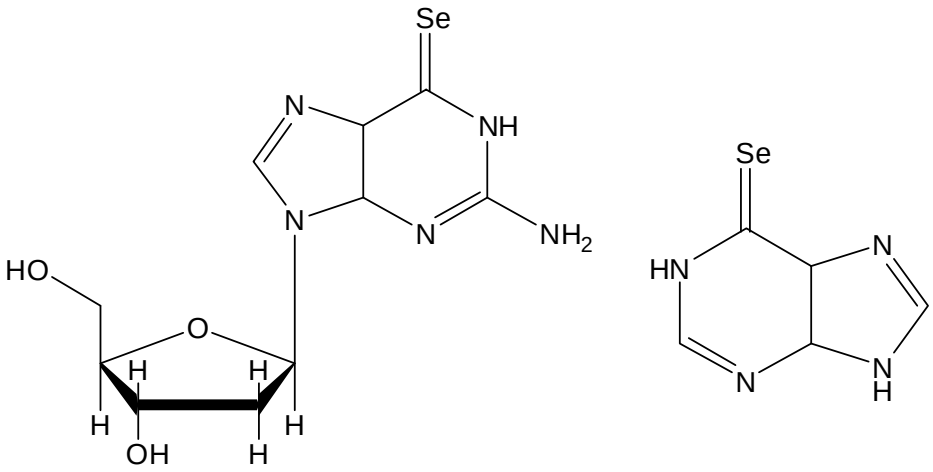


Figure 8

Recently, certain heterocyclic derivatives, such as Ebselen (Figure 9, left) [46] and its *p*-chloro analogue, selenazoles (Figure 9, right) [47] and selenomorpholines (Figure 9, middle) [48] have been evaluated for their antibacterial, antifungal and anti-inflammatory activities, joined together with extremely low toxicity. It is interesting to underline that their corresponding sulfur analogues did not present the same pharmaceutical activity.[44]

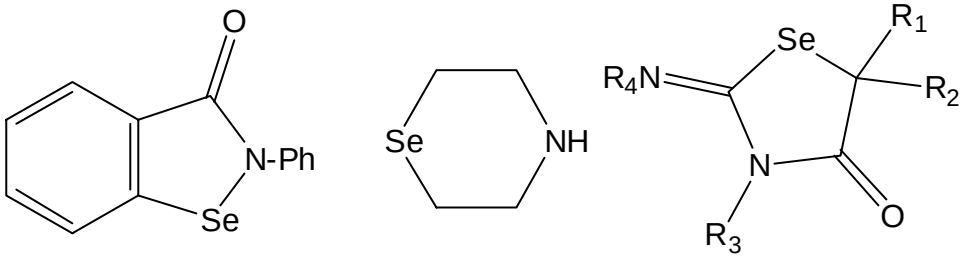


Figure 9

In conclusion, selenium containing molecules present wide applicability in the pharmacological and biological fields as potential drugs for the treatment of diseases, such as cancer and HIV-virus, due to the peculiarity of selenium atom.

Moreover, since last decades several chiral organoselenium reagents found chemical applications as ligands for asymmetric synthesis,[41a, 49] and more recently, selenides have been employed in organocatalysis,[49c] so disclosing the

vast importance of selenium chemistry in the chemical as well as in the biological fields.[41]

3.2.1. Selenosilanes in the ring opening reactions of three-membered heterocycles for the synthesis of β-hydroxy and β-mercapto diselenides, under TBAF catalysis

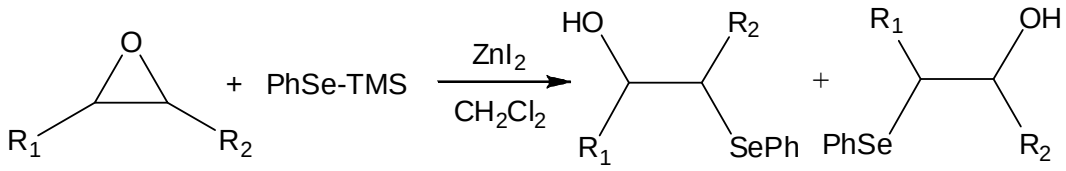
Once established the importance of selenated molecules in the biological, pharmaceutical and chemical fields, the need of developing efficient methodologies for their synthesis appears clear.

Selenated reagents are in fact used either as useful intermediates in the synthesis of heterocyclic compounds or in the synthesis of selenium containing cyclic structures. Although a number of synthetic processes based on selenium chemistry have been reported along the years, little is known about methodologies based on the reactivity of selenosilanes.

Our long dated interest in the chemical behaviour of HMDST, led us to elucidate its efficiency as a useful reagent in the generation of a variety of thiocarbonyl compounds, as well as β-mercapto-derivatives.[15c,d, 29]

On the other hand, the chemistry of the corresponding selenium derivative, bis(trimethylsilyl)selenide (HMDSS, TMS-Se-TMS) **23**[50] has received much less attention, despite the relevance that organoselenium compounds have actually gained.

To the best of our knowledge, only few examples dealing with the reactivity of silyl selenides with heterocyclic rings have been reported. In particular, reactions of phenylseleno(trimethylsilane) towards tetrahydrofurans[51] and epoxides,[52] under basic (*n*-BuLi) or Lewis acid conditions (Scheme 34) were described in the literature. In Scheme 34, the ring opening of differently substituted epoxides with PhSeTMS under catalysis of ZnI_2, afforded β-siloxy-alkyl phenyl selenides; the regioselectivity of the process was not total, depending on the substituting groups on the epoxides and on the reaction conditions.[52a]



Scheme 34

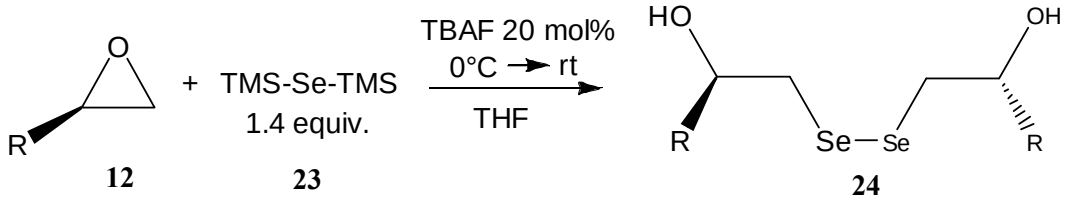
More recently, Tiecco *et al.* reported the synthesis of enantioenriched β-hydroxy selenides by asymmetric ring opening of *meso*-epoxides with different (phenylseleno)silanes, catalyzed by chiral salen(metal) complexes.[52d]

Lewis acid catalyzed reaction of epoxides with the related $PhSeSnBu_3$ has also been reported in the literature.[53]

On the contrary, a large number of papers concerning the reactivity of diselenides and different selenium anions with epoxides have been described in the literature.[54]

In our group, we have already investigated the reactivity of HMDSS **23** (synthesized from elemental selenium, see experimental section), with epoxides that afforded ring opening of these three-membered cycles under fluoride ion catalysis.[55] The reaction in the presence of catalytic amount of TBAF, as fluoride ion source, led to the isolation of β-hydroxy diselenides **24** with total regioselectivity, due to the attack of the nucleophile on the less bulky side of the substrate; when enantiopure heterocycles were reacted under the same conditions, optically active β-hydroxy diselenides were regioselectively formed (Scheme 35). The reaction proved quite general, occurring with aliphatic and aromatic substituents on the epoxide.

Only in the case of styrene oxide was the corresponding regioisomer, arising from the attack of the nucleophile on the more hindered side of the substrate, detected.



R = CH_2Oi-Pr, CH_3, CH_2OBn, (*R*)-CH_2OBn, Ph, CH_2OMe

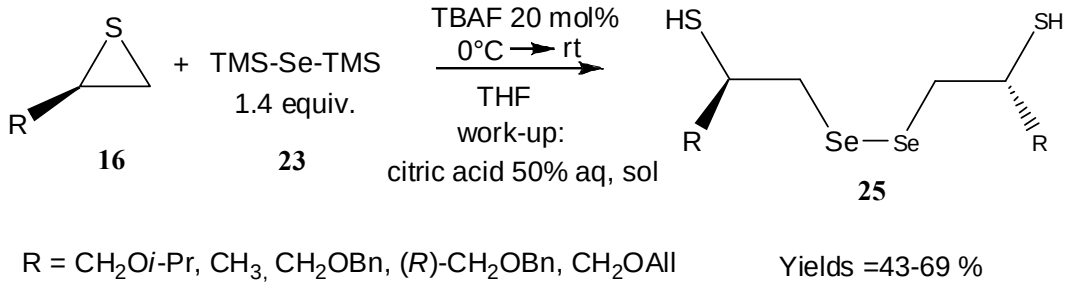
Yields =36-72 %

Scheme 35

In this first screening, several attempts to isolate the β-hydroxy silyl selenide (or selenol) intermediates were unsuccessful, and the corresponding β-hydroxy diselenides **24** were always obtained. In fact, while the treatment of the reaction mixture with anti-oxidant citric acid led to the isolation of β-mercapto alcohols and 1,2-dithiols, as already reported in Chapter 1, in the case of the corresponding selenated compounds the dimerization process occurred in any case, even when carrying the work-up under anti-oxidant conditions. The different behaviour was depending on the easier tendency of the selenols to oxidation, when compared with the corresponding thiols.

We could envisage a plausible reaction mechanism for the activation of the Si-Se bond, completely parallel to the activation mechanism published by Tanabe [26a]for the reaction of PhSTMS, under TBAF catalysis, towards oxiranes (Scheme 13, Chapter 1).

The described reactivity was not limited to epoxides, but was conveniently extended to other ring strained heterocycles, such as episulfides (Scheme 36),[55] leading to a convenient access to several β-mercapto diselenides **25** in good yields.

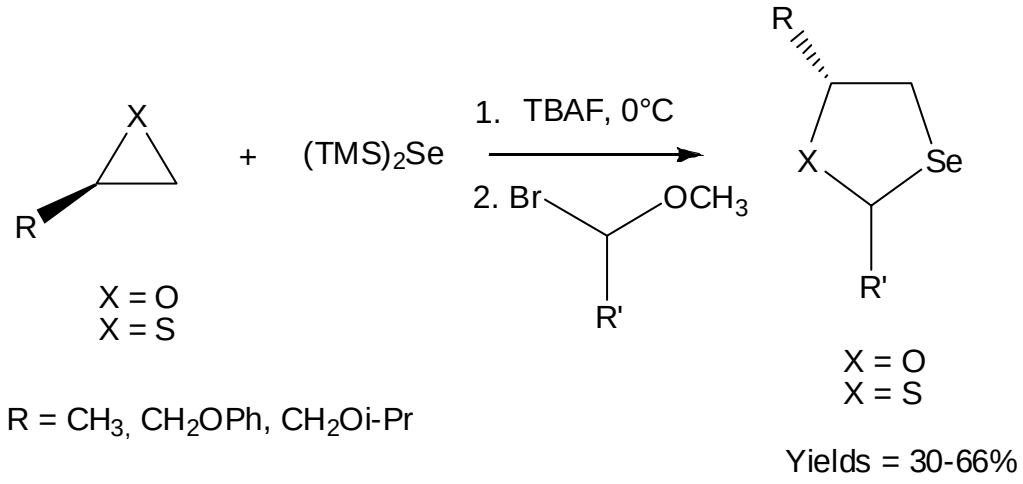


Scheme 36

Nucleophilic attack occurred on the less hindered position of the thiirane, thus providing ring-opening products with total regioselectivity.

Diselenide derivatives of this kind are useful building blocks in organic chemistry for the synthesis of more complex selenium containing molecules, such as heterocyclic compounds, which present biological and pharmaceutical activities. In this context, in the literature, few examples have been reported for the direct synthesis of selenium containing heterocycles, such as 1,3-oxaselenolane. In particular, two examples have been reported in which, after reduction of the Se-Se bond of diselenide intermediates by $NaBH_4$[56] or H_3PO_2,[57] the *in situ* trapping with aldehydes or bromo-acetals, afforded 1,3-oxaselenolanes. Moreover, the synthesis of 1,3-thiaselenolanes has been even more rarely reported.[58]

In our group, we found a direct and highly efficient methodology for the synthesis of 1,3-oxaselenolanes and 1,3-thiaselenolanes in good yields (Scheme 37). [55]



Scheme 37

In such a methodology, when oxiranes or thiiranes were treated with HMDSS in the presence of 1-bromo-1-methoxy derivatives, the expected 1,3-oxaselenolanes and 1,3-thiaselenolanes were obtained as mixtures of *cis* and *trans* diastereoisomers, arising from the in situ trapping of the β-hydroxy or β-mercapto selenol intermediates by the bromo derivatives.

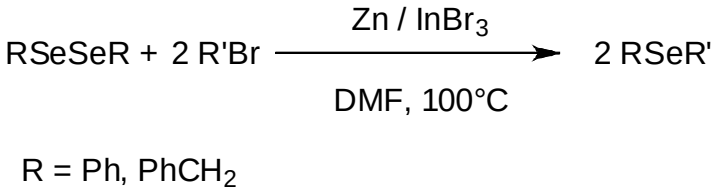
3.2.2. HMDSS as versatile reagent for the selective synthesis of β-hydroxy and β-mercapto selenides, under TBAF catalysis

Taking advantage of the previuosly reported reactivity of HMDSS, and considering that chiral products, such as β-mercapto diselenides and β-hydroxy diselenide could be used as ligands for suitable metals in the construction of optically pure metal complexes for asymmetric synthesis,[49] we turned our attention to find a general and efficacious methodology for the chemoselective synthesis of the corresponding chiral β-functionalized selenides.

In fact, the evaluation that β-functionalized diselenides and β-functionalized selenides could act as chiral bidentate ligands with different spacing, prompted us to find a general and direct methodology for their selective synthesis.

In the literature, many examples have been described for the synthesis of selenides through reduction of diselenides, affording selenium anions which were

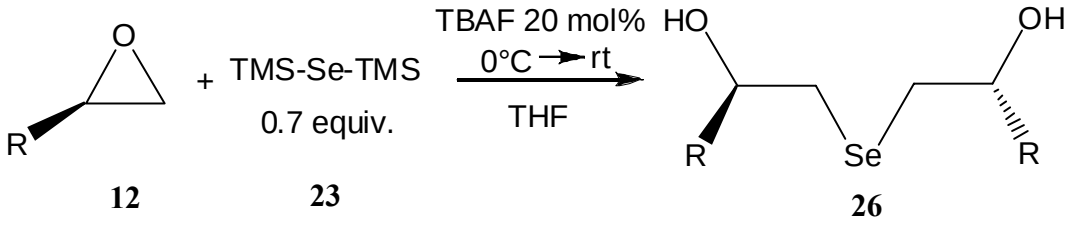
in situ trapped with electrophiles.[59] Nevertheless, selenides were often recovered in mixtures with the corresponding diselenides, and their purification was difficult, thus limiting the versatility of the processes. In Scheme 38 is reported an example in this direction, concerning the synthesis of asymmetric selenides through reductive cleavage of preformed diorganyl diselenides, catalyzed by In(III) and mediated by Zn.[59d]



Scheme 38

In this context, our intention was to investigate the possible selective and direct access to chiral diselenides or selenides, by using HMDSS in the ring opening reactions of epoxides and episulfides, under catalysis of fluoride ion. HMDSS turned out to be a versatile seleno nucleophile, effectively activated by fluoride ion catalysis under mild reaction conditions and as a consequence, we envisaged the possibility to synthesize chemoselectively diselenides or selenides only through the control of the stoichiometric ratio of the reagents.

The results outlined in the previous section showed that the reaction between ring strained cycles (as electrophiles), and 1.4 equivalents of HMDSS, led to the isolation of differently β-substituted diselenides; the further step was to carry out the reaction in the same reaction conditions, but using double amount of electrophiles, in comparison with HMDSS (Scheme 39).



12 **23** **26**

Scheme 39

With our delight, the reaction of epoxides with 0.7 equivalents of HMDSS under catalysis of TBAF, allowed to obtain with high selectivity, β-hydroxy-selenides **26** in moderate to good yields. The reaction proved totally regioselective, with the attack of the seleno nucleophile on the less hindered position of the substrate and, when enantiopure epoxides were reacted, optically active β-hydroxy-selenides were regioselectively formed (Table 9, entry 2).

Table 9. Synthesis of β-hydroxy selenides in THF under TBAF catalysis

entry	R	product	yield (%)[a,b]
1	(±)-CH_2OBn (**12a**)	**26a**	56
2	(*R*)-CH_2OBn (**12f**)	**26f**	59
3	CH_2OCH_3 (**12h**)	**26h**	61

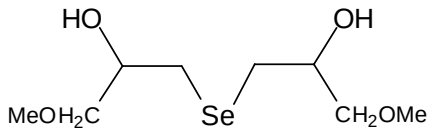
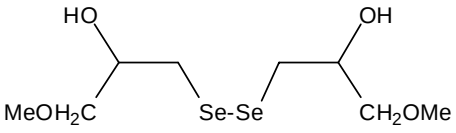
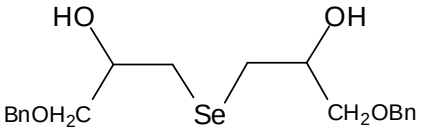
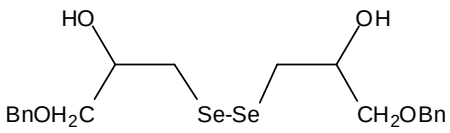
[a] Based on isolated yield.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{77}Se-NMR and mass spectroscopy.

The univocal assignment of the structures was not possible on the base of ^{1}H-NMR and ^{13}C-NMR spectroscopies**,** because the differences of the chemical shifts were usually not significant to distinguish between β-hydroxy diselenides and β-hydroxy selenides.

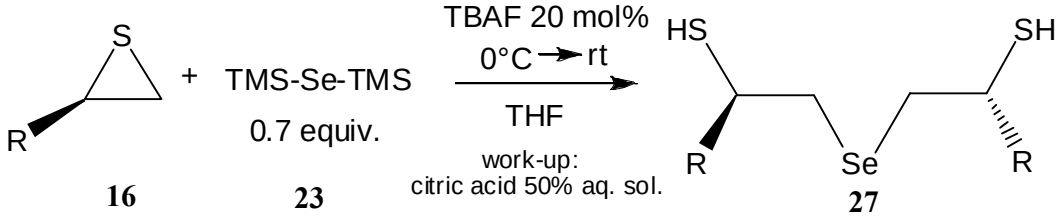
^{1}H-NMR and ^{13}C-NMR analysis of these two classes of compounds (β-hydroxy diselenides and β-hydroxy selenides) allowed to recognize a specific trend in which chemical shifts of the proton and carbon at α-position in selenides usually resonated at upfield from that of diselenides. Nevertheless, these differences were not enough for the univocal assignment of the structures.

On the other hand, the differences in the ^{77}Se-NMR chemical shifts were substantial and it was possible to find two specific ranges for the chemical shifts of the two classes of compounds, which were distant more than 200 ppm (Table 10). In this way the assignment of the structures was unambiguous.

Table 10

2-hydroxy selenide ^{77}Se-NMR (ppm)	2-hydroxy diselenide ^{77}Se-NMR (ppm)
 69	 280
 71	 278

The scope of the reaction was extended with success to the ring opening of thiiranes, affording under the same reaction conditions, β-mercapto selenides **27** with total regioselectivity and enantioselectivity (Scheme 40, Table 11).



16 **23** **27**

Scheme 40

The isolation of the compounds was possible through an easy work-up consisting in the treatment with an anti-oxidant citric acid solution, to avoid the oxidation of the thiol-groups. In same cases, the products were recovered from the reaction medium pure enough to be employed in further transformations without purification.

Table 11. Synthesis of β-mercapto selenides in THF under TBAF catalysis

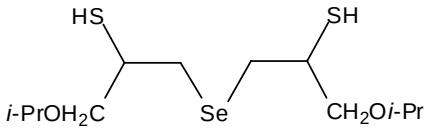
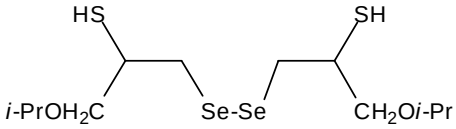
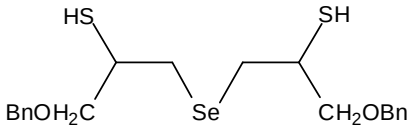
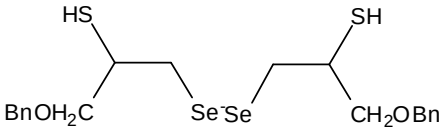
entry	R	product	yield (%)[a,b]
1	CH_2O*i*-Pr (**16c**)	**27c**	50
2	(±)-CH_2OBn (**16d**)	**27d**	52
3	(*R*)-CH_2OBn (**16e**)	**27e**	49

[a] Based on isolated yield.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{77}Se-NMR, and mass spectroscopy.

The assignment of the structures was possible through ^{77}Se-NMR spectroscopy, in accord with the already mentioned case for the corresponding β-hydroxy derivatives.

Also in this case, ^{77}Se-NMR analysis led to the finding of specific ranges of chemical shifts for β -mercapto selenides **27** and diselenides **25**, which were distant almost more 200 ppm (Table 12).

Table 12

2-mercapto selenide ^{77}Se-NMR (ppm)	2-mercapto diselenide ^{77}Se-NMR (ppm)
 122 - 123	 311 - 312
 123 - 124	 311

The ring opening reaction of racemic epoxides and episulfides with HMDSS afforded β-functionalized diselenides and selenides as mixtures of *syn* and *anti* diastereoisomers, which could be, in same cases, distinguished by ^{77}Se-NMR spectroscopy (Table 12).

In conclusion, we have devised a general and efficient methodology for the obtaining of β-hydroxy **26** and β-mercapto **27** selenides by regio- and stereoselective ring opening reaction of epoxides and thiiranes in the presence of HMDSS, under mild catalysis of fluoride ion in THF.

We highlighted the versatility of HMDSS as selenating reagent, with which it was possible to obtain, using the same methodology and only changing the stoichiometric ratios, the corresponding β-hydroxy **24** and β-mercapto **25** diselenides with high selectivity.

The possibility to obtain selenides or diselenides with selectivity has shown fundamental importance, because of the extreme difficulty to separate selenides and diselenides by chromatography.

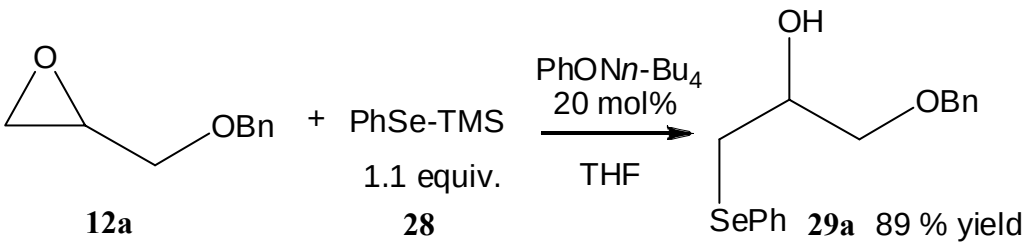
3.3.1. Reactivity of PhSeTMS under catalysis of phenoxide ion in THF

As a further step, we decided to evaluate the possible extension of the selenosilanes reactivity in the presence of phenoxide ion catalysts, due to the advantages that they present when compared with fluoride ion catalysts, as reported in Chapter 1.

In this context, we started to investigate the reactivity of PhSeTMS **28** as nucleophile for the ring opening reactions of three-membered heterocycles under catalysis of PhON*n*-Bu_4.

When benzylglycidol **12a** was reacted with phenylselenotrimethylsilane **28** under catalysis of PhON*n*-Bu_4 in THF, a clean reaction occurred, leading to the isolation in good yield of the β-hydroxy phenylseleno derivative **29a**, thus confirming the versatility of this new catalytic system (Scheme 41).

Compounds of this kind are interesting synthetic intermediates, due to the presence of the PhSe- group that is an excellent leaving group and that allows further transformations.[541]

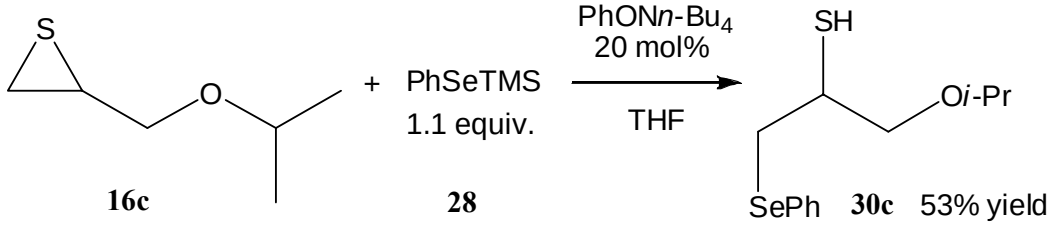


12a

Scheme 41

The nucleophilic attack occurred regioselectively on the less hindered side of **12a**, and no trace of the other regioisomer was detected. The crude was recovered as mixture of hydroxy compound and its trimethylsilyl ether, and simple work up under acidic conditions (citric acid aqueous solution) smoothly afforded the desired phenylselenoalcohol **29a**.

The ring opening of the thiirane **16c** under the same reaction conditions afforded the β-mercapto phenylseleno derivative **30c** with total regioselectivity (Scheme 42).



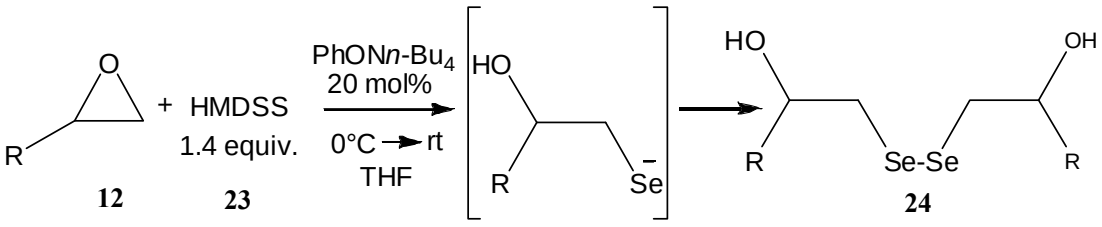
Scheme 42

In this case the work-up under anti-oxidant conditions (citric acid, aqueous solution) allowed to preserve the labile -SH group, even if, during the purification process on silica gel, dimerization occurred with consequent decreasing of the yield (53%).

3.3.2. Synthesis of β-hydroxy and β-mercapto diselenides, under catalysis of phenoxide ion in THF

The efficiency of the phenoxide ion catalysis in the activation of the Se-Si bond was further demonstrated by the use in such reactions of the much more labile, but more intriguing HMDSS **23**.

When differently substituted epoxides were reacted with HMDSS and PhON*n*-Bu_4, a smooth reaction occurred, leading to the synthesis of β-hydroxy diselenides **24**, arising from oxidation of the transient selenols, in comparable yields with those already obtained under fluoride ion conditions[55] (Scheme 43, Table 13).



Scheme 43

Table 13. Synthesis of β-hydroxy diselenides under phenoxide ion catalysis

entry	R	product	yield (%)[a,b]
1	(±)-CH_2OBn (**12a**)	**24a**	59
2	(*R*)-CH_2OBn (**12f**)	**24f**	62
3	CH_2O*i*-Pr (**12b**)	**24b**	57
4	Ph (**12c**)	**24c**	57[c]
5	CH_3 (**12g**)	**24g**	60

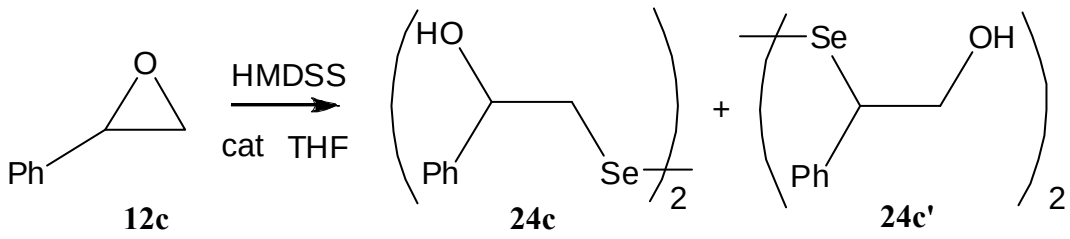
[a] Based on isolated yield.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{77}Se-NMR and mass spectroscopy.
[c] Mixture of two regioisomers.

Attempts to isolate the β-hydroxy silyl diselenide (or selenol) intermediates were unsuccessful.

The reaction proceeded with high regioselectivity and with enantioconservation when enantiopure oxiranes were used (Table 13, entry 2).

Only in the case of styrene oxide (Table 13 entry 4) was the regioisomer arising from the attack of the nucleophile on the more hindered position of the substrate, detected (Scheme 44, Table 14).

Interestingly, when we performed the reaction with styrene oxide under catalysis of both TBAF and PhON*n*-Bu_4, we obtained different regioisomeric ratios of the products **24c** and **24c'**, depending on the catalyst employed.



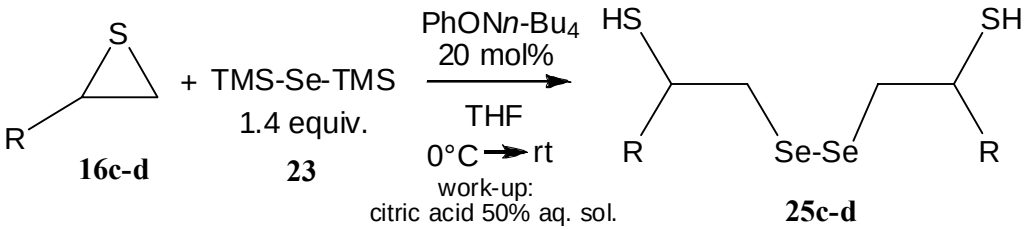
Scheme 44

The results are summarized in Table 14; the assignment of the structures was possible through NMR spectroscopy, and also in this context ^{77}Se-NMR analysis confirmed the presence of both regioisomers as mixture of two diastereoisomers.

Table 14. Regioisomeric ratios of styrene oxide derivatives

TBAF r.r. (**24c**:**24c'**)	PhON*n*-Bu$_4$ r.r. (**24c**:**24c'**)	^{77}Se-NMR (δ ppm) compound **24c**	^{77}Se-NMR (δ ppm) compound **24c'**
95 : 5	75 : 25	281.4 - 280.8	264 - 262

The methodology was extended with success to the ring opening of thiiranes affording, in the same reaction conditions, β-mercapto diselenides **25** in moderate to good yields (Scheme 45, Table 15) with total regioselectivity.



Scheme 45

Table 15. Synthesis of β-mercapto diselenides under phenoxide ion catalysis

entry	R	product	yield (%)[a,b]
1	CH_2O*i*-Pr (1**6c**)	**25c**	43
2	CH_2OBn (1**6d**)	**25d**	40

[a] Based on isolated yield.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{77}Se-NMR and mass spectroscopy.

The obtainment of β-mercapto diselenides **25c-d** resulted more complicate, due to the presence of the thiol-groups which easily undergo oxidation and as a consequence, the yields decreased when compared with those obtained for the β-hydroxy diselenides **24a-g**.

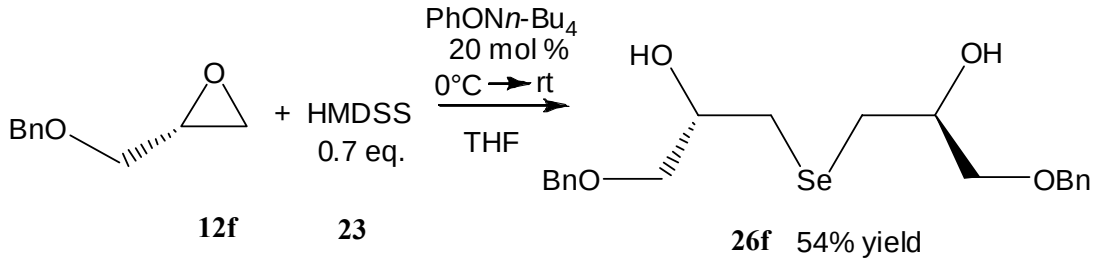
3.3.3. Synthesis of differently β-functionalized selenides under catalysis of phenoxide ion

Once established the efficiency of phenoxide ion in promoting the activation of the Se-Si bond of HMDSS for the synthesis of β-hydroxy and β-mercapto diselenides, it was interesting to evaluate the possibility to obtain differently β-functionalized selenides under catalysis of PhON*n*-Bu_4.

The results already reported for the obtainment of diselenides and selenides under fluoride ion catalysis outlined that a chemoselective synthesis of such molecules was possible simply by changing the stoichiometric ratio of the reagents.

On the ground of these results, we decided to apply the same reaction conditions which allowed to obtain selenides under TBAF catalysis, to the ring opening of epoxides and thiiranes with PhON*n*-Bu_4 as catalyst.

Thus, when 0,7 equivalents of HMDSS were reacted with (*R*)-benzylglicidol **12f**, in the presence of PhON*n*-Bu_4 in anhydrous THF, a smooth regio- and enantioselective reaction occurred, leading to the isolation of the compound **26f** in 54 % yield (Scheme 46).

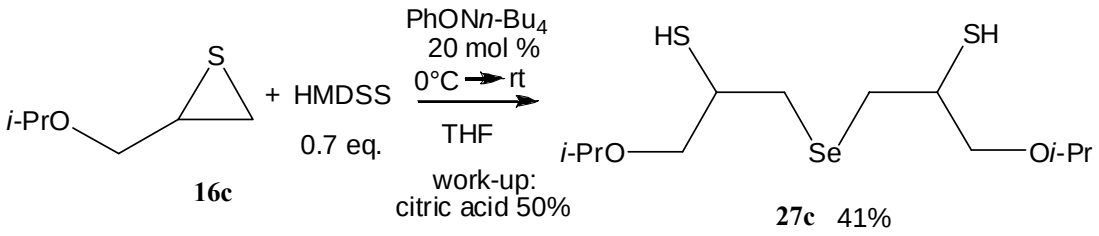


Scheme 46

A little amount (around 5%) of the corresponding β-hydroxy diselenide **24f** was detected in the crude, and several attempts to avoid its formation were unsuccessful.

Again, the reported procedure might represent a simple and versatile approach to access β-hydroxy selenides under PhON*n*-Bu_4 catalysis, as well as under TBAF catalysis.

In order to evaluate the possible extension to the ring opening of thiiranes, we reacted **16c** with HMDSS and PhON*n*-Bu_4 (Scheme 47).



Scheme 47

The reaction occurred regioselectively, leading to the formation of **27c** in quite good yield; also in this case, a little amount of the corresponding diselenide was detected in the crude.

The assignment of the structures was possible by ^{77}Se-NMR analysis, on the ground of the already reported results.

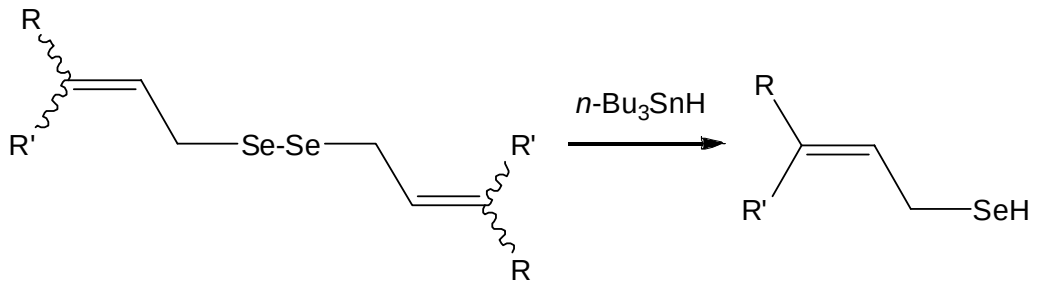
In conclusion, we showed that phenoxide ion catalysis could successfully activate the Se-Si bond of HMDSS for the selective synthesis of diselenides or selenides, versatile intermediates in organic synthesis.

3.4. Synthesis of β-hydroxy and β-mercapto selenols under phenoxide ion catalysis

The investigation concerning the use of phenoxide ion catalysts in the ring opening reactions of epoxides and episulfides allowed the isolation, with our surprise and delight, of β-hydroxy and β-mercapto selenols, synthetic intermediates with very limited stability, due to the presence of the selenol-group which undergoes easy oxidation to diselenide.

In the literature not so many examples have been reported for the synthesis of selenols, and usually they required drastic and long procedures.[60]

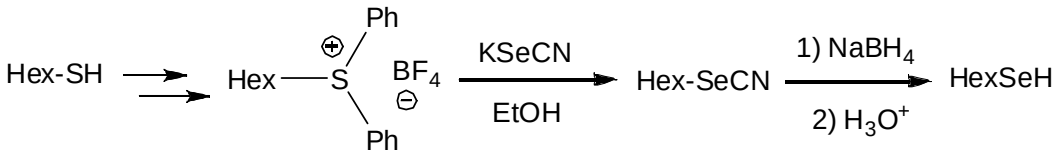
Guillemin *et al.* reported the synthesis of allylic and propargylic selenols starting from diselenides in the presence of *n*-Bu_3SnH, *via* a radical route (Scheme 48). The allylic selenols were prepared in a vacuum line by starting from the crude allylic diselenides by slow addition of *n*-Bu_3SnH, and it was not possible to avoid the formation of the corresponding alkenes. During the addition, selenols were continuously distilled off in vacuo from the reaction mixture, to avoid their oxidation, and conserved at low temperature.[61]



Scheme 48

Another synthetic route to allyl and alkynyl selenols involved selenocyanates as precursors and $LiAlH_4$ as the reagent to form selenolate salts which, after acidification, led to the corresponding selenols.[62]

Recently, Krief *et al.* reported the synthesis of primary-alkyl selenols from primary-alkyl thiols,[63] involving diphenyl sulfonium salts. In this procedure, alkyldiphenylsulfonium tetrafluoroborates reacted with potassium selenocyanate in ethanol affording alkyl selenocyanates which could be reduced to the corresponding sodium alkylselenoates in the presence of $NaBH_4$, to give alkyl selenols after acid hydrolysis (Scheme 49).

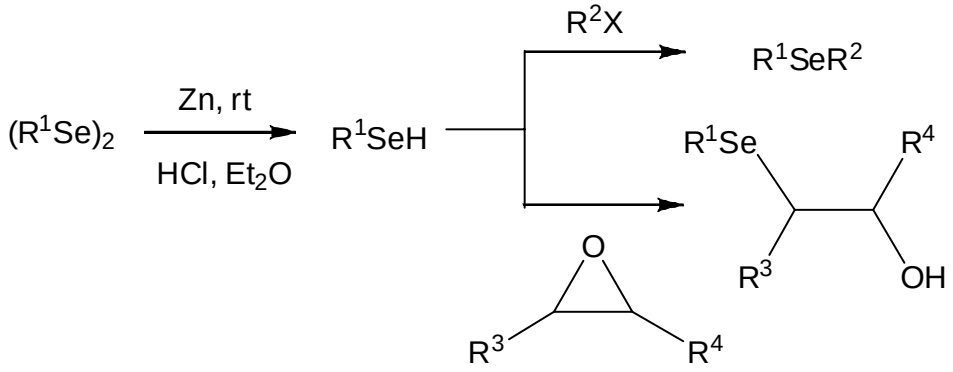


Scheme 49

This procedure allowed to obtain selenols in good yields, but involved several steps.

Usually selenols are trapped *in situ* with electrophiles, and several procedures in this direction have been described in the literature.[64]

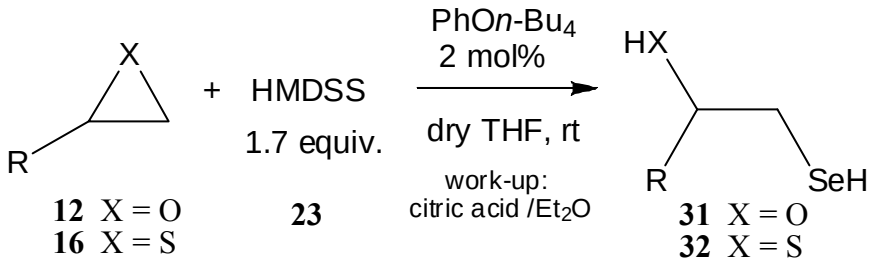
For example, Tiecco *et al.* very recently reported the use of zinc, under acidic conditions, in reducing diselenides to afford selenols, which were trapped with epoxides to give β-hydroxyselenides, or with halides to give selenides (Scheme 50).[64b]



Scheme 50

As showed in these examples, the syntheses of selenols is not direct and not easy. Nevertheless, selenols are interesting intermediates for the synthesis of more complex molecules with biological and pharmaceutical activities and when chiral, for a possible use as ligands in asymmetric synthesis. As a consequence of this wide versatility, an easier and direct access to them is of fundamental importance in organic chemistry, despite their well known instability towards oxidation.

Our investigation concerning the activation of the Se-Si bond of HMDSS promoted by PhON*n*-Bu_4, allowed to synthesize through a direct and easy approach, β-hydroxy selenols **31** and β-mercapto selenols **32** in good yields. In this context, the ring opening of epoxides and episulfides with HMDSS and a catalytic amount of PhON*n*-Bu_4 afforded, with our delight, β-hydroxy and β-mercapto selenols, arising from regioselective attack of HMDSS on the less hindered side of the substrates (Scheme 51).



Scheme 51

In Scheme 51, the optimized reaction conditions have been reported; unexpectedly 2 mol% of catalyst was enough to induce total conversion to the selenols. The possibility to reduce the amount of catalyst to 2 mol% was very important in this context, due to the lability and tendency to oxidation of selenols, that made their purification on silica gel not possible. As a consequence of the small amount of catalyst employed, the selenols could be used directly for further reactions.

The reaction proved completely general, occurring with epoxides as well as with episulfides bearing substituting groups of different nature, and the mildness of the experimental conditions allowed to apply the methodology also to labile glycidol derivatives (Table 16).

The obtainment of such labile compounds was possible by working under inert atmosphere and carrying the work-up in anti-oxidant conditions (addition of solid citric acid to the reaction medium).

Table 16. Synthesis of β-hydroxy and β-mercapto selenols

entry	X	R	product	yield (%)[a,b]	^{77}Se-NMR (δ ppm)
1	O	CH_2OBn (**12a**)	**31a**	67	-79
2	O	Ph (**12c**)	**31c**	44	-48
3	O	C_4H_9 (**12i**)	**31i**	53	-90
4	O	CH_2O*i*-Pr (**12b**)	**31b**	62	-79
5	S	CH_2O*i*-Pr (**16c**)	**32c**	63	-57

[a] Based on isolated yield.
[b] All the products were characterized by ^{1}H-NMR, ^{77}Se-NMR.

The assignment of the structures was supported by ^{77}Se-NMR analysis, that allowed to recognise a specific range of chemical shifts for such molecules.

The reactivity could be promoted also by TBAF, but a little amount of disulfides were observed in some cases.

Concerning the stability of the obtained selenols, we observed that it was strictly depending on the nature of the substituting groups. Precisely, selenols bearing

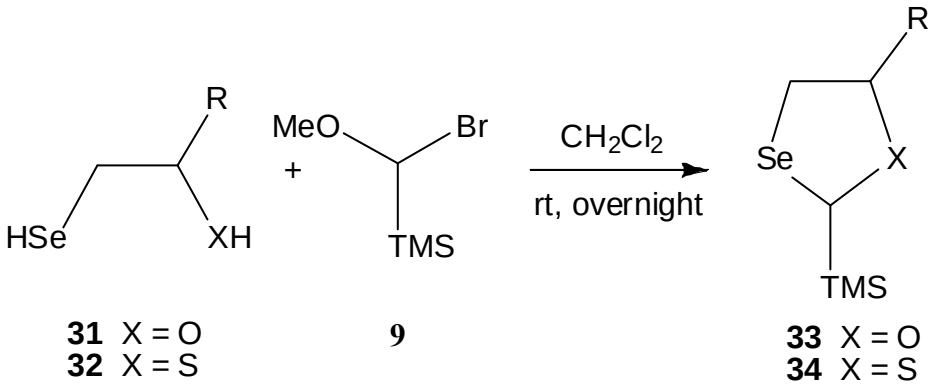
phenyl (Table 16, entry 2) and *n*-butyl group (Table 16, entry3) showed an extremely limited stability, undergoing oxidation to the corresponding diselenides after 3-4 hours, while selenols bearing an oxygen atom in the side chain (Table 16, entries 1, 4, 5) were stable for several days, without decomposition. A possible explanation of such peculiar behaviour was the formation of hydrogen bond which involved the oxygen in the side chain, to stabilize the structures, thus allowing a completely unexpected stability.

3.5. Synthesis of 2-trimethylsilyl 1,3-oxaselenolanes and 2-trimethylsilyl 1,3-thiaselenolanes

As a consequence of the unexpected obtainment and isolation of β-hydroxy and β-mercapto selenols, it was possible to employ them for the synthesis of five-membered selenated heterocyclic rings, bearing a trimethylsilyl-group at position 2, which represent important skeletons present in a number of molecules with biological activity. In fact, due to the presence of the trimethylsilyl-group, they can be further reacted, affording polyfuntionalized heterocyclic units of wide versatility.

The synthesis of 2-silyl-1,3-oxaselenolanes **33** and 2-silyl-1,3-thiaselenolanes **34** was possible by applying the same methodology already reported in Chapter 1 for the synthesis of the corresponding 2-trimethylsilyl-1,3-dithiolanes **2**.

Actually, the treatment of the bifunctionalized selenols in the presence of bromo(methoxy)methyl trimethylsilane **9** led to the isolation of the selenium containing cycles in moderate yields (Scheme 52).



31 X = O
32 X = S

9

33 X = O
34 X = S

Scheme 52

The methodology proved quite general, occurring with β-hydroxy (**31**) and β-mercapto selenols (**32**), and the results are reported in table 17. Due to the mildness of the experimental conditions, this process was successfully applied to useful but labile compounds, such as glycidol derivatives, which represent important structures in different fields.

Table 17. Synthesis of 2-silyl-1,3-oxaselenolanes and thiaselenolanes

entry	X	R	product	yield (%)[a,b]	^{77}Se-NMR (δ ppm)	d.r. (*cis : trans*)[c]
1	O	CH_2OBn (**31a**)	**33**	21	245	> 10 : 1
2	S	CH_2O*i*-Pr (**32c**)	**34**	26	322 - 344	1.5 : 1

[a] Based on isolated yield.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{77}Se-NMR.
[c] Determined by correlation spectroscopy.

^{77}Se-NMR analysis revealed the presence of the thiaselenolane **34** as mixture of two diastereoisomers (Table 17, entry 2), while in the case of 2-silyl-1,3-oxaselenolane **33** (Table 17, entry 1), ^{77}Se-NMR in accord with ^{1}H-NMR and ^{13}C-NMR, confirmed the presence of only one major stereoisomer.

3.6. Conclusions

In conclusion, in this section we outlined the peculiar reactivity of HMDSS as selenating reagent for selective synthesis of differently β-fuctionalized selenium containing molecules, which can be employed as building blocks for the synthesis of complex molecules, as well as possible ligands for asymmetric synthesis. In this context the obtainment of such intermediates was possible under different reaction conditions, such as different catalytic systems, highlighting the wide versatility of HMDSS as seleno nucleophile in ring opening reactions of ring strained heterocycles.

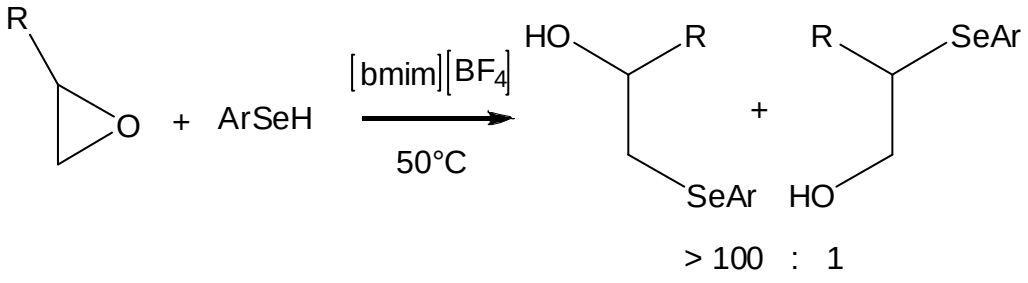
Finally, in the course of our investigation, it was possible, with our delight, to obtain and to isolate β-hydroxy and β-mercapto selenols, the synthesis of which is barely reported in the literature due to their lability. This important result confirmed once more the mildness of our reaction conditions for the obtainment of selenium containing structures.

Chapter 4

Synthesis of selenium containing polyfunctionalized molecules in ionic liquids

4.1. Introduction

The importance that environmentally friendly methodologies have acquired in the last years, turned our interest to the investigation of selenosilane reactivity in alternative and environmentally sustainable organic media, such as ionic liquids.
In Chapter 2 we showed that ionic liquids are excellent solvents for regio- and stereoselective synthesis of sulfur containing polyfunctionalized molecules.
Here, taking advantage of the previously reported results concerning the selenosilane reactivity in traditional conditions, we were interested to evaluate the possibility to extend these methodologies to the use of ionic liquids as reaction media.
To the best of our knowledge, besides few examples of ring opening of three-membered cycles with sulfurated[39] or silylated[40] nucleophiles in ILs, no example has been described of reactions of oxiranes and episulfides with selenosilanes. Very recently, a paper dealing with uncatalyzed highly regioselective ring opening reaction of epoxides promoted by [bmim][BF_4] with arylselenols has been reported, affording the corresponding selenium containing compounds in good yields[65] (Scheme 53).

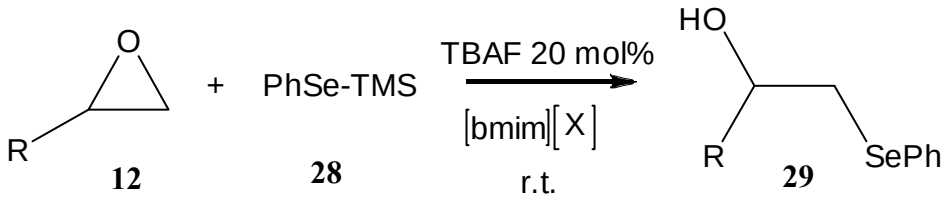


Scheme 53

The investigation of the selenosilane reactivity in ILs has been, until now, not explored; as a consequence, it was really interesting for us the evaluation of using selenosilanes for the synthesis of selenium containing molecules in ILs, also considering the already explained advantages connected with their use.

4.2.1. PhSeTMS reactivity in ring opening reactions of epoxides and episulfides promoted by fluoride ion catalysis, in ILs

The first step of this investigation foresaw the employing of PhSeTMS **28** in the ring opening reaction of epoxides and episulfides promoted by TBAF, to obtain differently β-functionalized phenylseleno-derivatives.
Thus, when epoxides **12** were reacted with PhSeTMS **28** under catalysis of TBAF, a smooth reaction occurred, leading to the isolation of the corresponding β-hydroxy phenylseleno-derivatives **29** in very good yields (Scheme 54, Table 18).



Scheme 54

The reaction was totally regioselective and, with chiral epoxides (Table 18, entry 4), enantioconservation was observed.
The mildness of the experimental conditions allowed, also in ILs, to apply the protocol to labile glycidol derivatives, without removing of the protective moieties.

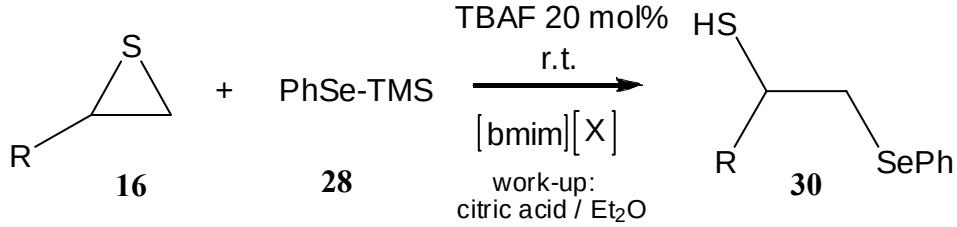
Table 18. Synthesis of β-hydroxy phenylselenides under TBAF catalysis

entry	R	[X]	product	yield (%)[a,b]
1	(±)-CH_2OBn (**12a**)	[BF_4]	**29a**	73
2	(*R*)-CH_2OBn (**12f**)	[BF_4]	**29f**	75
3	CH_2O*i*-Pr (**12b**)	[BF_4]	**29b**	83
4	CH_2O*i*-Pr (**12b**)	[PF_6]	**29b**	85

[a] Based on isolated yield.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{77}Se-NMR, and GC-MS.

Table 18 showed that the reaction was extended successfully to the use of [bmim][BF_4] as well as of [bmim][PF_6], affording comparable results.

The reactivity of **28** was not limited to the use of epoxides, but was conveniently applied to thiiranes, leading to a convenient access to several β-mercapto phenylselenides **30** in good yields (Scheme 55, Table 19). Attack occurred at the less hindered position of thiirane, affording the ring-opening products in good yields and with total regioselectivity.



Scheme 55

Table 19. Synthesis of β-mercapto phenylselenides under TBAF catalysis

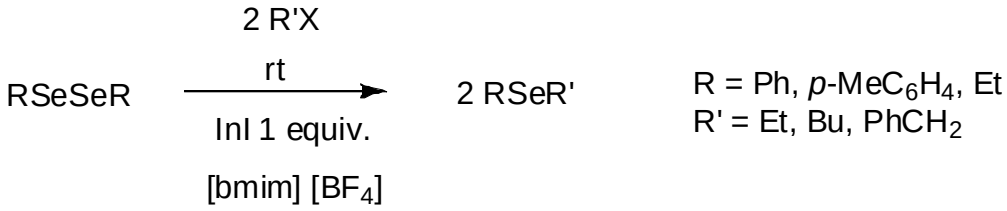
entry	R	[X]	product	yield (%)[a,b]
1	CH_2O*i*-Pr (**16c**)	[BF_4]	**30c**	45[c]
2	CH_2OBn (**16d**)	[PF_6]	**30d**	68
3	CH_2O*i*-Pr (**16c**)	[PF_6]	**30c**	71

[a] Refers to crude products.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{77}Se-NMR, and GC-MS.
[c] In the crude, the dimerization product in 13% yield was also detected.

The use of [bmim][PF_6] allowed to avoid the presence of disulfides, arising from the oxidation of -SH group (Table 19, entries 2-3), while in the presence of [bmim][BF_4] a little amount of disulfide was detected (Table 19, entry 1).

4.2.2. HMDSS in the synthesis of β-hydroxy and β-mercapto selenides and diselenides under fluoride ion catalysis, in ILs

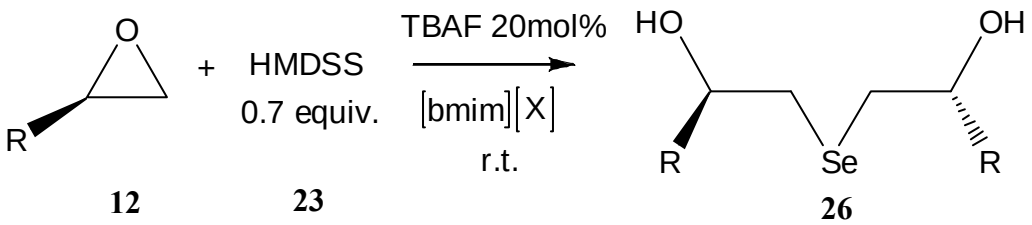
Once established the efficiency of the Se-Si bond activation of PhSeTMS promoted by TBAF, we moved to explore the reactivity of HMDSS for the synthesis of β-hydroxy and β-mercapto selenides and diselenides.
In this context, few examples have been reported in the literature, and in any case, the synthesis of selenides and diselenides involved preformed selenated species.[66]
Recently Braga *et al.*[67] reported the synthesis of unsymmetrical diorganyl selenides promoted by InI. In this methodology, selenides were obtained by reduction of diselenide species and consequent trapping of the intermediates in the presence of alkyl halides (Scheme 56).



Scheme 56

In this direction, our intention was to investigate the possibility to extend the already reported methodologies for the selective synthesis of diselenides or selenides to the use of ILs as reaction media. This possibility was not obvious, because of the completely different properties of such solvents, when compared with the traditional organic media. For example, the high polarity of the ILs could activate HMDSS, leading to a different reactivity than that observed in THF.

Firstly, we studied the ring opening reaction of epoxides in ILs under catalysis of TBAF with 0.7 equivalents of HMDSS, applying the same reaction conditions that in THF allowed to isolate selectively β-hydroxy selenides. It was possible to obtain selenides **26** in good yields with total selectivity (Scheme 57, Table 20), arising from regioselective attack of the seleno nucleophile on the less hindered side of the oxirane; when an enantiopure epoxide was reacted, the optically active β-hydroxy selenide **26f** was regioselectively obtained (Table 20, entry 2).



12 **23** **26**

Scheme 57

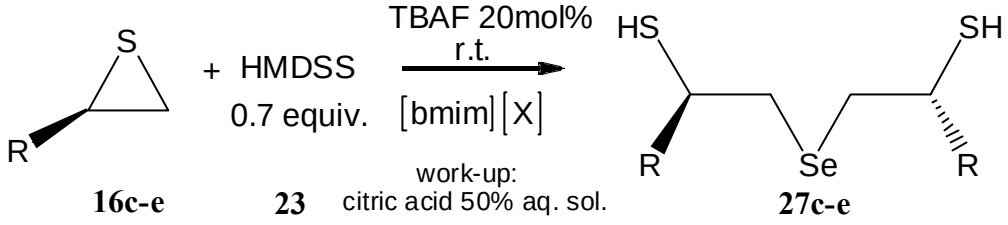
Table 20. Synthesis of β-hydroxy selenides in ILs, using TBAF

entry	R	[X]	product	yield (%)[a,b]
1	(±)-CH_2OBn (**12a**)	$[BF_4]$	**26a**	65
2	(*R*)-CH_2OBn (**12f**)	$[BF_4]$	**26f**	59
3	CH_2OCH_3 (**12h**)	$[BF_4]$	**26h**	69

[a] Refers to isolated products.
[b] All the products were characterized by ^1H-, ^{13}C-, ^{77}Se-NMR.

It is important to underline that our procedure allowed a direct synthesis of selenides, without employing preformed selenated species, as reported in the literature.

The procedure was extended to the ring opening of episulfides, affording in the same conditions, β-mercapto selenides **27** in quite good yields (Scheme 58, Table 21) with regioselectivity and enantioconservation.



16c-e **23** **27c-e**

Scheme 58

Table 21. Synthesis of β-mercapto selenides in ILs, using TBAF

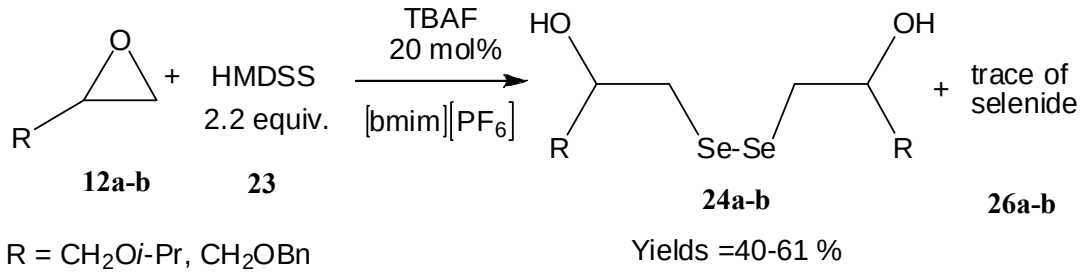
entry	R	[X]	product	yield (%)[a,b]
1	CH_2O*i*-Pr (**16c**)	$[BF_4]$	**27c**	48
2	(±)-CH_2OBn (**16d**)	$[PF_6]$	**27d**	59
3	(*R*)-CH_2OBn (**16e**)	$[PF_6]$	**27e**	55

[a] Refers to isolated products.
[b] All the products were characterized by ^{1}H-, ^{13}C-, ^{77}Se-NMR.

On the other hand, some difficulties were found in the selective obtainment of the corresponding β-functionalized diselenides in ILs. In fact, they could not be synthesized selectively in ILs, by changing the stoichiometric ratio of the reagents, as observed in THF.

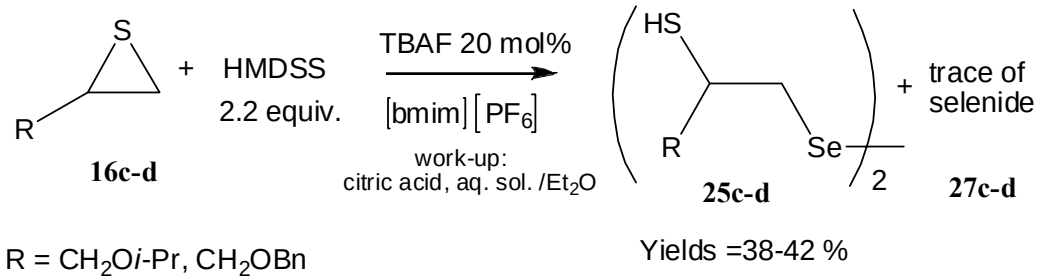
Probably in this context, the polarity of the ILs played a fundamental role in the activation of the species, facilitating the elongation of the Se-Si bond in the β-hydroxy silyl selenol intermediates, which gave nucleophilic attack onto a second molecule of electrophile, so leading to the formation of selenides rather than undergo dimerization. As a consequence selenides were isolated in mixture with the corresponding diselenides.

Attempts to avoid the second nucleophilic attack of the intermediate onto the electrophile were unsuccessful; nevertheless it was possible to reduce the amount of diselenide, by increasing the dilution of the reaction mixture and using 2.2 equivalents of HMDSS. Precisely, while the concentration used until now in ILs was around 0.6 M, we set up the reaction using an excess of HMDSS (2.2 equivalent) in 0.2 M solution. Thus, when we reacted epoxides in such new conditions under catalysis of TBAF, it was possible to obtain β-hydroxy diselenides **24** in good yields with total regioselectivity (Scheme 59), with a little amount of the corresponding selenides **26** (around 10-15%).



Scheme 59

The methodology proved quite general and was extended also to the ring opening of thiiranes, leading to the isolation of β-mercapto diselenides **25** and a little amount of the corresponding selenides **27** (Scheme 60).

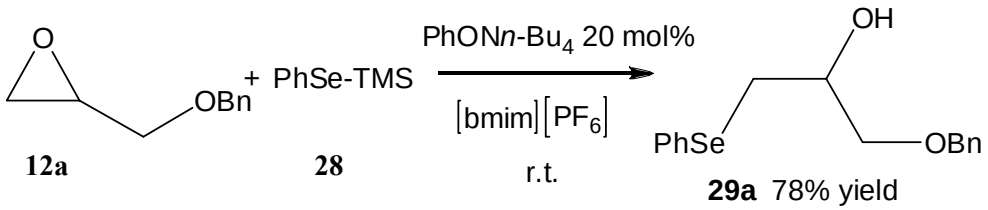


Scheme 60

In summary, the use of fluoride ion in promoting the reactivity of silyl selenides in ILs allowed to obtain differently β-functionalized selenium containing molecules, with high selectivity. Nevertheless, the different properties of ILs, when compared with traditional solvents, required to set up specific reaction conditions to increase the selectivity. Obviously, the advantages of this method included the possibility to reuse ILs for three or more runs, without any appreciable loss of the reactivity.

4.3.1. PhSeTMS reactivity in ILs for ring opening reactions of epoxides and episulfides, promoted by phenoxide ion catalysis

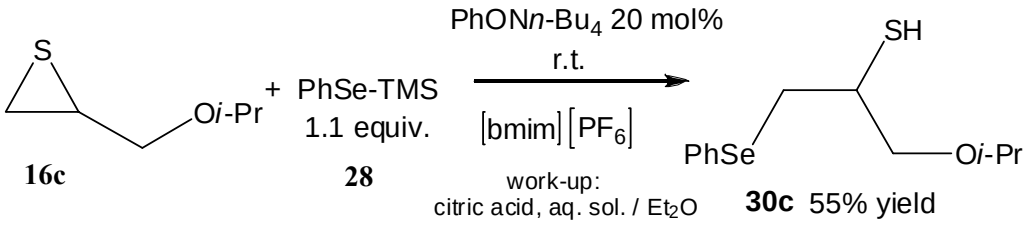
The drawbacks linked to the use of TBAF, such as the difficulties in having an anhydrous solution, and its stability along with time, prompted us to investigate the activation of the Se-Si bond in ILs induced by phenoxide ion catalysis.
In this direction, firstly we evaluated the ring opening reaction of three-membered heterocycles with PhSeTMS in ILs. Thus, when we reacted benzylglycidol **12a** with PhSeTMs **28** and a catalytic amount of PhON*n*-Bu_4 (20 mol%) in [bmim][PF_6], a clean reaction occurred, affording the β-hydroxy phenylselenide **29a** in good yield with total regioselectivity (Scheme 61).



12a **28** **29a** 78% yield

Scheme 61

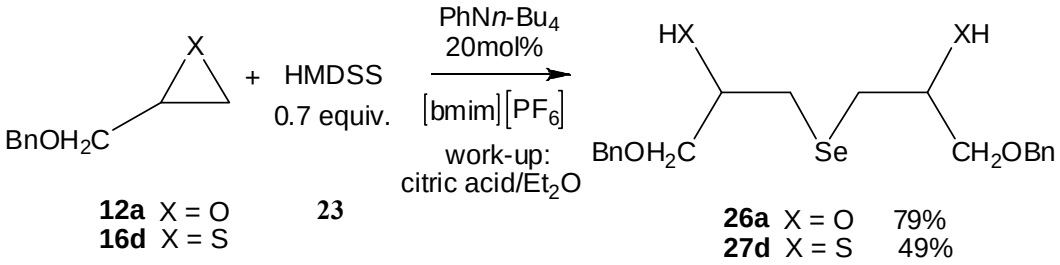
Performing the reaction in ILs, no trimethylsilyl ether formation was observed, like in THF, but only hydroxy compounds were isolated.
The procedure was successfully extended to the ring opening of the thiirane **16c**, leading to the corresponding β-mercapto phenylselenide **30c** with total regioselectivity in 55% yield (Scheme 62).



Scheme 62

4.3.2. HMDSS in the synthesis of β-hydroxy and β-mercapto selenides and diselenides under phenoxide ion catalysis, in ILs

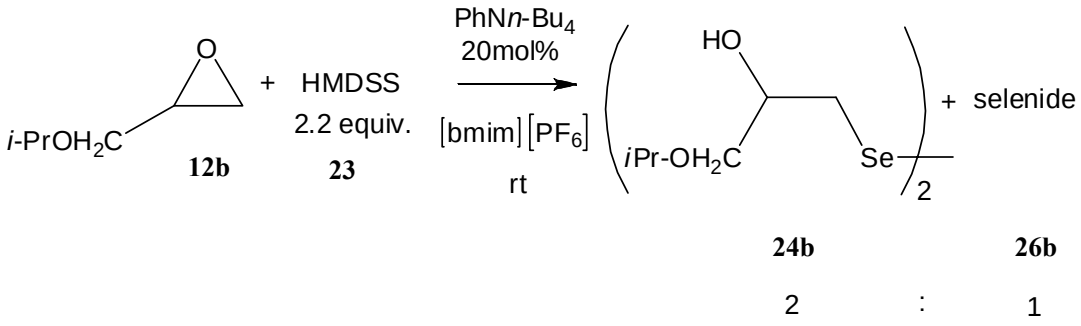
Finally, when we proceeded to apply this methodology to the use of HMDSS as nucleophile for the ring opening reactions of epoxides and episulfides, we found that the different chemical properties of ILs influenced the trend of the reactions.
In this context, when we reacted benzylglycidol **12a** and its thiirane **16d** with 0.7 equivalents of HMDSS under catalysis of PhON*n*-Bu_4, we obtained the β-hydroxy selenide **26a** and the analogous β-mercapto selenide **27d** with total regioselectivity, and no trace of the corresponding diselenides were detected (Scheme 63).



Scheme 63

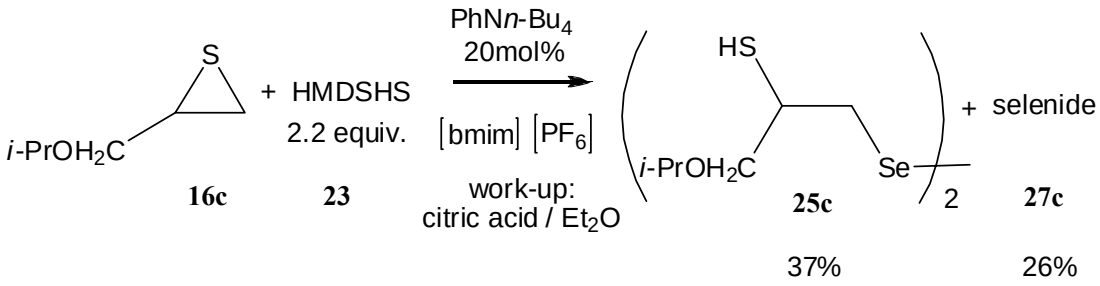
Nevertheless, the reaction to obtain the corresponding diselenides in ILs, as already observed for the reaction catalyzed by TBAF, was not totally selective, affording diselenides in mixture with selenides, also in the presence of a large amount of nucleophile.

Thus, when we reacted the oxirane **12b** in the presence of 2.2 equivalents of HMDSS under catalysis of PhON*n*-Bu_4 in [bmim][PF_6], we obtained a mixture of diselenide and selenide. As a consequence, taking advantage of the previously reported results for the corresponding reaction under catalysis of TBAF, we tried to increase the dilution, and in this case it was possible to reduce the amount of selenide, but not to avoid its formation (Scheme 64). The β-hydroxy diselenide **24b** was recovered in 45% yield.



Scheme 64

The same behaviour was pointed out for the ring opening of the thiirane **16c** under the same reaction conditions. Also in this case the β-mercapto diselenide **25c** was regioselectively formed together with a large amount of the analogous selenide **27c** (Scheme 65), and several attempts to avoid the formation of **27c** were unsuccessful.



Scheme 65

These results completely agreed with those already reported under fluoride ion conditions, thus confirming that the peculiar properties of ILs, such as their high polarity, influenced the activation of the Se-Si bond of the β-hydroxy or β-mercapto silyl selenide intermediates, facilitating a second nucleophilic attack onto the electrophile, rather than the dimerization to the corresponding diselenides.

4.4. Conclusions

In conclusion, the use of ionic liquids as reaction media for ring opening reactions of epoxides and episulfides with seleno nucleophiles led to the regioselective synthesis of differently β-functionalized selenium containing molecules, useful intermediates in organic chemistry.

The activation of seleno nucleophiles in ILs proceeded under fluoride ion catalysis, as well as under phenoxide ion catalysis, thus confirming the high versatility of our methodologies.

These results represented an important improvement in the perspective of environmental benign processes, which combined the use of environmentally friendly solvents with a new catalytic system, the PhON*n*-Bu$_4$, that allowed to overcome the aforementioned drawbacks linked to the use of fluoride ion catalysts.

Chapter 5

HMDSS in the synthesis of seleno-carboxylic acid derivatives

In these last years as previously reported, the syntheses of compounds containing selenium have been widely studied because of their interesting reactivities and their potential pharmaceutical and biological significances. Various methods for the synthesis of selenium-containing compounds, using different selenating reagents have been developed. Among them, the use of alkali metal salts of hydrogen selenide, which can be prepared *in situ* by the reaction of elemental selenium and a reducing reagent such as Li, $LiAlH_4$, Na, $NaBH_4$, $NaBEt_3H$ has been extensively studied.[68] However the use of these selenating reagents was often limited to the synthesis of specific selenated compound classes. In this context we investigated the use of PhSeTMS and HMDSS for the synthesis of seleno-carboxylic acid derivatives, so confirming once more the high versatility of these reagents in the synthesis of selenium containing molecules of different nature.

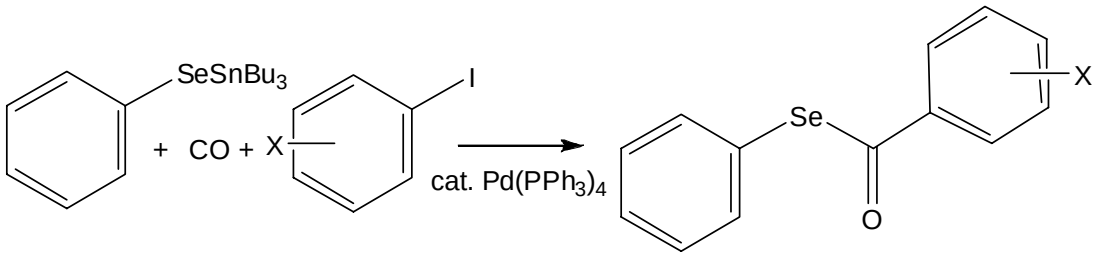
5.1. Synthesis of selenol esters

Selenol esters are important intermediates in organic synthesis and they present wide applicability in different fields: for example they have been used with success as liquid crystals[69] and in the synthesis of steroids and sex hormones.[70] These compounds exhibit also higher reactivity as acyl and aroyl transfer reagents than the corresponding O-analogs. As a consequence of their versatility, the development of a convenient method for their synthesis has attracted valuable attention.

In this context, although several synthetic methods for selenol esters have been reported in the literature,[71] they presented some disadvantages, for example problems connected with handling of organoselenium compounds, which usually are air and moisture unstable, difficulties in preparing organoselenium compounds, and in using acid chlorides which are easily hydrolyzed by water.

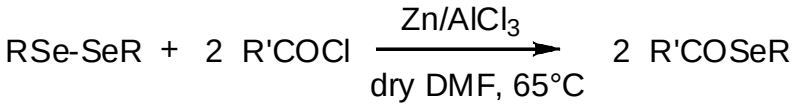
One of the most common synthetic route to selenol esters was the trapping of preformed selenocarboxylate salts with alkyl or aryl halides under different conditions, to give esters in moderate to good yields.[72, 73]

In 2002 Sonoda *et al*. reported an interesting synthesis of selenol esters through palladium-catalyzed coupling of phenyl tributylstannyl selenide, a reagent stable to air and moisture, with aryl iodides and carbon monoxide (Scheme 66). This three-component coupling reaction afforded selenol esters in moderate to good yields, depending on the position of the substituent on the aryl iodide.[74]



Scheme 66

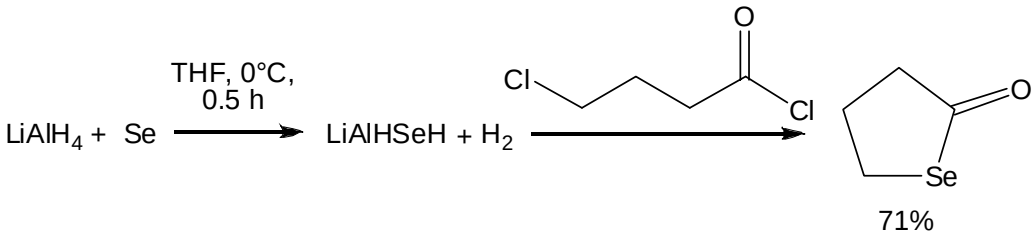
Another common procedure involved the reaction of diaryl or dialkyl diselenides with carboxilic acids derivatives. An example in this direction foresaw the treatment of diselenides with acid chlorides in the presence of $Zn/AlCl_3$ system (Scheme 67).[75]



Scheme 67

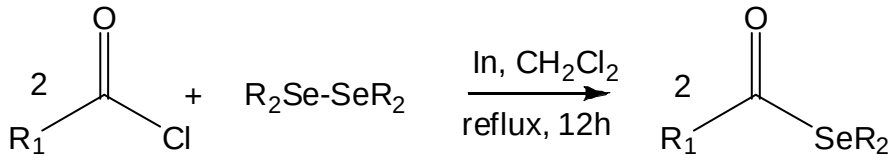
The reductive cleavage of the Se-Se bond led to zinc selenoate intermediates, which underwent nucleophilic displacement with acid chlorides in the presence of aluminium chloride, affording selenol esters.

Moreover, it was interesting to mention the synthesis of γ-selenobutyrolactone by reaction of 4-chlorobutyryl chloride with the *in situ* prepared LiAlHSeH (Scheme 68).[68]



Scheme 68

Finally, very recently Braga *et al.* reported the synthesis of selenol esters mediated by indium metal, which promoted the direct coupling of preformed diselenides and acyl chlorides (Scheme 69).[76]



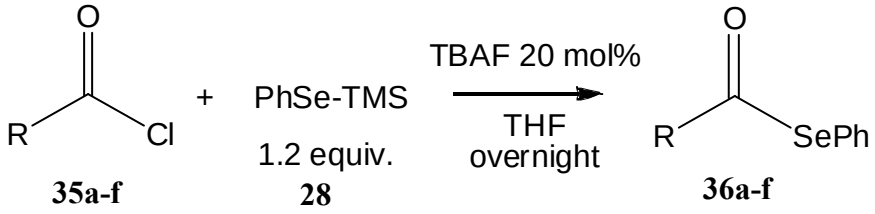
Scheme 69

Nevertheless, as shown by these examples, the synthesis of selenol esters required the use of preformed selenating compounds, which were often unstable to air and moisture, and tedious and long procedures.

As a consequence, the need to find a general and easy approach for the synthesis of such intermediates turned our attention to the possibility of using selenosilanes, activated by fluoride ion catalysts, in the obtainment of selenol esters in the presence of acyl chlorides.

In this context, the reactivity of PhSeTMS **28** induced by TBAF was investigate with several aliphatic, aromatic and heteroaromatic carboxylic acid derivatives **35** in THF.

With our delight, the reaction occurred successfully, leading to the isolation, after purification on silica gel, of phenyl-selenyl esters **36** in good yields (Scheme 70, Table 22).



35a-f **28** **36a-f**

Scheme 70

The fundamental improvement of our methodology, when compared with those previously reported in the literature, consisted in the use of stable and commercially available PhSeTMS as selenating reagent. Then, this general approach was applied with success to aromatic and aliphatic acid chlorides.

Table 22. Synthesis of selenol esters

entry	R	product	yield (%)[a,b]	^{77}Se-NMR (δ ppm)
1	C_6H_5 (**35a**)	**36a**	73	637
2	*p*-Cl-C_6H_4 (**35b**)	**36b**[71e]	75	638
3	*p*-CH_3O-C_6H_4 (**35c**)	**36c**	70	624
4	*o*-CF_3-C_6H_4 (**35d**)	**36d**	71	679
5	C_3H_7 (**35e**)	**36e**	61	655
6	$CH_3(CH)Cl$ (**35f**)	**36f**	59	651

[a] Based on isolated yield.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{77}Se-NMR and mass spectroscopy.

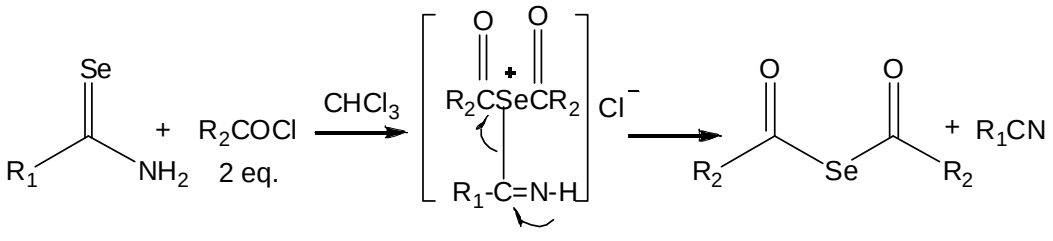
The structures were assigned by spectroscopic analysis, and ^{77}Se-NMR studies allowed to devise a specific range of chemical shifts for this class of molecules (Table 22). ^{77}Se-NMR spectroscopy is one of the most useful methods for structure identifications, however reports including ^{77}Se-NMR chemical shifts have scarcely appeared in the literature.

5.2. Synthesis of diacyl selenides and diacyl diselenides

Diacyl selenides and diselenides are useful transfer reagents for acyl or aroyl groups onto various organic compounds. Despite this, probably due to their instability, the synthesis of diacyl selenides and diselenides has been not frequently reported in the literature.

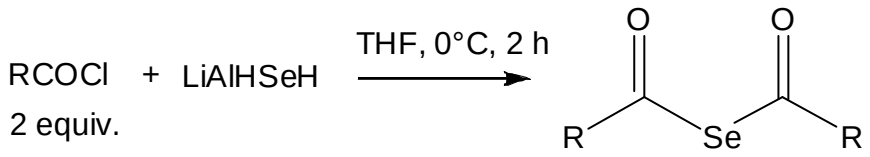
Some methods have been desribed during the years,[77] but they presented several disadvantages, as previously underlined in the case of selenol esters, such as the use of expensive and unstable reagents, the limited availability of the starting materials, the difficulties of purification, particularly evident for diacyl selenides and diselenides, and the high number of steps required.

An interesting procedure to obtain diacyl selenides involved the reactivity of selenoamides, prepared by the reaction of aryl nitriles with sodium hydroselenide, towards acyl chlorides (Scheme 71). The yields were satisfactory, but the method required the long preparation of selenoamides, which were very unstable.[78]



Scheme 71

In 2002 a paper dealing with LiAlHSeH as useful selenating reagent for the synthesis of a wide range of selenium-containing molecules, included diacyl selenides and diacyl diselenides, has been reported. This method allowed to isolate diacyl selenide in high yields by a single step, instead of the long previously reported procedures (Scheme 72).[68, 79]

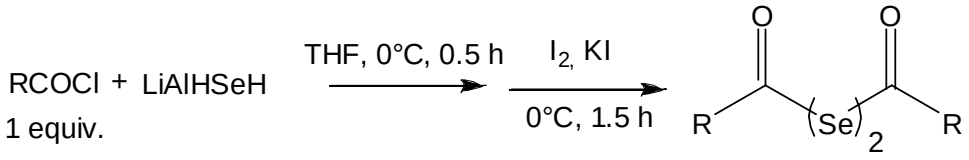


Scheme 72

Nevertheless, the selenating agent LiAlHSeH, synthesized *in situ* with elemental selenium and $LiAlH_4$, was unstable and it required to be used quickly once prepared, so limiting the applicability of such procedure.

Moreover, in the literature few examples have been described concerning the synthesis of diacyl diselenides.

A possible synthetic route to diacyl diselenides has been reported in the same paper,[79] in which oxidation in the presence of I_2 of the intermediate, arising from the already reported reaction of LiAlHSeH with one equivalent of acyl chloride, led to the isolation of the corresponding diacyl diselenide in good yields (Scheme 73).



Scheme 73

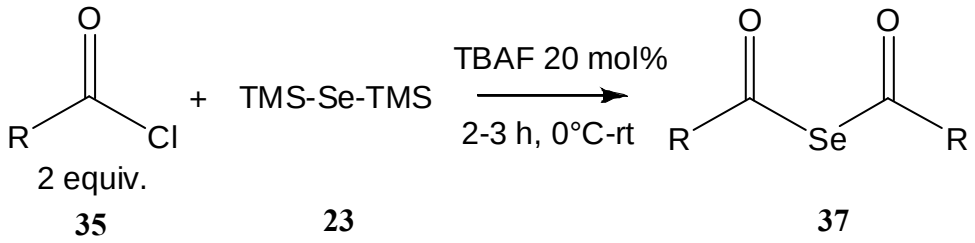
The present paper gave the selective preparation method of diacyl selenides and diacyl diselenides through the control of the reaction conditions, but the lability of LiAlHSeH was a drawback of this approach.

Finally, a direct way to the synthesis of such compounds was described by Nishiyama, where the possibility of the selective synthesis of bis(acyl) selenides or diselenides was investigated through the reaction of selenoate anions (HSe^- or HSe_2^-) with acyl chlorides, but the reaction conditions were quite drastic.[73]

In this context, our approach to the synthesis of diacyl selenides and diselenides was based on the reactivity of HMDSS, induced by fluoride ion catalysis, in the presence of acyl chlorides.

Selective obtainment of diacyl selenides or diselenides was possible only by changing the equivalent ratio of acid chloride used.

Actually, the reaction of HMDSS **23** with two equivalents of acyl chloride **35**, under fluoride ion catalysis in anhydrous THF, led to the selective isolation of diacyl selenides **37** in good yields (Scheme 74).



Scheme 74

The reactivity proved quite general and was applied successfully to aromatic, heteroaromatic

and aliphatic acid chlorides (Table 23).

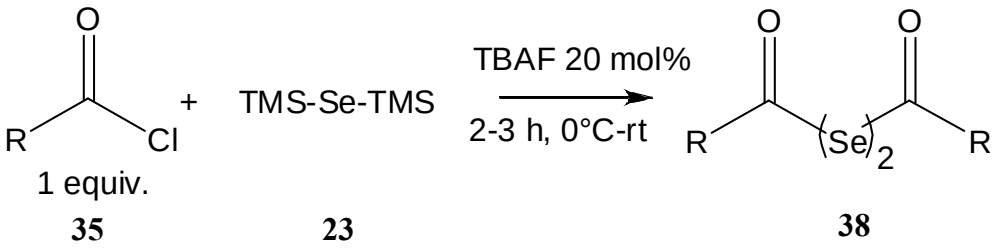
These results were very satisfactory, mostly considering the difficulties in obtaining aliphatic derivatives due to their instability; in our case it was possible to isolate the compound **37f** in 50% yield, after purification on silica gel column chromatography (Table 23, entry 5).

Table 23. Synthesis of diacyl selenides

entry	R	product	yield (%)[a,b]
1	C_6H_5 (**35a**)	**37a**	80
2	*p*-Cl-C_6H_4 (**35b**)	**37b**	76
3	*p*-CH_3O-C_6H_4 (**35c**)	**37c**	75
4	$CH_3(CH)Cl$ (**35f**)	**37f**	50
5	thienyl (**35g**)	**37g**	70

[a] Based on isolated yields.
[b] All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{77}Se-NMR.

With our delight, the reaction of HMDSS **23** in the same reaction conditions, but using an equimolar amount of acyl chloride **35**, allowed to obtain directly and selectively diacyl diselenides **38** (Scheme 75).



1 equiv.

35 **23** **38**

Scheme 75

Also in this case the reactivity was general and, due to the mild conditions, it was possible to extend the scope of the reaction to aromatic, heteroaromatic and aliphatic acyl chlorides with good yields (Table 24).

Table 24. Synthesis of diacyl diselenides

entry	R	product	yield (%)[a,b]
1	C_6H_5 (**35a**)	**38a**	83
2	*p*-Cl-C_6H_4 (**35b**)	**38b**	78
3	*p*-CH_3O-C_6H_4 (**35c**)	**38c**	72
4	CH_3(CH)Cl (**35f**)	**38f**	54
5	thienyl (**35g**)	**38g**	73

[a] Refers to isolated products.
[b] All the products were characterized by ^{1}H-, ^{13}C-, ^{77}Se-NMR.

The possibility to obtain diacyl selenides **37** or diselenides **38** with selectivity has shown fundamental importance, because of the extreme difficulty to separate selenide and diselenides by chromatography.

This methodology allowed a selective synthesis of such compounds by a simple change of reaction stoichiometry, so confirming the high versatility of HMDSS as selenating reagent in the obtaining selenated products of different nature.

The structure determination of diacyl selenides and diselenides was possible through ^{77}Se-NMR spectroscopy, in agreement with chemical shifts already reported in the literature.[79]

^{77}Se-NMR is one of the most useful methods to distinguish between selenides and diselenides; in fact on the base of ^{1}H-NMR and ^{13}C-NMR spectroscopy, the univocal assignment of the structures was not possible. For example, the chemical shift differences of C=O in the ^{13}C-NMR spectra of diacyl selenides and diselenides were not enough to distinguish between them, because usually the resonances were completely similar (around 1 ppm of difference).

On the other hand, the differences in the ^{77}Se-NMR chemical shifts were substantial and it was possible to devise two specific ranges for the two classes of compounds, which were distant more than 100 ppm (Table 25).

Table 25. Typical ^{77}Se-NMR chemical shifts of compounds **37** and **38**

	^{77}Se-NMR (δ ppm)	
R	compound **38**	compound **37**
C_6H_5	613	743
p-Cl-C_6H_4	619	749
p-CH_3O-C_6H_4	598	730
thienyl	614	777
$CH_3(CH)Cl$	601	784

5.3. Conclusions

In this section was reported the synthesis of selenol esters, diacyl selenides and diselenides through the reaction of selenosilanes, activated under fluoride ion catalysis, with acyl chlorides.

This methodology proved general and selective, leading to the chemoselective synthesis of different selenocarboxylate acid derivatives, by the simple control of the reaction conditions.

^{77}Se-NMR studies allowed the assignment of the structures and the individuation of specific chemical shift ranges for these classes of compounds.

Experimental section

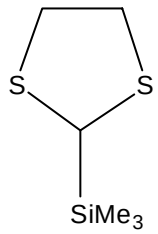
1. General Methods.

NMR spectra were acquired on a Varian Gemini 200 Spectrometer, running at 200, 50.3 and 38.1 MHz for ^{1}H, ^{13}C and ^{77}Se respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR; ^{77}Se NMR analysis are performed in $CDCl_3$ and chemical shifts (δ) are reported in ppm relative to signal of PhSeSePh, (461 ppm)). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a Shimadzu spectrometer connected with Gascromatograph (apolar column ZB-5 30m, 0.25 mm) using electron impact ionization techniques (EI-70eV). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates and glass-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ dip. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Fluka) was used. Optical rotations were measured on a Perkin-Elmer polarimeter (λ=589 nm). The enantioconservation of the products was determined by chiral stationary phase HPLC-Gilson (Kromasil 5-Cellucoat, 4.6 m X 250 mm column). THF was dried by a first distillation over Na and a second distillation over Na and benzophenone. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification.

2. Synthesis of 2-trimethyl-silyl-1,3-dithiolanes.

General procedure. A solution of methoxymethyl trimethylsilane **8** (400 μL, 2.57 mmol) in CCl_4 (5 mL), was treated dropwise with a solution of bromine (132 μL, 2.57 mmol) in CCl_4 (4 mL). The mixture was stirred, with release of HBr, until it became pale orange (around 6 h). The solvent was then evaporated under reduced pressure, and a solution of dithiol **10** (2.57 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added and the mixture was stirred overnight. After washing with water and brine, the organic layer was dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by chromatography on silica gel, to afford the pure compound **2**.

2a 2-trimethyl-silyl-1,3-dithiolane



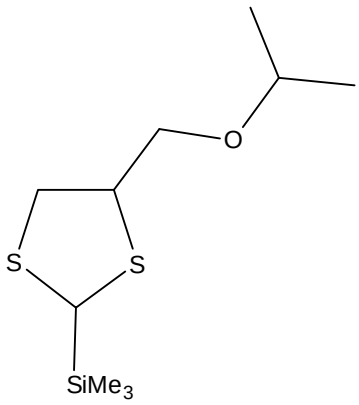
Following the general procedure, **2a** was isolated by chromatography on silica gel (petroleum ether/Et_2O 20:1) in 65 % yield as a yellowish oil.

^{1}H-NMR δ(ppm): 0.18 (9H, s, -Si$(CH_3)_3$), 3.06-3.29 (4H, m, -CH_2CH_2-), 3.53 (1H, s, CH).

^{13}C-NMR δ(ppm): -2.3 (Si$(CH_3)_3$), 37.6, 39.4.

MS m/z (%): 178 (2, M^+), 135 (17), 73 (100, $SiMe_3^+$), 59 (16, CH_2CHS^+).

2c (4-(isopropoxymethyl)- 1,3-dithiolan-2-yl)trimethylsilylane



Following the general procedure, **2c** was isolated by TLC (petroleum ether/Et_2O 100:1) in 44% yield as a yellowish oil, as a mixture of *cis* and *trans* diastereoisomers in ratio 2.5:1 respectively. The assignment of the diastereomeric structures, as well as of the d. r., were made by correlation spectroscopy (NOESY experiments).

Cis diastereoisomer:

^{1}H-NMR δ(ppm): 0.16 (9H, s, -Si(CH_3)$_3$); 1.14 (3H, d, J=6.2 Hz, (C**H$_3$**)$_2$-), 1.15 (3H, d, J=6.2 Hz, (C**H$_3$**)$_2$-), 2.92 (1H, dd, J=5.8, 12.2 Hz, C**H**$_2$S-), 2.93 (1H, dd, J=6.2, 12.2 Hz, C**H**$_2$S-), 3.2-3.42 (3H, m, -CH_2O + C**H**(CH_3)$_2$), 3.56 (1H, s, S-CH-S), 3.76-3.88 (1H, m C**H**-CH_2O-).

^{13}C-NMR δ(ppm): -2.3 (Si(CH_3)$_3$), 22.1 (**C**H_3)$_2$), 22.2 (**C**H_3)$_2$), 37.6; 42.1, 53.7, 70.1, 71.9.

MS m/z (%): 250 (3, M^+), 177 (3), 150 (12), 135 (28), 73 (100, $SiMe_3^+$), 59 (13, *i*-PrO^+).

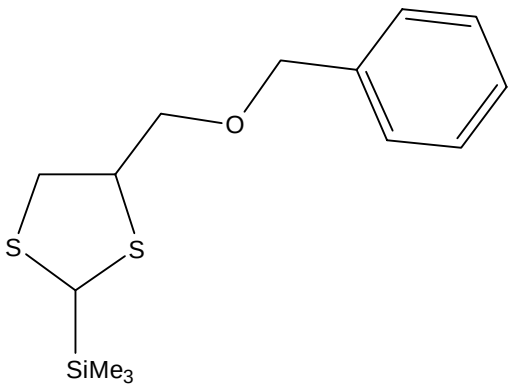
Trans diastereoisomer:

^{1}H-NMR δ(ppm): 0.16 (9H, s, -Si(CH_3)$_3$), 1.15 (6H, d, J=5.8 Hz, (C**H$_3$)$_2$**), 3.12 (1H, dd, J=5.2, 11.4 Hz, C**H**$_2$S-), 3.27 (1H, dd, J=5.6, 11.8 Hz, C**H**$_2$S-), 3.4-3.62 (3H, m, -CH_2O + C**H**(CH_3)$_2$), 3.56 (1H, s, S-CH-S), 3.8-3.92 (1H, m, C**H**-CH_2O).

^{13}C-NMR δ(ppm): -2.4 (Si(CH_3)$_3$), 22.1 (**C**H_3)$_2$), 22.2 (**C**H_3)$_2$), 36.1; 41.7, 54.9, 69.9, 72.1.

MS m/z (%): 250 (3, M^+), 177 (3), 150 (11), 135 (27), 73 (100, $SiMe_3^+$), 59 (12, *i*-PrO^+).

2d (4-(benzyloxymethyl)- 1,3-dithiolan-2-yl)trimethylsilylane



Following the general procedure, **2d** was isolated by TLC (cyclohexane/Et_2O 100:1) in 37% yield as a yellowish oil, as a mixture of *cis* and *trans* diastereoisomers in ratio 1.5:1 respectively. The assignment of the diastereomeric structures, as well as of the d. r., were

made by correlation spectroscopy (NOESY experiments).

Cis diastereoisomer:

^{1}H-NMR δ(ppm): 0.16 (9H, s, -Si(CH_3)$_3$), 2.95 (1H, dd, J=5.6, 12 Hz, C**H**$_2$S-), 2.96 (1H, dd, J=6.4, 11.8 Hz, C**H**$_2$S-), 3.38-3.6 (2H, m, CH-C**H$_2$**-O), 3.56 (1H, s, S-CH-S), 3.84-3.96 (1H, m, C**H**-CH_2O-), 4.53 (2H, s, C**H$_2$**Ph), 7.3-7.4 (5H, m, Ph).

MS m/z (%): 298 (1, M^+), 207 (10, M^+-OC_6H_5), 147 (45), 135 (38), 91 (84, $OC_6H_5^+$), 73 (100, $SiMe_3^+$).

Trans diastereoisomer:

^{1}H-NMR δ(ppm): 0.16 (9H, s, -Si(CH_3)$_3$), 3.12 (1H, dd, J=5.2, 11.4 Hz, C**H**$_2$S-), 3.30 (1H, dd, J=5.6, 11.6 Hz, C**H**$_2$S-), 3.38-3.6 (2H, m, CH-C**H$_2$**-O), 3.57 (1H, s, S-CH-S), 3.98-4.1 (1H, m, C**H**-CH_2O-), 4.55 (2H, s, C**H$_2$**OBn), 7.28-7.36 (5H, m, Ph).

MS m/z (%):298 (1, M^+), 207 (9, M^+-OC_6H_5), 147 (33), 135 (28), 91 (70, $OC_6H_5^+$), 73 (100, $SiMe_3^+$).

$[\alpha]^{rt}_D$ = +26.3 (c=0.9, $CHCl_3$) **2e**, major diastereoisomer.

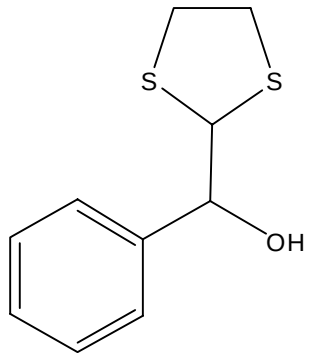
$[\alpha]^{rt}_D$ = +53.1 (c=0.77, $CHCl_3$) **2e**, minor diastereoisomer.

3. Functionalization of 2-trimethyl-silyl-1,3-dithiolanes.

Typical procedure: A solution of $PhONBu_4$ (prepared in accord with the literature)[il] (0.09 mmol, 0.4 equiv.) in dry DMF (0.2 mL) was added under inert atmosphere drop by drop with aldehyde **4** (0.24 mmol, 1.1 equiv.) and 2-trimethyl-silyl-1,3-dithiolane **2** (0.22 mmol, 1 equiv.). Progress of the reaction was monitored by TLC (petroleum ether/ethyl acetate 5:1) and GC/MS, and after 3.5 h the mixture was diluted with diethyl ether and washed with a saturated solution of NH_4Cl. The acqueous phase was extracted with diethyl ether and the combined organic phases were washed with brine and dried over Na_2SO_4.

Filtration and evaporation of solvent gave the crude α-hydroxy dithiolane **5** as yellow oil, that was purified on TLC to afford the pure compound.

5a (1,3-dithiolan-2-yl)(phenyl)methanol

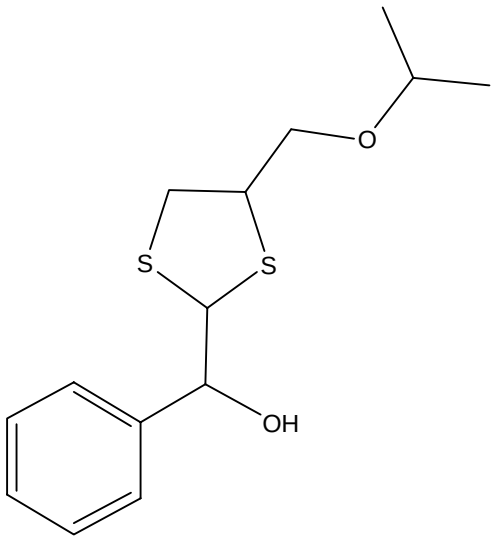


Following the general procedure, **5a** was isolated by TLC (petroleum ether/ethyl acetate 5:1) in 87% yield as a yellowish oil.

^{1}H-NMR δ(ppm): 3.14-3.32 (4H, m, -CH_2CH_2-), 4.62 (1H, d, J=7 Hz, C**H**OH,, 4.79 (1H, d, J=7 Hz, S-C**H**-S), 7.3-7.46 (5H, m, Ph).

MS m/z (%): 135 (0.5, M^+-77); 107 (18); 105 (100, $PhCO^+$); 79 (15); 77 (22).

5c (4(isopropylmethyl)-1,3-dithiolan-2-yl)(phenyl)methanol

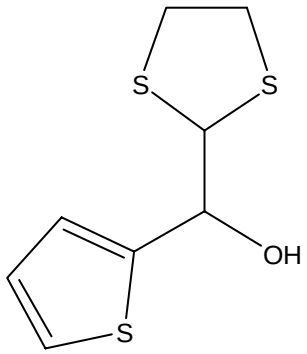


Following the general procedure, **5c** was isolated by TLC (petroleum ether/ethyl acetate 5:1) in 49% yield as a mixture of *cis* and *trans* stereoisomers, as a yellowish oil. Unluckily, the separation of the diastereoisomers was not possible.

^{1}H-NMR δ(ppm): 1.147-1.182 (6H, m, (C**H$_3$)$_2$**), 2.99-3.01 (1H, bs, O**H**), 3.21-3.64 (6H, m, C**H**$_2$S + C**H**-C**H$_2$**-O + C**H**(CH_3)$_2$), 4.63-4.79 (2H, m, SC**H**S + C**H**OH), 7.33-7.40 (5H, m, Ph).

MS m/z (%): 284 (1, M^+), 225 (3, M^+-O*i*-Pr), 193 (2, M^+-91), 177 (48), 135 (5), 119 (100), 91 (15, $OC_6H_5^+$), 73 (76, *i*-$PrOCH_2^+$).

5d (1,3-dithiolan-2-yl)(thiophen-2-yl)methanol.



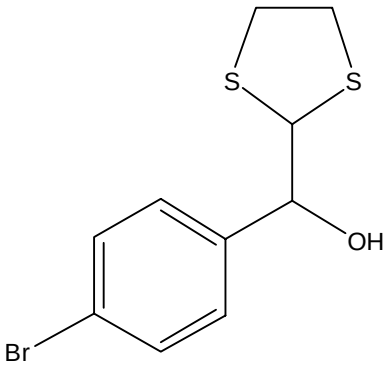
Following the general procedure, **5d** was isolated by TLC (petroleum ether/ethyl acetate 4:1) in 88% yield as a yellowish oil.

^{1}H-NMR δ(ppm): 3.21-3.23 (4H, m, -CH_2-CH_2-), 4.80 (1H, d, J=6.6 Hz, S-CH-S), 4.88 (1H, dd, J=6.6, 2.8 Hz, C**H**-OH); 7.02 (1H, dd, J=5.2, 3.6 Hz, CH (Het)), 7.11 (1H, dd, J=3.6, 1.2 Hz, CH (Het)), 7.31 (1H, dd, J=5, 1 Hz, CH (Het)).

^{13}C-NMR δ(ppm): 38.2 (CH_2), 39.0 (CH_2), 60.9 (S-CH-S), 74.0 (CHOH), 125.4 (CH, Het), 125.5 (CH, Het), 126.7 (CH, Het).

MS m/z (%): 221 (2), 200 (31, M^+-H_2O), 172 (12, M^+-SCH_2), 113 (25), 105 (100, $[dithiolan]^+$), 45 (39).

5e (4-bromophenyl)(1,3-dithiolan-2-yl)methanol.



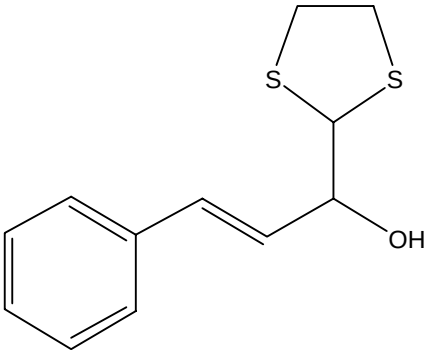
Following the general procedure, **5e** was isolated by TLC (petroleum ether/ethyl acetate 3:1) in 70% yield as a yellowish oil.

^{1}H-NMR δ(ppm): 3.19-3.21 (4H, m, -CH_2-CH_2-), 4.57 (1H, dd, J=6.8, 2.4 Hz, C**H**-OH), 4.70 (1H, d, J=7 Hz, S-CH-S), 7.28-7.32 (2H, m, Ph), 7.47-7.51 (2H, m, Ph).

^{13}C-NMR δ(ppm): 38.1 (CH_2), 39.1 (CH_2), 60.6 (S-CH-S), 76.7 (CHOH), 122.1, 128.6, 131.3, 139.4.

MS m/z (%): 291 (M^+-1), 212 (13, M^+-Br), 194, 105 (37, $[dithiolan]^+$), 91 (100, $PhCH_2^+$).

5f (*E*)-1-(1,3-dithiolan-2-yl)-3-phenylprop-2-en-1-ol.



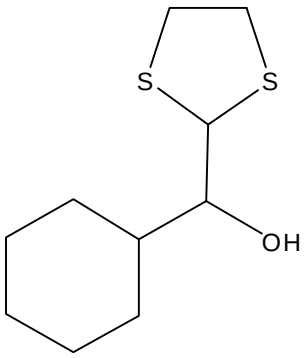
Following the general procedure, **5f** was isolated by TLC (petroleum ether/ethyl acetate 5:1) in 78% yield as a yellowish oil.

^{1}H-NMR δ(ppm): 3.19-3.31 (4H, m, -CH_2-CH_2-), 4.26 (1H, t, J=6.14 Hz, C**H**-OH), 4.49 (1H, d, J=6.22 Hz, S-CH-S), 6.23 (1H, dd, J=16, 6.1 Hz, C_{sp2}**H**-CHOH), 6.72 (1H, d, J=15.8 Hz, CH-Ph), 7.2-7.5 (5H, m, Ph).

^{13}C-NMR δ(ppm): 38.2 (CH_2), 39.0 (CH_2), 59.6 (S-CH-S), 75.8 (CHOH), 126.7 (CH), 127.9 (CH), 128.2, 128.5, 128.6, 132.7.

MS m/z (%): 220 (13, M^+-H_2O), 128 (100), 115 (81), 77 (33, $C_6H_5^+$), 45 (81).

5g cyclohexyl(1,3-dithiolan-2-yl)methanol.



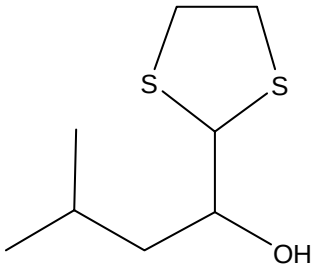
Following the general procedure, **5g** was isolated by TLC (petroleum ether/ethyl acetate 4:1) in 60% yield as a yellowish oil.

^{1}H-NMR δ(ppm): 1.0-1.57 (4H, m), 1.6-2.1 (7H, m), 3.15-3.32 (5H, m, -CH_2-CH_2-, C**H**-OH), 4.72 (1H, d, J=6 Hz, S-CH-S).

^{13}C-NMR δ(ppm): 25.9, 26.2, 27.6, 29.7, 30.1, 38.2 (CH_2), 39.0 (CH_2), 42.0, 57.3 (S-CH-S), 78.4.

MS m/z (%): 218 (1, M^+), 200 (1, M^+-H_2O), 106 (100), 105 (50, ([dithiolan]$^+$), 78 (13), 55 (25).

5h 1-(1,3-dithiolan-2-yl)-3-methylbutan-1-ol.



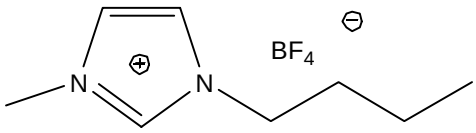
Following the general procedure, **5h** was isolated by TLC (petroleum ether/ethyl acetate 3:1) in 30% yield as a yellowish oil.

^{1}H-NMR δ(ppm): 0.88-0.96 (6H, 2d, $(CH_3)_2$), 1.3-1.5 (2H, m, CH_2), 3.1-3.4 (5H, m, S-CH_2-CH_2-S + C**H**$(CH_3)_2$), 3.54-3.63 (1H, m, C**H**-OH), 4.44 (1H, d, J=6 Hz, S-CH-S).

MS m/z (%): 192 (1, M^+), 174 (1, M^+-H_2O), 106 (96); 105 (100, ([dithiolan]$^+$); 78 (26); 69 (10); 61 (30).

4. Synthesis of ILs

Synthesis of 1-*n*-butyl-3-methylimidazolium tetrafluoroborate [BMI][BF_4]



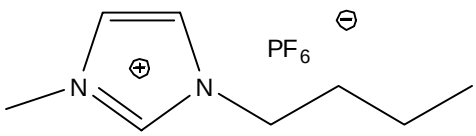
The procedure by Dupont *et al.* was followed.[iII]

To a solution of 1-*n*-butyl-methylimidazolium chloride (BMIC) (4.65 g, 26.64 mmol) in acetone (50 mL) at room temperature was added sodium tetrafluoroborate (2.92 g, 26.64 mmol). After 24 h stirring, the reaction mixture was filtered through a plug of celite and the volatiles were removed under reduced pressure to give the compound in 91% yield as a yellow dense oil.

^{1}H-NMR δ(ppm; DMSO-d_6, ref. 2.54 ppm) = 0.95 (3H, t, J=7.4 Hz, $CH_2C\mathbf{H_3}$), 1.28-1.46 (2H, m, $CH_2C\mathbf{H_2}CH_3$), 1.78-1.93 (2H, m, $CH_2C\mathbf{H_2}CH_2$), 3.96 (3H, s, $NC\mathbf{H_3}$), 4.18 (2H, t, J=7.4 Hz, $NC\mathbf{H_2}CH_2$), 7.28 (1H, s, NC**H**CHNCH_3), 7.32 (1H, s, CHC**H**NCH_3), 8.84 (1H, s, NC**H**N).

^{13}C-NMR δ(ppm) = 12.7 ($CH_2\mathbf{C}H_3$), 18.9 ($CH_2\mathbf{C}H_2CH_3$), 31.5 ($CH_2\mathbf{C}H_2CH_2$), 35.4 ($N\mathbf{C}H_3$), 49 ($N\mathbf{C}H_2CH_2$), 122 ($N\mathbf{C}HCHNCH_3$), 123.4 ($CH\mathbf{C}HNCH_3$), 136.4 ($N\mathbf{C}HN$).

Synthesis of 1-*n*-butyl-3-methylimidazolium hexafluoroborate [BMI][PF_6]



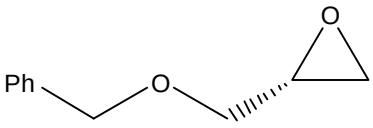
The procedure by Dupont *et al.* was followed.[iII]

To a solution of 1-*n*-butyl-methylimidazolium chloride (BMIC) (4.65 g, 26.64 mmol) in acetone (50 mL) at room temperature was added sodium hexafluoroborate (4.47 g, 26.64 mmol). After 24 h stirring, the reaction mixture was filtered through a plug of celite and the volatiles were removed under reduced pressure to give the compound in 83% yield as a yellow dense oil.

^{1}H-NMR δ(ppm; DMSO-d_6, ref. 2.54 ppm) = 0.94 (3H, t, J = 7.6 Hz, $CH_2C\mathbf{H_3}$), 1.20-1.40 (2H, m, $CH_2C\mathbf{H_2}CH_3$), 1.70-1.94 (2H, m, $CH_2C\mathbf{H_2}CH_2$), 3.88 (3H, s, $NC\mathbf{H_3}$), 4.19 (2H, t, J=7.4 Hz, $NC\mathbf{H_2}CH_2$), 7.73 (1H, s, $NCHC\mathbf{H}NCH_3$), 7.79 (1H, s, $NC\mathbf{H}CHNCH_3$), 9.14 (1H, s, $NC\mathbf{H}N$).

^{13}C-NMR δ(ppm) = 12.9 ($CH_2\mathbf{C}H_3$), 19.1 ($CH_2\mathbf{C}H_2CH_3$), 31.6 ($CH_2\mathbf{C}H_2CH_2$), 35.9 ($N\mathbf{C}H_3$), 50.0 ($N\mathbf{C}H_2CH_2$), 122.6 ($N\mathbf{C}HCHNCH_3$), 123.5 ($CH\mathbf{C}HNCH_3$), 136.9 ($N\mathbf{C}HN$).

5. Synthesis of (*R*)-2-(benzyloxymethyl)oxirane 12f



In a dried two-necked flask under inert atmosphere, was added NaH (60% dispersion in mineral oil) (594.6 mg, 14.86 mmol) to dry DMF (15 mL), and the mixture was cooled at -20°C. Then a solution of (*S*)-glycidol (896 µL, 13.5 mmol) in dry DMF (15 mL) was added dropwise to the suspension. The solution was stirred for 20 min, then benzyl bromide (1.6 mL, 13.5 mmol) was added dropwise. The solution was stirred for 4 h at -20°C, and for an

additional 1 h at room temperature. It was then diluted with diethyl ether and extracted with water (3X15 mL). The resulting organic phases were washed with brine and dried $NaSO_4$. The volatiles were remouved under reduced pressure to give the compound which was purified by FC (petroleum ether/ethyl acetate 8.1) on silica gel affording **12f** in 97% yield as a colorless oil.

^{1}H-NMR δ(ppm) = 2.63 (1H, dd, J = 2.4, 5 Hz, C**H$_2$**OCH$_2$Ph), 2.81 (1H, dd, J = 4.4, 5 Hz, C**H$_2$**OCH$_2$Ph), 3.14-3.24 (1H, m, OC**H**CH$_2$), 3.44 (1H, dd, J = 5.8, 11.4 Hz), 3.78 (1H, dd, J = 3, 11.4 Hz), 4.55 (1H, d, J = 12 Hz, C**H$_2$**Ph), 4.63 (1H, d, J = 12 Hz, C**H$_2$**Ph), 7.27-7.35 (5H, m, Ph).

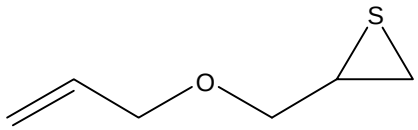
MS m/z (%) = 164 (17, [$M^{+\bullet}$]); 107 (87, [OBn] $^+$); 91 (100, $PhCH_2^+$); 87 (36, [$M^{+\bullet}$-Ph]); 65 (67), 77 (45, $[Ph]^+$).

Optical rotation : $[\alpha]^{rt}_D$ = +55 (c=1, $CHCl_3$).
This procedure afforded **12f** without loss of optical purity, as confirmed by HPLC-Gilson (Kromasil 5-Cellucoat, 4.6 m X 250 mm column; *ee*=98.3%).

6. Synthesis of thiiranes 16

General procedure. The procedure by Mobashery *et al.* was followed.[iIII] In a dried two-necked flask under inert atmosphere, were added, to anydrous MeOH (20 mL), epoxide **12** (8.62 mmol, 1 equiv.) and thiourea (10.34 mmol,1.2 equiv.). The solution was stirred at room temperature overnight then, after monitoring the reaction by TLC, it was concentrated under reduced pressure, diluted with 7 mL of DCM and quenched with 7 mL of water. The organic product was extracted with DCM (3X7 mL) and the combined organic layers were dried over dry $NaSO_4$. The volatiles were remouved under reduced pressure to give compound **16** which was used without purification.

16a 2-(allyloxymethyl)thiirane



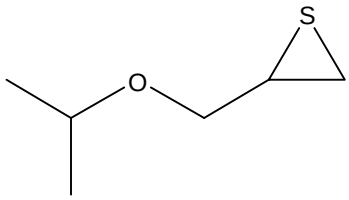
Following the general procedure **16a** was isolated in 67% yield as a yellow oil.

^{1}H-NMR δ(ppm) = 2.22 (1H, dd, J = 1, 5.2 Hz, C**H**$_2$S), 2.53 (1H, d, J = 6.2 Hz, C**H**$_2$S), 3.0-3.21 (1H, app. pent, J = 5.8, C**H**S), 3.45 (1H, dd, J = 6.6, 10.6 Hz, CHC**H$_2$**O), 3.65 (1H, dd, J = 5.8, 10.6 Hz, CHC**H$_2$**O), 4.03-4.07 (2H, m, C**H$_2$**All), 5.18-5.734 (2H, m, C**H**$_2$=CH), 5.82-6.02 (1H, m, CH$_2$=C**H**).

^{13}C-NMR δ(ppm) = 23.6 (**C**H$_2$S), 46.9 (**C**HS), 71.7 (CH**C**H$_2$O), 74.4 (**C**H$_2$CH=CH$_2$), 116.9 (**C**H$_2$=CH), 134.1 (CH$_2$=**C**H).

MS m/z (%) = 130 (0.5, $M^{+\bullet}$), 73 (100), 57 (25, $[OAll]^{+}$).

16c 2-(isopropoxymethyl)thiirane



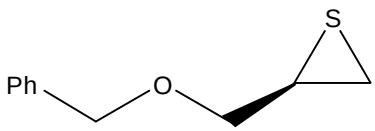
Following the general procedure **16c** was isolated in 74% yield as a yellow oil.

^{1}H-NMR δ(ppm) = 1.17 (3H, d, J = 6.4 Hz, (C**H$_3$**)$_2$), 1.18 (3H, d, J = 6.4 Hz, (C**H$_3$**)$_2$), 2.21 (1H, dd, J = 5.6, 1.2 Hz, C**H$_2$**S), 2.53 (1H, dd, J = 6.2, 1 Hz, C**H$_2$**S), 3.0-3.12 (1H, m, C**H**CH$_2$O), 3.38 (1H, dd, J = 10.6, 7.0 Hz, C**H$_2$**O), 3.59-3.72 (2H, m, C**H**$_2$O + OC**H**i-*Pr*).

^{13}C-NMR δ(ppm) = 22.0 (**C**H$_3$), 22.1 (**C**H$_3$), 24.0 (**C**H$_2$S), 32.6 (**C**HS), 71.9 (**C**H(O)), 72.8 (**C**H$_2$O).

MS m/z (%) = 134 (0.76, $[M^{+\bullet}+2]$), 132 (62, $[M^{+\bullet}]$), 99 (35, $[M^{+\bullet}-SH]$), 73 (95, $[M^{+\bullet}-OC_3H_7]$), 59 (100, $[C_2H_3S]$).

16e (*R*)-2-(benzyloxymethyl)thiirane



Following the general procedure (employing epoxide **12f**), **16e** was isolated in 78% yield as a colorless oil.

^{1}H-NMR δ(ppm) = 2.21 (1H, dd, J = 5.6, 1.2 Hz, CHC**H$_2$**S), 2.53 (1H, app d , J = 6.2 Hz, CHC**H$_2$**S), 3.11 (1H, pent, J = 6.2 Hz, SC**H**CH$_2$), 3.49 (1H, dd, J = 10.6, 6.6 Hz, CHC**H$_2$**OBn), 3.69 (1H, dd, J = 10.6, 5.8 Hz, CHC**H$_2$**OBn), 4.59 (2H, s, C**H$_2$**Ph), 7.25-7.4 (5H, m, Ph).

^{13}C-NMR δ(ppm) = 23.8 (**C**H$_2$S), 32.2 (**C**HCH$_2$), 73.0 (**C**H$_2$Ph), 74.6 (**C**H$_2$O), 127.4, 127.6, 128.2, 137.7.

MS m/z (%) = 180 (16, [M$^{+\bullet}$]), 147 (44, [M$^{+\bullet}$-SH]), 103 (87, [M$^{+\bullet}$-Ph]), 91 (100, PhCH$_2^+$).

This procedure afforded **16e**, through a S_N2 type mechanism, without loss of optical purity, as confirmed by HPLC analysis (Kromasil 5-Cellucoat, 4.6 m X 250 mm column; *n*-hexane (A) : 2-propanol (B); isocratic at 0% of B for 55 min, in 5 min to 5% of B for 5 min, in 20 min to 40% of B; τ_{major} = 94.9 min, τ_{minor} = 99.5 min (*ee*>98%)).

7. Synthesis of 1,2-dithiols 10 and β-mercapto alcohols 11

Method A: synthesis of 1,2-dithiols in THF, under catalysis of TBAF.

General procedure. A solution of thiirane **16** (1 mmol, 1 equiv.) and HMDST **13** (1,2 mmol, 1.2 equiv.) in THF (2.5 mL) was treated at 0°C with TBAF (1M in THF; 0.24 mmol, 0.2 equiv.) under inert atmosphere. The mixture became bright green and after few minutes pale yellow. After 10 minutes at 0°C, the mixture was warmed at room temperature, and the reaction was carried out for 30 min; the progress of the reaction was monitored by TLC. After addition of citric acid (50%

aq solution; 0.5 mL) the mixture was stirred for 10 min, then diluted with Et_2O. The organic phase was then washed with citric acid (20% aq solution; 0.5 mL), extracted with Et_2O and dried over $NaSO_4$. Evaporation of the solvent afforded dithiol **10** which was pure enough to be used without purification.

Method B: synthesis of 1,2-dithiols and β-mercapto alcohols in THF, under catalysis of $PhONBu_4$.

General procedure. A solution of $PhONBu_4$ (0.24 mmol, 0.2 equiv.) in THF (2.5 mL) was added with thiirane **16** or epoxide **12** (1 mmol, 1 equiv.) and HMDST **13** (1,2 mmol, 1.2 equiv.) at 0°C under inert atmosphere. The mixture became pale blue and after few minutes pale yellow. After 10 minutes at 0°C, the mixture was warmed at room temperature, and the reaction was carried out for 30 min; the progress of the reaction was monitored by TLC. After addition of citric acid (50% aq solution; 0.5 mL) the mixture was stirred for 10 min, then diluted with Et_2O. The organic phase was then washed with citric acid (20% aq solution; 0.5 mL), extracted with Et_2O and dried over $NaSO_4$. Evaporation of the solvent afforded product as a yellow oil, which was pure enough to be used without purification.

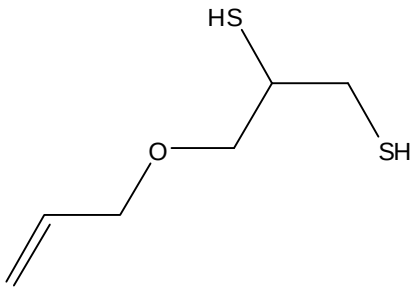
Method C: synthesis of 1,2-dithiols and β-mercapto alcohols in IL, under catalysis of TBAF.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 300 μL), HMDST **13** (0.22 mmol, 1.2 equiv.) and thiirane **16** or epoxide **12** (0,18 mmol, 1 equiv.) at room temperature under an inert atmosphere, was treated dropwise with TBAF (1M in THF; 0.04 mmol, 0.2 equiv.). After addtion of TBAF, the mixture became pale green and after few minutes, yellow. The reaction was carried out for around 1 h and 30 min and the progress was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the combined organic phases were treated with citric acid (50% aq solution; 1.0 mL). The resulting organic phase was then washed with citric acid (20% aq solution; 1.0 mL), and dried over $NaSO_4$. Evaporation of the solvent afforded product which was pure enough to be used without purification.

Method D: synthesis of 1,2-dithiols and β-mercapto alcohols in IL, under catalysis of $PhONBu_4$.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 300 μL) and $PhONBu_4$ (0.04 mmol, 0.2 equiv.) was added under inert atmosphere drop by drop with HMDST **13** (0.22 mmol, 1.2 equiv.) and thiirane **16** or epoxide **12** (0,18 mmol, 1 equiv.) at room temperature. The mixture became grey after few minutes. The reaction was carried out for around 2 h min and the progress of the reaction was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were treated with citric acid (50% aq solution; 1.0 mL). The resulting organic phase was then washed with with citric acid (20% aq solution; 1.0 mL), and dried over $NaSO_4$. Evaporation of the solvent afforded product.

10a 3-allyloxypropane-1,2-dithiol



^{1}H-NMR δ(ppm) = 1.45-1.62 (1H, m, CH_2S**H**), 1.87 (1H, d, J =8.6 Hz, CHS**H**), 2.67-3.28 (3H, m, C**H_2**S + C**H**SH), 3.47-3.74 (2H, m, C**H_2**O), 4.00 (2H, bs, OC**H_2**All), 5,16-5.32 (2H, m, CH=C**H_2**), 5.83-5.95 (1H, m,C**H**=CH_2).

^{13}C-NMR δ(ppm) = 23.4, 31.8, 71.6, 74.3, 117.0, 134,1.

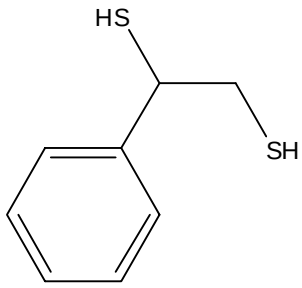
MS m/z (%) = 131 (4, [$M^{+\bullet}$-HS]), 106 (18), 73 (83, $PhCH_2^+$), 59 (100).

Yield:

Method A : 54%

Method C : 64%.

10b 1-phenylethane-1,2-dithiol



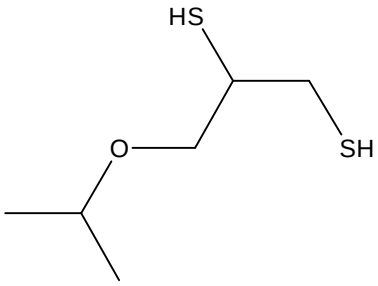
^{1}H-NMR δ(ppm) = 1.49 (1H, dd, J = 7.4, 9.2 Hz, CH_2S**H**), 2.30 (1H, d, J =5.2 Hz, CHS**H**), 2.86-3.20 (2H, m, C**H**$_2$S), 4.04-4.14 (1H, m, C**H**SH), 7.18-7.44 (5H, m,Ph).

^{13}C-NMR δ(ppm) = 34.6, 63.1, 128.5, 129.0, 129.3, 131,4.

Yield:

Method A : 75%.

10c 3-isopropoxypropane-1,2-dithiol



^{1}H-NMR δ(ppm) = 1.15 (6H, d, J=6 Hz, CH(C**H$_3$)$_2$**), 1.58 (1H, app t, J =8.6 Hz, CH_2S**H**), 1,87 (1H, d, J = 8.8 Hz, CHS**H**), 2.81-2.93 (2H, m, C**H$_2$**SH), 2.97-3.10 (1H, m, C**H**SH), 3.42-3.67 (3H, m, OC**H**$(CH_3)_2$+ C**H$_2$**Oi-*Pr*).

^{13}C-NMR δ(ppm) = 21.9 ((**C**$H_3)_2$), 29.8 (**C**H_2SH), 42.4 (**C**HSH), 70.5 (**C**H_2Oi-*Pr*), 71.9 (O**C**H$(CH_3)_2$).

MS m/z (%) = 166 (0.33, [$M^{+\bullet}$]), 132 (22, [$M^{+\bullet}$-H_2S]), 119 (1, [$M^{+\bullet}$-CH_2SH]), 106 (56, [$M^{+\bullet}$-Oi-*Pr*-H]), 99 (35, [$M^{+\bullet}$-SH-H_2S]), 73 (100, [CH_2Oi-*Pr*]), 59 (62, [Oi-*Pr*]).

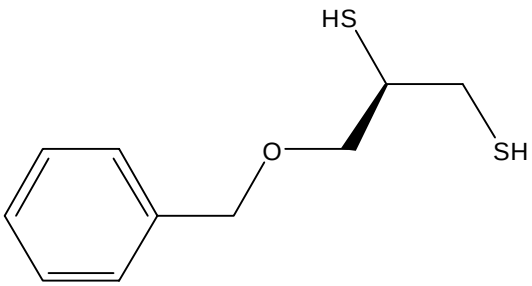
Yield:

Method A : 74%

Method B : 61%

Method C : 64%.

10e (*R*)-3-benzyloxypropane-1,2-dithiol



^{1}H-NMR δ(ppm) = 1.54 (1H, t, J = 8.8 Hz, CH_2S**H**), 1.89 (1H, d, J =4.4 Hz, CHS**H**), 2.88 (2H, dd, J=5.4, 8.8 Hz, C**H**$_2$S), 3.1-3.17 (1H, m, C**H**SH), 3.56 (1H, dd, J= 7.0, 9.6 Hz, C**H**$_2$O), 3.69 (1H, dd, J= 5.2, 9.6 Hz, C**H**$_2$O), 4,54 (2H, s, C**H**$_2$Ph), 7.3-7.4 (5H, m,Ph).

^{13}C-NMR δ(ppm) = 29.9 (**C**H_2SH), 42.1 (**C**HSH), 72.4 (**C**H_2OBn), 73.0 (**C**H_2Ph), 127.6, 127.8, 128.4, 137,8.

MS m/z (%) = 214 (0.34, $[M^{+\bullet}]$), 181 (4, $[M^{+\bullet}$-SH]), 149 (2, $[M^{+\bullet}$-SH-S]), 123 (14, $[M^{+\bullet}$-91]), 108 (15, $[C_3H_8S_2]$), 91 (100, $PhCH_2^+$), 77 (6, $[Ph]^+$), 65 (18).

Optical rotation : $[\alpha]^{rt}_D$ = -15 (c=1.1, $CHCl_3$).

Methods A-C afforded **10e** with total enantioconservation, as confirmed by HPLC analysis (Kromasil 5-Cellucoat, 4.6 m X 250 mm column; *n*-hexane (A) : 2-propanol (B); isocratic at 0% of B for 20 min, then ramp 30%, flow rate 0.8 mL/min; τ_{major} = 31.04 min, τ_{minor} = 33.09 min (*ee*>98%)).

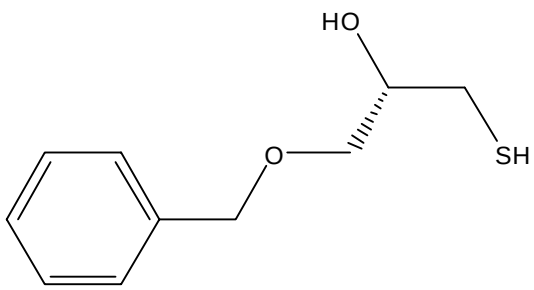
Yield:

Method A : **10e** was isolated in 77% yield; (±)-3-benzyloxypropane-1,2-dithiol (**10d**) was isolated in 80% yield.

Method C : **10e** was isolated in 77% yield (reaction carried in [BMI][PF_6]); **10d** in 75% yield (reaction carried in [BMI][BF_4]).

Method D : **10d** was isolated by TLC (petroleum ether/ethyl acetate 5:1) in 40% of yield.

11f (*S*)-1-(benzyloxy)-3-mercaptopropan-2-ol



^{1}H-NMR δ(ppm) = 1.45 (1H, app t, J = 8.6 Hz, $CH_2S\mathbf{H}$), 2.54 (1H, bs, O**H**), 2.64-2.72 (2H, m, $C\mathbf{H}_2SH$), 3.53-3.56 (2H, m, $C\mathbf{H}_2O$), 3.80-3.91 (1H, m, C**H**OH), 4,56 (2H, s, $C\mathbf{H_2}Ph$), 7.30-7.40 (5H, m, Ph).

^{13}C-NMR δ(ppm) = 28.1 (**C**H_2SH), 71.2 (**C**HOH), 72.1 (**C**H_2OBn), 73.5 (**C**H_2Ph), 127.7, 127.8, 127.9, 131.8.

MS m/z (%) = 198 (0.63, [$M^{+\bullet}$]), 180 (14, [$M^{+\bullet}$-H_2O]), 165 (5, [$M^{+\bullet}$-SH]), 122 (74, [$M^{+\bullet}$-76]), 107 (4, [$M^{+\bullet}$-91]), 91 (100, $PhCH_2^+$).

Optical rotation : $[\alpha]^{rt}_D$ = -9 (c=1, THF).

Method C afforded **11f** with total enantioconservation, as confirmed by HPLC analysis (Kromasil 5-Cellucoat, 4.6 m X 250 mm column; *n*-hexane (A) : 2-propanol (B); isocratic at 10% of B for 80 min; flow rate 0.5 mL/min; τ_{major} = 17.6 min, τ_{minor} = 19.4 min (*ee*>98%)).

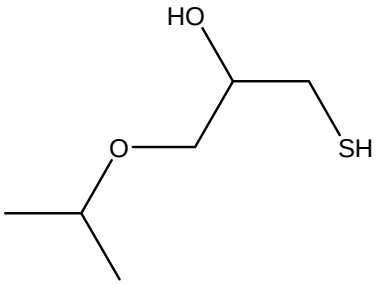
Yield:

Method B : (±)-1-(benzyloxy)-3-mercaptopropan-2-ol (**11a**) was isolated in 85% yield.

Method C : **11f** was isolated in 60% yield (reaction performed in [BMI][BF_4]); **11a** was isolated in 69% yield (reaction performed in [BMI][PF_6]).

Method D **: 11a** was recovered in 51% yield, when carrying the reaction in [BMI][PF_6].

11b 1-isopropoxy-3-mercaptopropan-2-ol



^{1}H-NMR δ(ppm) = 1.16 (6H, d, J=6.2 Hz, CH(C**H$_3$)$_2$**), 1,48 (1H, app t, J = 8.8 Hz, SH), 2.20 (1H, bs, OH), 2.63-2.71 (2H, m, C**H$_2$**SH), 3.44 (1H, dd, J=6.2, 9.4 Hz, C**H**$_2$O), 3.52 (1H, dd, J= 4.4, 9.2 Hz, C**H**$_2$O), 3.55-3.67 (1H, m, C**H**$(CH_3)_2$), 3.73-3.84 (1H, m, C**H**OH).

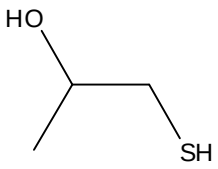
^{13}C-NMR δ(ppm) = 22.1 (CH(**C**$H_3)_2$), 28.1 (**C**H_2SH), 70.0 (**C**H_2O), 71.4 (**C**HOH), 72.2 (O**C**$H(CH_3)_2$).

MS m/z (%) = 151 (0.17, [$M^{+\bullet}$+1]), 132 (11, [$M^{+\bullet}$-H_2O]), 99 (88, [$M^{+\bullet}$-SH- H_2O]), 91 (13, [$M^{+\bullet}$-Oi-*Pr*]), 73 (94, [$CH_2OCH(CH_3)_2$]), 61 (100).

Yield:

Method C : 57% yield in [BMI][BF_4]; 73% yield in [BMI][PF_6].

11g 1-mercaptopropan-2-ol



^{1}H-NMR δ(ppm) = 1.22 (3H, d, J=6.2 Hz, CHC**H$_3$**), 1.46 (1H, dd, J = 9 Hz, CH_2S**H),** 2.26 (1H, bs, O**H**), 2.47 (1H, m, C**H**$_2$SH), 2.72 (1H, m, C**H**$_2$SH), 3.72-3.86 (1H, m, C**H**OH).

Yield:

Method C : 35% yield in [BMI][BF_4].

8. Synthesis of β-hydroxy and β-mercapto phenylthio-derivatives

Method A: synthesis of β-hydroxy and β-mercapto phenylthio-derivatives in THF, under catalysis of $PhONBu_4$.

General procedure. A solution of $PhONBu_4$ (0.04 mmol, 0.2 equiv.) in THF (0.4 mL) was added with thiirane **16** or epoxide **12** (0.2 mmol, 1 equiv.) and PhSTMS **17** (0,22 mmol, 1.1 equiv.) under inert atmosphere. The mixture was stirred at r.t. for around 1h and 30 min and the progress of the reaction was monitored by TLC. After quenching with water (in case of epoxide) or citric acid (50% aq solution, in case of episulfide) the mixture was diluted with Et_2O. The resulting organic phase was extracted with Et_2O and then washed with citric acid (20% aq solution; 1 mL) and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, in mixture with PhSSPh, that was purified on TLC.

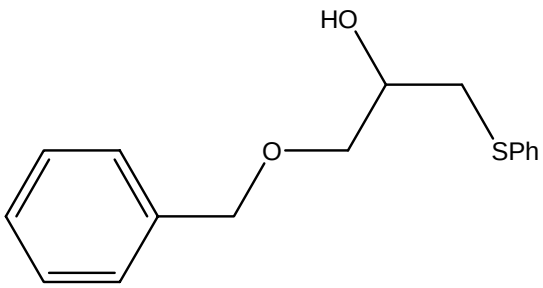
Method B: synthesis of β-hydroxy and β-mercapto phenylthio-derivatives in IL, under catalysis of TBAF.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 350 μL), PhSTMS **17** (0.22 mmol, 1.1 equiv.) and thiirane **16** or epoxide **12** (0,2 mmol, 1 equiv.) at room temperature under inert atmosphere, was treated dropwise with TBAF (1M in THF; 0.044 mmol, 0.2 equiv.). After the addtion of TBAF the mixture became pale yellow. The reaction was carried out for around 1 h and 30 min and the progress of the reaction was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were quenched with water (in case of epoxide) or citric acid (50% aq solution; 1 mL, in case of thiirane). The resulting organic phase was then washed with citric acid (20% aq solution), and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified on TLC.

Method C: synthesis of β-hydroxy and β-mercapto phenylthio-derivatives in IL, under catalysis of $PhONBu_4$.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 350 μL) and $PhONBu_4$ (0.044 mmol, 0.2 equiv.) was added, under inert atmosphere, drop by drop with PhSTMS **17** (0.22 mmol, 1.1 equiv.) and thiirane **16** or epoxide **12** (0,2 mmol, 1 equiv.) at room temperature. The mixture became grey after few minutes. The reaction was carried out for around 2 h min and the progress of the reaction was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were quenched with water (in case of epoxide) or citric acid (50% aq solution; 1 mL, in case of thiirane). The resulting organic phase was then washed with with citric acid (20% aq solution), and dried over $NaSO_4$. Evaporation of the solvent afforded crude product as a yellow oil, which was purified on TLC.

18a 1-(benzyloxy)-3-(phenylthio)propan-2-ol



^{1}H-NMR δ(ppm) = 2.58-2.76 (1H, bs, O**H**), 3.02 (1H, dd, J=6.8, 13.4 Hz, C**H_2**S), 3.12 (1H, dd, J=5.8, 13.8 Hz, C**H_2**S), 3.50 (1H, dd, J= 5.4, 9.6 Hz, C**H_2**O), 3.57 (1H, dd, J= 4.0, 9.6 Hz, C**H_2**O), 3.84-3.96 (1H, m, C**H**OH), 4.50 (2H, s, C**H_2**Ph), 7.17-7.34 (10H, m, Ph).

^{13}C-NMR δ(ppm) = 37.51 (**C**H_2S), 68.9 (**C**HOH), 72.4 (**C**H_2Ph), 73.4 (**C**H_2O), 127.4, 127.7, 129.6, 128.2, 128.4, 129.0, 135.3, 137.7.

MS m/z (%) = 274 (13, [$M^{\bullet}$]), 165 (13, [$M^{+\bullet}$-PhS]), 123 (51, [$PhSCH_2$]), 109 (29, [PhS]), 91 (100, $PhCH_2^+$), 77 (25, $[Ph]^+$).

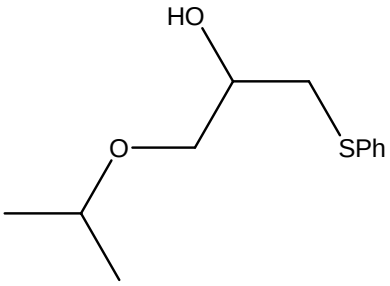
Yield:

Method A : **18a** was purified by TLC (petroleum ether/EtOAc, 9:1), affording 78% yield.

Method B : 73% yield (reaction carried in [BMI][BF_4]); 75% (reaction carried in [BMI][PF_6]).

Method C **:** 69% (reaction carried in [BMI][PF_6]).

18b 1-isopropoxy-3-(phenylthio)propan-2-ol



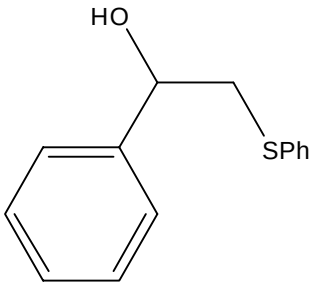
^{1}H-NMR δ(ppm) = 1.14 (6H, d, J = 5.8 Hz, CH(C**H$_3$)$_2$**), 2.69-2.78 (1H, bs, O**H**), 3.05-3-10 (2H, m, C**H**$_2$SPh), 3.35-3.65 (3H, m, C**H**$(CH_3)_2$ + C**H$_2$**O), 3.76-3.9 (1H, m, C**H**OH), 7.1-7.4 (5H, m, Ph).

MS m/z (%) = 226 (58, [$M^{+\bullet}$]), 135 (63, [$M^{+\bullet}$-91]), 123 (69), 110 (68, [PhSH]$^+$), 99 (100).

Yield:

Method B : the product was purified by TLC (petroleum ether/EtOAc, 8:1), affording 81% yield in [BMI][BF_4].

18c 1-phenyl-2(phenylthio)ethanol

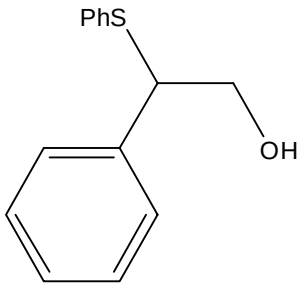


^{1}H-NMR δ(ppm) = 2.8 (1H, s, O**H**), 3.09 (1H, dd, J =9.2, 13.6 Hz, C**H**$_2$SPh), 3.34 (1H, dd, J =3.8, 13.4 Hz, C**H**$_2$SPh), 4.73 (1H, dd, J =3.6 Hz, C**H**OH), 7.24-7.45 (10 H, m,Ph).

^{13}C-NMR δ(ppm) = 43.9 (**C**H_2SPh), 71.9, 126.1, 126.8, 128.1, 128.7, 129.3, 130.2.

MS m/z (%) = 230 (9, [$M^{+\bullet}$]), 124 (100, [$PhSCH_2$]$^+$), 107 (37), 91 (14, $PhCH_2^+$), 77 (32, [Ph] $^+$).

18c' 2-phenyl-2(phenylthio)ethanol



^{1}H-NMR δ(ppm) = 2.02 (1H, bs, O**H**), 3.89-3.92 (2H, m, C**H$_2$**OH), 4.32 (1H, t, J =3.8 Hz, C**H**Ph), 7.23-7.35 (10 H, m,Ph).

^{13}C-NMR δ(ppm) = 55.6 (**C**H$_2$OH), 67.2, 127.3, 127.6, 127.9, 128.5, 128.8, 132.3.

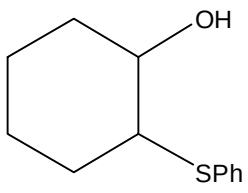
MS m/z (%) = 230 (42, [M$^{\bullet+}$]), 199 (78), 121 (97, M$^{\bullet+}$-PhS), 110 (99), 103 (76), 91 (100, PhCH$_2^+$).

Yield:

Method B : the reaction was performed in [BMI][BF$_4$]. The product was purified by TLC (petroleum ether/EtOAc, 8:1), affording the pure product in 67% yield, as mixture of both regioisomers **18c** and **18c'** in ratio 6:1.

Method C : the reaction was carried in [BMI][BF$_4$]. The crude was purified by TLC (petroleum ether/EtOAc, 9:1), affording the pure product in 51% yield, as mixture of both regioisomers **18c** and **18c'** in ratio 2:1.

18d 2-(phenylthio)cyclohexanol



^{1}H-NMR δ(ppm) = 1.13-1.45 (4H, m), 1.52-2.03 (2H, m), 2.06-2.31 (2H, m), 2.65-2.83 (1H, m, C**H**SPh) 2.9-3.01 (1H, bs, O**H**), 3.23-3.45 (1H, m, C**H**OH), 7.3-7.57 (5 H, m, Ph).

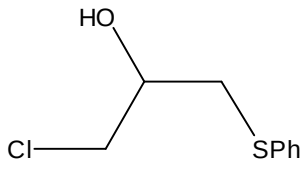
^{13}C-NMR δ(ppm) = 24.3, 26.2, 32.7, 33.9, 56.4 (**C**HSPh), 72.0 (**C**HOH), 127.5, 128.7, 132.5, 133.5.

MS m/z (%) = 208 (25, [M$^{+\bullet}$]), 110 (100), 98 (16), 81 (20), 65 (12).

Yield:

Method B : **18d** was isolated by TLC (petroleum ether/EtOAc, 9:1) in 59% yield as a yellow oil.The reaction was carried in [BMI][PF_6]. In the crude, cyclohexene-oxide was recovered in 15%.

18e 1-chloro-3-(phenylthio)propan-2-ol



^{1}H-NMR δ(ppm) = 2.64 (1 H, bs, O**H**), 3.07 (1H, dd, J = 7, 13.8 Hz, C**H**$_2$SPh), 3.18 (1H, dd, J = 5.4, 13.8 Hz, C**H**$_2$SPh), 3.67-3.69 (2H, m, C**H$_2$**Cl), 3.87-3.4 (1H, m, C**H**OH), 7.25-7.43 (5 H, m, Ph).

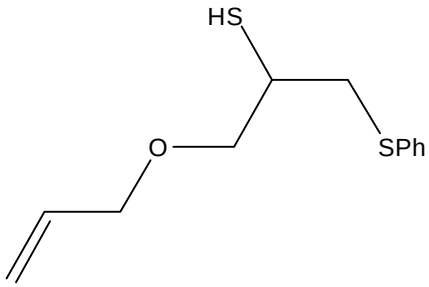
^{13}C-NMR δ(ppm) = 38.3 (**C**H_2SPh), 48.0 (**C**H_2Cl), 69.5 (**C**HOH), 126.9, 129.1, 130.1, 134.5.

MS m/z (%) = 204 (14, [$M^{+\bullet}$+2]), 202 (39, [$M^{+\bullet}$]), 158 (17), 123 (100), 77 (22, $[Ph]^+$).

Yield:

Method B : the reaction was carried in [BMI][PF_6]. **18e** was isolated in 47% yield as a yellow oil.

19a 1-(allyloxy)-3-(phenylthio)propane-2-thiol



^{1}H-NMR δ(ppm) = 2.05 (1H, bs, S**H**), 3.23.-3.34 (3H, m, C**H$_2$**SPh + C**H**SH), 3.56-3.71 (2H, m, OC**H$_2$**CH), 3.92-4.0 (2H, m, OC**H$_2$**CH=CH_2), 5,15-5.32 (2H, m, CH=C**H$_2$**), 5.78-5.97 (1H, m,C**H**=CH_2), 7.24-7.41 (5H, m, Ph).

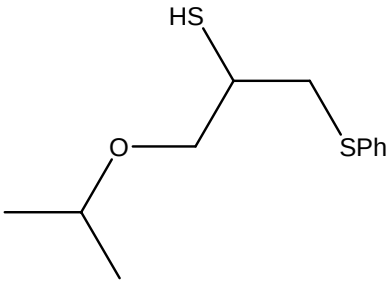
^{13}C-NMR δ(ppm) = 39.4 (**C**H_2SPh), 60.4, 69.9, 72.0 (O**C**H_2CH=CH_2), 117.2, 126.4, 128.9, 129.3, 129.7, 134.3.

MS m/z (%) = 240 (0.5, $M^{+\bullet}$), 182 (20, [$M^{+\bullet}$-OAll]), 149 (24), 110 (64, $PhSH^{+}$), 73 (100).

Yield:

Method B : the product was isolated by TLC (petroleum ether/EtOAc, 8:1) in 43% yield as a yellow oil. The reaction was carried out in [BMI][PF_6].

19c 1-(isopropoxy)-3-(phenylthio)propane-2-thiol

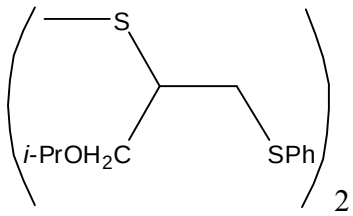


^{1}H-NMR δ(ppm) = 1.14 (6H, d, J = 6.2 Hz, CH(C**H$_3$)$_2$**), 2.11 (1H, d, J = 7.2 Hz, S**H**), 3.04-3-37 (3H, m, C**H**SH + C**H$_2$**SPh), 3.48-3.70 (3H, m, C**H**$(CH_3)_2$ + C**H$_2$**O*i*-Pr), 7.19-7.41 (5H, m, Ph).

^{13}C-NMR δ(ppm) = 22.1 ((**C**H_3)$_2$), 39.3 (**C**H_2SPh), 39.9 (**C**HSH), 70.7 (**C**H_2O*i*-Pr), 72.1 (**C**H$(CH_3)_2$), 126.0, 128.9, 129.6, 129.1.

MS m/z (%) = 244 (2, [$M^{+\bullet}$+2]), 243 (3, [$M^{+\bullet}$+1]), 242 (24, [$M^{+\bullet}$]), 208 (4, [$M^{+\bullet}$-H_2S]), 182 (5, [$M^{+\bullet}$-O*i*-Pr-H]), 133 (21, [$M^{+\bullet}$-SPh]), 123 (20, [$M^{+\bullet}$-CHSHCH_2O*i*-Pr]), 110 (73, $[PhSH]^{+}$), 99 (53, [$M^{+\bullet}$-H_2S-PhS]), 73 (100, $[CH_2O$*i*-Pr$]^{+}$).

20c 1-(isopropoxy)-3-(phenylthio)propyl-2-disulfide



^{1}H-NMR δ(ppm) = 1.11 (12 H, d. J = 6.2 Hz, CH(C**H$_3$)$_2$**), 2.97-3.09 (2H, m, C**H**$(CH_3)_2$), 3.25-3.29 (4H, m, C**H$_2$**SPh), 3.44-3.75 (6H, m, C**H**$(CH_3)_2$ + C**H$_2$**O*i*-Pr), 7.16-7.40 (10 H, m, Ph).

MS m/z (%) = 482 (0.5, [$M^{+\bullet}$]), 273 (1), 209 (44), 167 (49, [$M^{+\bullet}$-PhS CH_2CHCH_2O]), 123 (100, $[PhSCH_2]^{+}$), 73 (17, $[CH_2O$*i*-Pr$]^{+}$).

Yield:

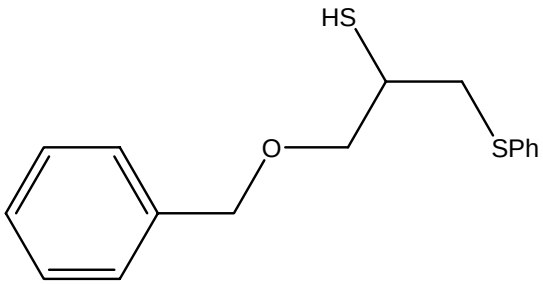
Method A: **19c** was isolated in 61% yield.

Method B : **19c** was isolated by TLC (petroleum ether/EtOAc, 8:1) in 37% yield, as a yellow oil.

In the crude, **20c** was also detected in 23% yield, when carrying the reaction in [BMI][BF_4].

When carrying the reaction in [BMI][PF_6], only **19c** was detected in the crude and it was obtained, after purification, in 64% yield.

19d 1-(benzyloxy)-3-(phenylthio)propane-2-thiol

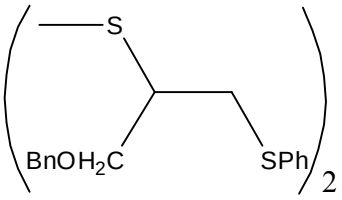


^{1}H-NMR δ(ppm) = 2.12 (1H, d, J = 7.6 Hz, CHS**H**), 3.09-3.36 (3H, m, C**H$_2$**SPh + C**H**SH), 3.60 (1H, dd, J= 5.2, 9.6 Hz, C**H$_2$**OBn), 3.73 (1H, dd, J= 4.8, 9.6 Hz, C**H$_2$**OBn), 4,48 (2H, s, C**H$_2$**Ph), 7.19-7.40 (10 H, m, Ph).

^{13}C-NMR δ(ppm) = 39.4 (**C**H_2SPh), 39.6 (**C**HSH), 72.7 (**C**H_2O), 73.8 (**C**H_2OBn), 126.1, 126.3, 127.5, 128.2, 128.8, 129.6, 135.5, 137.7.

MS m/z (%) = 292 (0.82, [$M^{+\bullet}$+2]), 291 (1, [$M^{+\bullet}$+1]), 290 (11, [$M^{+\bullet}$]), 256 (1, [$M^{+\bullet}$-H_2S]), 181 (7, [$M^{+\bullet}$-SPh]), 147 (10, [$M^{+\bullet}$-SPh-H_2S]), 123 (7, [$M^{+\bullet}$-$BnOCH_2CHSH$]), 110 (15, $[PhSH]^+$), 91 (100, $PhCH_2^+$).

20d bis(1-(benzyloxy)-3-(phenylthio)propyl)-2-disulfide



^{1}H-NMR δ(ppm) = 3.02-3.09 (2H, m, C**H**SS), 3.24-3.27 (4H, m, C**H$_2$**SPh), 3.63 (2H, dd, J= 4.8, 10.2 Hz, C**H$_2$**OBn), 3.73 (2H, dd, J= 5.8, 10.4 Hz, C**H$_2$**OBn), 4,42 (4H, d, J = 2.6 Hz, C**H$_2$**Ph), 7.19-7.41 (20 H, m, Ph).

MS m/z (%) = 578 (0.4, [$M^{+\bullet}$]), 321 (1), 290 (0,7), 257 (35), 123 (8, [$M^{+\bullet}$-$BnOCH_2CHSH$]), 91 (100, $PhCH_2^+$).

Yield:

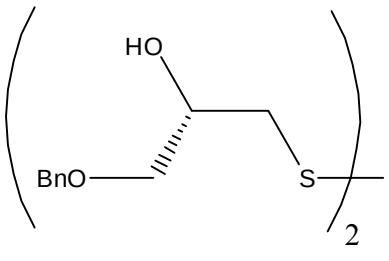
Method B : **19d** was purified by TLC (petroleum ether/EtOAc, 9:1), affording 55% yield, when performing the reaction in [BMI][BF_4]. In the crude, the corresponding disulfide **20d** was also detected in 10% yield.

When carrying the reaction in [BMI][PF_6], **19d** was obtained in 69% yield.
Method C **: 19d** was obtained in 48% yield in [BMI][PF_6].

9. Synthesis of β-functionalized disulfides in ILs, without catalysis

General procedure. A mixture of IL ([BMI][BF_4], 350 μL) and thiirane **16** or epoxide **12** (0,2 mmol, 1 equiv.) at room temperature under inert atmosphere, was added dropwise with HMDST **13** (0.24 mmol, 1.2 equiv.). The reaction was carried out for around 2-4 days and the progress was monitored by TLC. Due to the long reaction time and to low conversion degree, the system was heated at 80-90°C, nevertheless epoxide (or episulfide) was recovered in the crude.After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were treated with citric acid (50% aq solution; 1 mL in case of thiirane) or with water (in case of epoxide). The resulting organic phase was then washed with citric acid (20% aq solution), and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified on TLC.

21f (2*S*, 2'*S*)-3,3'-disulfanediylbis (1-benzyloxypropan-2-ol)



^{1}H-NMR δ(ppm) = 2.72 (2H, bs, O**H**), 2.82 (2H, dd, J = 7.2, 13.8 Hz, C**H**$_2$S), 2.92 (2H, dd, J = 5.2, 13.6 Hz, C**H**$_2$S), 3.50 (2H, dd, J = 5.8, 9.4, C**H**$_2$O), 3.60 (2H, dd, J = 4, 9.6, C**H**$_2$O), 4.02-4.15 (2H, m, C**H**OH), 4,56 (4H, s, C**H**$_2$Ph), 7.26-7.42 (10H, m, Ph).

^{13}C-NMR δ(ppm) = 42.5 (**C**H_2SH), 69.3 (**C**HOH), 72.5 (**C**H_2Ph), 73.5 (**C**H_2O), 127.7, 127.8, 128.4, 137.7.

MS m/z (%) = 394 (7, [$M^{+\bullet}$]), 197 (14), 124 (6), 107 (9, $[OBn]^+$), 91 (100, $PhCH_2^+$).

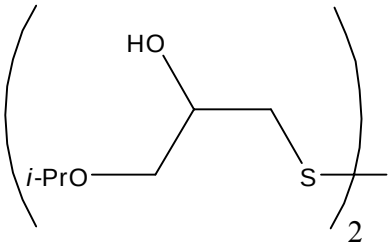
$[\alpha]^{rt}_D$ = - 25 (c=1, $CHCl_3$).

Yield

21f was isolated by TLC (petroleum ether/EtOAc 2:1.5) in 31% yield.

(±)-3,3'-disulfanediylbis (1-benzyloxypropan-2-ol) (**21a**) was isolated in 27% yield.

21b 3,3'-disulfanediylbis (1-isopropoxypropan-2-ol)



^{1}H-NMR δ(ppm) : 1.17 (12H, d, J = 6 Hz, CH(C**H$_3$)$_2$**), 2.28 (2H, bs, O**H**), 2.83 (2H, dd, J = 5.8, 13.6 Hz, C**H**$_2$S), 2.92 (2H, dd, J = 5.4, 13.6 Hz, C**H**$_2$S), 3.4-3.68 (6H, m, C**H$_2$**O + C**H**$(CH_3)_2$), 4.0-4.05 (2H, m, C**H**OH).

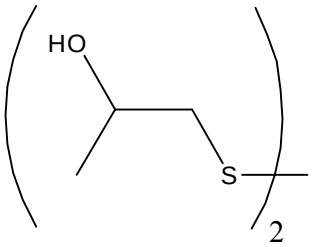
^{13}C-NMR δ(ppm) = 22.07 (CH(**C**$H_3)_2$), 22.1 (CH(**C**$H_3)_2$), 42.5, 42.6 (**C**H_2SH), 69.3 (**C**HOH), 70.4 (**C**H_2O), 72.3 (O**C**H$(CH_3)_2$).

MS m/z (%) = 298 (4, [$M^{+\bullet}$]), 207 (2), 99 (88), 99 (22), 89 (18), 73 (37), 57 (100).

Yield

21b was isolated by TLC (petroleum ether/EtOAc 1:1.5) in 25% yield as a yellow oil.

21g 1,1'-disulfanediyldipropan-2-ol



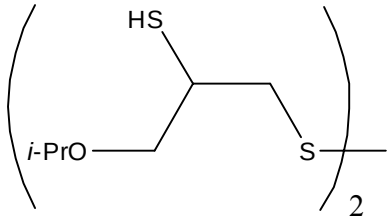
^{1}H-NMR δ(ppm) = 1.31 (6H, d, J= 5.6 Hz, CHC**H$_3$**), 2.21 (2 H, bs, O**H**), 2.82-2.93 (2H, m, C**H$_2$**SH), 3.10 (2H, dd, J = 4.6, 12 Hz, C**H$_2$**SH), 4.15-4.22 (2H, m, C**H**OH).

MS m/z (%) = 182 (8, [$M^{+\bullet}$]), 138 (6), 91 (11), 59 (53), 45 (100).

Yield

21g was isolated by TLC (petroleum ether/EtOAc 2:1.5) in 21% yield, as a yellow oil.

22c 3,3'-disulfanediylbis (1-isopropoxypropane-2-thiol)



^{1}H-NMR δ(ppm) = 1.13 (12H, d, J=6.2 Hz, CH(C**H$_3$)$_2$**), 2.1 (2H, d, J= 7.0 Hz, S**H**), 2.91-2.99 (2H, m, C**H**$(CH_3)_2$), 3.2-3.3 (4H, m, C**H$_2$**S), 3.50-3.70 (6H, m, C**H$_2$**O + C**H**SH).

Yield

22c was isolated by TLC (petroleum ether/EtOAc 1:1) in 19% yield, as a yellow oil.

10. Synthesis of β-hydroxy and β-mercapto phenylselenides

Method A: synthesis of β-hydroxy and β-mercapto phenylseleno-derivatives in THF, under catalysis of $PhONBu_4$.

General procedure. A solution of $PhONBu_4$ (0.044 mmol, 0.2 equiv.) in dry THF (0.4 mL) was treated under inert atmosphere with thiirane **16** or epoxide **12** (0.2 mmol, 1 equiv.) and PhSeTMS **28** (0,22 mmol, 1.1 equiv.). The mixture was stirred at r.t. for 1h and the progress of the reaction was monitored by TLC. After a quenching with water (in case of epoxide) or citric acid (50% aq solution, in case of episulfide) the mixture was diluted with Et_2O. The organic phase was extracted with Et_2O and then washed with citric acid (20% aq solution) and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, in mixture with PhSeSePh, which was purified on TLC.

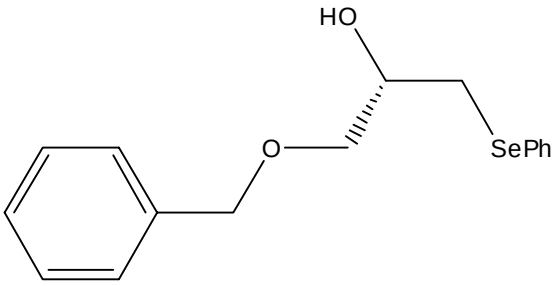
Method B: synthesis of β-hydroxy and β-mercapto phenylseleno-derivatives in IL, under catalysis of TBAF.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 350 μL), PhSeTMS **28** (0.23 mmol, 1.1 equiv.) and thiirane **16** or epoxide **12** (0,21 mmol, 1 equiv.) at room temperature under inert atmosphere, was treated dropwise with TBAF (1M in THF; 0.046 mmol, 0.2 equiv.). The reaction was carried out for around 1 h and 30 min and the progress of the reaction was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were treated with water (in case of epoxide) or citric acid (50% aq solution; 0.5 mL, in case of thiirane). The resulting organic phase was then washed with citric acid (20% aq solution), and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, in mixture with PhSeSePh.

Method C: synthesis of β-hydroxy and β-mercapto phenylseleno-derivatives in IL, under catalysis of $PhONBu_4$.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 350 μL) and $PhONBu_4$ (0.046 mmol, 0.2 equiv.) was added under inert atmosphere drop by drop with PhSeTMS **28** (0.23 mmol, 1.1 equiv.) and thiirane **16** or epoxide **12** (0,21 mmol, 1 equiv.) at room temperature. The mixture became grey after few minutes. The reaction was carried out for around 1 h and 30 min and the progress of the reaction was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were treated with water (in case of epoxide) or citric acid (50% aq solution, in case of thiirane). The resulting organic phase was then washed with with citric acid (20% aq solution; 0.5 mL), and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified by TLC.

29f (*S*)-1-(benzyloxy)-3-(phenylselanyl)propan-2-ol



^{1}H-NMR δ(ppm) = 2.36 (1H, bs, O**H**), 3.03 (1H, dd, J=7.0, 12.4 Hz, C**H**$_2$Se), 3.12 (1H, dd, J=5.8, 12.8 Hz, C**H**$_2$Se), 3.51 (1H, dd, J=6.0, 9.6 Hz, C**H**$_2$O), 3.58 (1H, dd, J=4.4, 9.6Hz, C**H**$_2$O), 3.88-3.99 (1H, m, C**H**OH), 4.50 (2H, s, C**H**$_2$Ph), 7.24-7.39 (10H, m, Ph).

^{13}C-NMR δ(ppm) = 31.9 (**C**H_2Se), 69.4 (**C**H_2Ph), 72.8 (**C**H_2OBn), 73.3 (**C**HOH), 127.1, 127.6, 127.7, 128.3, 129.1, 129.5, 132.7, 137.7.

^{77}Se-NMR. δ(ppm) = 241.5.

MS m/z (%) = 322 (15, [$M^{+\bullet}$]); 201 (4, [$M^{+\bullet}$-CH_2OBn]); 183 (12, [$M^{+\bullet}$-CH_2OBn-H_2O]); 157 (11, [SePh]$^+$); 91 (100, Bn^+).

Optical rotation : $[\alpha]^{rt}_D$ = -48 (c=2.1, $CHCl_3$).

Method B afforded **29f** with total enantioconservation, as confirmed by HPLC analysis (*n*-hexane (A) : 2-propanol (B); isocratic at 0% of B for 55 min, then ramp 30%, flow rate 0.8 mL/min; τ_{major} = 71.9 min, τ_{minor} = 72.3 min (*ee*>98%)).

Yield:

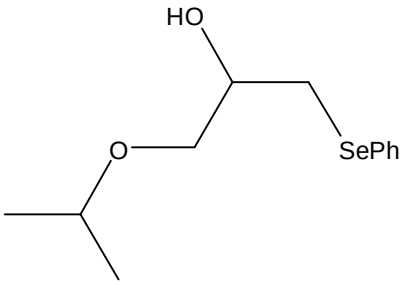
Method A : (±)-1-(benzyloxy)-3-(phenylselanyl)propan-2-ol (**29a**) was isolated by TLC (petroleum ether/EtOAc, 9:1) in 89% yield as a yellow oil.

Method B : **29a** was isolated by TLC (petroleum ether/EtOAc, 9:1) in 73% yield; the reaction was carried in [BMI][BF_4].

29f was isolated in 75% yield; the reaction was carried in [BMI][BF_4].

Method C : **29a** was isolated in 78% yield; the reaction was carried in [BMI][PF_6].

29b 1-isopropoxy-3-(phenilselanyl)propan-2-ol



^{1}H-NMR δ(ppm) = 1.15 (6H, d, J=6.4 Hz, CH(C**H$_3$**)$_2$), 2.72-2.82 (1H, bs, O**H**), 3.03 (1H, dd, J=6.6, 12.6 Hz, C**H**$_2$Se), 3.10 (1H, dd, J=6.2, 12.8 Hz, C**H**$_2$Se), 3.43 (1H, dd, J=6.2, 9.4 Hz, C**H**$_2$O), 3.54 (1H, dd, J= 4, 9.4 Hz, C**H**$_2$O), 3.54-3.63 (1H, m, C**H**(CH$_3$)$_2$), 3.84-3.95 (1H, m, C**H**OH), 7.25-7.30 (5H, m, Ph).

^{13}C-NMR δ(ppm) = 22.1 (CH(**C**H$_3$)$_2$), 31.9 (**C**H$_2$Se), 69.6 (**C**H$_2$O), 70.7 (O**C**H(CH$_3$)$_2$), 72.2 (**C**HOH), 126.9, 129.0, 129.6, 132.5.

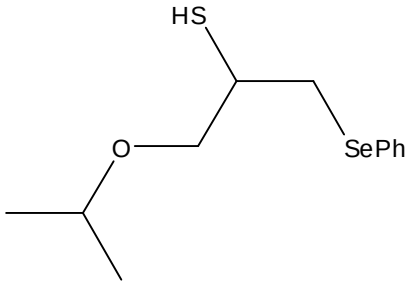
^{77}Se-NMR. δ(ppm) = 243.2.

MS m/z (%) = 274 (26, [M$^{+\bullet}$]), 201 (8, [M$^{+\bullet}$-CH$_2$OCH(CH$_3$)$_2$]), 183 (30); 157 (3, [SePh]$^+$); 99 (59, [M$^{+\bullet}$-OH-SePh]), 73 (48, [CH$_2$OCH(CH$_3$)$_2$]$^+$), 57 (100).

Yield:

Method B : **29b** was isolated by TLC (petroleum ether/EtOAc, 8:1) in 83% yield, when carrying the reaction in [BMI][BF_4]. **29b** was isolated in 85% yield, when carrying the reaction in [BMI][PF_6].

30c 1-(isopropoxy)-3-(phenylselanyl)propane-2-thiol



^{1}H-NMR δ(ppm) = 1.12 (6H, d, J=6.2 Hz, CH(C**H$_3$)$_2$**), 2.12 (1H, d, J= 7.4 Hz, S**H**), 3.05-3.36 (3H, m, C**H**$_2$Se + C**H**SH), 3.45-3.58 (2H, m, C**H**$_2$O + C**H**$(CH_3)_2$), 3.65 (1H, dd, J=4.8, 9.6 Hz, C**H**$_2$O), 7.24-7.27 (5H, m, Ph).

^{13}C-NMR δ(ppm) = 22.0 (CH(**C**$H_3)_2$), 33.8 (**C**H_2Se), 40.5, 69.2 (**C**H_2O), 72.0 (O**C**$H(CH_3)_2$), 126.9, 129.1, 130.0, 131.4.

^{77}Se-NMR. δ(ppm) = 277.6.

MS m/z (%) = 290 (2, $[M^{+\bullet}]$), 157 (6, $[SePh]^+$), 133 (13), 91 (21), 73 (100, $[CH_2OCH(CH_3)_2]^+$), 57 (27).

Yield:

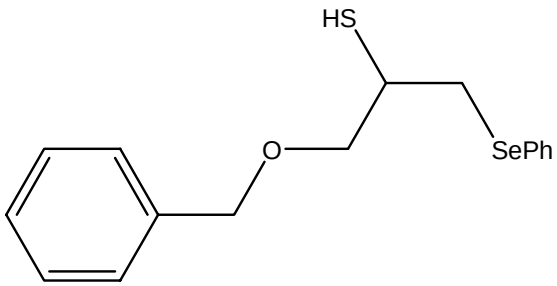
Method A : **30c** was isolated by TLC (petroleum ether/EtOAc, 10:1) in 53% yield as a yellow oil.

Method B : **30c** was isolated by TLC (petroleum ether/EtOAc, 10:1) in 45% yield when carrying the reaction in [BMI][BF_4].

30c was isolated in 71% yield, when carrying the reaction in [BMI][PF_6].

Method C : **30c** was isolated in 55% yield; the reaction was carried in [BMI][PF_6].

30d 1-(benzyloxy)-3-(phenylselanyl)propane-2-thiol



^{1}H-NMR δ(ppm) = 2.12 (1H, d, J = 7.6 Hz, CHS**H**), 3.15-3.33 (3H, m, C**H$_2$**SePh + C**H**SH), 3.59 (1H, dd, J= 4.6, 9.4 Hz, C**H$_2$**OBn), 3.71 (1H, dd, J= 4.8, 9.4 Hz, C**H$_2$**OBn), 4,44 (2H, s, C**H$_2$**Ph), 7.20-7.51 (10H, m, Ph).

^{13}C-NMR δ(ppm) = 33.8 (**C**H$_2$SePh), 51.1 (**C**HSH), 73.0 (**C**H$_2$Ph), 73.3 (**C**H$_2$OBn), 127.1, 127.11, 127.6, 128.3, 129.1, 130.0, 132.5, 137.8.

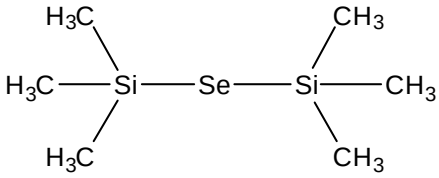
^{77}Se-NMR. δ(ppm) = 280.7.

MS m/z (%) = 340 (0.7, [$M^{+\bullet}$+2]), 338 (4, [$M^{+\bullet}$]), 230 (0.3, [$M^{+\bullet}$-OBn-H]), 181 (15, [$M^{+\bullet}$-SePh]), 157 (3, [PhSe]), 107 (4, [OBn]$^+$), 91 (100, Bn$^+$).

Yield:

Method B : **30d** was isolated by TLC (petroleum ether/EtOAc, 9:1) in 68% yield; the reaction was carried in [BMI][PF_6].

11. Synthesis of bis(trimethylsilyl)selenide (HMDSS) 23



In a flame-dried Schlenk flask under nitrogen atmosphere, $NaBH_4$ (27.8 mmol, 2.2 equiv.) was added portionwise to anhydrous THF (30 mL). The mixture was stirred at rt for 10 minutes, then elemental Se (12.65 mmol, 1 equiv.) was added in portions. The heterogeneous mixture, firstly dark brown, became quickly pale brown and after few hours white, with release of hydrogen. After 24 hours strirring at rt, the mixture was cooled at 0°C and TMSCl (29.1 mmol, 2.3 equiv.) was added drop by drop. After additionally 4

h at rt, the mixture was diluted with 150 mL of pentan, to allow the precipitation of inorganic salts. The organic layer was filtered through a plug of celite under inert atmosphere, due to the tendency of the compound to oxidation, and the salts were washed with pentane. The filtered organic layers were combined and the solvent was evaporated under reduced pressure to give **23** in 60% yield, as a yellow oil, which was used without further purification.

^{1}H-NMR δ(ppm) = 0.46 (18H, CH_3)

^{13}C-NMR δ(ppm) = 4.7

^{77}Se-NMR. δ(ppm) = -337.2

MS m/z (%) = 226 (27, [$M^{+\bullet}$]), 211 (56, [$M^{+\bullet}$- CH_3]), 73 (100, [$(CH_3)_3$-Si]).

12. Synthesis of β-hydroxy and β-mercapto diselenides

The assignment of the structures was confirmed by synthesizing the products through an alterantive synthetic route.[iIV]

Method A: synthesis of β-hydroxy and β-mercapto diselenides in THF, under catalysis of $PhONBu_4$.

General procedure. A solution of $PhONBu_4$ (0.056 mmol, 0.2 equiv.) in dry THF (0.4 mL) was added with thiirane **16** or epoxide **12** (0.2 mmol, 1 equiv.) and drop by drop with HMDSS **23** (0,28 mmol, 1.4 equiv.) at 0°C under inert atmosphere. After 10 minutes at 0°C, the mixture was warmed at room temperature, and the reaction was carried out for 1 h; the progress of the reaction was monitored by TLC. After addition of citric acid (50% aq solution) the mixture was stirred for 10 min, then diluted with Et_2O. The organic phase was then washed with citric acid (20% aq solution), extracted with Et_2O and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified on TLC.

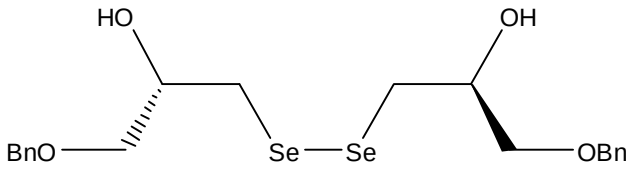
Method B: synthesis of β-hydroxy and β-mercapto diselenides in IL, under catalysis of TBAF.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 800 μL), HMDSS **23** (0.4 mmol, 2.2 equiv.) and thiirane **16** or epoxide **12** (0,18 mmol, 1 equiv.) at room temperature under inert atmosphere, was treated dropwise with TBAF (1M in THF; 0.08 mmol, 0.2 equiv.). The reaction was carried out for around 1 h and 30 min and the progress was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were treated with citric acid (50% aq solution; 1 mL). The resulting organic phase was then washed with citric acid (20% aq solution), and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified on TLC.

Method C: synthesis of β-hydroxy and β-mercapto diselenides in IL, under catalysis of $PhONBu_4$.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 800 μL) and $PhONBu_4$ (0.08 mmol, 0.2 equiv.) was added under inert atmosphere drop by drop with HMDSS **23** (0.4 mmol, 2.2 equiv.) and thiirane **16** or epoxide **12** (0,18 mmol, 1 equiv.) at room temperature. The reaction was carried out for around 2 h and the progress of the reaction was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were treated with citric acid (50% aq solution; 1 mL). The resulting organic phase was then washed with with citric acid (20% aq solution), and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified on TLC.

24f (2*S*,2*S*′)-3,3'-diselanediylbis(1-(benzyloxy)propan-2-ol)



^{1}H-NMR δ(ppm) = 2.30 (2H, bs, O**H**), 3.09 (2H, dd, J=4.8, 12.8 Hz, C**H**$_2$Se), 3.16 (2H, dd, J=7.6, 12.8 Hz, C**H**$_2$Se), 3.50-3.62 (4H, m, C**H**$_2$O), 4.03-4.08 (2H, m, C**H**OH), 4.56 (4H, s, C**H**$_2$Ph), 4.6-4.8 (2H, bs, O**H**), 7.30-7.36 (10H, m, Ph).

^{13}C-NMR δ(ppm) = 34.1 (**C**H$_2$Se), 70.2, 72.9, 73.5, 127.6, 127.7, 128.3, 137.6.

^{77}Se-NMR. δ(ppm) = 277.5

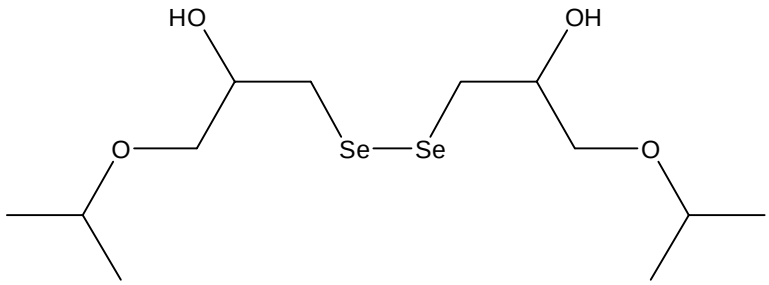
MS m/z (%) = 488 (1, [$M^{+\bullet}$]), 367 (17), 244 (52), 91 (100, Bn^{+}).

Optical rotation : $[\alpha]^{rt}_{D}$ = -82 (c=1.1, $CHCl_3$).

Yield

Method A : (±)-3,3'-diselanediylbis(1-(benzyloxy)propan-2-ol) (**24a**) was isolated by TLC (1.5:1 petroleum ether/ethyl acetate) in 59% yield as a yellow oil.
24f was isolated by TLC (1.5:1 petroleum ether/ethyl acetate) in 62% yield.
Method B : **24a** was isolated by TLC (1.5:1 petroleum ether/ethyl acetate) in 61% yield. In the crude the corresponding selenide **26a** was also detected (15%). The reaction was carried in [BMI][PF_6].

24b 3,3'-diselanediylbis(1-isopropoxypropan-2-ol)



^{1}H-NMR δ(ppm) = 1.16 (12H, d, J=5.8 Hz, CH(C**H**$_3$)$_2$), 2.7-2.85 (2H, bs O**H**), 3.09-3.15 (4H, m, C**H**$_2$Se), 3.44-3.68 (6H, m, C**H**$_2$O + C**H**(CH$_3$)$_2$), 3.9-4-09 (2H, m ,C**H**OH).

^{13}C-NMR δ(ppm) = 22.2 (CH(**C**H_3)**$_2$**), 34.2 (**C**H_2Se), 70.4 (**C**HOH), 70.9 (**C**H_2O), 72.3 (O**C**H(CH_3)$_2$).

^{77}Se-NMR. δ(ppm) = 279.8, 280.4 (mix of two diastereoisomers).

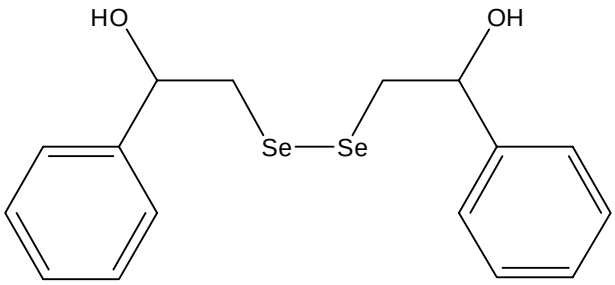
Yield:

Method A : **24b** was isolated in 57% yield as a yellow oil.

Method B : **24b** was isolated by TLC (petroleum ether/ethyl acetate 2:1) in 40% yield. The reaction was carried in [BMI][PF_6]. In the crude the corresponding selenide **26b** was also detected.

Method C : **24b** was isolated in 45% yield in mixture with the corresponding selenide in ratio 2:1.

24c 2,2'-diselanediylbis(1-phenylethanol)

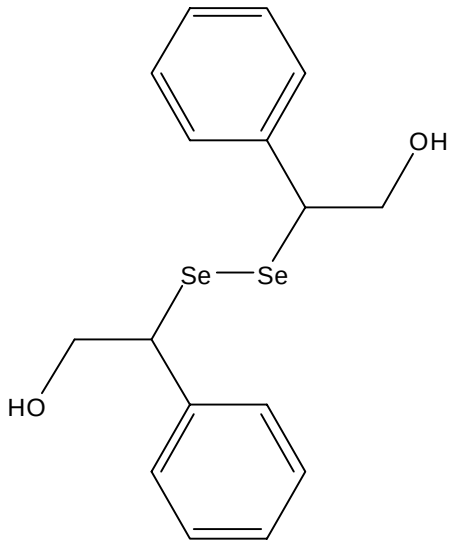


^{1}H-NMR δ(ppm) = 3.17-3.40 (4H, m, C**H$_2$**Se), 4.91-4.98 (2H, m, C**H**OH), 7.22-7.43 (10H, Ph).

^{13}C-NMR δ(ppm) = 39.6, 39.8 (**C**H_2Se, mix of two diastereoisomers), 73.2, 73.3 (**C**HOH, mix of two diastereoisomers), 125.8, 127.9, 128.6, 142.3.

^{77}Se-NMR. δ(ppm) = 280.8, 281.4 (mix of two diastereoisomers).

24c' 2,2'-diselanediylbis(2-phenylethanol)



^{1}H-NMR δ(ppm) = 3.44-3.63 (4H, m, C**H$_2$**O), 5.03-5.11 (2H, m, C**H**Se), 7.28-7.39 (10H, Ph).

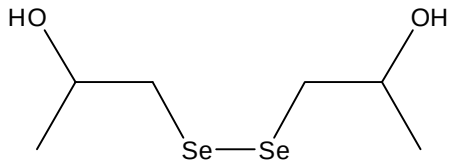
^{13}C-NMR δ(ppm) = 41.4 (**C**H$_2$Se), 72.6, 125.2, 125.4, 128.1, 141.8.

^{77}Se-NMR. δ(ppm) = 262.5, 264.5 (mix of two diastereoisomers

Yield

Method A : **24c** +**24c'** were isolated by TLC (2.5:1 petroleum ether/ethyl acetate) in 57% yield in regioisomeric ratio 75:25.

24g 1,1'-diselanediyldipropan-2-ol



^{1}H-NMR δ(ppm) = 1.25 (6H, d, J=6.2 Hz, C**H$_3$**), 2.40 (2H, bs, O**H**), 2.90-3.15 (4H, m, C**H$_2$**Se), 3.98-4.07 (2H, m, C**H**OH).

^{13}C-NMR δ(ppm) = 22.5 (**C**H$_3$), 39.8 (**C**H$_2$Se), 67.1.

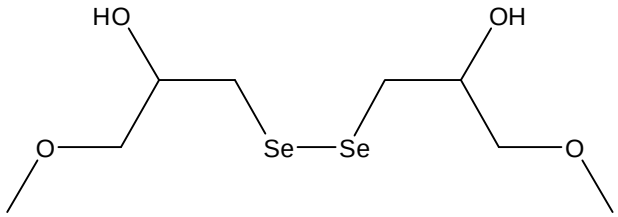
^{77}Se-NMR. δ(ppm) = 268.2.

MS m/z (%) = 278 (9, [$M^{+\bullet}$]), 219 (0.6), 160 (14), 121 (3), 93 (4), 59 (100, $[CH_3CH(OH)CH_2]^+$).

Yield

Method A : **24g** was isolated by TLC (1:1 petroleum ether/ethyl acetate) in 60% yield as a yellow oil.

24h 3,3'-diselanediylbis(1-methoxypropan-2-ol)

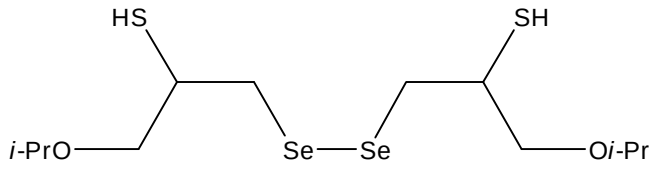


^{1}H-NMR δ(ppm) = 2.94-3.05 (4H, m, C**H$_2$**Se), 3.40 (6H, s, C**H$_3$**O), 3.42-3-53 (4H, m, C**H$_2$**O), 4.0-4.05 (2H, m, C**H**OH).

^{13}C-NMR δ(ppm) = 32.8, 32.9 (**C**CH_2Se, mix of two diastereoisomers), 62.26, 62.34 (**C**HOH), 69.5, 71.6.

^{77}Se-NMR. δ(ppm) = 280.3.

25c 3,3'-diselanediylbis(1-isopropoxypropane-2-thiol)



^{1}H-NMR δ(ppm) = 1.16 (12H, d, J=6.2 Hz, CH(C**H$_3$**)**$_2$**), 2.04 (2H, d, J= 7.2 Hz, S**H**), 2.89-2.96 (2H, m, C**H**$(CH_3)_2$), 3.18-3.29 (4H, m, C**H$_2$**Se), 3.49-3.68 (6H, m, C**H$_2$**O + C**H**SH).

^{13}C-NMR δ(ppm) = 22.2 (CH(**C**H_3)**$_2$**), 36.36, 36.42 (**C**H_2Se, mix of two diastereoisomers), 41.1 (**C**HSH), 71.6 (**C**H_2O), 72.2 (O**C**H$(CH_3)_2$).

^{77}Se-NMR. δ(ppm) = 311, 312.4 (mix of two diastereoisomers).

MS m/z (%) = 344 (4), 99 (28), 73 (100, CH_2O*i*-Pr$^+$).

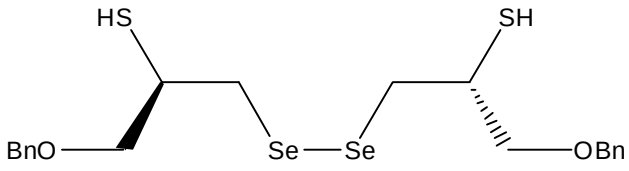
Yield

Method A : **25c** was isolated by TLC (3:1 petroleum ether/ethyl acetate) in 43% yield as a yellow oil.

Method B : **25c** was isolated in 38% yield. In the crude the corresponding selenide was also detected (around 10%).

Method C : **25c** was isolated in 37% yield in mixture with the corresponding selenide **27c** in 26% yield.

25e (2*R*,2*R'*)-3,3'-diselanediylbis(1-benzyloxypropane-2-thiol)



^{1}H-NMR δ(ppm) = 2.04 (2H, d, J=7.8 Hz, S**H**), 3.21-3.37 (6H, m, C**H$_2$**Se + C**H**SH), 3.55-3.75 (4H, m, C**H$_2$**O), 4.54 (4H, s, C**H$_2$**Ph), 7.34 (10H, m, Ph).

^{13}C-NMR δ(ppm) = 33.9 (**C**H$_2$Se), 54.6 (**C**HSH), 68.1, 75.6, 127.6, 128.1, 129.8, 136.2.

^{77}Se-NMR. δ(ppm) = 310.8.

Optical rotation : $[\alpha]^{rt}_{D}$ = +14 (c=1.2, $CHCl_3$).

Yield

Method A : (±)-3,3'-diselanediylbis(1-benzyloxypropane-2-thiol) (**25d**) was isolated by TLC (3:1 petroleum ether/ethyl acetate) in 40% yield as a yellow oil.

Method B : **25d** was isolated in 42% yield. In the crude the corresponding selenide was also detected (12%).

13. Synthesis of β-hydroxy and β-mercapto selenides

The assignment of the structures was confirmed by synthesizing the products through an alterantive synthetic route.[iV]

Method A: synthesis of β-hydroxy and β-mercapto selenides in THF, under catalysis of TBAF.

General procedure. A solution of thiirane **16** or epoxide **12** (0.2 mmol, 2 equiv.) and HMDSS **23** (0.14 mmol, 0.7 equiv.) in dry THF (0.4 mL) was treated at 0°C with TBAF (1M in THF; 0.028 mmol, 0.2 equiv.) under inert atmosphere. After addition of TBAF, the mixture became bright green and after few minutes pale yellow. After 10 minutes at 0°C, the mixture was warmed at room temperature, and the reaction was carried out for 1 h; the progress of the reaction was monitored by TLC. After addition of citric acid (50% aq solution) the mixture was stirred for 10 min, then diluted with Et_2O. The organic phase was then washed with citric acid (20% aq solution; 1 mL), extracted with Et_2O and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified on TLC.

Method B: synthesis of β-hydroxy and β-mercapto selenides in THF, under catalysis of $PhONBu_4$.

General procedure. A solution of $PhONBu_4$ (0.028 mmol, 0.2 equiv.) in dry THF (0.4 mL) was added with thiirane **16** or epoxide **12** (0.2 mmol, 1 equiv.) and dropwise with HMDSS **23** (0,14 mmol, 0.7 equiv.) at 0°C under inert atmosphere. After 10 minutes at 0°C, the mixture was warmed at room temperature, and the reaction was carried out for 1 h; the progress of the reaction was monitored by TLC. After addition of citric acid (50% aq solution; 1 mL) the mixture was stirred for 10 min, then diluted with Et_2O. The organic phase was then washed with citric acid (20% aq solution), extracted with Et_2O and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified on TLC.

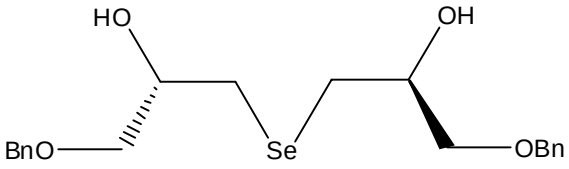
Method C: synthesis of β-hydroxy and β-mercapto selenides in IL, under catalysis of TBAF.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 340 μL), HMDSS **23** (0.13 mmol, 0.7 equiv.) and thiirane **16** or epoxide **12** (0,18 mmol, 1 equiv.) at room temperature under inert atmosphere, was treated dropwise with TBAF (1M in THF; 0.03 mmol, 0.2 equiv.). After the addtion of TBAF the mixture became yellow. The reaction was carried out for around 1 h and 30 min and the progress was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were treated with citric acid (50% aq solution; 1 mL). The resulting organic phase was then washed with citric acid (20% aq solution), and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified on TLC.

Method D: synthesis of β-hydroxy and β-mercapto selenides in IL, under catalysis of $PhONBu_4$.

General procedure. A mixture of IL ([BMI][BF_4] or [BMI][PF_6], 340 μL) and $PhONBu_4$ (0.03 mmol, 0.2 equiv.) was added under inert atmosphere drop by drop with HMDSS **23** (0.13 mmol, 0.7 equiv.) and thiirane **16** or epoxide **12** (0,18 mmol, 1 equiv.) at room temperature. The reaction was carried out for around 2 h and the progress of the reaction was monitored by TLC. After addition of Et_2O in the reaction flask, the organic product was directly extracted from IL (3X1 mL) and the organic phases were treated with citric acid (50% aq solution; 1 mL). The resulting organic phase was then washed with with citric acid (20% aq solution; 1 mL), and dried over $NaSO_4$. Evaporation of the solvent afforded crude product, which was purified on TLC.

26f (2*S*,2*S*′)-3,3'-selenobis(1-benzyloxypropan-2-ol)



^{1}H-NMR δ(ppm) = 2.70 (2H, dd, J=7.2, 12.8 Hz, C**H**$_2$Se), 2.81 (2H, dd, J=4.4, 12.8 Hz, C**H**$_2$Se), 3.41-

3.58 (4H, m, C**H**$_2$O), 3.9-4.04 (2H, m, C**H**OH), 4.54 (24H, s, C**H**$_2$Ph), 4.6-4.8 (2H, bs, O**H**), 7.24-7.39 (10H, m, Ph).

^{13}C-NMR (APT) δ(ppm) = 28.9 (**C**H$_2$Se), 69.9 (**C**HOH), 73.2, 73.3, 127.6, 127.8, 128.2, 137.4.

^{77}Se-NMR. δ(ppm) = 71.2.

MS m/z (%) = 410 (3, [$M^{+\bullet}$]), 358 (73), 343 (16), 136 (21), 91 (100, Bn^{+}).

Optical rotation : $[\alpha]^{rt}_{D}$ = -61 (c=1.1, $CHCl_3$).

Yield:

Method A : (±)-3,3'-selenobis(1-benzyloxypropan-2-ol) (**26a**) was isolated by TLC (petroleum ether/EtOAc, 2:1) in 56% yield as a yellow oil.

26f was isolated in 59% yield as a yellow oil.

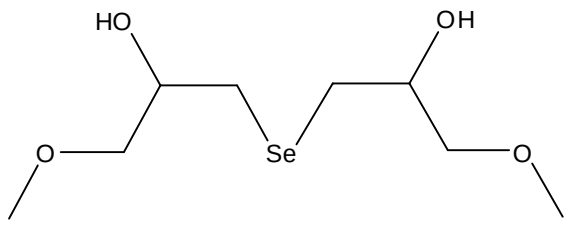
Method B : **26f** was isolated by TLC (petroleum ether/EtOAc, 1:1) in 54%.

Method C : **26a** was isolated in 65% yield; the reaction was carried in [BMI][BF_4].

26f was isolated in 59% yield; the reaction was carried in [BMI][BF_4].

Method D : **26a** was isolated in 79% yield; the reaction was carried in [BMI][PF_6].

26h 3,3'-selenobis(1-isopropoxypropan-2-ol)



^{1}H-NMR δ(ppm) = 2.70 (2H, dd, J=7.2, 12.8 Hz, C**H**$_2$Se), 2.81 (2H, dd, J=4.8, 13.2 Hz, C**H**$_2$Se), 2.90-3.10 (2H, bs, O**H**), 3.38 (6H, s, C**H**$_3$O), 3.41-3-50 (4H, m, C**H**$_2$O), 3.91-3.97 (2H, m, C**H**OH).

^{13}C-NMR δ(ppm) = 28.9 (**C**H$_2$Se), 59.2 (**C**HOH), 69.9, 75.7.

^{77}Se-NMR. δ(ppm) = 69.

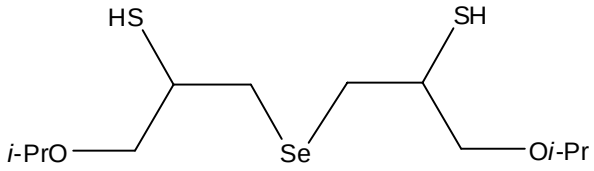
MS m/z (%) = 258 (6, [$M^{+\bullet}$]), 195 (8, [$M^{+\bullet}$- $(CH_3O)_2$]), 151 (9), 71 (100).

Yield:

Method A : **26h** was isolated by TLC (petroleum ether/EtOAc, 1:1) in 61% yield as a yellow oil.

Method C : **26h** was isolated by TLC in 69%; the reaction was carried in [BMI][BF_4].

27c 3,3'-selenobis(1-isopropoxypropane-2-thiol)



^{1}H-NMR δ(ppm) = 1.15 (12H, d, J=5.8 Hz, CH(C**H$_3$)$_2$**), 2.06 (2H, d, J= 7.6 Hz, S**H**), 2.8-3.05 (4H, m, C**H$_2$**Se), 3.4-3.72 (8H, m, C**H$_2$**O + C**H**$(CH_3)_2$ + C**H**SH).

^{13}C-NMR δ(ppm) = 22.2 (CH(**C**$H_3)_2$), 31.3 (**C**H_2Se), 40.9 (**C**HSH), 71.7 (**C**H_2O), 72.1 (O**C**$H(CH_3)_2$).

^{77}Se-NMR. δ(ppm) = 121.9, 122.9 (mix of two diastereoisomers).

MS m/z (%) = 346 (5, [$M^{+\bullet}$]), 313 (1, [$M^{+\bullet}$-SH]), 153 (10), 133 (15), 99 (38), 73 (100, CH_2O*i*-Pr^+).

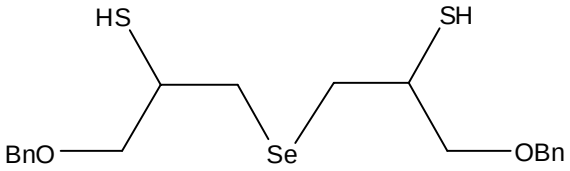
Yield:

Method A : **27c** was isolated by TLC (petroleum ether/EtOAc, 2.5:1) in 50% yield as a yellow oil.

Method B : **27c** was isolated by TLC in 41% yield.

Method C : **27c** was isolated in 48% yield; the reaction was carried in [BMI][BF_4].

27d 3,3'-selenobis(1-benzyloxypropane-2-thiol)



^{1}H-NMR δ(ppm) = 2.05 (2H, d, J=7.8 Hz, S**H**), 2.80-3.05 (4H, m, C**H$_2$**Se), 3.4-3.8 (6H, m, C**H**SH + C**H$_2$**O), 4.53 (4H, s, C**H$_2$**Ph), 7.19-7.4 (10H, m, Ph).

^{13}C-NMR δ(ppm) = 31.3 (**C**H$_2$Se), 40.5 (**C**HSH), 73.1, 73.6, 127.5, 127.6, 128.2, 137.6.

^{77}Se-NMR. δ(ppm) = **27d**: 123.5, 124.4 (mix of two diastereoisomers). (2*R*,2*R'*)-3,3'-selenobis(1-benzyloxypropane-2-thiol) (**27e**): 123.6.

MS m/z (%) = 442 (4, $[M^{+\bullet}]$), 409 (0.4, $[M^{+\bullet}$-SH]), 181 (14), 147 (10), 107 (29, $[PhCH_2O]^+$), 91 (100, Bn^+).

Yield:

Method A : **27d** was isolated by TLC (petroleum ether/EtOAc, 2.5:1) in 52% yield as a yellow oil.

27e was isolated in 49% yield as a yellow oil.

Method C : **27d** was isolated by TLC (petroleum ether/EtOAc, 2.5:1) in 59% yield as a yellow oil; the reaction was carried in [BMI][PF_6].

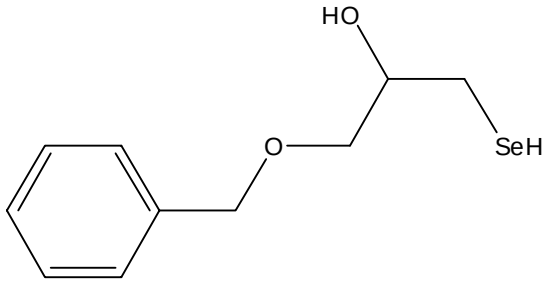
27e was isolated in 55% yield.

Method D : **27d** was isolated by TLC (petroleum ether/EtOAc, 2.5:1) in 49% yield; the reaction was carried in [BMI][PF_6].

14. Synthesis of β-hydroxy selenols

General procedure. A solution of $PhONBu_4$ (0.005 mmol, 0.02 equiv.) in THF (0.4 mL) was added with epoxide **12** (0.15 mmol, 1 equiv.) and HMDSS **23** (0,26 mmol, 1.7 equiv.) at 0°C under inert atmosphere. After 10 minutes at 0°C, the mixture was warmed at room temperature, and the reaction was carried out for 45 min; the progress of the reaction was monitored by TLC. After addition of solid citric acid, the mixture was stirred under inert atmosphere for 15 min, then diluted with Et_2O. H_2O was then added, and the organic phase was extracted with Et_2O (2x3 mL) and dried over $NaSO_4$. Evaporation of the solvent afforded product as a yellow oil, which was pure enough to be used without purification.

31a 1-(benzyloxy)-3-hydroselenopropan-2-ol



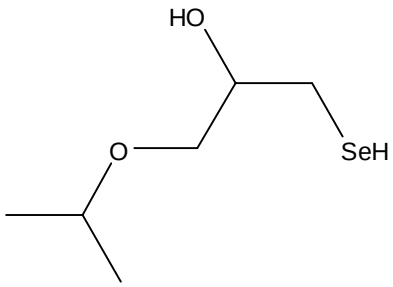
Following the general procedure **31a** was isolated in 67% yield.

^{1}H-NMR δ(ppm) = -0.60 (1H, t, J=7.4 Hz, Se**H**), 2.69-2.78 (2H, m, C**H$_2$**Se), 3.52-3.59 (2H, m, C**H$_2$**O), 3.84-3.95 (1H, m, C**H**OH), 4.56 (2H, s, C**H$_2$**Ph), 7.3-7.4 (5H, m Ph).

^{13}C-NMR δ(ppm) = 21.5 (**C**H$_2$Se), 70.9 (O**C**H$_2$Ph), 72.6 (**C**H$_2$CH), 73.4 (**C**HOH), 127.6, 127.7, 128.4, 137.6.

^{77}Se-NMR. δ(ppm) = -79.4

31b 1-hydroseleno-3-isopropoxypropan-2-ol



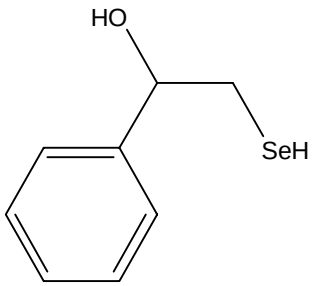
Following the general procedure **31b** was isolated in 62% yield.

^{1}H-NMR δ(ppm) = -0.58 (1H, t, J=7.6 Hz, Se**H**), 1.16 (6H, d, J=6.2 Hz, (C**H$_3$**)**$_2$**), 2.68-2.76

(2H, m, C**H**$_2$Se), 3.39-3.68 (3H, m, C**H**$_2$O + C**H***i*-Pr), 3.94-4.02 (1H, m, C**H**OH).

^{77}**Se-NMR**. δ(ppm) = -78.6

31c 2-hydroseleno-1-phenylethanol

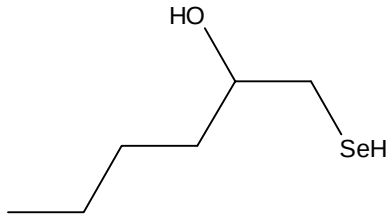


Following the general procedure **31c** was isolated in 44% yield.

^{1}**H-NMR** δ(ppm) = -0.57 (1H, t, J=7.6 Hz, Se**H**), 2.86-2.99 (2H, m, C**H**$_2$Se), 4.79 (1H, dd, J=4.4, 8 Hz, C**H**OH), 7.28-7.39 (5H, m Ph).

^{77}**Se-NMR**. δ(ppm) = -48.4

31i 1-hydroselenohexan-2-ol



Following the general procedure **31i** was isolated in 53% yield.

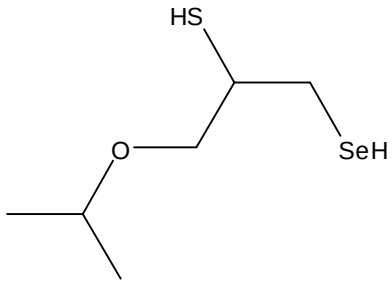
^{1}**H-NMR** δ(ppm) = -0.69 (1H, t, J=7.8 Hz, Se**H**), 0.90 (3H, t, J=7 Hz, C**H**$_3$), 1.31-1.53 (6H, m, CH$_3$(C**H**$_2$)$_3$), 2.50-2.64 (1H, m, C**H**$_2$Se), 2.82 (1H, ddd, J=3.6, 7.4, 11 Hz, C**H**$_2$Se), 3.59-3.70 (1H, m, C**H**OH).

^{77}**Se-NMR**. δ(ppm) = -90.2

MS m/z (%) = 164 (15, [$M^{+\bullet}$-17]), 135 (15, [$M^{+\bullet}$-17-CH_2-CH_3]), 69 (32), 55 (100).

15. Synthesis of β-mercapto selenol

32c 1-hydroseleno-3-isopropoxypropane-2-thiol



A solution of $PhONBu_4$ (0.004 mmol, 0.02 equiv.) in THF (0.35 mL) was added with episulfide **16c** (0.12 mmol, 1 equiv.) and HMDSS **23** (0,20 mmol, 1.7 equiv.) at 0°C under inert atmosphere. After 10 minutes at 0°C, the mixture was warmed at room temperature, and the reaction was carried out for 45 min; the progress of the reaction was monitored by TLC. After addition of solid citric acid, the mixture was stirred under inert atmosphere for 15 min, then diluted with Et_2O. H_2O was then added, and the organic phase was extracted with Et_2O (2x3 mL) and dried over $NaSO_4$. Evaporation of the solvent afforded product **32c** as a yellow oil in 63% yield (16.2 mg, 0.076 mmol), which was pure enough to be used without purification.

^{1}H-NMR δ(ppm) = -0.46 (1H, t, J=7.6 Hz, Se**H**), 1.15 (6H, d, J=6.2 Hz, CH(C**H$_3$)$_2$**), 1.93 (1H, d, J= 8 Hz, S**H**), 2.92 (2H, app t, C**H$_2$**Se), 3.02-3.12 (1H, m, C**H**$(CH_3)_2$), 3.42-3.7 (3H, m, C**H$_2$**O + C**H**SH).

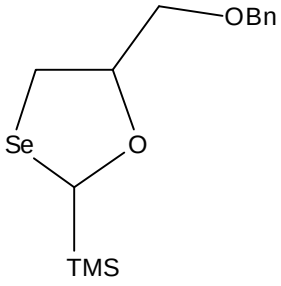
^{13}C-NMR δ(ppm) = 22.19, 22.23 (CH(**C**$H_3)_2$), 23.7 (**C**H_2Se), 41.9 (**C**HSH), 71.3 (**C**H_2O), 72.1 (O**C**$H(CH_3)_2$).

^{77}Se-NMR. δ(ppm) = -57.2

MS m/z (%) = 154 (64, [$M^{+\bullet}$-iPrO]), 121 (13, [$M^{+\bullet}$-iPrO-SH]), 73 (54, CH_2O*i*-Pr $^+$), 57 (100).

16. Synthesis of 2-trimethylsilyl 1,3-oxaselenolane

33 (5-(benzyloxymethyl)-1,3-oxaselenolan-2-yl)trimethylsilane



A solution of methoxymethyl trimethylsilane **8** (109 μL, 0.7 mmol) in CCl_4 (1.4 mL), was treated dropwise with a solution of bromine (36 μL, 0.7 mmol) in CCl_4 (1.0 mL). The mixture was stirred, with release of HBr, until it became pale orange (around 6 h). Then the solvent was evaporated under reduced pressure and a solution of selenol **31a** (172.2 mg, 0.7 mmol, 1 equiv.) in CH_2Cl_2 (1.4 mL) was added and the mixture was stirred overnight. After washing with water and brine, the organic layer was dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified on TLC (petroleum ether/EtOAc 10:1), to afford the pure compound in 21% yield (48.5 mg, 0.147 mmol) as a major diastereoisomer.

^{1}H-NMR δ(ppm): 0.14 (9H, s, -Si(CH_3)$_3$), 2.65 (1H, dd, J=1.2, 9.2 Hz, C**H**$_2$Se), 3.24 (1H, dd, J=5.2, 9.2 Hz, C**H**$_2$Se), 3.64 (1H, dd, J=4, 10.4 Hz, CHC**H$_2$**O), 3.71 (1H, dd, J=6, 10.8 Hz, CHC**H$_2$**O), 3.90-3.97 (1H, m, OC**H**CH_2), 4.58 (1H, d, J=12 Hz, C**H**$_2$Ph), 4.62 (1H, d, J=12 Hz, C**H**$_2$Ph), 5.05 (1H, s, SeC**H**O), 7.34 (5H, ap s, Ph).

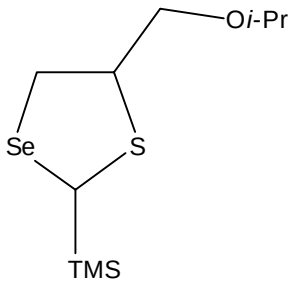
^{13}C-NMR δ(ppm) = -3.2 (Si(**C**H_3)$_3$), 29.3 (**C**H_2Se), 71.0 (CH**C**H_2O), 73.4 (O**C**H_2Ph), 74.9, 87.7 (**C**HO), 127.7, 128.39, 128.42, 138.1.

^{77}Se-NMR. δ(ppm) = 245.1.

MS m/z (%): 254 (9, [$M^{+\bullet}$-Ph]), 239 (3, [$M^{+\bullet}$-91]), 237 (12), 211 (5), 151 (5), 73 (100, $SiMe_3^+$).

17. Synthesis of 2-trimethylsilyl 1,3-thiaselenolane

34 (5-(isopropoxymethyl)-1,3-thiaselenolan-2-yl)trimethylsilane



A solution of methoxymethyl trimethylsilane **8** (187μL, 1.2 mmol) in CCl_4 (2.4 mL), was treated dropwise with a solution of bromine (62 μL, 1.2 mmol) in CCl_4 (2.0 mL). The mixture was stirred, with release of HBr, until it became pale orange (around 6 h). Then the solvent was evaporated under reduced pressure and a solution of selenol **32c** (254.4 mg, 1.2 mmol, 1 equiv.) in CH_2Cl_2 (2.4 mL) was added and the mixture was stirred overnight. After washing with water and brine, the organic layer was dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by TLC (petroleum ether/EtOAc 13:1), to afford the pure compound in 26% yield (92 mg, 0.3 mmol) as a mixture of *cis* and *trans* diastereoisomers in ratio 1.5:1. The assignment of the structure of the diastereoisomers was made by correlation spectroscopy (NOESY experiments).

^{1}H-NMR δ(ppm): 0.16 (18H, s, -Si(C**H$_3$)$_3$**), 1.16 (12H, d, J=6.2 Hz, (C**H$_3$)$_2$**), 3.14-3.79 (12H, m), 3.92-4.04 (2H, m, C**H**S).

Cis-diastereoisomer:

^{13}C-NMR δ(ppm) = -1.8 (Si(**C**H$_3$)$_3$), 22.2 ((**C**H$_3$)$_2$), 26.7 (Se**C**HS), 34.89 (**C**H$_2$Se), 56.3 (**C**HS), 69.0, 72.1.

Trans-diastereoisomer:

^{13}C-NMR δ(ppm) = -1.8 (Si(**C**H$_3$)$_3$), 22.1 ((**C**H$_3$)$_2$), 26.7 (Se**C**HS), 34.94 (**C**H$_2$Se), 58.3 (**C**HS), 69.9, 72.1.

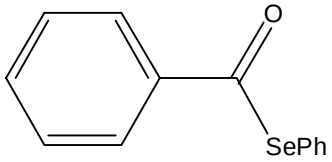
^{77}Se-NMR. δ(ppm) = 322.3, 343.7 (mix of *trans* and *cis* diastereoisomers, respectively).

MS m/z (%): 298 (2, [$M^{+\bullet}$]), 198 (37), 181 (6), 73 (100, $SiMe_3^+$).

18. Synthesis of selenol esters

General procedure. A solution of dry THF (500 μL) and acyl chloride **35** (0.214 mmol, 1 equiv.) was added under inert atmosphere with PhSeTMS **28** (0.26 mmol, 1.2 equiv.) and it was cooled at 0°C. Then TBAF (1M in THF; 0.05 mmol, 0.2 equiv.) was added dropwise. The mixture was warmed at rt and stirred overnight. The mixture was then diluted with diethyl ether (2 mL) and washed with saturated NaCl solution. The organic layer was dried over $NaSO_4$, and evaporated to dryness. The residue was purified by FC on silica gel with dichlorometane / *n*-hexane (1:2), to give the pure product.

36a *Se*-phenyl benzoselenoato



Following the general procedure, **36a** was isolated in 73% yield.

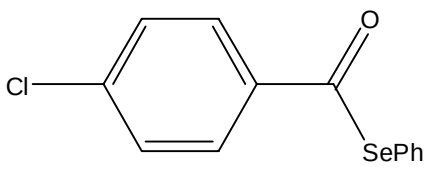
^{1}H-NMR δ(ppm): 7.21-7.27 (3H, m); 7.43-7.54 (5H, m); 7.59-7.6 (2H, m).

^{13}C-NMR δ(ppm): 125.6; 125.7; 127.2; 127.5; 130.0; 133.4; 133.7; 136.1; 193.2 (C=O).

MS m/z (%): 264 (0.74, M^{+}+2); 262 (4, M^{+}); 157 (10, $PhSe^{+}$); 155 (5); 105 (98, Ph-C=O^{+}); 77 (100, Ph^{+}).

^{77}Se-NMR. δ(ppm) = 637.2.

36b *Se*-phenyl 4-chlorobenzoselenoato



Following the general procedure, **36b** was isolated in 75% yield.

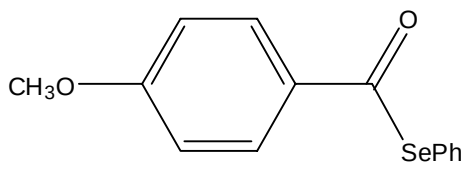
^{1}H-NMR δ(ppm): 7.17-7.34 (3H, m); 7.40-7.51 (4H, m); 7.56-7.60 (2H, m).

^{13}C-NMR δ(ppm): 121.5; 126.3; 127.5; 129.3; 131.4; 132.6; 136.1; 139.9; 192.0 (C=O).

MS m/z (%): 298 (0.57, M^++2); 297 (0.20, M^++1); 296 (1, M^+); 157 (6.1, -$PhSe^+$); 141 (50); 139 (100, Cl-Ph-C=O^+); 113 (16); 111 (44).

^{77}Se-NMR. δ(ppm) = 638.1.

36c *Se*-phenyl 4-methoxybenzoselenoato



Following the general procedure, **36c** was isolated in 70% yield.

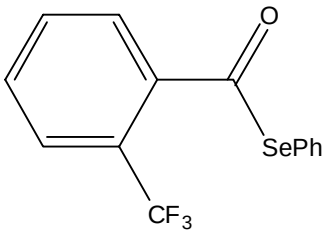
^{1}H-NMR δ(ppm): 3.88 (3H, s, CH_3O-); 6.94-6.98 (2H, m); 7.25-7.27 (1H, m); 7.41-7.44 (2H, m); 7.58-7.63 (2H, m); 7.90-7.94 (2H, m).

^{13}C-NMR δ(ppm): 55.6 (CH_3O); 114.0; 127.6; 129.0; 129.1; 129.5; 131.3; 136.2; 163.9; 191.0.

MS m/z (%): 294 (0.1, M^++2); 292 (0.13, M^+); 184 (0.14); 135 (100, CH_3OPhCO^+); 107 (15); 92 (14); 77 (33, Ph^+).

^{77}Se-NMR. δ(ppm) = 624.2.

36d *Se*-phenyl 2-(trifluoromethyl)benzoselenoato



Following the general procedure, **36d** was isolated in 71% yield.

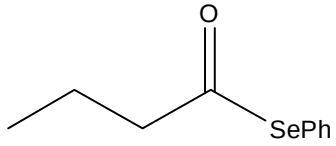
^{1}H-NMR δ(ppm): 7.25-7.28 (1H, m); 7.42-7.45 (3H, m); 7.59-7.67 (3H, m); 7.74-7.84 (2H, m).

^{13}C-NMR δ(ppm): 120.3; 126.3; 127.0; 127.8; 129.1; 129.4; 131.2; 131.6; 135.6; 138.9; 194.0 (C=O).

MS m/z (%): 330 (0.34, M^+); 173 (100, CF_3-Ph-C=O^+); 157 (5, $PhSe^+$); 145 (44, CF_3-Ph-$^+$); 125 (4); 77 (12).

^{77}Se-NMR. δ(ppm) = 679.1.

36e *Se*-phenyl butaneselenoato



Following the general procedure, **36e** was isolated in 61% yield.

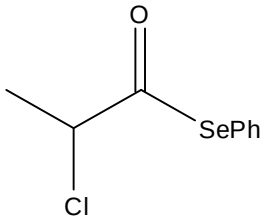
^{1}H-NMR δ(ppm): 1.00 (3H, t, J=7.4 Hz, CH_3); 1.76 (2H, sext, J=7.4 Hz, CH_3-C**H_2**-); 2.69 (2H, t, J=7.4 Hz, -C**H_2**-CO); 7.25-7.30 (1H, m); 7.37-7.42 (2H, m); 7.49-7.54 (2H, m).

^{13}C-NMR δ(ppm): 13.7; 19.8; 49.4; 126.2; 128.7; 129.1; 135.7; 194.2 (C=O).

MS m/z (%): 230 (1, M^++2); 228 (6, M^+); 158 (7); 157 (12, $PhSe^+$); 155 (6); 117 (3); 77 (22, Ph^+); 71 (100, $CH_3(CH_2)_2C=O^+$).

^{77}Se-NMR. δ(ppm) = 655.2.

36f *Se*-phenyl 2-chloropropane-selenoato



Following the general procedure, **36f** was isolated in 59% yield.

^{1}H-NMR δ(ppm): 1.75 (3H, d, J=7 Hz, CH_3); 4.58 (1H, q, J=7 Hz, Cl-CH-); 7.41-7.51 (3H, m); 7.53-7.55 (2H, m).

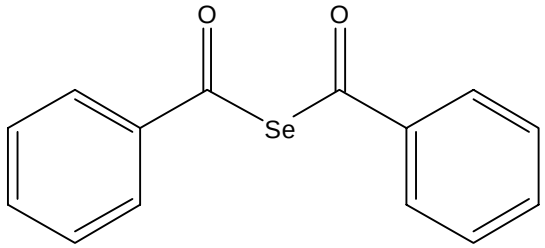
MS m/z (%): 250 (12, M^++2); 249 (3, M^++1); 248 (26, M^+); 246 (13); 192 (22); 158 (39); 157 (38, $PhSe^+$); 155 (24); 105 (11); 91 (44, CH_3CHCl-C=O^+); 77 (50, Ph^+); 63 (100, CH_3CHCl^+).

^{77}Se-NMR. δ(ppm) = 650.6.

19. Synthesis of diacyl selenides

General procedure. A solution of dry THF (500 μL) and acyl chloride **35** (0.214 mmol, 2 equiv.) was added under inert atmosphere with TBAF (1M in THF; 0.023 mmol, 0.2 equiv., with respect to **23**). The mixture was cooled at 0°C and HMDSS **23** (0.118 mmol, 1 equiv. + 10%) was added dropwise. The mixture became red and after 5 min pale yellow. The mixture was warmed at rt and stirred for 2-3 h. The mixture was then diluted with diethyl ether (2 mL) and washed with saturated NaCl solution. The organic layer was dried over $NaSO_4$, and evaporated to dryness. The residue was purified by FC on silica gel with dichlorometane / *n*-hexane (1:1), to give the pure product.

37a benzoic selenoanhydride



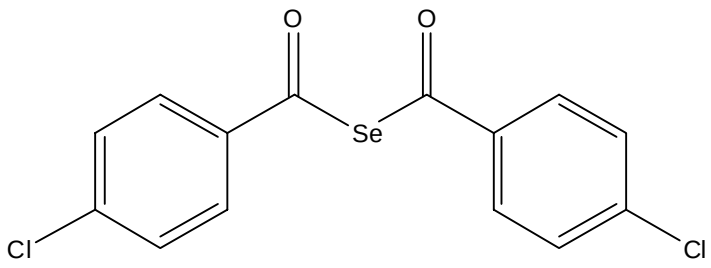
Following the general procedure, **37a** was isolated in 80% yield, as a yellow solid.

^{1}H-NMR δ(ppm): 7.42-7.51 (4H, m); 7.59-7.62 (2H, m); 7.95-8.02 (4H, m).

^{13}C-NMR δ(ppm): 128.2; 128.9; 134.5; 138.1; 188.5 (C=O).

^{77}Se-NMR. δ(ppm) = 743.

37b 4-chlorobenzoic selenoanhydride



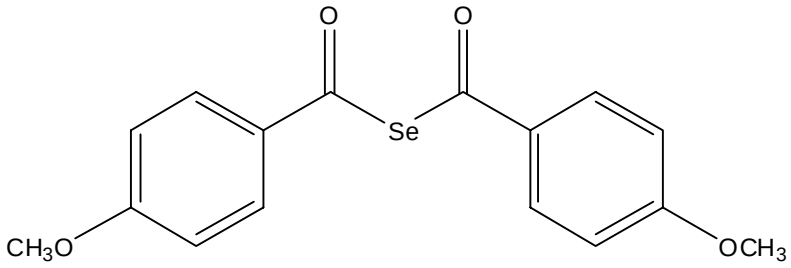
Following the general procedure, **37b** was isolated in 76% yield, as a yellow solid.

^{1}H-NMR δ(ppm): 7.45-7.47 (4H, m), 7.85-7.92 (4H, m).

^{13}C-NMR δ(ppm): 129.2, 129.5, 136.2, 139.9, 186.6 (C=O).

^{77}Se-NMR. δ(ppm) = 749.1

37c 4-methoxybenzoic selenoanhydride



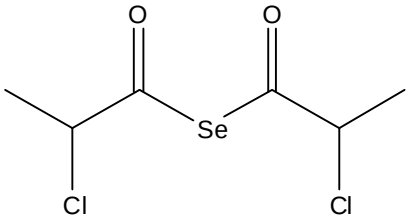
Following the general procedure, **37c** was isolated in 75% yield, as a yellow solid.

^{1}H-NMR δ(ppm): 3.88 (6H, s, CH_3O); 6.93-6.98 (4H, m); 7.92-7.96 (4H, m).

^{13}C-NMR δ(ppm): 55.6; 114.1; 131.0; 131.5; 164.6; 185.9 (C=O).

^{77}Se-NMR. δ(ppm) = 730.0.

37f 2-chloropropanoic selenoanhydride



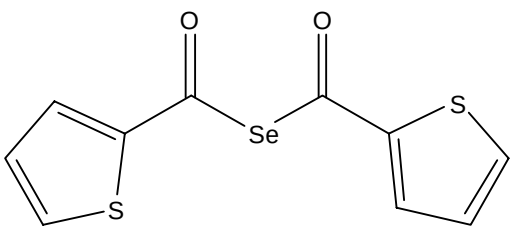
Following the general procedure, **37f** was isolated in 50% yield, as a yellow oil.

^{1}H-NMR δ(ppm): 1.73 (6H, d, J=7 Hz, CH_3); 4.46 (2H, q, J=7.2 Hz, CH).

^{13}C-NMR δ(ppm): 22.2; 63.8; 169.8 (C=O).

^{77}Se-NMR. δ(ppm) = 783.9.

37g thiophene-2-carboxylic selenoanhydride



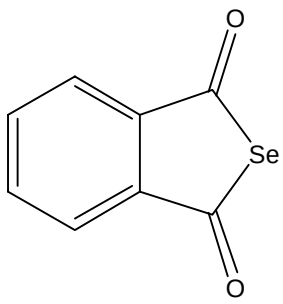
Following the general procedure, **37g** was isolated in 70% yield, as a yellow oil.

^{1}H-NMR δ(ppm): 7.18-7.20 (2H, m); 7.77-7.89 (4H, m).

^{13}C-NMR δ(ppm): 127.7; 132.9; 133.5; 134.0; 184.7 (C=O).

^{77}Se-NMR. δ(ppm) = 776.8.

37h benzeselenophene-1,3-dione



Following the general procedure, N was isolated in 63% yield, as a yellow solid.

^{1}H-NMR δ(ppm): 7.74-7.80 (2H, m); 7.90-7.99 (2H, m).

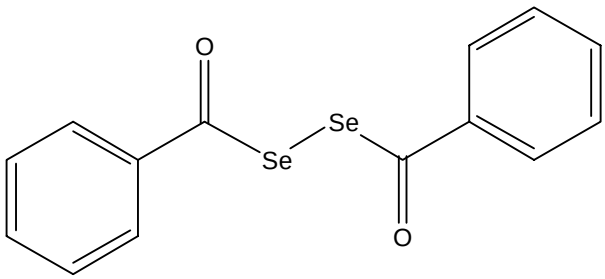
^{13}C-NMR δ(ppm): 123.6; 134.8; 141.6; 193.9 (C=O).

^{77}Se-NMR. δ(ppm) = 610.2.

20. Synthesis of diacyl diselenides

General procedure. A solution of dry THF (500 μL) and acyl chloride **35** (0.214 mmol, 1 equiv.) was added under inert atmosphere with HMDSS **23** (0.235 mmol, 1 equiv. + 10%) and it was cooled at 0°C. Then TBAF (1M in THF; 0.047 mmol, 0.2 equiv., with respect to **23**) was added dropwise. The mixture became red and, after 5 min, pale yellow. The mixture was warmed at rt and stirred for 2-3 h. The mixture was then diluted with diethyl ether (2 mL) and washed with saturated NaCl solution. The organic layer was dried over $NaSO_4$, and evaporated to dryness. The residue was purified by FC on silica gel with dichlorometane / *n*-hexane (1:1), to give the pure product.

38a benzoic diselenoperoxyanhydride



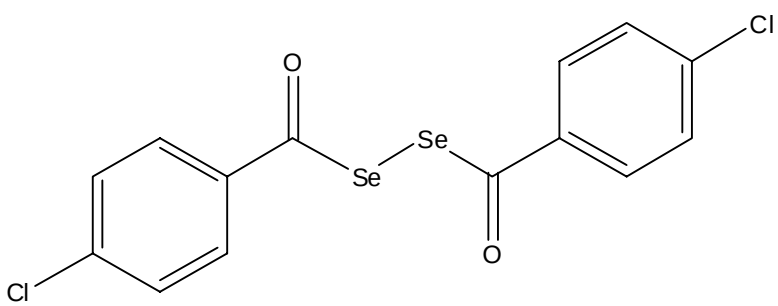
Following the general procedure, **38a** was isolated in 83% yield as a yellow igroscopic solid.

^{1}H-NMR δ(ppm): 7.47-7.54 (4H, m); 7.61-7.65 (2H, m); 7.99-8.16 (4H, m).

^{13}C-NMR δ(ppm): 128.0; 129.0; 134.2; 136.6; 186.1 (C=O).

^{77}Se-NMR. δ(ppm) = 613.0.

38b 4-chlorobenzoic diselenoperoxyanhydride



Following the general procedure, **38b** was isolated in 78% yield, as a yellow igroscopic

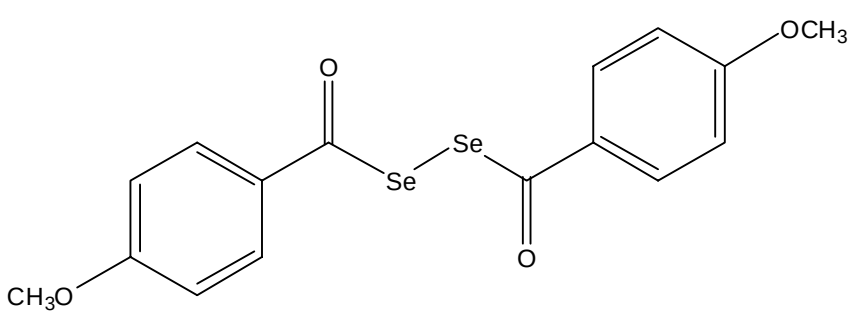
solid.

^{1}H-NMR δ(ppm): 7.40-7.51 (4H, m); 7.72-8.08 (4H, m).

^{13}C-NMR δ(ppm): 129.4; 129.5; 134.9; 141.0; 186.0 (C=O).

^{77}Se-NMR. δ(ppm) = 619.4.

38c 4-methoxybenzoic diselenoperoxyanhydride



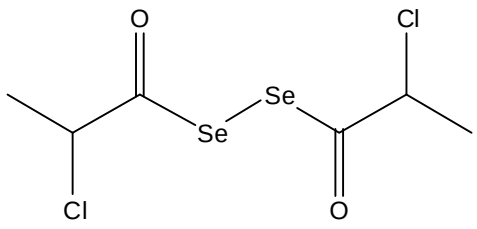
Following the general procedure, **38c** was isolated in 72% yield.

^{1}H-NMR δ(ppm): 3.88 (6H, s, CH_3O); 6.92-6.98 (4H, m); 7.91-8.07 (4H, m).

^{13}C-NMR δ(ppm): 55.6; 114.2; 129.3; 130.5; 164.4; 185.4 (C=O).

^{77}Se-NMR. δ(ppm) = 598.5.

38f 2-chloropropanoic diselenoperoxyanhydride



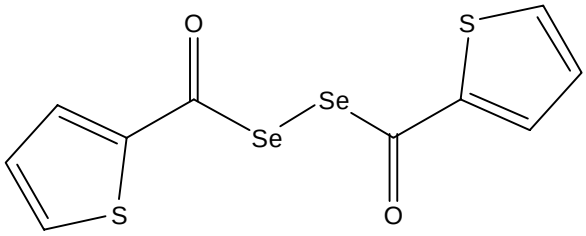
Following the general procedure, **38f** was isolated in 54% yield, as a yellow oil.

^{1}H-NMR δ(ppm): 1.68 (6H, d, J=7 Hz, CH_3); 4.46 (2H, q, J=7 Hz, CH).

^{13}C-NMR δ(ppm): 22.2; 62.2; 170.0 (C=O).

^{77}Se-NMR. δ(ppm) = 601.

38g thiophene-2-carboxylic diselenoperoxyanhydride



Following the general procedure, **38g** was isolated in 73% yield, as a yellow oil.

^{1}H-NMR δ(ppm): 7.15-7.20 (2H, m); 7.77-7.89 (4H, m).

^{13}C-NMR δ(ppm): 128.0; 132.9; 133.5; 135.4; 185.0 (C=O).

^{77}Se-NMR. δ(ppm) = 614.4.

iI R. Goddard, H. M. Herzog, M. T. Reetz, *Tetrahedron* **2002**, 58, 7847.

iII P. A. Z. Suarez, J. E. L. Dullius, S. Einlot, R. F. De Souza, J. Dupont, *Polyhedron* **1996**, 15 (7), 1217.

iIII M. Lee, M. M. Bernardo, S. O. Meroueh, S. Brown, R. Fridman, S. Mobashery, *Org. Lett.* **2005**, *7*, 4463.

iIV P.P. Phadnis, G. Mugesh, *Org. Biomol. Chem.* **2005**, 3, 2476.

iV J. A. Gladysz, J. L. Hornby, J. E. Garbe, *J. Org. Chem.* **1978**, 43 (6), 1204.

Bibliography

[1] R. I. Fox, *Adv. in Experimental Medicine and Biology*, **2002**, 506.

[2] a) J. Branalt, I. Kvarnstrom, *et al,. J. Org. Chem.* **1996**, 61, 3604. b) J. Nokami, K. Ryokume *et al*., *Tetrahedron Lett.* **1995**, 36, 6099.

[3] a) E. Teodori, F. Gualtieri, P. Angeli, L. Brasili, M. Giannella, M. Pigini,. *J. Org. Chem.* **1986**, 29, 1610. b) M. N. Romanelli, F. Gualtieri, G. Valle, L. Brasili, P. Angeli, *J. Med. Chem.* **1988**, 31, 1703.

[4] B. H. Wilmore, P. B. Cassidy, R. L. Warters, J. C. Roberts, *J. Med. Chem.* **2001**, 44, 2661.

[5] Y. Le Merrer, L. Poitout, J.-C. Depezay, I. Dosboaa, S. Geoffroy, M.-J. Foglietti, *Bioorg. Med. Chem.* **1997**, 5, 519.

[6] F. Huang, M. Zhao, X. Zhang, C. Wang, *et al*., *Bioorg. Med. Chem.* **2009**, 17, 6085.

[7] M. Taroua, C. Ribuot, M. H. Péra, G. Taillandier, M. Fatome, J. D. Laval, P. Demenge, G. Leclerc, *Eur. J. Med. Chem.* **1996**, 31, 589.

[8] T. A. Hase, *Umpoled Synthons: A Survey of Sources and Uses in Synthesis*, Wiley Interscience, New York, **1987**.

[9] a) P. J. Kocienski, *Tetrahedron Lett*. **1980**, 21, 1559. b) D. J. Ager, M. B. East, *J. Org. Chem.* **1986**, 51, 3983.

[10] a) T. Cohen, S. M. Nolan, *Tetrahedron Lett*. **1978**, 3533. b) S. Sengupta, V. Snieckus, *J. Org. Chem.* **1990**, 55, 5680.

[11] a) D. Seebach, *Angew. Chem. Int. Ed. Engl*. **1969**, 8, 639. b) D. Seebach, E. J. Corey, *J. Org. Chem.* **1975**, 40, 231. c) N. H. Andersen, D. A. Mc Crae, D. B. Grotjahn, S. Y. Gabhe, L. J. Theodore, R. M. Ippolito, T. K. Sarkar, *Tetrahedron*, **1981**, 37, 4068.

[12] E. L. Eliel, A. A. Hartmann, A. G. Abatjoglou, *J. Am. Chem. Soc.* **1974**, 96, 1807 and references cited therein.

[13] a) S. R. Wilson, G. M. Georgiadis, H. N. Khatri, J. E. Bartmess, *J. Am. Chem. Soc.* **1980**, 102, 3577. b) S. R. Wilson, P. Caldera, M. A. Jester, , *J. Org. Chem.* **1982**, 47, 3319. c) T. Oida, S. Tanimoto, H. Terao, M. Okano, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1715.

[14] a) H. Paulsen, W. Koebernich, H. Koebernick, *Tetrahedron Lett*. **1976**, 17, 2297. b) M. Yamashita, R. Suemitsu, *J. Chem. Soc., Chem. Comm.* **1977**, 691.

[15] a) A. Degl'Innocenti, A. Capperucci, T. Nocentini, *Tetrahedron Lett*. **2001**, 42, 4557. b) A. Capperucci, V. Ceré, A. Degl'Innocenti, T. Nocentini, S. Pollicino, *Synlett.* **2002**, 9, 1447. c) A. Degl'Innocenti, S. Pollicino, A. Capperucci, *Chem. Comm*. **2006**, 4881. d) A. Capperucci, A. Degl'Innocenti, S. Pollicino, M. Acciai, G. Castagnoli, I, Malesci, C. Tiberi, *Heteroatom Chem.* **2007**, 18 (5), 516.

[16] S. Rendler, M. Oestreich, *Synthesis* **2005**, 11, 1727.

[17] a) R. K. Sharma, J. L. Fry, *J. Org. Chem.* **1983**, 48, 2112. b) D. P. Cox, J. Terpinski, W. Lawrynowicz, *J. Org. Chem.* **1984**, 49, 3216. c) G. Majetich, A. Casares, D. Chapman, M. Behnke, *J. Org. Chem.* **1986**, 51, 1745. d) H. Sun, S. G. DiMagno, *J. Am. Chem. Soc.* **2005**, 127, 2050.

[18] a) M. Michida, T. Mukaiyama, *Chem. Lett.* **2008**, 37, 26. b) M. Michida, T. Mukaiyama, *Chem. Asian, J*. **2008**, 3, 1592. c) T. Kitazawa, T. Minoua, T. Mukaiyama, *Chem Lett.* **2006**, 35 (9), 1002.

[19] A. Capperucci; C. Tiberi; S. Pollicino; A. Degl'Innocenti, *Tetrahedron Letters* **2009**, 50 (23), 2808.

[20] a) F. H. Elsner, H. G. Woo, T. D. Tilley, *J. Am. Chem. Soc.* **1988**, 110, 313. b) J. A. Soderquist, E I. Miranda, *J. Am. Chem. Soc.* **1992**, 114, 10078.

[21] A. Capperucci, G. Castagnoli, A. Degl'Innocenti, I. Malesci, T. Nocentini, *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, 180, 1297.

[22] Inter alia: a) W. Lidy, W. Sundermeyer, *Tetrahedron Lett*. **1973**, 1449. b) C. H. Behrens, K. B. Sharpless, *J. Org. Chem.* **1985**, 50, 5696. c) V. Kesavan, D. Bonnet-Delpon, J.-P. Bégué, *Tetrahedron Lett.* **2000**, 41, 2895: and references cited therein.

[23] Inter alia: a) M. Chini, P. Crotti, E. Giovani, F. Macchia, M. Pineschi, *Synlett*. **1992**, 303. b) M. H. Wu, E. N. Jacobsen, *J. Org. Chem.* **1998**, 63, 5252. c) B. Movassagh, S. Sobhani, F. Kheirdoush, Z. Fadaei, *Synth. Commun*. **2003**, 33, 3103. d) F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, *Tetrehedron Lett.* **2003**, 44, 6785.

[24] a) B. N. Steger, U.S. Patent 4564710, **1986**. b) H. Morishiri, K. Shimakawa, A. Ryu, N. Kawato, S. Kobayashi, Jpn. Kokai Tokyo Koho JP 2003155269, **2003**.

[25] F. G. Bordwell, H. M. Anderson, *J. Am. Chem. Soc.* **1953**, 75, 4959.

[26] Inter alia: a) Y. Tanabe, K. Mori, Y. Yoshida, *J. Chem. Soc., Perkin Trans. 1* **1997**, 671. b) E. W. Abel, D. J. Walker, *J. Chem. Soc. A* **1968**, 2338. c) B. M. Trost, T. S. Scanlan, *Tetrahedron Lett*. **1986**, 27, 4141. d) J. Rokach, Y. Girard, Y. Guindon, J. G. Atkinson, M. Larue, R. N. Young, P. Masson, G. Holme, *Tetrahedron Lett.* **1980**, 21, 1485. e) Y. Guindon, R. N. Young, R. Frenette, *Synth. Commun.* **1981**, 11, 391.

[27] J. Brittain, Y. Gareau, *Tetrahedron Lett*. **1993**, 34, 3363.

[28] J. C. Justo de Pomar, J. A. Soderquist, *Tetrahedron Lett*. **1998**, 39, 4409.

[29] a) A. Degl'Innocenti and A. Capperucci, *Eur. J. Org. Chem*. **2000**, 2171. b) A. Degl'Innocenti, A. Capperucci, G. Castagnoli and I. Malesci, *Synlett*. **2005**, 1965.

[30] a) N. Iranpoor, H. Firouzabadi, A. A. Jafari, *Synth. Commun.* **2003**, 33, 2321. b) M. G. Silvestri, and C. H. Wong, *J. Org. Chem.* **2001**, 66, 910. c) Y. Usui, J. Noma, M. Hirano, and S. Komiya, *J. Chem. Soc., Dalton Trans.* **1999**, 4397. d) N. V. Schwartz, *J. Org. Chem.* **1968**, 33, 2895.

[31]*Targets in Heterocyclic Synthesis*; Eds. O. A. Attanasi, D. Spinelli; (**2004**), Vol.8, Pg. 33; Published By Societa' Chimica Italiana.

[32] J. S. Wilkes, J. A. Levinsky, R. A. Wilson, C. A. Hussey, *Inorg. Chem.* **1982**, 21, 1263.

[33] J. S. Wilkes, M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.* **1992**, 965.

[34] a) R. Sheldon, *Chem. Comm.* **2001**, 2399. b) T. Welton, *Chem. Rev.* **1999**, 99, 2071.

[35] a) S. Chowdhury, R. S. Mohan, J. L. Scott, *Tetrahedron* **2007**, 63, 2363. b) M. J. Earle, K. R. Seddon, *Pure Appl. Chem.* **2000**, 72 (7), 1391.

[36] D. R. MacFarlane, J. M. Pringle, K. M. Johansson, S. A. Forsyth, M. Forsyth, *Chem. Comm.* **2006**, 1905.

[37] a) M. T. Garcia, N. Gathergood, P. J. Scammells, *Green. Chem.* **2005**, 7, 9. b) K.J. Kulacki, G. A. Lamberti, *Green. Chem.* **2008**, 10, 104.

[38] Inter alia: a) H. Yoshino, K. Nomura, S. Matsubara, K. Oshima, K. Matsumoto, R. Hagiwara, Y. Ito, *Journal of Fluorine Chemistry* **2004**, 125, 1127. b) J. S. Yadav, B. V. S. Reddy, B. Jyothirmai, M. S. R. Murty, *Tetrahedron Lett.* **2005**, 46, 6559. c) C. Betti, D. Landini, A. Maia, *Synlett.* **2006**, 9, 1335. d) A. Horvat, R. Skoda-Földes, S. Maho, Z. Berente, L. Kollar, *Steroids* **2006**, 71, 706.

[39] a) A. R. Khosropour, M. M. Khodaei, K. Ghozati, *Chem. Lett.* **2004**, 33, 1378. b) A. R. Khosropour, M. M. Khodaei, K. Ghozati, *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, 180, 2525. c) J. Chen, H. Wu, C. Jin, X. Zhang, Y. Xie, W. Su, *Green. Chem.* **2006**, 8, 330. d) B. C. Ranu, T. Mandal, S. Banerjee, S. S. Dey, *Aust. J. Chem.* **2007**, 60 (4), 278. e) B. C. Ranu, L. Adak, S. Banerjee, *Can. J. Chem.* **2007**, 85, 366.

[40] L.-W. Xu, L. Li, C.-G. Xia, P.-Q. Zhao, *Tetrahedron Lett*. **2004**, 45, 2435.

[41] Inter alia: a) A. Krief, *Comprehensive Organometallic Chemistry*, E. W. Abel, E. G. A. Stone, G. Wilkinson, Eds. (Pergamon, Oxford, **1995**), Vol. 11, P. 515. b) A Wendel, Ed., *Selenium in Biology and Medicine* (Springer-Verlag, Berlin, **1989**). c) J. Nève, A. Favier, Eds. *Selenium in Medicine and Biology* (Walter de Gruyter, Berlin, **1989**).

[42] M. Tiecco, L. Testaferri, L. Bagnoli, F. Marini, C. Santi, A. Temperini, C. Scarponi, S. Sternativo, R. Terlizzi and C. Tomassini, *Arkivoc*, vii, 186 (**2006**), and references cited therein. b) J. Młochowski, K. Kloc, R. Lisiak, P. Potaczek, H. Wojtowicz, *Arkivoc*, vi, 14, (**2007**), and references cited therein.

[43] a) M. P. Rayman, *The Lancet* **2000**, 356, 233 and references cited therein. b) A. T. Diplock, *Mol Aspects Med.* 1**994**, 15, 293. c) R. A. Sunde Selenium. In: B. L. O'Dell, R. A. Sunde, eds. *Handbook of nutritionally essential mineral elements.* New York; Marcel Dekker Inc, **1997**, 493-556. d) E. Bloch, M. Birringer, W. Jiang, T. Nakahodo, H. J. Thompson, P. J. Toscano, H. Uzar, X. Zhang, Z. Zhu, *J. Agric. Food Chem.* **2001**, 49, 458. e) Y. Xie, M. D. Short, P. B. Cassidy, J. C. Roberts, *Bioorg. Med. Chem. Lett.* **2001**, 11, 2911. f) L. A. Wessjohann, A. Schneider, M. Abbas, W. Brandt, *Biological Chemistry* **2007**, 388 (10), 997.

[44] G. Mugesh, W.-W. du Mont, H. Sies, *Chem. Rev.* **2001**, 101, 2125.

[45] H. E. Ganther, *Bioorg. Med. Chem.* **2001**, 9, 1459.

[46] G. H. Milne, L. B. Townsend, *J. Med. Chem.* **1974**, 17, 263.

[47] L. Xi, L. Yi, W. Jun, Q. Songsheng, *Termochimica Acta* **2001**, 375, 109.

[48] a) M.Renson, N. Dereu, *J. Pharm. Belg.* **1990**, 45, 322. b) V. Narayanaswami, H. Sies, *Free Radical Res. Comm.* **1990**, 10, 237.

[49] Inter alia: a) *Organoselenium Chemistry - A Pratical Approach*; T. G. Back Ed.; Oxford: New York **2000**. b) A. L. Braga, D. S. Lüdtke, F. Vargas, R. C. Braga, *Synlett.* **2006**, 1453. c) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches, V. K. Aggarwal, *Chem. Rev.* **2007**, 107, 5841.

[50] a) A. Ogawa and N. Sonoda, *Encyclopedia of Reagents for Organic Synthesis* (John Wiley and Sons, **2001**), DOI: 10.1002/047084289X.rb221. b) L. Syper and J. Młochowski, *Tetrahedron* **1988**, 44, 6119. c) M. R. Detty, M. D. Siedler, *J. Org. Chem.* **1982**, 47, 1354.

[51] N. Miyoshi, Y. Hatayama, I. Ryu, N. Kambe, T. Murai, S. Murai, and N. Sonoda, *Synthesis* **1988**, 175.

[52] a) N. Miyoshi, K. Kondo, S. Murai, and N. Sonoda, *Chem. Lett.* **1979**, 909. b) M. R. Detty, *Tetrahedron Lett.* **1978**, 5087. c) N. Miyoshi, Y. Hatayama, I. Ryu, N. Kambe, T. Murai, S. Murai, N. Sonoda, *Synthesis* **1988**, 175. d) M. Tiecco, L. Testaferri, F. Marini, S. Sternativo, F. Del Verme, C. Santi, L. Bagnoli, A. Temperini, *Tetrahedron* **2008**, 64, 3337.

[53] Y. Nishiyama, H. Ohashi, K. Itoh, and N. Sonoda, *Chem. Lett.* **1998**, 159.

[54] Inter alia: a) S. Santoro, B. Battistelli, L. Testaferri, M. Tiecco, C. Santi, *Eur. J. Org. Chem.* **2009**, 29, 4921. b) B. Mayassagh and M. Shamsipoor, *Synlett.* **2005**, 1316. c) M. Joshaghani, A. R. Khosropour, H. Jafary, I. B. Mohammadpoor, *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, 180 (1), 117. d) M. Tiecco, L. Testaferri, L. Bagnoli, V. Purgatorio, A. Temperini, F. Marini, C. Santi, *Tetrahedron: Asymmetry* **2004**, 15, 405. e) A. P. Kozikowski and A. Ames, *Tetrahedron* **1985**, 41, 4821. f) P. A. Barlett and L. A. McQuaid, , *J. Am. Chem. Soc.* **1984**, 106, 7854. g) A. Cravador and A. Krief, *Tetrahedron Lett.* **1981**, 22, 2941. h) M. R. Detty and M. D. Seidler, *J. Org. Chem.* **1981**, 46, 1283. i) G. H. Posneri and D. Z. Rogers, *J. Am. Chem. Soc.* **1977**, 99, 8208. l) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.* **1973**, 95, 2697.

[55] A. Degl'Innocenti, A. Capperucci, G. Castagnoli, I. Malesci, C. Tiberi, B. Innocenti *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, 183, 966.

[56] C. K. Chung, I. Ma, S. Olgen, C. Pierra, J. Du, G. Gumina, E. Gullen, Y. C. Cheng, R. Schinazi, *J. Med. Chem.* **2000**, 43, 3906.

[57] J. Du, S. Surzhykov, J. Sheng Lin, M. G. Newton, Y. C. Cheng, R. F. Schinazi, C. K. Chu, *J. Med. Chem.* **1997**, 40, 2991.

[58] a) S. V. Amosova, M. V. Penzik, A. I. Albanov, V. A. Potapov, *Journal of Organometallic Chemistry* **2009**, 694 (20), 3369. b) S. V. Amosova, M. V. Penzik, A. I. Albanov, V. A. Potapov, *Tetrahedron Lett.* **2009**, 50, 306.

[59] Inter alia: a) C.C. Silveira, F. Rinaldi, R.C. Guadagnin, A. L. Braga, *Synth.* **2009**, 3, 469. b) A. Sharma, R. S. Schwab, A. L. Braga, T. Barcellos, M. W. Paixão, *Tetrahedron Lett.* **2008**, 49, 5172. c) J.Salon, J. Sheng, J. Jiang, G. Chen, J. Caton-Williams, Z. Huang, *J. Am. Chem. Soc.* **2007**, 129, 4862. d) A. L. Braga, P. H. Schneider, M. W. Paixão, A. M. Deobald, *Tetrahedron Lett.* **2006**, 47, 7195. e) B. C. Ranu, T. Mandal, S. Samanta, *Org. Lett.* **2003**, 5 (9), 1439.

[60] For some examples, see: a) M. Clarembeau, A. Krief, *Tetrahedron Lett.* **1984**, 25, 3625. b) D. J. Procter, *J. Chem. Soc., Perkin Trans. 1* **1999**, 641. c) A. Krief, M. Trabelsi, W. Dumont, M. Derock, *Synlett.* **2004**, 10, 1751. d) A. Spurg, S. R. Waldvogel, *Synlett.* **2007**, 19, 3042. e) E. P. Levanova, E. A. Sukhomazova, L. V. Klyba, *Russian Journal of General Chemistry* **2008**, 78 (4), 608. f) L. C. Song, W. Gao, C. P. Feng, D. F. Wang, Q. M. Hu, *Organometallics* **2009**, 28 (20), 6121.

[61] E. H. Riague, J.-C. Guillemin, *Organometallics* **2002**, 21, 68.

[62] J.-C. Guillemin, G. Bajor, E. H. Riague, B. Khater, T. Veszprémi, *Organometallics* **2007**, 26, 2507.

[63] A. Krief, W. Dumont, M. Robert, *Chem. Comm.* **2005**, 2167.

[64] See for example: a) W. H. H. Günther, *J.Org. Chem.* **1966**, 31, 1202. b) C. Santi, S. Santoro, L. Testaferri, M. Tiecco, *Synlett.* **2008**, 10, 1471.

[65] M.-H. Yang, G.-B. Yan, Y.-F. Zheng, *Tetrahedron Lett*. **2008**, 49, 6471.

[66] a) S. Devender, E. E. Alberto, O. E. Rodrigues, A. L. Braga, *Green Chem.* **2009**, 11 (10), 1521. b) E. J. Lenardão, L. G. Dutra, M. T. Saraiva, R. G. Jacob, G. Perin, *Tetrahedron Letters* **2007**, 48, 8011. c) D. Chang, W. Bao, *Synlett.* **2006**, 11, 1786.

[67] S. Narayanaperumal, E. E. Alberto, F. Molinos de Andrade, E. J. Lenardão, P. S. Taube, A. L. Braga, *Org. Biomol. Chem.* **2009**, 7, 4647.

[68] H. Ishihara, M. Koketsu, Y. Fukuta, F. Nada, *J. Am. Chem. Soc.* **2001**, 123, 8408.

[69] G. Happke, J. Martence, K. Praefcke, H. Simon, *Angew. Chem. Int.Ed.* **1977**, 16, 318.

[70] J. Pheninger, C. Heuberger, W. Graf, *Helv. Chim. Acta* **1980**, 63, 2308.

[71] See for example: a) P. A. Grieco, J. Y. Jaw, D. A. Claremon, K. C. Nicolaou, *J. Org. Chem*. **1981**, 46, 1215. b) S. Zhang, Y. Zhang, *Synth. Commun.* **1998**, 28, 3999. c) C. C. Silveira, A. L. Braga, E. L. Larghi, *Organometallics* **1999**, 18, 5183. d) L. Wang, Y. Zhang, *Synth. Commun.* **1999**, 29, 3107. e) O. A. Wallner, K. J. Szabó, *J. Org. Chem*. **2005**, 70 (23), 9215, and references cited therein.

[72] S.-I. Fujiwara, A. Asai, T. Shin-ike, N. Kambe, N. Sonoda, *J. Org. Chem*. **1998**, 63, 1724.

[73] Y. Nishiyama, A. Katsuura, A. Negoro, S. Hamanaka, *J. Org. Chem*. **1991**, 56, 3776.

[74] Y. Nishiyama, K. Tokunaga, H. Kawamatsu, N. Sonoda, *Tetrahedron Letters* **2002**, 43, 1507.

[75] B. Movassagh, F. Mirshojaei, *Monatshefte für Chemie* **2003**, 134, 831.

[76] G. Marin, A. L. Braga, A. S. Rosa, F. Z. Galetto, R. A. Burrow, H. Gallardo, M. W. Paixão, *Tetrahedron* **2009**, 65, 4614.

[77] a) O. Niyomura, K. Tani, S. Kato, *Heteroat. Chem.* **1999**, 10, 373. b) J.-X. Wang, C.-H. Wang, W.-F. Wang, W.-F. Cui, Y.-L. Hu, S.-S. Zang, *J. Chem. Res. (S)* **1990**, 230. c) Y. Nishiyama, A. Katsuura, Y. Okamoto, S. Hamanaka, *Chem. Lett.* **1989**, 1825. d) K. A. Jensen, L. Bøje, L. Henriksen, *Acta Chem. Scand.* **1972**, 26, 1465.

[78] a) H.-R. Zhao, X.-J. Zhao, X. Huang, *Synth. Commun.* **2002**, 32 (21), 3383. b) H.-R. Zhao, X.-J. Zhao, X. Huang, *Chinese Chemical Letters* **2001**, 12 (10), 873.

[79] M. Koketsu, F. Nada, S. Hiramatsu, H. Ishihara, *J. Chem. Soc., Perkin Trans. 1* **2002**, 737.

Part II

Asymmetric organocatalysis: a versatile approach for the synthesis of chiral compounds.

Chapter 1

Organocatalysis: a brief introduction of some fundamental principles

1.1. Introduction: the genesis and expansion of organocatalysis

Stereoselective synthesis has been the focus for a large number of organic chemists for many years, and methods for the construction and manipulation of stereocenters are central tools in organic chemistry. Traditionally, stereocenters have been obtained and transformed from natural sources, but the use of asymmetric catalysis has allowed for the *'de novo'* construction of non-racemic stereocenters using substoichiometric amounts of a catalyst. Obviously, the design of these catalysts and the study of their working mechanisms are of fundamental importance.

Prior to the year 2000, the field of asymmetric catalysis was mainly divided into two branches: organometallic catalysis[1] and enzymatic catalysis[2]. Enzymes are characterized by high turnover numbers but also high substrate specificity, while metal catalysts, that have high turnover numbers and good substrate scopes, are sometimes limited by the demands for inert reaction conditions and by the risk of trace metal contaminants in the products. However, starting in the late 1990s, a third discipline arose in the field of asymmetric catalysis. Later called *Organocatalysis*[3] this new concept was based on the use of small organic molecules as rate enhancers and chiral inducers in stereoselective synthesis. Precisely, organocatalysis is "the catalysis with small organic molecules, where an inorganic element is not part of the active principle", as reported by List in 2007[4]. Between 1998 and 2008, not less than 1500 publications have evolved on this topic, and new developments will continue to arise in the near future (Figure 1)[5].

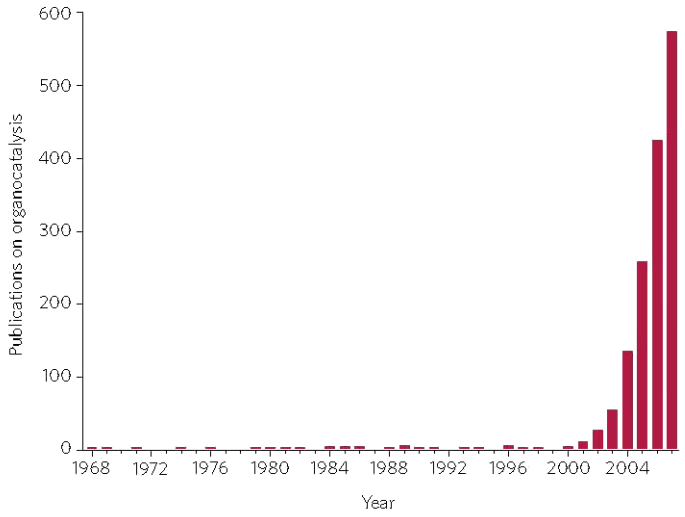


Figure 1

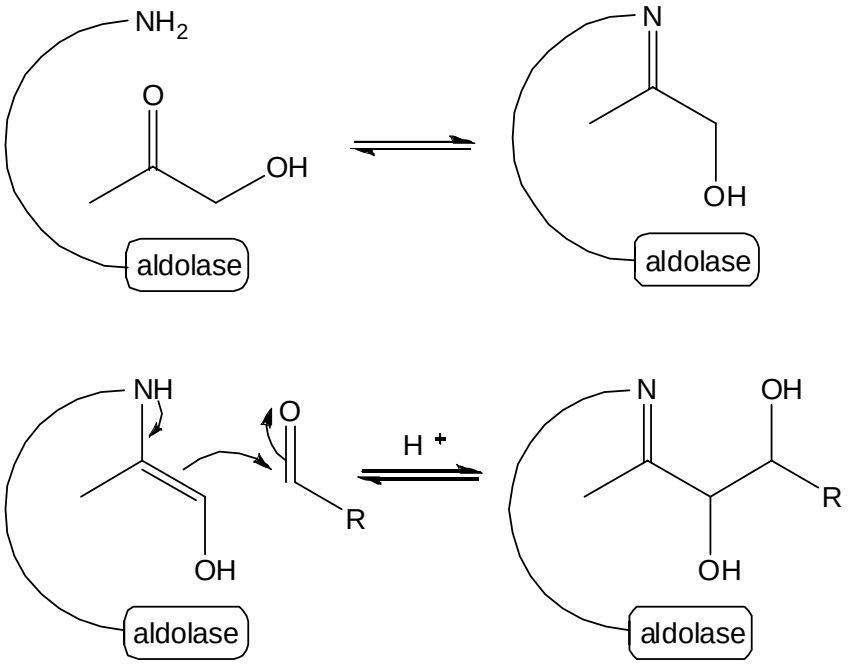
A decade ago, organocatalysis had been limited to few reports of selected transformations, but today, especially in the field of asymmetric synthesis, organocatalysis has become a key player.

Organocatalysis is still limited by relatively low turnover numbers, but is rarely dependent on inert experimental conditions. Furthermore, the diversity with respect to substrates and reagents expressed by many organocatalysts make them interesting catalysts for the small scale synthesis of chiral molecules. Many organocatalysts are now commercially available, which is an important improvement towards larger applications.

Nowadays, a variety of different organocatalytic activation modes have been described, such as chiral phase transfer catalysis (PTC)[6], amino-catalysis[7], hydrogen bonding catalysis[8]. Among the mentioned sub-branches of organocatalysis, amino-catalysis and H-bonding catalysis are probably the two that have made greatest impact in this research area.

1.2. Amino-catalysis

The use of amine-functionality as catalytic motif has been a long recognized phenomenon in enzymatic catalysis[9]. Rutter *et al.* studied aldolase type enzymes in the 1960, describing their activation of carbonyls through iminium-enamine formation, so generating an enzyme-bound carbanion equivalent as nucleophilic species[9b] (Scheme 1).

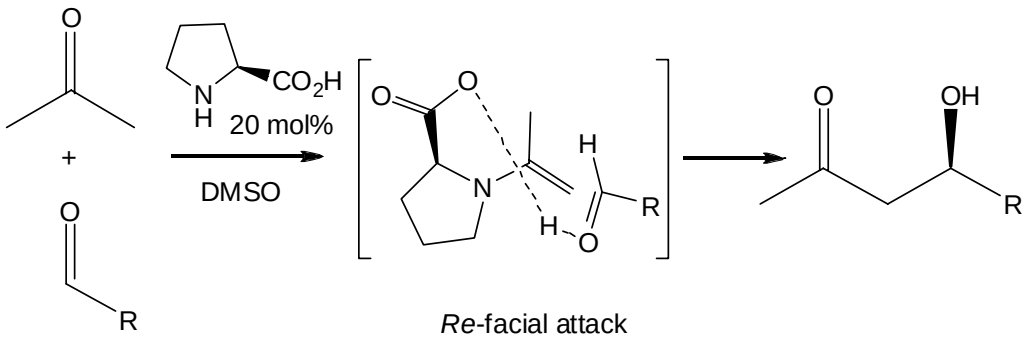


Scheme 1

Also in the field of organic chemistry, the use of enamines as nucleophiles to form new C-C bonds has been acknowledged for over half a century. The landmark leading to the genesis of organocatalysis came in 1971, with the Hajos-Wiechert reaction in which a proline catalyzed a Robinson annulation.[10]

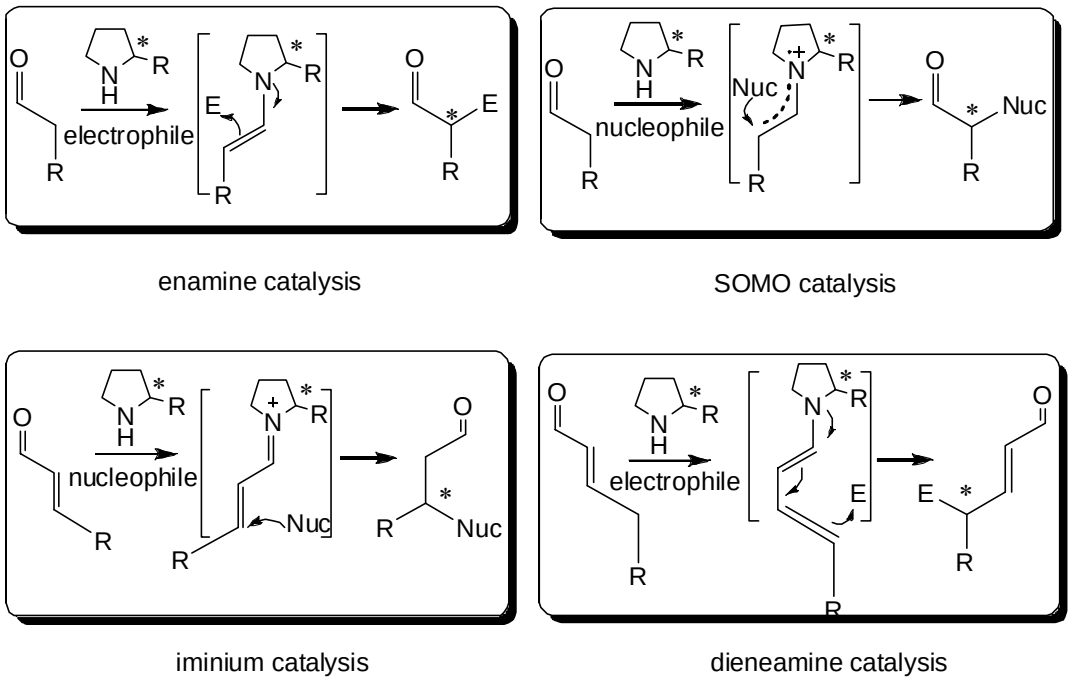
Nevertheless, the real genesis came in year 2000, when Barbas, Lerner and List, during their studies of catalytic antibodies, discovered that proline was able to mimic aldolase type enzymes. The use of proline as catalyst in an asymmetric catalytic aldol reaction[11] demonstrated that simple amino acids could be considered as 'open-site' enzymes allowing substrate freedom, when compared

with enzymatic catalysis, and however maintaining the activity and stereoselectivity (Scheme 2).



Scheme 2

Today, there are four recognized variants of amino-catalysis in the literature: enamine, iminium-ion, SOMO[7,12] and dieneamine[7,13] catalysis (Scheme 3) .

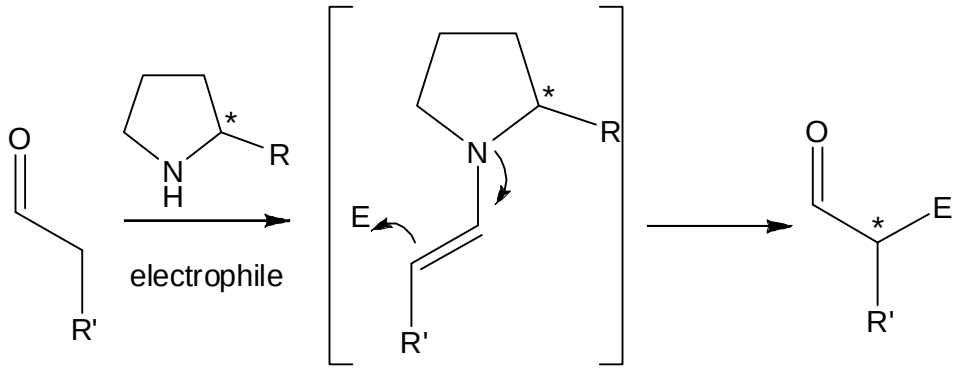


Scheme 3

In this section enamine[7, 8a, 14], iminium-ion[7, 8a, 15] and hydrogen-bonding catalysis[8] will be briefly introduced, and some specific aspects will be examined in the later section.

1.3.1. The concept of enamine activation

This activation concept is based on the reversible condensation of a secondary amine catalyst with a ketone or aldehyde to give an iminium species which, after tautomerization, leads to the formation of an enamine intermediate that can be subsequently trapped in the presence of an electrophile (Scheme 4).



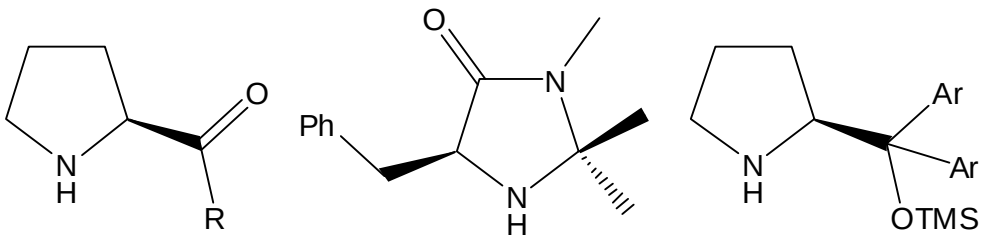
Scheme 4

Enamine catalysis involves the highest occupied molecular orbital (HOMO) and results in a raise of the energetic potential of carbonyls and adjacent α-carbonyl carbons, *via* formation of electron-rich amine-substituted olefins, that have enough π-electron density to give nucleophilic attack onto a variety of electrophiles.

The scope of the enantioselective enamine activation has been developed during the recent years, leading to efficient organocatalytic routes to many important transformations of carbonyl compounds including α-functionalizations, such as aldol-,[16] Mannich-,[17] α-amination-,[18] α-halogenation-,[19] and α-hydroxylation-[20] reactions.

As a consequence of the importance of this activation mode, the choice of the catalyst in relation to the specific reaction in which it is involved, as well as the development of new catalysts, have attracted a great deal of attention. One of the most versatile catalyst for enamine activation has been proline (or its amide, Figure 2, **1a-b**), which is a cheap amino acid commercially available in both enantiomeric forms. However, recently it was demonstrated that proline is not the best choice for transformations which involve α-functionalization of carbonylic compounds.

New versatile catalysts, developed by MacMillan (imidazolidinone, Figure 2, **2**)[21] and Jørgensen (pyrrolidines, Figure 2, **3a-b**)[19a] for iminium-ion catalysis, showed also high efficiency for enamine activation mode, with respect to enantioselectivity and versatility towards several reactions.



1a R = OH
1b R = NH_2

2

3a Ar = Ph
3b Ar = 3,5-$(CF_3)_2$-Ph

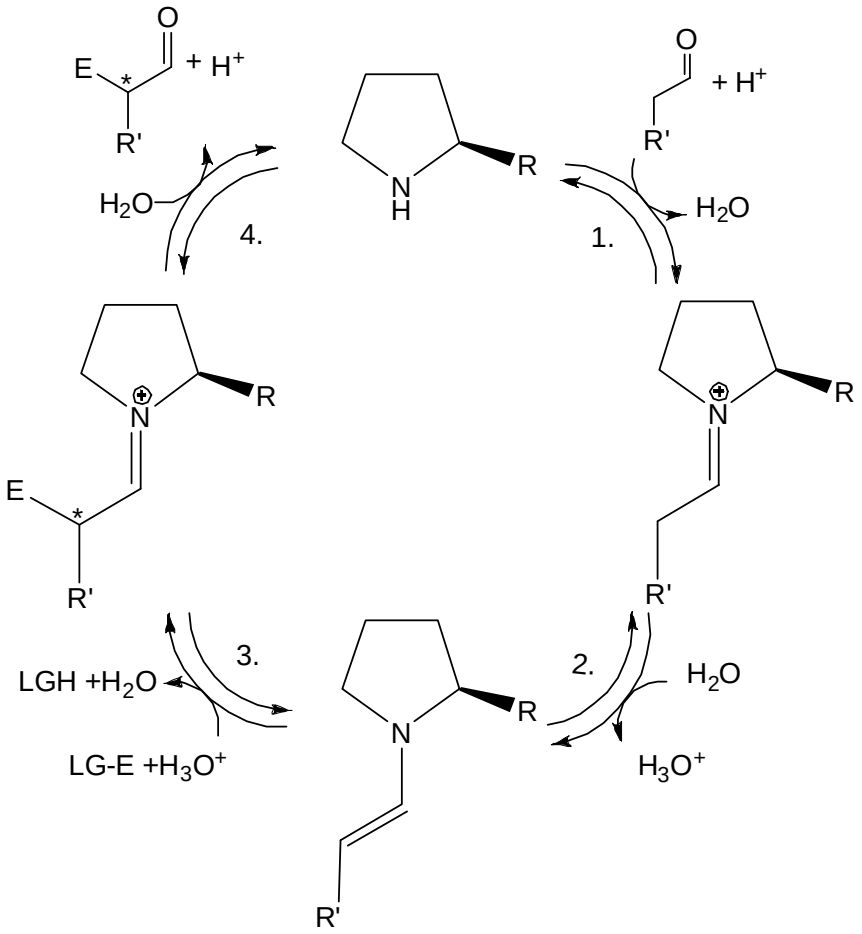
Figure 2

1.3.2. Enamine activation in the α-functionalization of aldehydes

The following section provides some mechanistic clarifications and explanation about organocatalytic α-functionalization of aldehydes through the formation of enamine intermediates with the catalyst.

It is interesting to underline how the choice of the catalyst influences the stereochemistry of the products, as reported later in this section.

The mechanism of organocatalytic α-functionalization of aldehydes catalyzed by an asymmetric cyclic secondary amine catalyst is reported in Scheme 5.



Scheme 5

The cycle is initiated by the formation of an iminium-ion arising from the condensation of an aldehyde and the catalyst (Scheme 5, step 1). Deprotonation at the α-position in the iminium-ion leads to the nucleophilic enamine intermediate (step 2) which attacks the incoming electrophile with enantioselectivity, while reforming the iminium-ion (step 3). Hydrolysis of the iminium-ion releases the α-functionalized aldehyde and the catalyst, which can participate in a new catalytic cycle (step 4). Using chiral pyrrolidine catalysts, these transformations usually generate products with excellent enantiomeric excess.

The chemical nature of the substituent in the catalyst determinates the stereochemical outcome, directing the electrophile either by steric or electronic shielding (Figure 3). [19a]

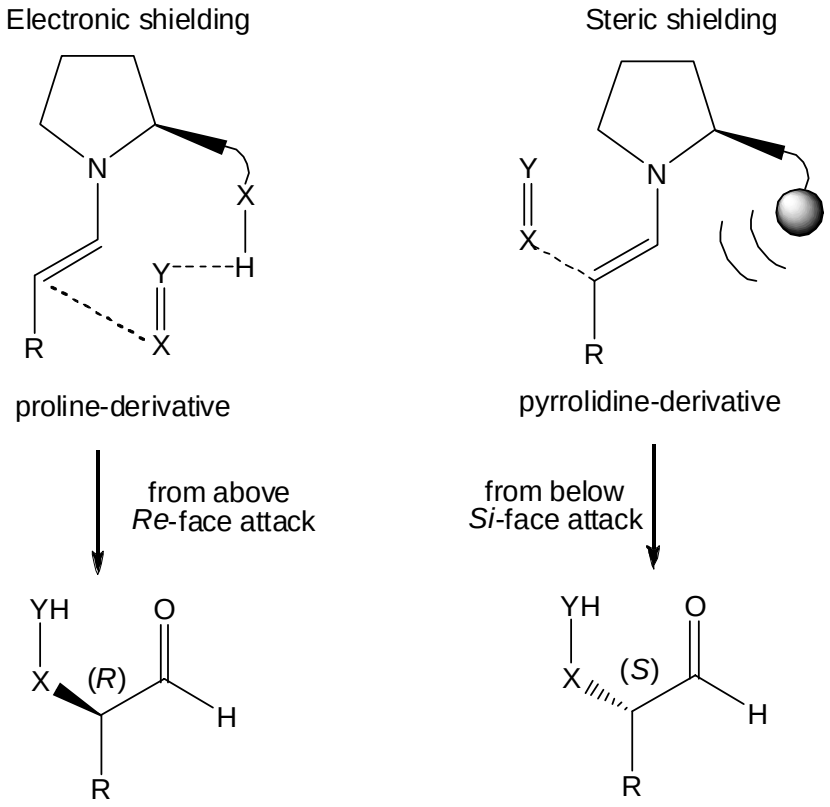


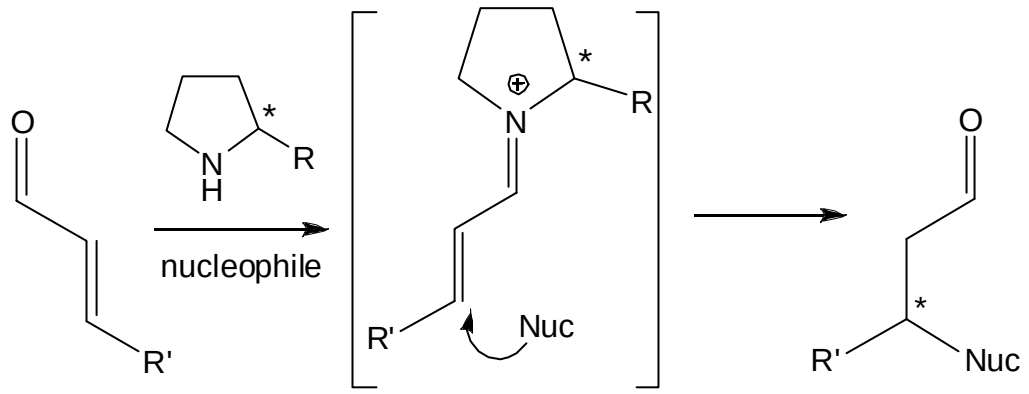
Figure 3

When the catalyst is a proline (**1a-b**), the stereochemistry of the product is induced by electronic effects through the formation of an hydrogen-bond with the incoming electrophile (Figure 3, left), so favouring a *Re*-faced nucleophilic attack. On the other hand, bulky pyrrolidine catalyst (**3a-b**) shields the *Re*-face of the enamine intermediate, favouring the electrophilic approach to the *Si*-face (Figure 3, right). Thus the different effects observed with these two catalysts, lead to the formation of the opposite enantiomers.

1.3.3. The concept of iminium activation

In the year 2000, MacMillan's group discovered a new strategy for asymmetric catalysis,[21] based on the use of chiral amines as enantioselective catalysts for a number of transformations that usually involve Lewis acids.

The catalytic concept was that the reversible formation of iminium-ion between α,β-unsaturated aldehydes and amines could mimic the π-orbital electronics that are inherent to Lewis acid catalysis. Actually, by the formation of an electron positive iminium-ion through amine-α,β-unsaturated aldehydes condensation, the energetic potential of the lowest unoccupied molecular orbital (LUMO) is lowered and rate enhancement and chiral induction are provided in the corresponding Michael acceptor (Scheme 6).



Scheme 6

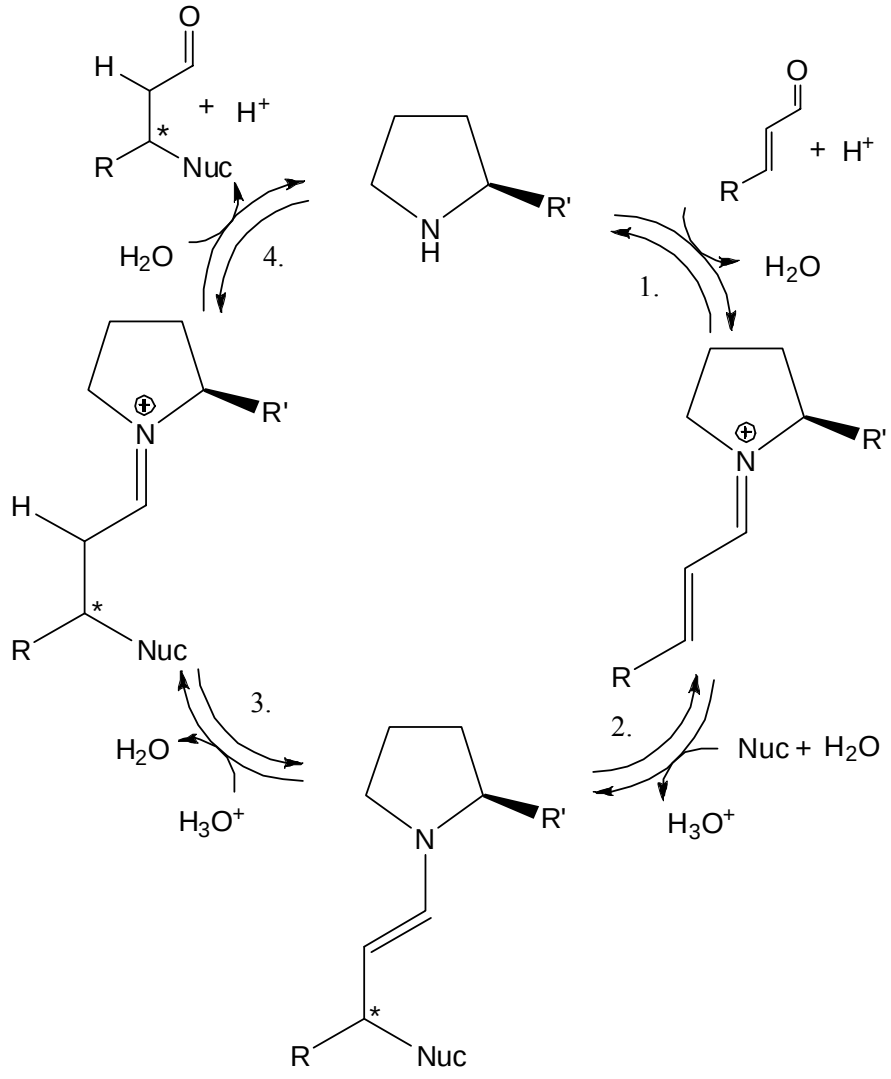
This approach has been later generalized to include enantioselective 1,4-additions of hydride,[22] sulphur,[23] amine,[24] oxygen[25] and carbon [21, 26] nucleophiles to α,β-unsaturated carbonyl compounds.

1.3.4. Iminium-ion activation in the β-functionalization of α, β-unsaturated aldehydes

The β-functionalization of α,β-unsaturated aldehydes is mechanistically close to enamine chemistry. In fact, an initial condensation between the secondary amine catalyst and the aldehyde gives an iminium-ion (Scheme 7, step 1), which is the reactive species in the catalytic cycle and leads to an energetic lowering of the LUMO, thus activating the β-position of the aldehyde for nucleophilic attack.

Addition of a nucleophile to the β-carbon of the iminium-ion forms a β-functionalized enamine (step 2), which is in a tautomeric equilibrium with the corresponding iminium-ion (step 3).

As in the case of α-functionalizations, the iminium-ion is now hydrolyzed to release the functionalized, saturated aldehyde and the catalyst, which can re-enter the catalytic cycle (step 4).



Scheme 7

Scheme 7 shows a close relationship between enamine and iminium-ion activation methods.

Computational studies have produced models of the structure of various iminium ion and transition states, showing an energetic favouring for the *trans-trans*

iminium-ion, with nucleophile leading to an approach to the *Re*-face of the intermediate (Figure 4, left).[27]

In contrast to α-functionalizations, in which H-bonding can play an important role in directing the incoming electrophile, β-functionalizations depend on steric hindrance to shield one diastereotopic face.

The control of the configuration of both double-bonds, as well as the directing of the nucleophile have fundamental importance to ensure high enantioselectivity.

The chemical nature of the incoming nucleophile has also great importance in β-functionalizations.

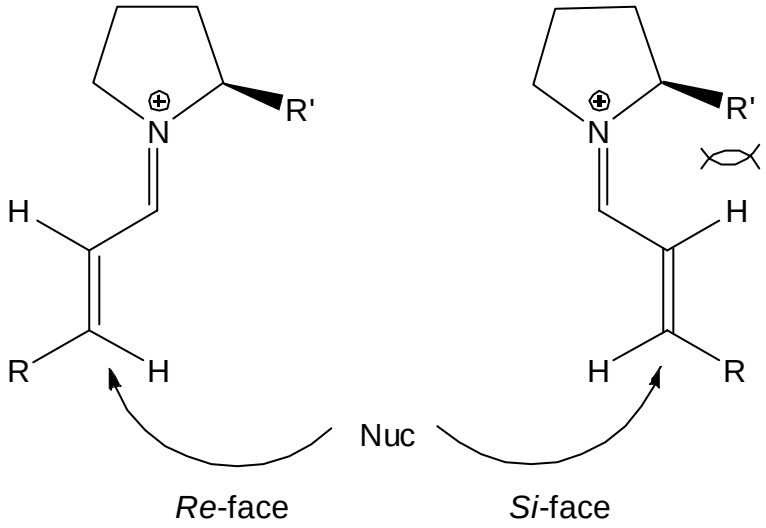
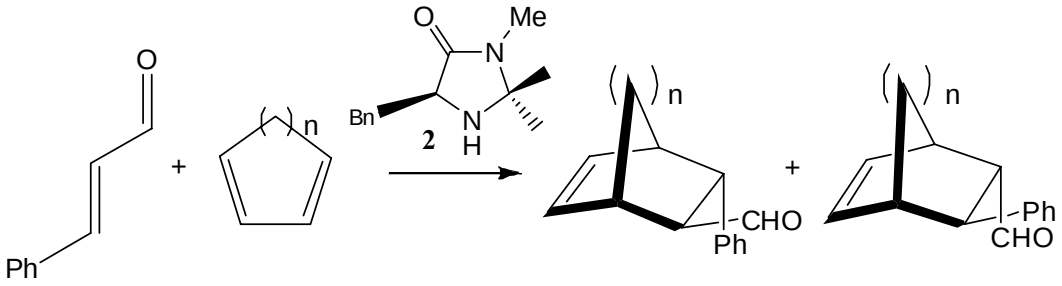


Figure 4

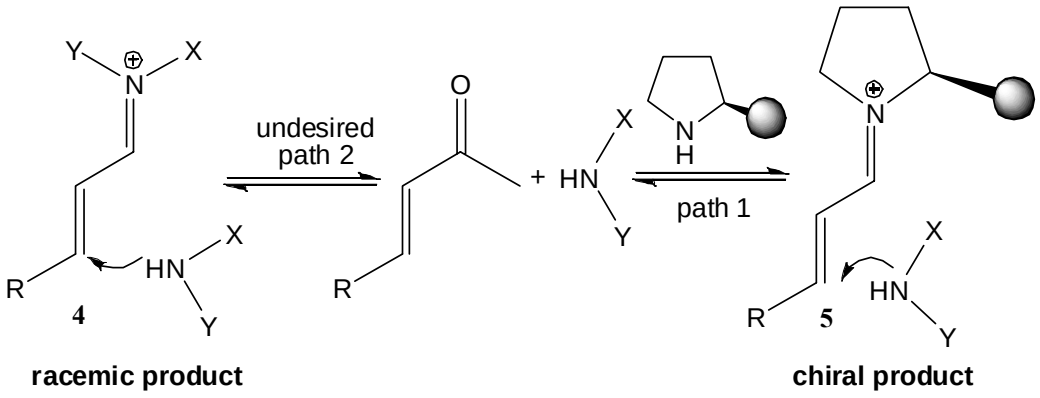
Among several examples reported in the literature,[22-26] the starting point of modern β-functionalizations is considered the MacMillan's JACS paper in which is reported an imidazolidinone (**2**) catalyzed asymmetric Diels-Alder reaction (Scheme 8).[21]



Scheme 8

Conjugate additions of nucleophiles to α,β-unsaturated carbonyl compounds is one of the most important C-C, C-N, C-S, C-O bond forming in asymmetric synthesis, leading to the formation of products such as α,β-amino acids, 1,3-amino alcohols, 1,3-mercapto alcohols, 1,3-diols.

About 1,4-addition of nitrogen based nucleophiles, while a number of reports based on different Lewis acidic organometallic catalysts have been reported in the literature, the same reaction using the amino-catalysis approach seems less obvious, since both the catalyst and the nucleophile are nitrogen based. In the amino-catalytic approach, the choice of the nucleophile is fundamental, because the carbonyl group of the aldehyde could undergo nucleophilic attack and condensation with the nitrogen-centred nucleophile, to form the undesired iminium-ion intermediate **4**, leading to the formation of racemic products (Scheme 9, path 2).



Scheme 9

As a consequence, the nitrogen source of choice must be chemo- and regioselective, demonstrating its ability to add to the catalyst activated α,β-unsaturated aldehyde **5** in an enantioselective pathway (Scheme 9, path 1), and limiting the formation of the unwanted **4**.

MacMillan *et al.* firstly described a solution to this problem, using *N,O*-diprotected hydroxylamine as nucleophile in 1,4-addition to α,β-unsaturated aldehydes with imidazolidinone **2** as catalyst.[24a]

Otherwise, the use of cheaper and commercially available succinimide as nucleophile was interestingly reported by Jørgensen *et al.* in 2007,[28] thereby offering a more convenient approach to the same β-aminated aldehydes, with excellent regio- and stereoselectivity. This concept will be examined in Chapter 2.

The discussion concerning the study of the reaction conditions for the organocatalytic β-amination with succinimide will be presented in detail in Chapter 2, with the aim to show all the variables that we have to consider in the optimizing the reactivity and the enantioselectivity of the process.

1.4. Cascade reactions

In the recent years, much effort has also been aimed to one-pot, cascade reactions leading to a highly efficient method for multiple bond and stereocenter formations without intermediate purifications.[29] The simplicity of these reactions which minimize the number of manual operations, make them a very interesting choice for organic synthesis.

Due to the capacity of both enamine and iminium-ion activation mode, amino-catalysis is perfectly suitable for performing cascade reactions. The number of transformations associated with each of the activation modes has in the latest years grown explosively, providing a versatile approach to the synthesis of complex organic molecules by cascade one-pot processes.

1.5. H-bonding catalysis

Hydrogen bonding catalysis[8] is one of the fundamental forces in nature, responsible for essential functionalities of life, such as protein folding, DNA base pairing and receptor recognition. Moreover, enzymes use H-bonding forces to ensure substrate affinity and to stabilize the transition state, facilitating in this way nucleophilic attack. Taking inspiration from nature, chemists started to study the use of organic hydrogen donors in synthetic catalytic systems.

Enantioselective hydrogen bonding catalysis, or Brønsted acid catalysis, is an important area of organocatalysis, which has grown since last decade.

Hydrogen bond catalysis involves the activation of the substrate by lowering of the LUMO orbital, *via* proton or hydrogen association.

Precisely, Brønsted acid activation proceeds through substrate protonation, leading to ion-pair formation between the activated substrate (cation) and the resulting catalyst conjugate base (anion). In contrast, hydrogen bond catalysis involves the sharing of an hydrogen atom by the substrate and the catalyst (hydrogen bond donor) with consequent lowering of the energetic potential of the substrate LUMO-orbital.

Nevertheless, in organocatalysis the term hydrogen-bonding activation is used to indicate both hydrogen bond catalysis and Brønsted acid catalysis.

A number of chiral organic molecules, such as guanidine, urea[30] and thiourea[31] derivatives (for example cinchona alkaloid-based thiourea catalysts) can give hydrogen bond interactions with carbonyl compounds, imines, amides, showing wide versatility for enantioselective applications, such as 1,2-, 1,4-additions, rearrangements and cycloaddition reactions.[8]

Bifunctional H-bonding catalysis

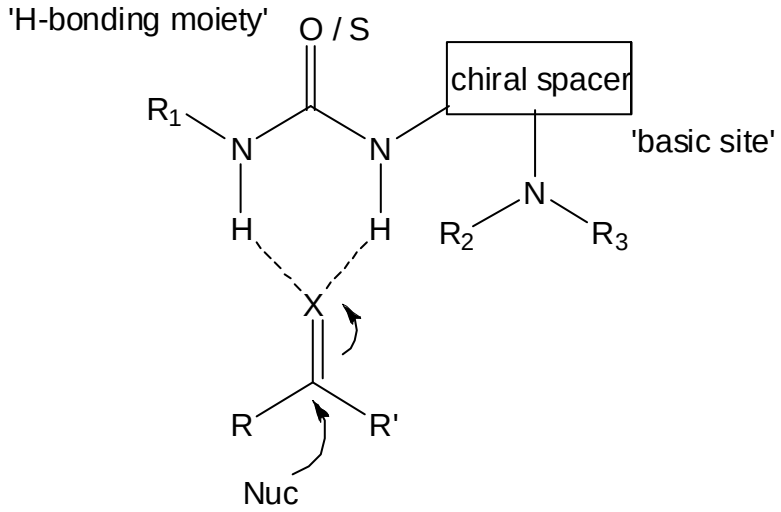


Figure 5

Usually this mechanism involves bi- or multidentate catalysts, which allow the formation of strictly oriented hydrogen bonds (Figure 5), with consequent limitation of the substrate freedom, thus ensuring high enantioselective discrimination.

1.6. Conclusions

In this first chapter we reported some general principles of organocatalysis, with particular attention to different activation modes with which chiral organic catalysts play an important role in the chirality transfer in different synthetic methodologies.

This brief introduction has been focused on the explanation of the most common mechanisms; deepenings concerning iminium-ion catalysis with pyrrolidine catalysts **3a-b**, have been treated in the Chapter 2, with application to the synthesis of propargylic and homo-propargylic compounds.

Chapter 2

Organocatalysis in one-pot strategies for the synthesis of chiral polyfunctionalized molecules

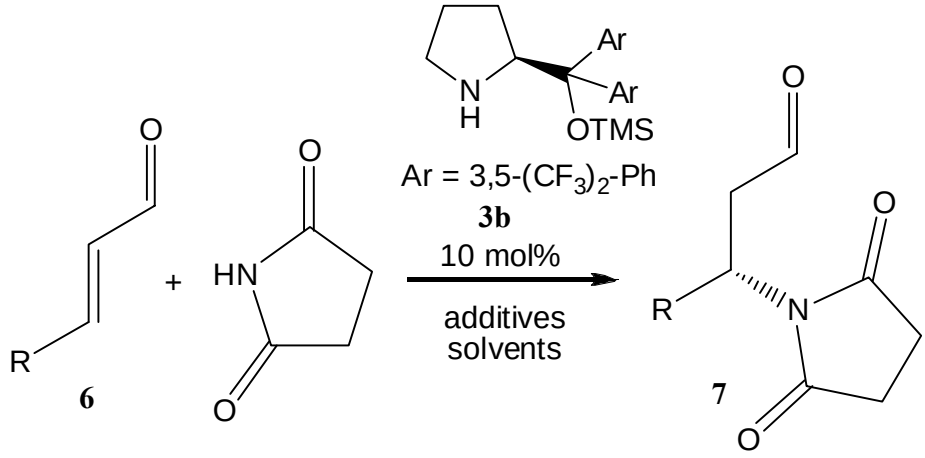
2.1. Iminium-ion activation in the β-amination reactions of α, β-unsaturated aldehydes

While the asymmetric addition of carbon-based nucleophiles has achieved substantial attention in organocatalysis, considerably less effort has been put in the development of conjugate addition of heteroatoms to Michael acceptor systems.

As reported in Chapter 1, MacMillan *et al.*[24a] first described in 2006 the direct β - amination of α, β-unsaturated aldehydes, with *N*-silyloxy carbamate nucleophiles. Subsequently, Cordova *et al.* presented the application of the simpler *N*-protected hydroxylamines (with an unprotected hydroxyl group) as nucleophiles, catalyzed by an *O*-TMS protected diarylprolinol catalyst.[32]

As an alternative to the *N*-centred nucleophiles reported by MacMillan and Cordova, Jørgensen's group reported the addition of N-heterocyclic nucleophiles to enals.[27a,28]

The use of succinimide as nucleophile for conjugate additions to α, β-unsaturated aldehydes **6** led to β-aminated aldehydes **7** (Scheme 10), [28] that could be further utilized in interesting transformations, such as α-amination reactions and reductive aminations.



R = Et, Me, *n*Pr, *n*Bu, *n*Hep, CH_2-OTBDMS

Yields = 65-74% *ee* = 78-90%

Scheme 10

This method allowed to obtain protected optically active β-amino aldehydes **7** in good yields and enantioselectivities. These products represent a common motif in bioactive peptidomimetics, such as fibrinogen receptor antagonists.[33]

An initial screening revealed that in CH_2Cl_2 succinimide could react as a nucleophile in the conjugate addition towards iminium-ion activated α,β-unsaturated aldehydes **5**, by using pyrrolidine derivative (**3b**) as catalyst; in the absence of the catalyst, no reaction was observed.

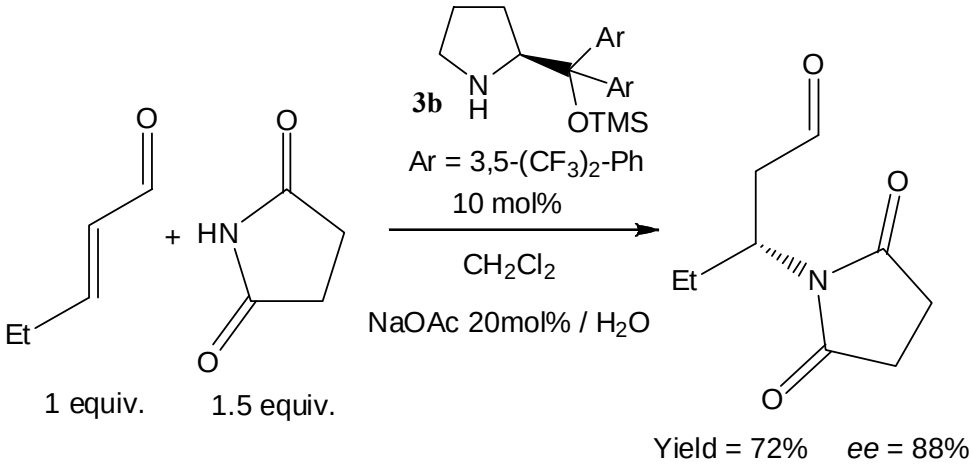
One of the advantage of this methodology was that succinimide was a stable N-protecting group, which could survive most manipulations, but which could be removed, when desired, by easy protocols.[34]

The screening process showed that the β-amination reaction was dependent on the catalyst, but also on the presence of additives and on the temperature.

In fact, in presence of (*S*)-2-[bis(3,5-bistrifluoromethyl-phenyl)trimethylsilanyloxymethyl]pyrrolidine (**3b**) as catalyst, the reaction between trans-2-pentenal and succinimide in CH_2Cl_2 (Scheme 11), in the absence of additives, led to moderate conversion. In order to increase the conversion, a number of additives were evaluated, and the presence of NaOAc (20 mol%) or H_2O/NaOAc gave a significant improvement in conversion. Probably, the role of

NaOAc was to facilitate the deprotonation of succinimide, making it a better nucleophile. The presence of water allowed the reduction of the reaction time, probably due to the role of the water to make the catalytic cycle faster.[16g]

These conditions led to the isolation of the β-amination product with 72% of yield and 88% *ee* (Scheme 11).

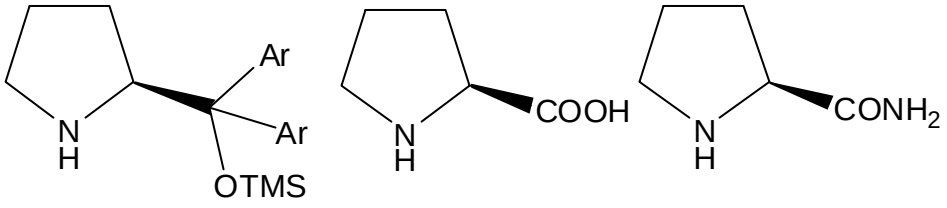


Scheme 11

The use of strong acids as additives, such as HCl, resulted in protonation of the secondary amine and deprotection of TMS-group of the catalyst; nevertheless, by using a weaker acid such as $PhCO_2H$, the reaction took place, but at a lower rate.

Moreover, under acidic conditions, as well as in the absence of additive, a number of side reactions took place.

A number of other catalysts were tested, for example proline **1a** and proline amide **1b**, but they resulted much less effective, in terms of conversion and stereoselective control, than **3b** (Figure 6).



3b **1a** **1b**

Figure 6

The reactivity depended also on the temperature, as mentioned before. in fact while at -24°C no conversion occurred, at higher temperature (40°C), it was possible to increase the conversion, but the enantioselectivity decreased. The best results were obtained carrying out the reaction at room temperature.

Finally, after a screening of the most common solvents with different polarities and hydrogen-bonding properties, the solvent which gave better results in terms of conversion was CH_2Cl_2.

The organocatalytic enantioselective β-amination reaction here reported[28] was completely general and was applied to a number of α,β-unsaturated aldehydes in presence of succinimide with good results in terms of yields and enantioselectivities.

In this first section, we reported in detail some problems (the choice of the reagents, catalyst, additives and in general reaction conditions) that we meet when performing organocatalytic reactions. We referred to the optimized reaction conditions here reported for the β-amination reactions with succinimide, in the following section. Moreover, in the following section, we applied such reactivity to one-pot syntheses of polyfuctionalized molecules.

2.2. Iminium-ion activation as an efficient strategy for divergent synthesis of optically active propargylic and homo-propargylic compounds[35]

Taking advantage of the previously reported considerations concerning the β-amination reactions of α, β-unsaturated aldehydes with succinimide as nucleophile,[28] we turned our attention to the application of the iminium-ion activation strategy to the synthesis of chiral compounds, which could be used as useful building blocks for the construction of more complex molecules.

In this context, the acetylenic motif serves as a common synthon in many C-X and C-C bond disconnessions.[36]

Propargylic and homo-propargylic compounds are particularly important as chiral building blocks in the course of stereoselective synthesis,[37] due to their transformational diversity and their condition tolerance.[38]

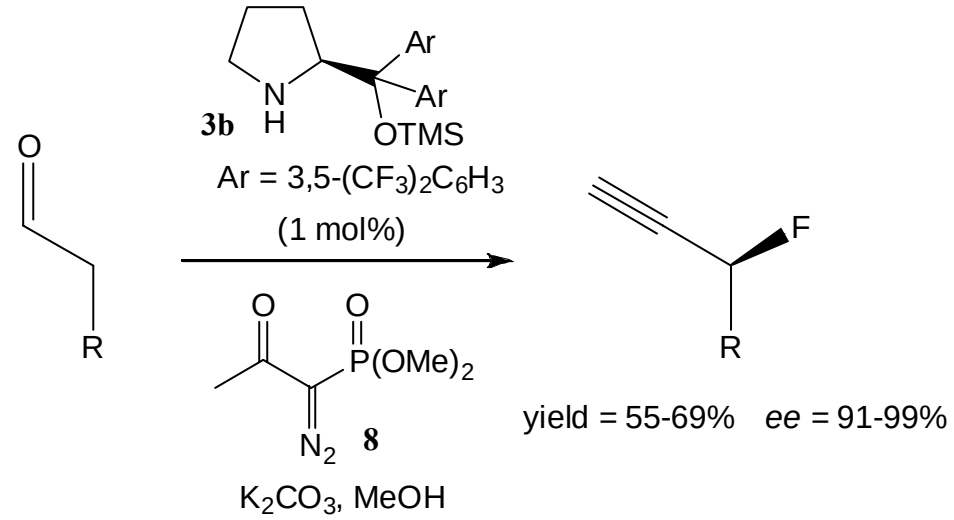
The synthesis of propargylic and homopropargylic compounds remains an attractive, yet, challenging task pursued by many research groups. Nowadays, modern synthesis and synthetic methods oftentimes include new and important aspects such as time-cost control and sustainability.

One of the possible methods to reduce time-costs is the development of more chemospecific reactions, thereby avoiding the use of protective groups and superfluous redox manipulations.[39] An alternative, but equally efficient solution to the problem is the incorporation of one-pot procedures, with consequential *in situ* entrapment of intermediates, making product isolation unnecessary. Moreover, other issues such as structural lability, a frequent cause for product oxidation/reduction/protections, can also be prevailed with high degree by the use of one-pot strategies.

In this context, organocatalysis is a robust and reliable synthetic tactic, not dependent on the presence of air or water, and therefore being exceedingly suitable for this type of ”a*ssemble and build strategy*”, where simple and available components are assembled to form a chiral structural skeleton, upon which molecular complexity can be built, in a one-pot fashion.

Recently, Jørgensen's group reported the enamine-catalyzed enantioselective electrophilic fluorination of aldehydes and subsequent Seyferth-Gilmann homologation by using the Ohira-Bestmann reagent **8**, to form highly

enantioenriched propargylic fluorides in one-pot from all commercially available reagents (Scheme 12).[19d]



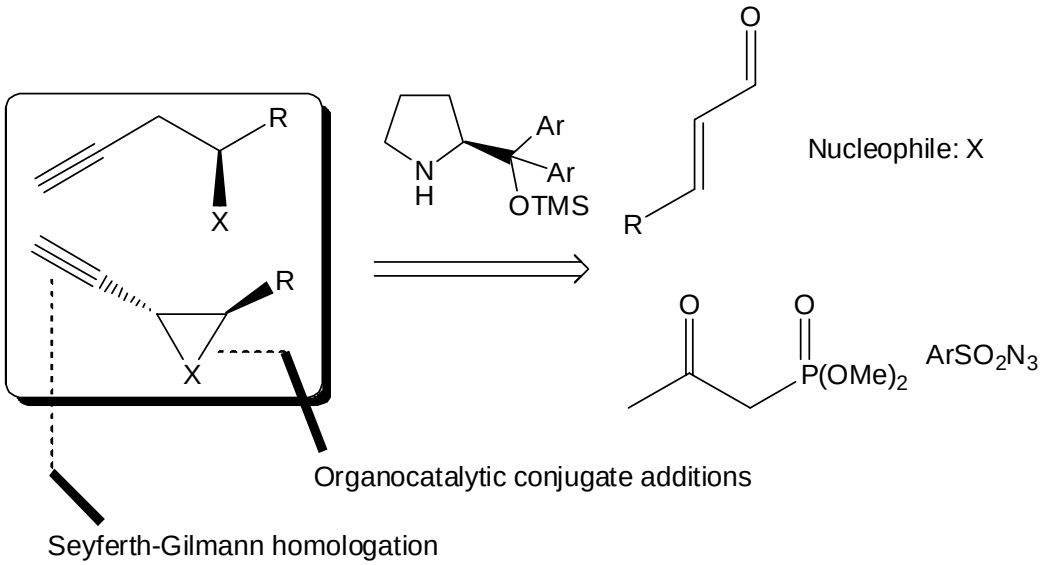
R = -Bn, $-(CH_2)_{13}CH_3$, $-(CH_2)_7CH_3$, *p*-Br-$C_6H_4CH_2$-, *p*-OCH_3-$C_6H_4CH_2$-

Scheme 12

Due to the importance of optically active acetylenes, conceptual generalization leading to diversity-oriented synthesis of optically active propargylic compounds was a highly desirable and important synthetic methodology. However this approach encountered unavoidable difficulties, such as decomposition of the products and racemization, when substituting the α-fluorination reaction with other organocatalytic α-functionalizations.

As a consequence, we turned our attention toward the use of iminium-ion activation, assuming better stability of the reaction intermediates and products.

In this direction, herein it was reported a series of chiral iminium-ion activated conjugate addition – homologation sequences, forming highly enantioenriched propargylic and homo-propargylic compounds in a simple and benign way (Scheme 13).



Scheme 13

Explications concerning the mechanism of the processes have been reported in the course of this section.

Terminal propargylic epoxides[40] represent a privileged class of intermediates, used often for the synthesis of intricate molecular structures and natural products.[40f,g]

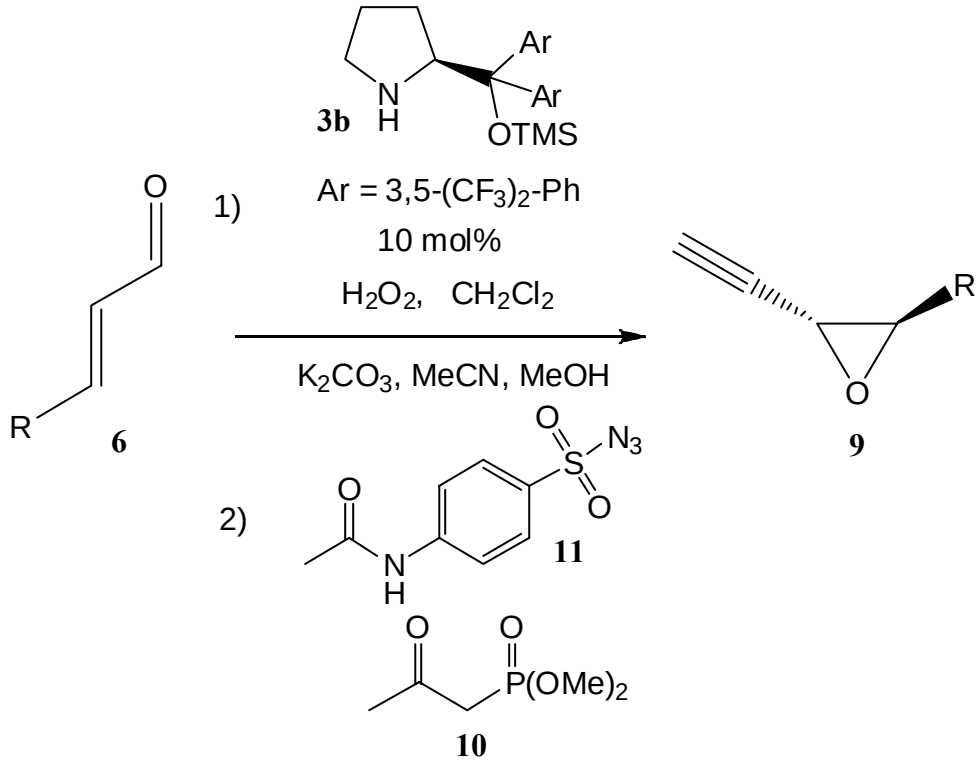
Despite their importance, few methodologies have been reported in the literature for their synthesis, and often these required long reaction times. Among these synthetic routes, the most common strategies proceeded through the ring-closure reaction of chiral halohydrines,[40a,b] or by enantioselective epoxidation of enynes.[40c,d]

Recently, in 2001, Martin *et al*. reported a three-step procedure to the same class of compounds, starting from pure epoxyaldehydes.[40e]

In this context, we envisioned that a more simple approach could be devised by combining the organocatalyzed epoxidation reaction[41] of α,β-unsaturated aldehydes with the Ohira modification[42] of the Seyferth-Gilmann homologation (Scheme 14) and the results are as outlined in Table 1.

To our delight, we discovered that the Ohira-Bestmann modification of the Seyferth-Gilmann method provided full compatibility with the organocatalyzed approach.

Despite the presence of base, no racemization was observed affording the desired products in excellent enantioselectivities.



Scheme 14

Table 1. The organocatalytic synthesis of chiral propargylic epoxides[a]

entry	R	d.r.[d]	Product	Yield [%] [b]	*ee* [%] [c]
1	*n*-Butyl	>20:1	**9a**	83	99
2	*i*-Propyl	>20:1	**9b**	63	99
3	*n*-Hexyl	>20:1	**9c**	81	98
4	Ph	>20:1	**9d**	66	98
5	*o*-NO_2-Ph	>20:1	**9e**	86	99
6	CH_2OBn	>20:1	**9f**	73	91
7 [e]	CO_2Et	>20:1	**9g**	58	97

[a] Reaction performed on 0.2 mmol scale (see experimental section).
[b] Isolated yields after column chromatography.
[c] *ee* determined by chiral stationary phase HPLC or GC.
[d] Determined by NMR spectroscopy.
[e] Complete trans-esterification to the methyl ester.

The first step in the one-pot formation of optically active epoxides **9a-g** was the reaction of α,β-unsaturated aldehydes **6** with H_2O_2, catalyzed by (*S*)-2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine **3b** in CH_2Cl_2. The intermediate *trans*-epoxy aldehydes were subsequently trapped by the Ohira-Bestmann reagent **8**, generated *in situ* from dimethyl 2-oxopropylphosphonate **10** and 4-acetamidobenzenesulfonyl azide **11**, furnishing the homologated products **9a-g** in high yields and excellent enantioselectivities.

Both simple or substituted alkyl and aryl side-chains were allowed, furnishing the desired *trans*-propargylic epoxides **9a-e** in 63-86% yield and 91-99% *ee* (Table 1, entries 1-5).

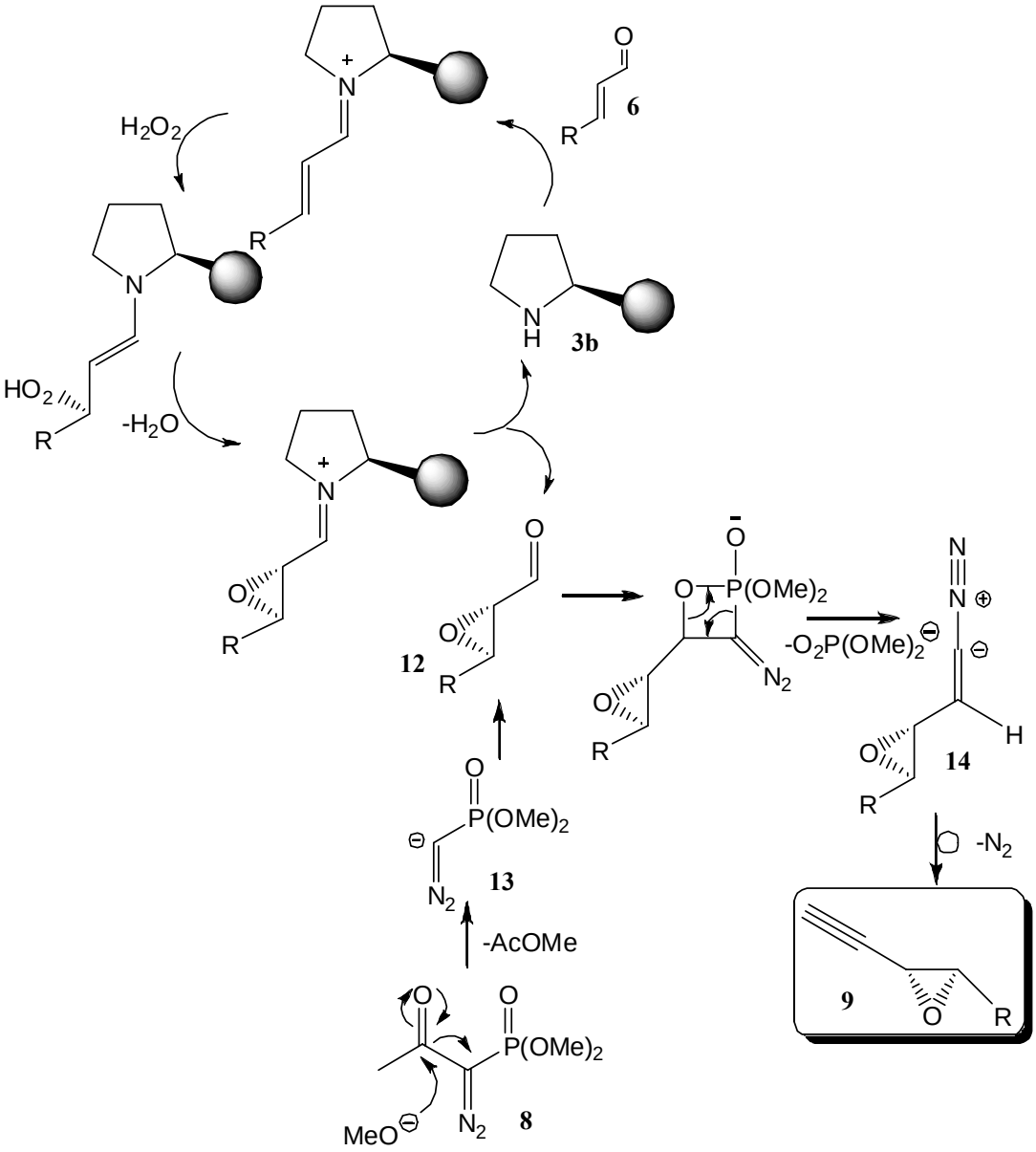
When employing substrates carrying other functional groups, for example ester group (Table 1, entry 7) or hydroxybenzyl group (Table 1, entry 6), the same levels of yield and optical purity were obtained; however, for compound **9g**, complete transesterification to the methyl ester was accomplished. It should be noted that the reported reaction was almost complete diastereoselective (d.r. 20:1), and easily scaled- up to 5 mmol without affecting the obtained yield and enantioselectivity.

The absolute configuration of product **9a** was determined by chemical correlation, [40a] confirming the (2*R*,3*R*)-configuration, as expected by comparison to the epoxyaldehyde intermediates. The remaining configurations are assumed by analogy.

The proposed mechanisms for the formation of propargylic epoxides was outlined in Scheme 15.

The reaction started with the condensation of the catalyst **3b** and aldehyde **6**, leading to the formation of a reactive iminium-ion species, which favoured conjugate attack of H_2O_2 from the *Re*-face, due to the steric shielding of the *Si*-face by the catalyst.

Next, epoxide formation and catalyst hydrolysis provided the enantiomerically enriched *trans*-epoxyaldehyde **12**. The intermediate product **12** was trapped by the Ohira-Bestmann reagent **8**, which formed the carbene species **13** by methanolysis. This reactive species trapped the intermediate **12** to give the species **14**, by which the epoxide was formed by a 1,2-proton shift and elimination of N_2.



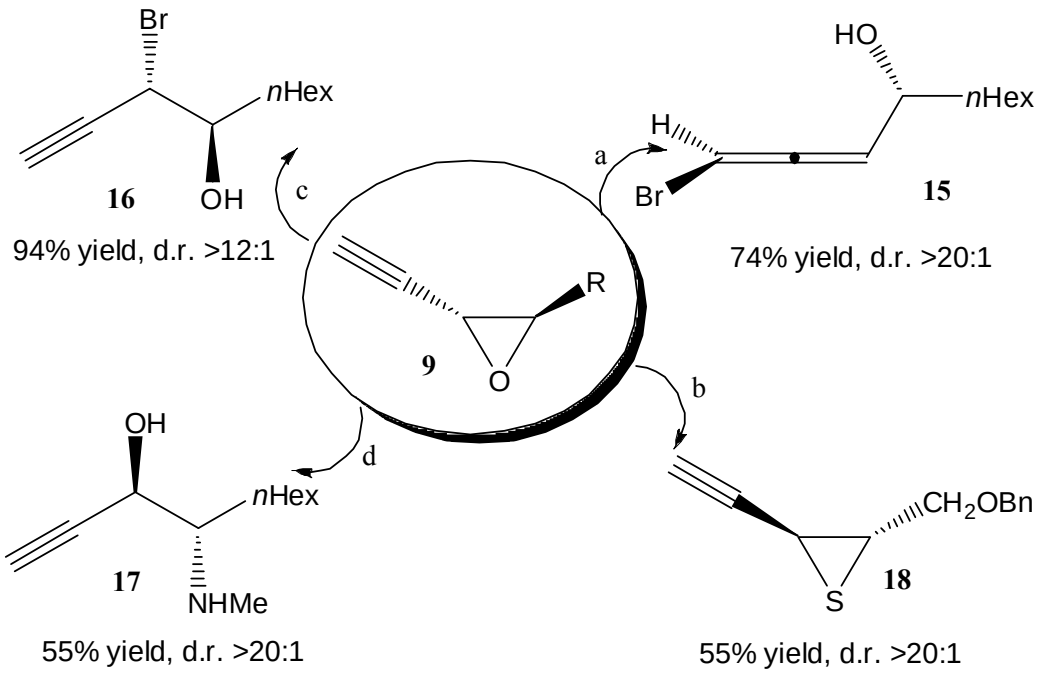
Scheme 15

As further step, rivaling the intriguing demands for easy access to molecular complexity, we aimed to demonstrate the simplicity and diversity with which our products can be transformed (Scheme 16). In fact, chiral propargylic epoxides of this kind are highly versatile intermediates in organic synthesis, which can be transformed by direct and easy procedures in chiral compounds of different nature, some of which are reported in Scheme 16.

For example, enantiomerically enriched allenes[43] are valuable chiral building blocks in contemporary organic synthesis. Following the procedure reported by Chemla *et al.*,[443c] the allenic alcohol **15** was obtained in 74% yield, as a single diastereomer, by treating compound **9c** with NH_4Br, in the presence of copper reagents.

To demonstrate further utility of the propargylic epoxides, ring opening reactions of **9c** with heteroatom-based nucleophiles, such as halide or nitrogen, were conducted, providing the optically active halohydrin **16** in 94 % yield, and 1,2-aminoalcohol **17** in 55% yield.

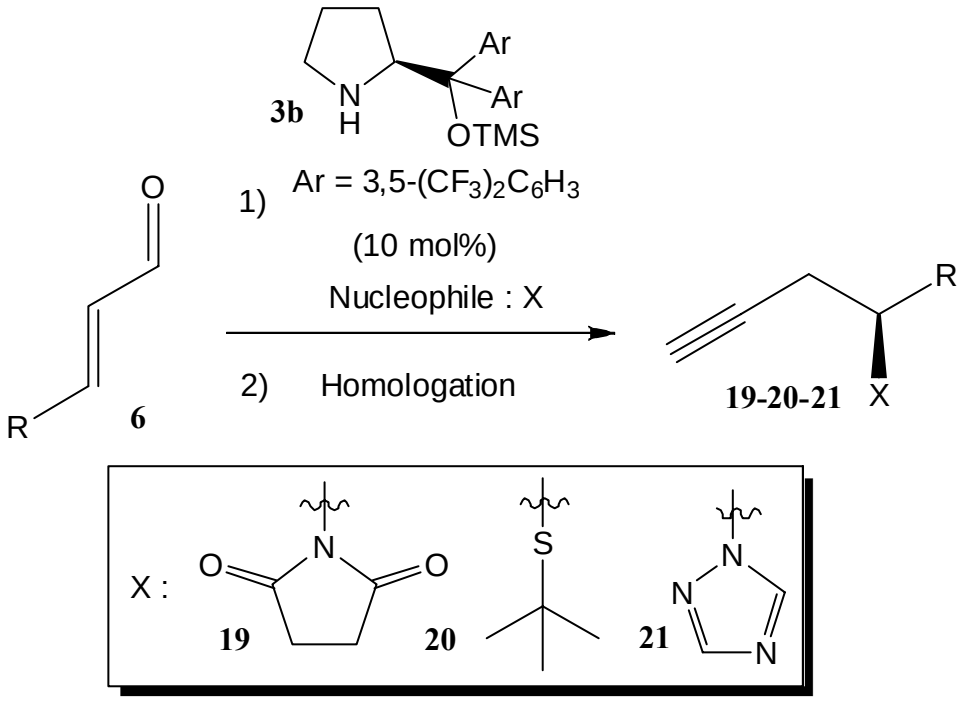
Moreover, the chiral synthesis of propargylic thiiranes[44] was accomplished by a double S_N2 type mechanism in the presence of thiourea, giving the desired product **18** (from the epoxide **9f**) in 55% yield based on recovered starting material, and with no loss of optical purity (Scheme 16).



a) NH_4Br, CuBr, Cu, HBr, Et_2O, -50°C to -10°C, 2h.
b) $CS(NH_2)_2$, MeOH, RT, 1d.
c) PPh_3, Br_2, RT, 15 min.
d) $MeNH_2$, H_2O, 60°C, 3d.

Scheme 16

Encouraged by the previous results, we decided to exploit the possibility of combining other β-heterofunctionalizations with the *in situ* homologation strategy. Actually, the predicted versatility and robustness of this *"assemble and build"* type tactic for synthesis of homo-propargylic compounds could be realized for nucleophiles, such as amines, sulfides and triazoles, as described in Scheme 17 and in Table 2.



Scheme 17

Table 2. Scope of the organocatalytic synthesis of diverse homo-propargylic compounds[a]

entry	R	X	Product	Yield [%] [b]	*ee* [%][c]
1	*n*-butyl	suc	**19a**	43	87
2	*n*-propyl	suc	**19b**	41	87
3	CH_2OBn	suc	**19c**	40	85
4	ethyl	suc	**19d**	44	85
5 [d]	ethyl	suc	ent-**19d**	42	-85
6	*n*-heptyl	suc	**19e**	43	88
7	*cis*-$(CH_2)_2CH{=}CHC_2H_5$	suc	**19f**	48	85
8	$(CH_2)_2Ph$	suc	**19g**	30	88
9	*i*-propyl	*t*BuSH	**20a**	34	89
10	Ph	*t*BuSH	**20b**	48	85
11	*i*-propyl	triaz.	**21a**	44	79
12	ethyl	triaz.	**21b**	47	81
13	*n*-propyl	triaz.	**21c**	49	80

[a] Reaction performed on 0.2 mmol scale; suc=succinimide; triaz=1,2,4-triazole.
[b] Yields of isolated products, after column chromatography.
[c] *ee* determined by chiral stationary phase HPLC. The homo-propargyl triazoles were transformed in order to determinate the *ee* (see Experimental Section).
[d] The enantiomer of catalyst **3b** was employed.

The use of succinimide as nucleophilic nitrogen source allowed to obtain homo-propargylic protected amines **19** in quite good yields, by a convenient and one-pot methodology, merging the organocatalyzed β-amination reaction of α,β-unsaturated aldehydes, whose reaction conditions were discussed in detail in the previous section, with the Ohira-Bestmann homologation.

Homo-propargylic amines have been typically prepared by a Barbier-type reaction of propargylic bromides and aldimines, using stoichiometric amounts of metals, such as indium.[45] Recently Soderquist *et al.* reported an asymmetric allenylboration giving chiral homo-propargylic amines.[45b]

In our approach it was possible to avoid the use of metals, with consequent benign effect on the pollution, employing an easy and highly efficient methodology (Scheme 17, Table 2).

Table 2 outlined that, with succinimide, the reactivity was generalized to aldehydes with different substituting chain sizes (entries 1-2 and 4-6), as well as

to aldehydes with unsaturated chains (Table 2, entry 7), leading to the isolation of desired chiral products **19a,b,d-f** in moderate to good yields and high enantioselectivities. In the presence of aldehydes carrying other functionalities, such as hydroxybenzyl (Table2, entry 3), or phenyl group (Table2, entry 8), the reaction also proceeded smoothly and in 85-88% *ee*.

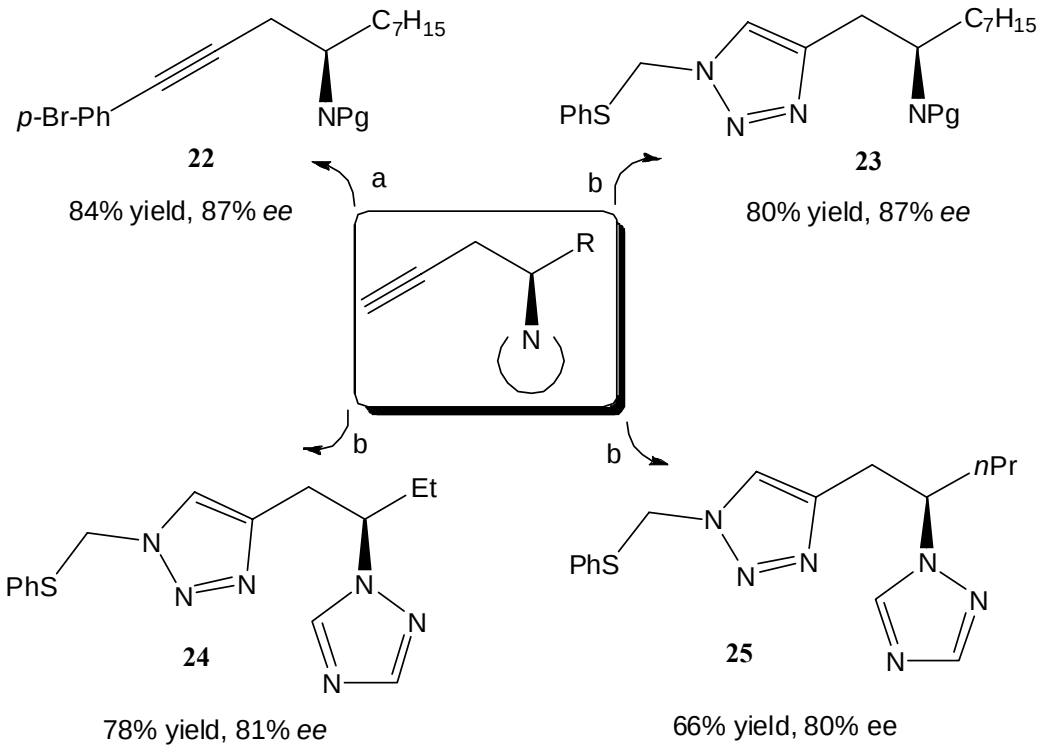
The use of *tert*-butyl sulfide as nucleophile in the organocatalytic step led to the isolation of homo-propargylic sulfides **20a-b** (Table 2, entries 9-10) in moderate yields but with high enantioselectivity, in the presence of both, aliphatic (Table 2, entry 9) and aromatic (Table 2, entry 10) substituents on the substrate. The low yield in the case of **20a** was due to the volatility of the homo-propargylic compound.

Finally, using 1,2,3-triazole as nucleophile it was possible to isolate, after the one-pot procedure, homo-propargylic *N*-heterocycles **21a-c** (Table 2, entries 11-13) in quite good yields and high enantioselectivities. However, in this case, pre-prepared Ohira-Bestmann reagent was used, instead of the *in situ* generated reagent, to combat the diminishing yields.

Having remarked the transformational diversity of the homo-propargylic adducts, we next employed the obtained protected optically active amines in several general and reliable transformations (Scheme 18).

In doing so, compound **19e** was coupled with an aryl iodide under standard Sonogashira conditions[46] providing the internal homo-propargylic amine **22** in 84% yield and with full conservation of the optical integrity.

Moreover, given the importance of the *N*-heterocyclic structure in life science, we demonstrated that enantiomerically enriched triazoles could be obtained by ”clicking” the same starting alkyne **19e** with organic azides (following the Sharpless procedure[47]), as exemplified by the formation of compound **23** in 80% yield and 87% ee. Alternatively, by starting from the homo-propargylic triazoles **21b-c**, optically active 1,2-ditriazoles (**24**, **25**) with differentiated substitution pattern were obtained (Scheme 18).



NPg = succinimide.
a) CuI, $Pd(PPh_3)_4$, *p*-Br-PhI, Et_3N, 60°C, 4h.
b) sodium ascorbate, $CuSO_4$, $PhSCH_2N_3$, H_2O / *t*BuOH, RT, overnight.

Scheme 18

Scheme 18 showed how the obtained homo-propargyl compounds can be differently reacted through easy strategies, thus underlining their transformational diversity for the synthesis of different classes of chiral compounds.

2.3. Conclusions

In summary, we have demonstrated that the iminium-ion activation mode could be conceptually extended to a highly efficient "assemble and build strategy" for divergent synthesis of chiral propargylic, homo-propargylic and allenic compounds. The structural types produced by the reactions described in this section included propargylic epoxides and thiiranes; homo-propargylic amines, sulfides, and triazoles and allenic alcohols, all derived entirely from readily available starting materials.

The flexibility with which organocatalyzed functionalizations was joined with the Ohira-Bestmann homologation reaction highlighted the wide versatility of organocatalytic strategies, which can be merged with different synthetic methodologies for the one-pot synthesis of widely applicable polyfunctionalized chiral molecules.

Experimental section

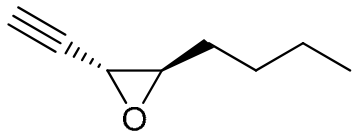
1. General Methods.

NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionization techniques. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ dip. Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD and Daicel Chiralcel OD columns) or by GC using a chiral Chrompack CP Chiralsil-Dex Cβ column. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Fluka) or Iatrobeads 6RS-8060 (spherical silica gel) was used. (*E*)-4-(benzyloxy)but-2-enal and (*E*)-5-phenylpent-2-enal,[iI] and the Ohira-Bestmann reagent **8**[iII] were synthesized according to literature.

2. Propargylic epoxides

General Procedure: A vial equipped with a magnetic stirring bar was charged with the aldehyde **6** (0.2 mmol, 1 equiv), the catalyst **3b** (0.02 mmol, 0.1 equiv), 35 %wt H_2O_2 (0.26 mmol, 1.3 equiv) and CH_2Cl_2 (0.4 mL). Upon completion of reaction (usually 5 h), the mixture was diluted with MeOH (1 mL) and quantitatively transferred to a pre-stirred (stirred for 2 h) suspension of dimethyl 2-oxopropylphosphonate **10** (0.27 mmol, 1.35 equiv), 4-acetamidobenzene-sulfonyl azide **11** (0.27 mmol, 1.35 equiv) and K_2CO_3 (0.8 mmol, 4 equiv) in MeCN (3 mL). After additionally 18 h of stirring, the crude reaction mixture was diluted with Et_2O and filtered through a short pad of silica (wash with Et_2O), concentrated *in vacuo* and purified by FC on silica gel.

9a (2*R*,3*R*)-2-Butyl-3-ethynyloxirane



Following the general procedure **9a** was isolated by FC (gradient: pentane to pentane/Et_2O 49:1) in 83% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 3.12-3.07 (m, 2H), 2.31-2.29 (m, 1H), 1.60-1.52 (m, 2H), 1.50-1.32 (m, 4H), 0.92 (t, J = 7.1 Hz, 3H).

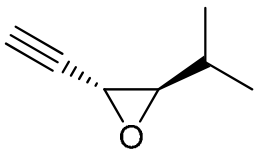
^{13}C NMR (100 MHz, $CDCl_3$) : 80.6, 71.7, 60.4, 44.9, 31.3, 27.7, 22.4, 13.9.

MS (EI): m/z = 124.1 [M^+].

The *ee* was determined by GC using a chiral Chrompack CP Chiralsil-Dex Cβ column; temperature ramp: 70 to 90 °C (10 °C/min), then isotherm for 5 min; τ_{major} = 4.8 min, τ_{minor} = 4.7 min (99% *ee*).

$[\alpha]_D^{rt}$: +5.0 (c = 1.0, Et_2O).

9b (2*R*,3*R*)-2-Ethynyl-3-isopropyloxirane



Following the general procedure **9b** was isolated by FC (gradient: pentane to pentane/Et_2O 49:1) in 34% yield (Volatile product, 63% yield based on internal standard) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 3.13 (dd, J = 1.7, 1.9 Hz, 1H), 2.91 (dd, *J* = 2.2, 6.7 Hz, 1H), 2.30 (d, *J* = 1.7 Hz, 1H), 1.58-1.49 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H).

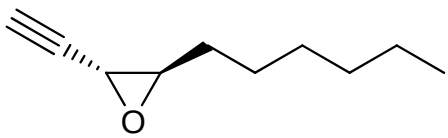
^{13}C NMR (100 MHz, $CDCl_3$): 71.6, 65.9, 43.9, 30.3, 18.6, 18.0(2C).

MS (EI): m/z = 110.1 [M^+].

The *ee* was determined by GC using a chiral Chrompack CP Chiralsil-Dex Cβ column; temperature ramp: 60 °C, isotherm for 10 min; τ_{major} = 5.3 min, τ_{minor} = 4.8 min (99% *ee*).

$[\alpha]_D^{rt}$: -12.1 (c = 1.3, $CHCl_3$).

9c (2*R*,3*R*)-2-Ethynyl-3-hexyloxirane



Following the general procedure **9c** was isolated by FC (gradient: pentane to pentane/Et_2O 49:1) in 81% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 3.11-3.07 (m, 2H), 2.30 (d, *J* = 1.5 Hz, 1H), 1.59-1.50 (m, 2H), 1.49-1.39 (m, 2H), 1.38-1.23 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H).

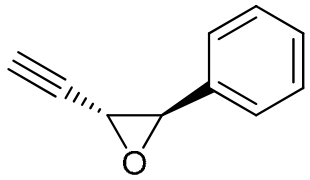
^{13}C NMR (100 MHz, $CDCl_3$): 80.6, 71.6, 60.4, 44.8, 31.6(2C), 28.9, 25.5, 22.5, 14.0.

MS (EI): m/z = 152.1 [M^+].

The *ee* was determined by HPLC using a Chiralcel OB column [hexane/*i*-PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 4.9 min, τ_{minor} = 4.6 min (98% *ee*).

$[\alpha]_D^{rt}$: +0.7 (c = 1.66, $CHCl_3$).

9d (2*R*,3*R*)-2-Ethynyl-3-phenyloxirane



Following the general procedure **9d** was isolated by FC (gradient: pentane to pentane/Et_2O 49:1) in 66% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.37-7.30 (m, 3H), 7.27-7.22 (m, 2H), 4.02 (d, *J* = 1.9 Hz, 1H), 3.33-3.32 (m, 1H), 2.38 (d, *J* = 1.6 Hz, 1H).

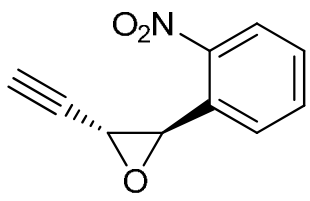
^{13}C NMR (100 MHz, $CDCl_3$): 135.3, 128.8, 128.6(2C), 125.5(2C), 79.8, 72.2, 59.8, 48.9.

MS (EI): m/z = 144.0 [M^+].

The *ee* was determined by GC using a chiral Chrompack CP Chiralsil-Dex Cβ column; temperature ramp: 70 to 140 °C (10 °C/min), then isotherm for 5 min; τ_{major} = 7.6 min, τ_{minor} = 7.5 min (98% *ee*).

$[\alpha]_D^{rt}$: +96.8 (c = 1.6, $CHCl_3$).

9e (2*R*,3*R*)-2-Ethynyl-3-(2-nitrophenyl)oxirane



Following the general procedure **9e** was isolated by FC (gradient: pentane to pentane/Et_2O 9:1) in 86% yield as a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$): 8.21-8.18 (m, 1H), 7.72-7.65 (m, 1H), 7.59-7.49 (m, 2H), 4.66 (d, *J* = 1.6 Hz, 1H), 3.28-3.26 (m, 1H), 2.47 (d, *J* = 1.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 147.5, 134.4, 132.4, 129.2, 127.0, 124.8, 79.0, 73.0, 57.9, 48.3.

HRMS: Calculated for $[C_{10}H_7NNaO_3]^+$: 212.0318; found: 212.0316.

M.p.: 88 °C.

The *ee* was determined by GC using a chiral Chrompack CP Chiralsil-Dex Cβ column; temperature ramp: 70 to 180 °C (10 °C/min), then isotherm for 5 min; τ_{major} = 12.0 min, τ_{minor} = 11.8 min (99% *ee*).

$[\alpha]_D^{rt}$: +175.0 (c = 1.36, $CHCl_3$).

9f (2*R*,3*R*)-2-(Benzyloxymethyl)-3-ethynyloxirane

Following the general procedure **9f** was isolated by FC (gradient: pentane to pentane/Et_2O 4:1) in 73% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.40-7.28 (m, 5H), 4.56 (s, 2H), 3.73 (dd, *J* = 2.9, 11.7 Hz, 1H), 3.55 (dd, *J* = 4.5, 11.8 Hz, 1H), 3.38-3.36 (m, 1H), 3.35-3.34 (m, 1H), 2.33 (d, *J* = 1.6 Hz, 1H).

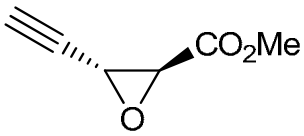
^{13}C NMR (100 MHz, $CDCl_3$): 137.5, 128.4(2C), 127.9, 127.7(2C), 79.7, 73.4, 72.3, 68.4, 58.5, 42.4.

HRMS: Calculated for $[C_{12}H_{12}NaO_2]^+$: 211.0730; found: 211.0733.

The *ee* was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.8 min, τ_{minor} = 9.6 min (91% *ee*).

$[\alpha]_D^{rt}$: +3.0 (c = 0.60, $CHCl_3$).

9g (2*S*,3*R*)-Methyl 3-ethynyloxirane-2-carboxylate



Following the general procedure **9g** was isolated by FC (gradient: pentane to pentane/Et_2O 3:1) in 58% yield as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): 3.80 (s, 3H), 3.64-3.62 (m, 1H), 3.61-3.59 (m, 1H), 2.38 (d, *J* = 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 167.6, 77.9, 73.1, 53.9, 52.9, 44.5.

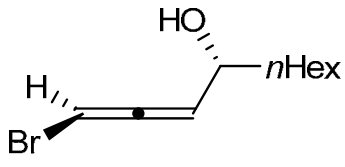
HRMS: Calculated for $[C_6H_6NaO_3]^+$: 149.0215; found: 149.0211.

The e*e* was determined by GC using a chiral Chrompack CP Chiralsil-Dex Cβ column; temperature ramp: 70 to 100 °C (10 °C/min), then isotherm for 5 min; τ_{major} = 4.3 min, τ_{minor} = 4.2 min (97% *ee*).

$[\alpha]_D^{rt}$: +15.5 (c = 0.77, $CHCl_3$).

3. Transformations of the propargylic epoxides

15 (2*R*,4*R*)-1-Bromodeca-1,2-dien-4-ol



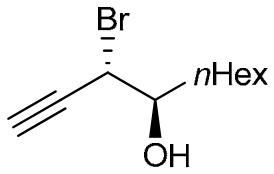
The procedure by Chemla *et al.* was followed.[iIII] The propargylic epoxide **9c** (0.5 mmol, 1 equiv) was dissolved in dry Et_2O (0.25 mL) under argon and cooled to -50 °C. A 48% aqueous solution of HBr (0.375 mmol, 0.75 equiv) was then added, followed by CuBr (0.5 mmol, 1 equiv), NH_4Br (0.25 mmol, 0.5 equiv) and Cu^0 (0.05 mmol, 0.1 equiv). The reaction mixture was warmed to -5 ^oC over 3 h, then quenched by addition of a NH_3/NH_4Cl mixture (1:4) and extracted with Et_2O (3 x 5 mL). The ether phases were washed with NH_3/NH_4Cl (2 x 5 mL), dried and concentrated *in vacuo*. The residue was subjected to FC on Iatrobeads (gradient: pentane/Et_2O 9:1 to 5:1) to give the product **15** in 74% yield as a colorless oil.

^{1}H NMR (400 MHz, CDCl3): 6.09 (dd, *J* = 1.8, 5.7 Hz, 1H), 5.44 (apparent t, *J* = 5.8 Hz, 1H), 4.34-4.26 (m, 1H), 1.87 (d, *J* = 4.8 Hz, 1H), 1.69-1.52 (m, 2H), 1.49-1.23 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, CDCl3): 200.5, 104.4, 74.2, 69.2, 37.0, 31.7, 29.1, 25.1, 22.6, 14.1.

$[\alpha]_D^{rt}$: -157.7 (c = 2.08, $CHCl_3$).

16 (3*S*,4*R*)-3-Bromodec-1-yn-4-ol



The procedure by Martín *et al.* was followed.[iIV] To a solution of PPh_3 (0.57 mmol, 1.2 equiv) in dry CH_2Cl_2 (3 mL) was added bromine (0.57 mmol, 1.2 equiv) under nitrogen at 0 °C. The mixture was stirred for 15 min after which time a solution of **9c** (0.47 mmol, 1 equiv) in dry CH_2Cl_2 was added. The mixture was stirred for another 15 min and quenched by the addition of water. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to FC on silica gel (gradient: pentane to pentane/Et_2O 3:1) to give the product **16** in 94% yield as a colorless oil.

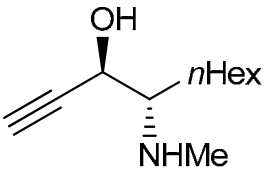
^{1}H NMR (400 MHz, $CDCl_3$): 4.56 (dd, *J* = 2.5, 3.8 Hz, 1H), 3.81-3.72 (m, 1H), 2.71 (d, *J* = 2.4 Hz, 1H), 2.20 (d, *J* = 6.0 Hz, 1H), 1.79-1.24 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 79.1, 77.3, 74.2, 43.1, 33.7, 31.7, 29.1, 25.6, 22.6, 14.1.

HRMS: Calculated for $[C_{10}H_{17}BrNaO]^+$: 255.0355; found: 255.0364.

$[\alpha]_D^{rt}$: +2.1 (c = 1.0, CH_2Cl_2).

17 (3*R*,4*S*)-4-(Methylamino)dec-1-yn-3-ol



The procedure by Manisse *et al.* was followed.[iV] The propargylic epoxide **9c** (0.2 mmol, 1 equiv) was dissolved in 0.4 mL of a 30% aqueous solution of $MeNH_2$ and stirred for 3 d at 55 °C. The reaction mixture was then diluted with Et_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Final purification by FC on silica gel (gradient: EtOAc/pentane 3:1 to EtOAC/MeOH 4:1) gave the product **17** in 55% yield as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): 3.71-3.61 (m, 1H), 3.32-3.29 (m, 1H), 2.51 (s, 3H), 2.34 (d, *J* = 2.2 Hz, 1H), 2.04 (bs, 2H), 1.65-1.21 (m, 10H), 0.88 (t, *J* = 6.6 Hz, 3H).

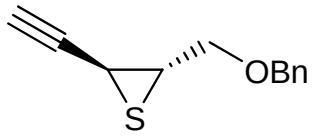
^{13}C NMR (100 MHz, $CDCl_3$): 81.5, 74.0, 72.4, 57.3, 34.3, 33.8, 31.7, 29.2, 25.8, 22.6, 14.1.

HRMS: Calculated for $[C_{11}H_{21}NNaO]^+$: 206.1521; found: 206.1511.

M.p.: 64 °C.

$[\alpha]_D^{rt}$: +15.3 (c = 1.52, $CHCl_3$).

18 (2*S*,3*S*)-2-(Benzyloxymethyl)-3-ethynylthiirane



The procedure by Mobashery *et al.* was followed.[iVI] To a solution of the propargylic epoxide **9f** (0.11 mmol, 1 equiv) in MeOH (0.3 mL) under nitrogen atmosphere was added thiourea (0.17 mmol, 1.5 equiv) and the reaction mixture was stirred at rt for 24 h, by which time water was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by FC on silica gel (gradient: pentane/Et_2O 15:1 to 4:1) to give the product **18** in 55% yield (based on recovered starting material) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.43-7.28 (m, 5H), 4.59 (s, 2H), 3.70 (dd, *J* = 5.5, 10.6 Hz, 1H), 3.48 (dd, *J* = 6.6, 10.8 Hz, 1H), 3.32 (dd, *J* = 5.6, 11.1 Hz, 1H), 3.10 (dd, *J* = 2.0, 4.8 Hz, 1H), 2.25 (d, *J* = 2.0 Hz, 1H).

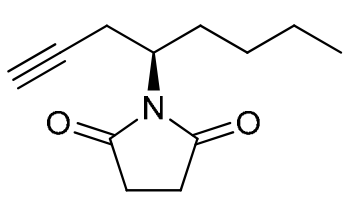
^{13}C NMR (100 MHz, $CDCl_3$): 137.6, 128.5(2C), 127.9, 127.7(2C), 81.7, 73.2, 73.0, 69.9, 40.4, 25.0.

$[\alpha]_D^{rt}$: -106.5 (c = 0.38, MeOH).

4. Homo-propargylic amines

General Procedure: A vial equipped with a magnetic stirring bar was charged with the aldehyde **6** (0.2 mmol, 1 equiv), the catalyst **3b** (0.02 mmol, 0.1 equiv), NaOAc (0.04 mmol, 0.2 equiv), H_2O (0.4 mmol, 2 equiv), succinimide (0.3 mmol, 1.5 equiv) and CH_2Cl_2 (0.4 mL). Upon completion of reaction (usually 24 h), the mixture was diluted with MeOH (1 mL) and quantitatively transferred to a pre-stirred (stirred for 2 h) suspension of dimethyl 2-oxopropylphosphonate **10** (0.51 mmol, 2.04 equiv), 4-acetamidobenzene-sulfonyl azide **11** (0.51 mmol, 2.04 equiv) and K_2CO_3 (1.52 mmol, 6.08 equiv) in MeCN (6 mL). After additionally 18 h of stirring, the crude reaction mixture was diluted with Et_2O and filtered through a short pad of silica (wash with Et_2O), concentrated *in vacuo* and purified by FC (gradient: pentane to pentane/Et_2O 49:1) on silica gel.

19a (*R*)-1-(Oct-1-yn-4-yl)pyrrolidine-2,5-dione



Following the general procedure **19a** was isolated by FC (pentane/EtOAc 3:1) in 43% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 4.33-4.22 (m, 1H), 2.89 (ddd, *J* = 2.7, 10.0, 16.8 Hz, 1H), 2.70 (s, 4H), 2.54 (ddd, *J* = 2.6, 5.8, 16.8 Hz, 1H), 2.03-1.93 (m, 1H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.75-1.65 (m, 1H), 1.39-1.08 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H).

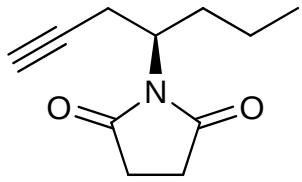
^{13}C NMR (100 MHz, $CDCl_3$): 177.3(2C), 80.5, 69.9, 51.4, 30.6, 28.6, 27.9(2C), 22.2, 21.5, 13.9.

HRMS: Calculated for $[C_{12}H_{17}NNaO_2]^+$: 230.1157; found: 230.1153.

The e*e* was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 13.9 min, τ_{minor} = 16.0 min (87% *ee*).

$[\alpha]_D^{rt}$: +3.6 (c = 0.45, MeOH).

19b (*R*)-1-(Hept-1-yn-4-yl)pyrrolidine-2,5-dione



Following the general procedure **19b** was isolated by FC (pentane/EtOAc 3:1) in 41% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 4.34-4.25 (m, 1H), 2.89 (ddd, *J* = 2.7, 16.8 Hz, 1H), 2.73-2.66 (m, 4H), 2.54 (dd, *J* = 2.6, 16.8 Hz, 1H), 2.02-1.93 (m, 1H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.71-1.61 (m, 1H), 1.29-1.16 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H).

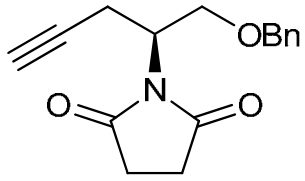
^{13}C NMR (100 MHz, $CDCl_3$): 177.3(2C), 80.5, 69.9, 51.2, 32.9, 27.9(2C), 21.5, 19.7, 13.6.

HRMS: Calculated for $[C_{11}H_{15}NNaO_2]^+$: 216.0995; found: 216.1004.

The *ee* was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.4 min, τ_{minor} = 14.5 min (87% *ee*).

$[\alpha]_D^{rt}$: -3.8 (c = 0.80, $CHCl_3$).

19c (*S*)-1-(1-(Benzyloxy)pent-4-yn-2-yl)pyrrolidine-2,5-dione



Following the general procedure **19c** was isolated by FC (pentane/EtOAc 3:1) in 44% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.38-7.25 (m, 5H), 4.64-4.57 (m, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 3.91 (dd, *J* = 8.9, 10.0 Hz, 1H), 3.74-3.67 (m, 1H), 2.84 (ddd, *J* = 2.7, 9.6, 16.9, 9.6, Hz, 1H), 2.67 (s, 4H), 2.67-2.61 (m, 1H), 1.94 (t, *J* = 2.7 Hz, 1H).

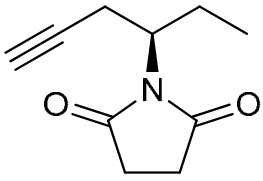
^{13}C NMR (100 MHz, $CDCl_3$): 177.2(2C), 137.7, 128.4(2C), 127.8, 127.6(2C), 79.7, 72.8, 70.3, 67.9, 50.3, 27.9(2C), 18.4.

HRMS: Calculated for $[C_{16}H_{17}NNaO_3]^+$: 294.1114; found: 294.1106.

The *ee* was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 20.6 min, τ_{minor} = 25.5 min (85% *ee*).

$[\alpha]_D^{rt}$: +10.3 (c = 1.0, CH_2Cl_2).

19d (*R*)-1-(Hex-5-yn-3-yl)pyrrolidine-2,5-dione



Following the general procedure **19d** was isolated by FC (pentane/EtOAc 3:1) in 44% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 4.25-4.11 (m, 1H), 2.89 (ddd, *J* = 2.7, 10.0, 16.8 Hz, 1H), 2.70 (s, 4H), 2.56 (ddd, *J* = 2.6, 5.9, 16.8, Hz, 1H), 2.01-1.94 (m, 1H), 1.92 (t, *J* = 2.7 Hz, 1H), 1.82-1.72 (m, 1H), 0.85 (t, *J* = 7.5 Hz, 3H).

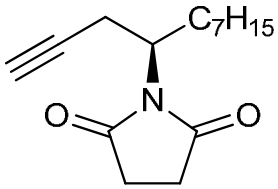
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4(2C), 80.5, 69.9, 53.0, 27.9(2C), 24.1, 21.3, 15.3.

HRMS: Calculated for $[C_{10}H_{13}NNaO_2]^+$: 202.0844; found: 202.0838.

The *ee* was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 15.6 min, τ_{minor} = 18.2 min (85% *ee*).

$[\alpha]_D^{rt}$: -10.3 (c = 0.86, MeOH).

19e (*R*)-1-(Undec-1-yn-4-yl)pyrrolidine-2,5-dione



Following the general procedure **19e** was isolated by FC (pentane/EtOAc 3:1) in 43% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 4.32-4.23 (m, 1H), 2.89 (ddd, *J* = 2.7, 10.0, 16.8 Hz, 1H), 2.70 (s, 4H), 2.54 (ddd, *J* = 2.6, 5.8, 16.8 Hz, 1H), 2.03-1.93 (m, 1H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.75-1.65 (m, 1H), 1.35-1.19 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H).

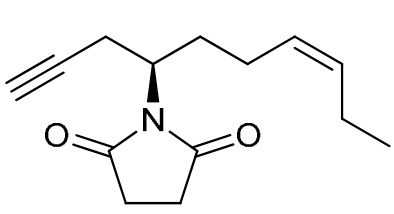
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4(2C), 80.5, 69.9, 51.4, 31.7, 30.8, 29.0, 29.0, 27.8(2C), 26.4, 22.5, 21.5, 14.0.

HRMS: Calculated for $[C_{15}H_{23}NNaO_2]^+$: 272.1626; found: 230.1633.

The *ee* was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 13.1 min, τ_{minor} = 18.1 min (88% *ee*).

$[\alpha]_D^{rt}$: +5.1 (c = 0.8, MeOH).

19f (*R*,*Z*)-1-(Dec-7-en-1-yn-4-yl)pyrrolidine-2,5-dione



Following the general procedure **19f** was isolated by FC (pentane/EtOAc 3:1) in 48% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 5.43-5.32 (m, 1H), 5.28-5.20 (m, 1H), 4.35-4.26 (m, 1H), 2.88 (ddd, *J* = 2.7, 9.9, 16.8 Hz, 1H), 2.69 (s, 4H), 2.55 (ddd, *J* = 2.6, 5.9, 16.8 Hz, 1H), 2.14-2.03 (m, 1H), 2.02-1.94 (m, 4H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.82-1.72 (m, 1H), 0.93 (t, *J* = 7.6 Hz, 3H).

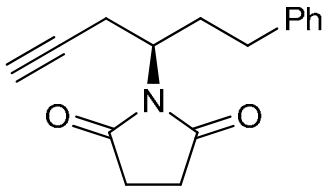
^{13}C NMR (100 MHz, $CDCl_3$): 177.3(2C), 132.8, 127.2, 80.4, 70.0, 51.2, 30.7, 27.9(2C), 24.2, 21.6, 20.5, 14.2.

HRMS: Calculated for $[C_{14}H_{19}NNaO_2]^+$: 256.1313; found: 256.1310.

The *ee* was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 13.7 min, τ_{minor} = 14.7 min (85% *ee*).

$[\alpha]_D^{rt}$: +4.7 (c = 1.8, $CHCl_3$).

19g (*R*)-1-(1-Phenylhex-5-yn-3-yl)pyrrolidine-2,5-dione



Following the general procedure **19g** was isolated by FC (pentane/EtOAc 3:1) in 30% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.29-7.13 (m, 5H), 4.39-4.30 (m, 1H), 2.87 (ddd, *J* = 2.7, 9.6, 16.8 Hz, 1H), 2.77-2.68 (m, 1H), 2.64-2.47 (m, 3H), 2.46-2.36 (m, 4H), 2.06-1.97 (m, 1H), 1.94-1.91 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 177.3(2C), 140.6, 128.3(2C), 128.2(2C), 126.1, 80.3, 70.1, 51.6, 33.2, 30.9, 27.8(2C), 22.0.

HRMS: Calculated for $[C_{16}H_{17}NNaO_2]^+$: 278.1157; found: 278.1144.

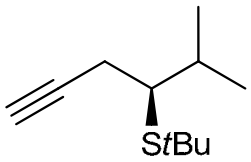
The *ee* was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 24.3 min, τ_{minor} = 30.4 min (88% *ee*).

$[\alpha]_D^{rt}$: -25.3 (c = 0.4, $CHCl_3$).

5. Homo-propargylic sulfides

General Procedure: A vial equipped with a magnetic stirring bar was charged with the aldehyde **6** (0.38 mmol, 1.5 equiv), the catalyst **3b** (0.025 mmol, 0.1 equiv), $PhCO_2H$ (0.025 mmol, 0.1 equiv) and toluene (1 mL). After cooling the reaction mixture to -20 °C, *t*-butyl sulfide (0.25 mmol, 1 equiv) was added and stirring was continued for further 30 h. Upon completion of reaction, the mixture was diluted with MeOH (2 mL) and quantitatively transferred to a pre-stirred (stirred for 2 h) suspension of dimethyl 2-oxopropylphosphonate **10** (0.27 mmol, 1.35 equiv), 4-acetamidobenzene-sulfonyl azide **11** (0.27 mmol, 1.35 equiv) and K_2CO_3 (0.8 mmol, 4 equiv) in MeCN (3 mL). After additionally 18 h of stirring, the crude reaction mixture was diluted with Et_2O and filtered through a short pad of silica (wash with Et_2O), concentrated *in vacuo* and purified by FC (pentane/Et_2O 49:1) on silica gel.

20a (*S*)-*tert*-Butyl(2-methylhex-5-yn-3-yl)sulfane



Following the general procedure **20a** was isolated by FC in 34% yield as a colorless oil.

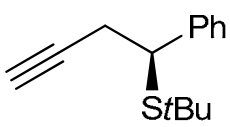
^{1}H NMR (400 MHz, $CDCl_3$): 2.64-2.52 (m, 3H), 2.29-2.18 (m, 1H), 2.00 (t, *J* = 2.5 Hz, 1H), 1.33 (s, 9H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 82.8, 69.3, 48.2, 42.7, 31.5(3C), 30.8, 26.1, 20.6, 17.7.

The *ee* was determined by HPLC using a Chiralcel OJ column [hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 3.7 min, τ_{minor} = 4.4 min (89% *ee*).

$[\alpha]_D^{rt}$: +16.3 (c = 1.2, $CHCl_3$).

20b (*S*)-*tert*-Butyl(1-phenylbut-3-ynyl)sulfane



Following the general procedure **20b** was isolated by FC in 48% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.36-7.15 (m, 5H), 3.95 (dd, *J* = 8.15, 6.39 Hz, 1H), 2.72 (ddd, *J* = 2.6, 6.3, 16.8 Hz, 1H), 2.66 (ddd, *J* = 2.6, 8.1, 16.9 Hz, 1H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.20 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): 143.5, 128.3(2C), 127.6(2C), 127.1, 81.6, 70.2, 46.3, 44.2, 31.3(3C), 28.9.

HRMS: Calculated for $[C_{14}H_{18}NaS]^+$: 241.1016; found: 241.1024.

The *ee* was determined by HPLC using a Chiralcel OJ column [hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 5.5 min, τ_{minor} = 8.0 min (85% *ee*).

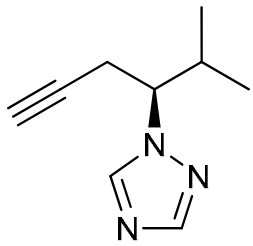
$[\alpha]_D^{rt}$: -104.3 (c = 0.8, $CHCl_3$).

6. Homo-propargylic triazoles

General Procedure: A vial equipped with a magnetic stirring bar was charged with the aldehyde **6** (0.3 mmol, 1 equiv), the catalyst **3b** (0.02 mmol, 0.1 equiv), 1,2,4-triazole (re-crystallized, 0.2 mmol, 1 equiv), $PHCO_2H$ (0.02 mmol, 0.1 equiv) and toluene (2 mL). The stirring was continued for 20 h and MeOH (4.5 mL), dimethyl 1-diazo-2-oxopropylphosphonate **8** (0.26 mmol, 1.32 equiv) and K_2CO_3 (0.53 mmol, 2.64 equiv) was added. After additionally 18 h of stirring, the crude reaction mixture was diluted with EtOAc and filtered through a short pad of silica (wash with EtOAc), concentrated *in vacuo* and purified by FC (gradient: pentane/EtOAc 1:1 to 1:2) on silica gel.

Determination of ee: The homo-propargylic triazoles were transformed by a simple click-reaction in order to determine the enantiomeric excess. An ordinary vial equipped with a magnetic stirring bar was charged with the homo-progargylic triazole **21** (0.1 mmol, 1 equiv), sodium ascorbate (0.01 mmol, 0.1 equiv), $CuSO_4 \cdot 5H_2O$ (0.01 mmol, 0.1 equiv), azidomethyl phenyl sulfide (0.11 mmol, 1.1 equiv) and 1:1 *t*-BuOH/H_2O (0.5 mL). The mixture was stirred at ambient temperature for 18 h, upon which the mixture was diluted with NH_4Cl, extracted with EtOAc (3 x 5 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by FC (gradient: pentane/EtOAc 1:1 to pure EtOAc) on silica gel.

21a (*S*)-1-(2-Methylhex-5-yn-3-yl)-1*H*-1,2,4-triazole



Following the general procedure **21a** was isolated by FC in 44% yield as a colorless oil.

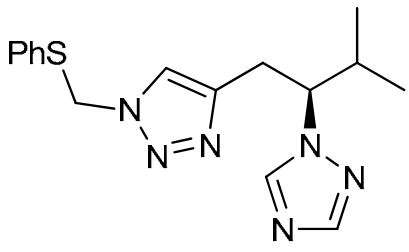
^{1}H NMR (400 MHz, $CDCl_3$): 8.14 (s, 1H), 7.97 (s, 1H), 4.11-3.99 (m, 1H), 2.84 (ddd, *J* = 2.0, 7.9, 15.8 Hz, 1H), 2.78 (ddd, *J* = 2.0, 4.2, 7.5 Hz, 1H), 2.37-2.26 (m, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, CDCl3): 151.9, 143.3, 79.5, 71.2, 65.7, 31.9, 22.8, 19.6, 18.9.

HRMS: Calculated for $[C_9H_{13}N_3Na]^+$: 186.1007; found: 186.1014.

$[\alpha]_D^{rt}$: -8.1 (c = 0.65, $CHCl_3$).

26 (*S*)-4-(3-Methyl-2-(1*H*-1,2,4-triazol-1-yl)butyl)-1-(phenylthiomethyl)-1*H*-1,2,3-triazole



Following the general procedure **26** was isolated by FC in 62% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.91 (s, 1H), 7.75 (s, 1H), 7.32-7.28 (m, 3H), 7.21-7.18 (m, 2H),

6.87 (s, 1H), 5.48 (d, J = 14.4 Hz, 1H), 5.43 (d, J = 14.4 Hz, 1H), 4.32-4.24 (m, 1H), 3.36-3.23 (m, 2H), 2.31-2.19 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H).

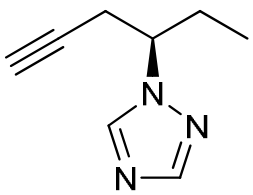
^{13}C NMR (100 MHz, $CDCl_3$): 152.0, 144.2, 144.0, 132.3(2C), 131.6, 129.5(2C), 128.7, 121.2, 66.6, 53.8, 32.7, 28.6, 19.7, 19.0.

HRMS: Calculated for $[C_{16}H_{20}N_6NaS]^+$: 351.1362; found: 351.1368.

The *ee* was determined by HPLC using a Chiralpak AD column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 14.2 min, τ_{minor} = 24.2 min (79% *ee*).

$[\alpha]_D^{rt}$: -16.0 (c = 0.38, $CHCl_3$).

21b (*R*)-1-(Hex-5-yn-3-yl)-1*H*-1,2,4-triazole



Following the general procedure **21b** was isolated by FC in 47% yield as a colorless oil.

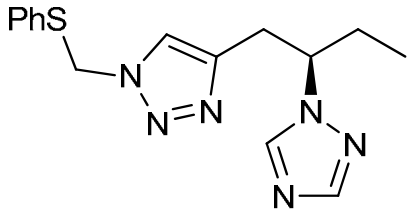
^{1}H NMR (400 MHz, $CDCl_3$: 8.14 (s, 1H), 7.97 (s, 1H), 4.32-4.23 (m, 1H), 2.82-2.67 (m, 2H), 2.11-1.95 (m, 2H), 2.00 (t, J = 2.6 Hz, 1H), 0.84 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 152.1, 142.9, 79.2, 71.4, 61.3, 26.7, 25.1, 10.4.

HRMS: Calculated for $[C_8H_{11}N_3Na]^+$: 172.0845; found: 172.0851.

$[\alpha]_D^{rt}$: -7.6 (c = 0.67, $CHCl_3$).

24 (*R*)-4-(2-(1*H*-1,2,4-Triazol-1-yl)butyl)-1-(phenylthiomethyl)-1*H*-1,2,3-triazole



Following the general procedure **24** was isolated by FC in 78% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.94 (s, 1H), 7.79 (s, 1H), 7.33-7.20 (m, 5H), 6.92 (s, 1H), 5.51 (d, *J* = 14.4 Hz, 1H), 5.46 (d, *J* = 14.4 Hz, 1H), 4.54-4.45 (m, 1H), 3.27 (dd, *J* = 9.4, 14.9 Hz, 1H), 3.21 (dd, *J* = 5.0, 14.8 Hz, 1H), 2.10-1.97 (m, 1H), 1.97-1.88 (m, 1H), 0.82 (t, *J* = 7.4 Hz, 3H).

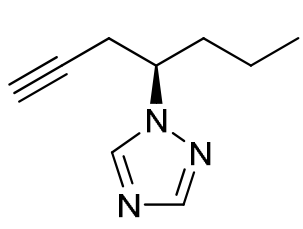
^{13}C NMR (100 MHz, $CDCl_3$): 152.5, 144.1, 143.8, 132.6(2C), 131.6, 129.7(2C), 129.0, 121.5, 62.6, 54.1, 31.5, 28.0, 10.8.

HRMS: Calculated for $[C_{15}H_{18}N_6NaS]^+$: 337.1206; found: 337.1211.

The *ee* was determined by HPLC using a Chiralpak AD column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 15.9 min, τ_{minor} = 25.9 min (81% *ee*).

$[\alpha]_D^{rt}$: -18.0 (c = 0.25, $CHCl_3$).

21c (*R*)-1-(Hept-1-yn-4-yl)-1H-1,2,4-triazole



Following the general procedure **21c** was isolated by FC (pentane/EtOAc 1:1) in 48% yield as a colorless oil.

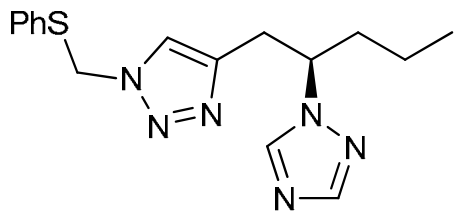
^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (s, 1H), 7.96 (s, 1H), 4.41-4.33 (m, 1H), 2.81-2.65 (m, 2H), 2.12-1.95 (m, 2H), 1.94-1.84 (m, 1H), 1.33-1.09 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 152.0, 142.9, 79.2, 71.5, 59.5, 35.5, 25.4, 19.1, 13.5.

HRMS: Calculated for $[C_9H_{13}N_3Na]^+$: 186.1002; found: 186.1010.

$[\alpha]_D^{rt}$: -7.3 (c = 0.6, $CHCl_3$).

25 (*R*)-4-(2-(1*H*-1,2,4-Triazol-1-yl)pentyl)-1-(phenylthiomethyl)-1*H*-1,2,3-triazole



Following the general procedure **25** was isolated by FC in 66% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.92 (s, 1H), 7.77 (s, 1H), 7.33-7.27 (m, 3H), 7.23-7.19 (m, 2H), 6.90 (s, 1H), 5.50 (d, *J* = 14.4 Hz, 1H), 5.45 (d, *J* = 14.4 Hz, 1H), 4.64-4.55 (m, 1H), 3.29-3.14 (m, 2H), 2.08-1.94 (m, 1H), 1.88-1.75 (m, 1H), 1.30-1.04 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 152.1, 143.8, 143.4, 132.3(2C), 131.6, 129.4(2C), 128.7, 121.2, 60.4, 53.8, 36.4, 31.4, 19.1, 13.5.

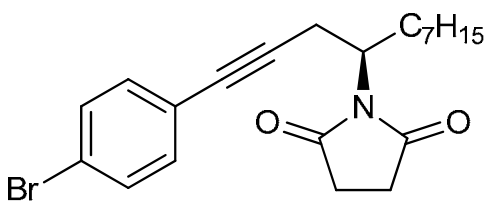
HRMS: Calculated for $[C_{16}H_{20}N_6NaS]^+$: 351.1368; found: 351.1375.

The *ee* was determined by HPLC using a Chiralpak AD column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 17.0 min, τ_{minor} = 29.9 min (80% *ee*).

$[\alpha]_D^{rt}$: -13.6 (c = 0.13, $CHCl_3$).

7. Transformations of the homo-propargylic amines

22 (*R*)-1-(1-(4-Bromophenyl)undec-1-yn-4-yl)pyrroli-dine-2,5-dione



The procedure by Hayashi *et al.* was followed.[iVII] A solution of **19e** (0.20 mmol, 1 equiv), 1-bromo-4-iodobenzene (0.4 mmol, 2 equiv), $Pd(PPh_3)_4$ (0.01 mmol, 0.05 equiv) and CuI (0.01 mmol, 0.05 equiv) in Et_3N (0.4 mL) was stirred at 60 ^oC for 4 h. Upon completion of the reaction, the crude mixture was passed through a short pad of celite and silica, washed with Et_2O and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (pentane/EtOAc 3:1) to give the product **22** in 84% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.39 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.39-4.30 (m, 1H), 3.05 (dd, *J* = 9.8, 17.0 Hz, 1H), 2.74 (dd, *J* = 5.9, 16.9 Hz, 1H), 2.67 (s, 4H), 2.09-1.96 (m, 1H), 1.81-1.69 (m, 1H), 1.36-1.13 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H).

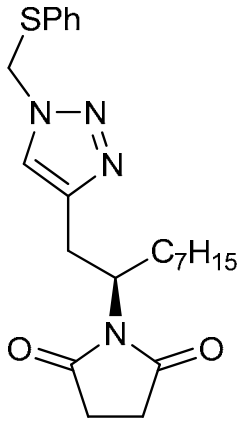
^{13}C NMR (100 MHz, CDCl3): 177.3(2C), 132.9(2C), 131.4(2C), 122.2, 122.0, 87.4, 81.1, 51.7, 31.7, 30.8, 29.1, 29.0, 27.9(2C), 26.5, 22.6, 22.6, 14.1.

HRMS: Calculated for $[C_{21}H_{26}NNaO_2Br]^+$: 426.1045; found: 426.1049.

The *ee* was determined by HPLC using a Chiralcel OD column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 11.9 min, τ_{minor} = 18.1 min (87% *ee*).

$[\alpha]_D^{rt}$: -24.3 (c = 0.6, CH_2Cl_2).

23 (*R*)-1-(1-(1-(Phenylthiomethyl)-1H-1,2,3-triazol-4-yl)nonan-2-yl)pyrrolidine-2,5-dione



An ordinary vial equipped with a magnetic stirring bar was charged with the homo-progargylic amine **19e** (0.1 mmol, 1 equiv), sodium ascorbate (0.01 mmol, 0.1 equiv), $CuSO_4 \cdot 5H_2O$ (0.01 mmol, 0.1 equiv), azidomethyl phenyl sulfide (0.11 mmol, 1.1 equiv) and 1:1 *t*-BuOH/H_2O (0.5 mL). The mixture was stirred at ambient temperature for 18 h, upon which the mixture was diluted with NH_4Cl, extracted with EtOAc (3 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by FC (EtOAc/pentane 9:1) on silica gel to give **23** in 80% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.33 (s, 1H), 7.29-7.21 (m, 5H), 5.54 (d, *J* = 14.4 Hz, 1H), 5.49 (d, *J* = 14.4 Hz, 1H), 4.31-4.20 (m, 1H), 3.40 (dd, *J* = 10.8, 14.7, Hz, 1H), 2.91 (dd, *J* = 4.9, 14.7 Hz, 1H), 2.58-2.39 (m, 4H), 2.11-1.98 (m, 1H), 1.73-1.62 (m, 1H), 1.33-1.11 (m, 10H), 0.83 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 177.6(2C), 145.2, 131.9(2C), 131.9, 129.4(2C), 128.5, 120.9, 53.5, 52.6, 31.7, 31.2, 29.1(2C), 27.8(2C), 27.3, 26.5, 22.5, 14.0.

HRMS: Calculated for $[C_{22}H_{30}N_4NaO_2S]^+$: 437.1982; found: 437.1985.

The *ee* was determined by HPLC using a Chiralpak AD column [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 52.5 min, τ_{minor} = 45.4 min (87% *ee*).

$[\alpha]_D^{rt}$: -21.4 (c = 0.9, CH_2Cl_2).

iI J. Kang, G. J. Lim, S. K. Yoon, M. Y. Kim, *J. Org. Chem.* **1995**, 60, 564.

iII G. J. Roth, B. Liepold, S. G. Müller, H. J. Bestmann, *Synthesis* **2004**, 59.

iIII F. Chemla, N. Bernard, J. Normant, *Eur. J. Org. Chem.* **1999**, 2067.

iIV D. Díaz, T. Martín, V. S. Martín, *J. Org. Chem.* **2001**, 66, 7231.

iV N. Manisse, J. Chuche, *Tetrahedron* **1977**, 33, 2399.

iVI M. Lee, M. M. Bernardo, S. O. Meroueh, S. Brown, R. Fridman, S. Mobashery, *Org. Lett.* **2005**, 7, 4463.

iVII T. Nishimura, X.-X. Guo, N. Uchiyama, T. Katoh, T. Hayashi, *J. Am. Chem. Soc.* **2008**, 130, 1576.

Bibliography

[1] a) L.S. Hegedus, *Transition Metals in the Synthesis of Complex Molecules*, University Science Books, USA, **1999**. b) D. Astruc, *Organometallic Chemistry and Catalysis*, Springer Berlin, Heidelberg, **2007**.

[2] *Enzyme Catalysis in Organic Synthesis*, (Eds: K. Drauz, H. Waldmann), Wiley-VCH Verlag GmbH, Germany, **2008**. b) G. I. Likhtenshtein, *New Trends in Enzyme Catalysis and Biomimetic Chemical Reactions*, Springer, Kluwer Academic Publishers, **2003**.

[3] For general reviews and essays, see: a) P.L. Dalko, L. Moisan , *Angew. Chem. Int. Ed.* **2004**, 43, 5138. b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, **2004**. c) C. F. Barbas III, *Angew. Chem. Int. Ed.* **2007**, 47, 42, and references cited therein.

[4] B. List, *Chem. Rev.* **2007**, 107, 5413.

[5] D. W. C. MacMillan, *Nature* 2**008**, 455, 304.

[6] For general reviews, see: a) *Asymmetric Phase Transfer Catalysis*, (Ed. K. Maruoka), Wiley-VCH: Weinheim, Germany, **2008**. b) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, 46, 4222. c) P. Elsner, L. Bernardi, G. Dela Salla, J. Overgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, 130, 4897.

[7] For general reviews, see: a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, , *Angew. Chem. Int. Ed.* **2008**, 47, 6138. b) A. Dondoni, A. Massi, , *Angew. Chem. Int. Ed.* **2008**, 47, 4638. c) B. List, *Chem. Comm.* **2006**, 819.

[8] Inter alia: a) *New Frontiers in Asymmetric Catalysis*, Ed. K. Mikami and M. Lautens, Wiley-VCH, Germany **2007**; and references cited therein. b) M. S. Taylor, E. N. Jacobsen, , *Angew. Chem. Int. Ed.* **2006**, 45, 1520. c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, 107, 5713.

[9] a) W. P. Jenks, *Catalysis in Chemistry and Enzymology*, Dover, New York, **1969**. b) W. J. Rutter, *Fed. Proc.* **1964**, 23, 1248. c) C. Y. Lai, N. Nakai, D. Chang, *Science* **1974**, 183, 1204.

[10] a) Z. G. Hajos, D. R. Parrish, German Patent DE 2102623, **1971**. b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, 39, 1615. c) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, 10, 496.

[11] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, 122, 2395.

[12] a) S. Bertelsen, M. Nielsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2007**, 46, 7356. b) H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, 130, 398. c) T. H. Graham, C. M. Jones, N. T. Jui, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, 130, 16494. d) K. C. Nicolaou, R Reingruber, D. Sarlah, S. Bräse, *J. Am. Chem. Soc.* **2009**, 131, 6640.

[13] Inter alia: S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, 128, 12973.

[14] For recent reviews on α-functionalizations using enamine activation, see: a) M. Marigo, K. A. Jørgensen, *Chem. Comm.* **2006**, 2001. b) G. Guillena, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, 17, 1465.

[15] For recent reviews on conjugated additions using iminium-ion activation, see for example: a) S. B. Tsogoeva, *Eur. J. Org.* **2007**, 1701. b) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065.

[16] For reviews on organocatalytic aldol reactions see for example: a) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, 123, 5260. b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, 124, 6798. c) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2004**, 43, 2152. d) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Comm.* **2002**, 620. e) D. Enders, C. Grondal, *Angew. Chem. Int. Ed.* **2005**, 44, 1210. f) J. T. Suri, S. Mitsumori, K. Albertshofer, F. Tanaka, C. F. Barbas III, *J. Org. Chem.* **2006**, 71, 3822. g) I. Ismail, A, Córdova, *Tetrahedron Lett.* **2005**, 3363.

[17] S. Mitsumori, H. Zhang, P. H. Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, 128, 1040. b) T. Kano, Y. Yamaguchi, O. Tokuda, K. Maruoka, *J. Am. Chem. Soc.* **2005**, 127, 16408.

[18] Inter alia: a) B. List, *J. Am. Chem. Soc.* **2002**, 124, 5656. b) S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, 126, 8120. c) X. Liu, H. Li, L. Deng, *Org. Lett.* **2005**, 7, 167.

[19] For some selected examples, see: a) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjaesgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, 127, 18296. b) S. Bertelsen, N. Halland, S. Bachmann, M. Marigo, A. Braunton, , K. A. Jørgensen, *Chem, Commun.* **2005**, 4821. c) S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard, K. A. Jørgensen, *Chem. Eur. J.* **2006**, 12, 6039. d) H. Jiang, A. Falcicchio, K. L. Jensen, M. W. Paixao, S. Bertelsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2009**, 131, 7153.

[20] a) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, 125, 10808. b) G. Zhong, *Angew. Chem. Int. Ed.* **2004**, 43, 1983.

[21] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, 122, 4243.

[22] a) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, 127, 32. b) S. Mayer, B. List, *Angew. Chem. Int. Ed.* **2006**, 45, 4193.

[23] a) R. B. Woodward, E. Logusch *et al*., *J. Am. Chem. Soc.* **1981**, 103, 3210. b) M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, 127, 15710. c) R. Rios, H. Sundén, I. Ibrahem, G. Zhao, L. Eriksson, A. Córdova, *Tetrahedron Lett.* **2006**, 47, 8547. d) S. Brandau, E. Maerten, , K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, 128, 14986.

[24] a) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, 128, 9328. b) J. Vasely, I. Ibrahem, G. Zhao, R. Rios, A. Córdova, *Angew. Chem. Int. Ed.* **2007**, 46, 778. c) G. L. Zhao, R. Rios, J. Vasely, L. Eriksson, A. Córdova, *Angew. Chem. Int. Ed.* **2008**, 47, 8468.

[25] S. Bertelsen, P. Dinér, R. L. Johansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, 129, 1536.

[26] a) S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, 45, 4305. b) H. Gotoh, R. Masui, H. Ogino, M. Shoji, Y. Hayashi, *Angew. Chem. Int. Ed.* **2006**, 45, 6853.

[27] a) P. Dinér, M. Nielsen, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2007**, 46, 1983. b) D. Seebach, U. Grošelj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta*, **2008**, 91, 1999.

[28] H. Jiang, J. B. Nielsen, M. Nielsen, , K. A. Jørgensen, *Chem. Eur. J.* **2007**, 7, 9068.

[29] For general reviews, see for example: a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, 45, 7134. b) G. L. Zhao, R. Rios, J. Vasely, L. Eriksson, A. Córdova, *Angew. Chem. Int. Ed.* **2008**, 47, 8468. c) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, 441, 861. d) M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, 127, 15710.

[30] Inter alia: a) D. P. Curran, L. H. Kuo, *J. Org. Chem.* **1994**, 59, 3259. b) D. P. Curran, L. H. Kuo, *Tetrahedron Lett*. **1995**, 36, 6647.

[31] Inter alia: a) M. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, 120, 4901. b) E. J. Corey, M. Grogan, *Org. Lett*. **1999**, 1, 157.

[32] I. Ibrahem, R. Rios, J. Vasely, G. L. Zhao, A. Córdova, *Chem. Comm.* **2007**, 849.

[33] a) J. A. Zablocki, *J. Med. Chem.* **1995**, 38, 2378. b) W. J. Hoekstra, *J. Med. Chem.* **1999**, 42, 5254.

[34] a) E. Göβnitzer, A. Punkenhofer, A. Amon, B. Favre, *Eur. J. Pharm. Sci.* **2003**, 19, 151. b) N. Defacqz, R. Touillaux, A. Cordi, J. Marchand-Brynaert, *J. Chem. Soc. Perkin Trans. 1*, **2001**, 2632. c) R. Haftendorn, R. Ulbrich-Hofmann, *Tetrahedron* **1995**, 51, 1177.

[35] H. Jiang, N. Holub, M. W. Paixão, C. Tiberi, A. Falcicchio, K. A. Jørgensen, *Chemistry- A European Journal*, **2009**, 15 (38), 9638.

[36] S. Warren, P. Wyatt, in *Organic Synthesis: The Disconnection Approach*, Wiley-VCH, Weinheim, 2nd Ed., **2009**, Ch. 16, pp. 115.

[37] For recent examples, see: a) B. M. Trost, G. Dong, *Nature* **2008**, *456*, 485. b) K. C. Nicolaou, Y. Tang, J. Wang, *Angew. Chem. Int. Ed.* **2009**, *48*, 1.

[38] a) *Modern Acetylene Chemistry*, (Eds. P. J. Stang, F. Diederich), VCH, Weinheim, **1995**. b) L. S. Hegedus, in *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, USA, **1999**, and references herein. c) C. A. de Parrodi, P. J. Walsh, *Angew. Chem. Int. Ed.* **2009**, *48*, DOI: 10.1002/anie.200900900.

[39] a) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 2854. b) R. A. Shenvi, D. P. O'Malley, P. S. Baran, *Acc. Chem. Res.* **2009**, *42*, 530.

[40] For synthesis, see: a) T. Kanger, P. Niidas, A. Müürisepp, T. Pehk, M. Lopp, *Tetrahedron: Asymmetry* **1998**, *9*, 2499. b) F. Chemla, N. Bernard, F. Ferreira, J. F. Normant, *Eur. J. Org. Chem.* **2001**, 3295. c) R. S. Coleman, R. Carg, *Org. Lett.* **2001**, *3*, 3487. d) C. P. Burke, Y. Shi, *J. Org. Chem.* **2007**, *72*, 4093. e) D. Díaz, T. Martín, V. S. Martín, *J. Org. Chem.* **2001**, *66*, 7231. For application in total synthesis, see *e.g.*: f) C. Mukai, Y. Sugimoto, K. Miyazawa, S. Yamaguchi, M. Hanaoka, *J. Org. Chem.* **1998**, *63*, 6281. g) A. Fürstner, E. Kattnig, O. Lepage, *J. Am. Chem. Soc.* **2006**, *128*, 9194.

[41] M.Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K.A. Jørgensen, *J. Am. Chem. Soc.* **2005**, 127, 6964.

[42] a) S. Ohira, *Synth. Commun*. **1989**, *19*, 561. b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521. c) G. J. Roth, B. Liepold, S. Müller, H. J. Bestmann, *Synthesis* **2004**, 59.

[43] Recent review, see: a) M. Ogasawara, *Tetrahedron: Asymmetry* **2009**, 20, 259. For synthesis, see e.g.: b) A. Alexakis, L. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, 47, 1677. c) F. Chemla, N. Bernard, J. Normant, *Eur. J. Org. Chem.* **1999**, 2067. For application, see e.g.: d) J. A. Marshall, *J. Org. Chem*. **2007**, 72, 8153.

[44] M. Lee, M. Bernardo, S. O. Meroueh, S. Brown, R. Fridman, S. Mobashery, *Org. Lett.* **2005**, 7, 4463.

[45] For Barbier type reaction, see: a) A Yanagisawa, T Suzuki, T. Koide, S. Okitsu, T. Arai, *Chem. Asian J.* **2008**, 3, 1793, and references therein. For allenyl boration, see: b) A. Z. Gonzalez, J. A. Soderquist, *Org. Lett.* **2007**, 9, 1081.

[46] R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, 107, 874.

[47] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, 40, 2004.

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