Synthesis and Applications of Organic Selenols

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Abstract. The synthesis and the study of organoselenium compounds have received much attention over the past decades. Selenium-containing organic molecules are widely used in organic synthesis, materials science, and medicinal chemistry. Selenium – and more specifically the amino acid selenocysteine, bearing a selenol (SeH) moiety – is present in at least 25 human protein families, whose biological functions have not been completely identified. Amongst the variety of organoselenium compounds, selenols are a versatile class of molecules easily undergoing a broad array of useful transformations. Because of the unique properties of the SeH group, selenol chemistry has important applications in chemical sciences, spanning from organic synthesis to materials chemistry and biology. This review summarises currently available methodologies for the synthesis of selenols and highlights applications of selenols in chemical sciences and biology.

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Keywords: Selenols; Selenium; Organic synthesis; Selenides; Diselenides; Antioxidants; Glutathione peroxidase.

1. Introduction

Organoselenium compounds include a wide variety of molecules with broad application in organic synthesis, materials science, medicinal chemistry, and biology.[1-3] A growing repertoire of selenium-containing small molecules have been employed as catalysts, ligands, and unconventional synthetic intermediates for the construction of complex structures. For example, the total syntheses of lycorine,[4] (—)-galanthamine,[5] (+)-deoxypancratistatin,[6] (—)-haliclonin A[7] rely on the use of organoselenium chemistry. The redox chemistry of oganoselenium compounds has been widely exploited to develop an array of selenium-mediated oxidative functional group interconversions.[8-10]

Among the variety of organoselenium compounds, selenols – characterised by the presence of the selenol moiety (SeH) – are a versatile class of molecules with unique reactivity and properties. The features of the SeH moiety (*i.e.* acidity, nucleophilicity) enable selenols to be functionalised with a variety of electrophilic partners under mild reaction conditions to form new selenium-carbon or selenium-heteroatom bonds.

Despite the range of transformations that can be carried out with selenols, their synthetic application has been tempered for long time by their air sensitivity and the consequent paucity of general methodologies for their preparation. Compared to related thiols, selenols are significantly more prone to undergo oxidation, rapidly providing the corresponding diselenides. However, over the past years several reliable and direct routes for the synthesis of selenols have been described. The selenol protecting group chemistry also received attention, mainly in the field of solid phase peptide synthesis. [11] Such advances led to a deeper investigation of the chemical behaviour of selenols, enabling to explore new frontiers of selenium chemistry and biochemistry. Therefore, selenols have been efficiently employed in a broad range of highly selective transformations that would be hardly feasible using diselenides as precursors of nucleophilic selenolate anions. Densely functionalised organoselenium compounds, bearing labile groups and characterised by high molecular complexity, can be prepared exploiting the reactivity of selenols. Selenols are also employed as catalysts for the synthesis of peptide thioesters or peptide ligation from bis(2-sulfanylethyl)amido (SEA) peptides[12-13] Catalytic amounts of selenols were

demonstrate to have a beneficial effect on the chain propagation step of the radical fragmentation of β-lactones, thus enabling to improve the efficiency of the process.[14]

On the other hand, investigating the chemical behaviour of suitably substituted stabilised selenols is of paramount importance in order to elucidate the mechanism of selenoenzymes.

In a comparative study on the kinetic and the thermodynamic properties of selenocysteine (Sec) and cysteine (Cys), Nauser *et al*. highlighted how several reactions involving Sec occur faster (up to four order of magnitude) with respect to related transformations where Cys is involved.[15] Selenols are stronger acids and more active reducing agents than related thiols.[16] On the other hand, selanyl radicals – selenol one-electron oxidised products – are less oxidising than thiyl radicals. Selenoproteins are characterised by unique properties and offer significant advantages in terms of biological activity. Although the biosynthesis of selenocysteine has been described as "costly" and "inefficient,"[17] its incorporation into proteins in place of cysteine enables living systems to accomplish a variety of essential biological functions.

The enzymatic activity of mammalian selenoproteins such as glutathione peroxidase (GPx),[18,19] iodothyronine deiodinase,[20] and thioredoxin reductase (TrxR)[21] relies on the properties of a selenocystein residue and, more specifically, on the reactivity of its selenol moiety (or selenolate anion). For example, the two-step mechanism explaining the very fast reactivity of GPx relies on the acidity and nucleophilicity of the selenol moiety of the Sec residue present in the enzyme active site. The proton of the SeH group of Sec is shuttled to a tryptophan residue, highly conserved in the enzymatic pocket of all GPx and playing the role of proton acceptor. This proton-transfer reaction leads to a high energy zwitterionic form in which the nucleophilicity of the selenolate anion is enhanced with respect to the neutral selenol.[22]

In this paper, we review the methodologies that are currently available for the synthesis of aliphatic and aromatic selenols. Procedures where selenols – or related selenolates – are formed as intermediates without isolation have been omitted.[23] The transformations covered include i) reaction of alkyl halides with selenylating agents; ii) ring-opening reactions of strained heterocycles with selenylating agents; iii) reductive cleavage of diselenides and selenocyanates; iv) selenium insertion into carbon-metal bonds. Application of selenols to the synthesis of various selenium-containing small molecules as well as selenol-based probes, metal clusters, and complexes are also reviewed. Furthermore, the role of selenol chemistry in elucidating the biological activity of selenoenzymes, with particular emphasis to the mechanistic aspects, is presented in this article.

Damiano Tanini received his PhD degree in Chemistry in 2015 from the University of Florence. He carried out part of his doctoral research at the University of Bristol, working with Prof. V. K. Aggarwal. D. Tanini is currently a researcher in Organic Chemistry at the University of Florence. Very recently he received a positive evaluation to become Associate Professor. His research interests currently center on organic synthesis, ranging from the development of novel sustainable methodologies towards synthetic intermediates and bioactive molecules to the study of chalcogen-catalysed transformations and molecular chirality.

Antonella Capperucci was born in Florence and in 1987 she obtained her PhD in Chemistry at the University of Florence (Italy) working on the synthesis and the reactivity of thiocarbonyl compounds mediated by group 14 organometallic derivatives. She was a postdoctoral fellow at the University of Bordeaux (France) and Toulouse (France). In 1997 she began her carrier as researcher at the University of Florence, and in 2005 she was appointed Associate Professor. Very recently she received a positive evaluation to become Full Professor in Organic Chemistry. In recent years her scientific interests include the synthesis and selective functionalisation of silylated heterocyclic systems; the synthesis of chalcogenated organic derivatives (S, Se, Te), also mediated by organosilanes, and the study of their properties as novel antioxidant systems and enzyme modulators.

2. Synthesis of selenols

Selenols are often accessed by reduction of the corresponding diselenides or by introduction of the SeH moiety into organic skeletons under suitable controlled reaction conditions. Both selenols and diselenide precursors are commonly synthesised exploiting the reactivity of inorganic selenium nucleophiles, such as Na_2Se, NaHSe, Na_2Se_2, KSeCN, Li_2Se_2, K_2Se_2 with electrophiles. Among the variety of reducing agents available, sodium borohydride ($NaBH_4$) is arguably the reagent of choice to generate inorganic selenium nucleophiles from elemental selenium (Scheme 1). Aqueous solution of NaHSe can be prepared upon reaction of Se(0) with two molar equivalents of $NaBH_4$ in H_2O (Scheme 1, *equation a*).

(a) Generation of NaHSe from Se(0) and $NaBH_4$ in water

$$4NaBH_4 + 2Se + 7H_2O \longrightarrow 2NaHSe + Na_2B_4O_7 + 14H_2$$

(b) Generation of NaHSe from Se(0) and $NaBH_4$ in ethanol

$$NaBH_4 + Se + 3EtOH \longrightarrow NaHSe + B(OEt)_3 + 3H_2$$

(c) Generation of Na_2Se_2 from Se(0) and $NaBH_4$ in water

$$2NaHSe + Na_2B_4O_7 + 2Se + 5H_2O \longrightarrow 2Na_2Se_2 + H_3BO_3$$

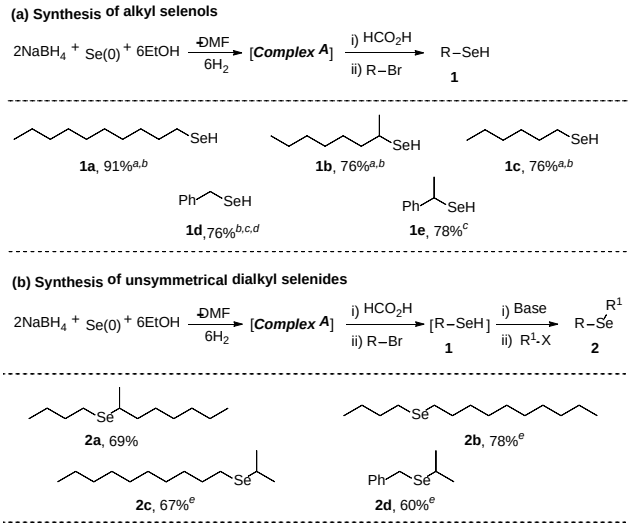
Scheme 1. Examples of generation of inorganic selenium nucleophiles through $NaBH_4$-mediated reduction of elemental selenium.

The comparison of the pK_1 and pK_2 of H_2Se with the pH of the obtained solution suggests that the concentration of hydrogen selenide ions (HSe^-) is much higher with respect to the concentration of selenide ions (Se^{2-}).[1] Aqueous NaHSe solution-based methodologies for the synthesis of dialkyl selenides have been developed. $NaBH_4$-promoted reduction reactions of elemental selenium in methanol or ethanol have also been reported. However, when methanol is used as the solvent a rapid selenium-triggered decomposition of borohydryde occurs and, therefore, large excesses of $NaBH_4$ are required to achieve complete Se(0) reduction. On the other hand, the borohydryde decomposition was found to be slower in ethanol and its reaction with Se(0) leads to the formation of NaHSe and triethyl borate (Scheme 1, eq. b).[24] Sodium diselenide was also generated by variating the stoichiometry of the reaction of elemental selenium with $NaBH_4$ (Scheme 1, eq. c). The reactivity of such inorganic selenium nucleophiles has been widely exploited to access selenides, selenols, and diselenides. For example, whereas treatment of aqueous NaHSe with benzyl chloride afforded dibenzyl selenide, benzeneselenol was achieved upon using the ethanolic NaHSe solution.[24]

2.1. Synthesis of aliphatic selenols

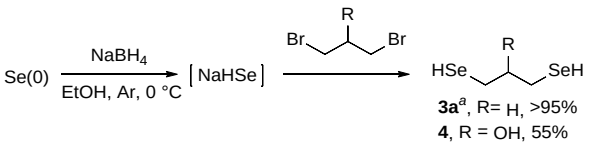
2.1.1. Selenols from alkyl halides and selenylating reagents

Krief and co-workers reported a convenient one pot procedure for the synthesis of aliphatic selenols by using readily available alkyl halides, elemental selenium and sodium borohydride.[25] A selenide complex (Complex A, Scheme 2, eq. a), formed *in situ* upon treatment of Se(0) with two molar equivalents of $NaBH_4$ in the presence of six equivalents of ethanol, was sequentially reacted with formic acid and alkyl halides, to afford the corresponding selenols in good yields (Scheme 2, *equation b*).



Scheme 2. Synthesis of alkyl selenols and unsymmetrical dialkyl selenides. Selected examples. [a]2.5 eq. of HCO_2H were used; [b]2-8% of the corresponding diselenides (RSeSeR) were detected; [c]4.0 eq. of HCO_2H were used; [d] benzyl chloride was used; [e]10-15% of symmetrical selenides (RSeR) were detected.

The method shown in the Scheme 2 was also exploited for developing a multistage approach towards unsymmetrical dialkyl selenides. Selenols **1** were indeed deprotonated by using an excess of a base (NaOH or NaH) to form the corresponding selenolates, which were *in situ* reacted with alkyl halides to afford unsymmetrical dialkyl selenides **2** (Scheme 2).



Scheme 3. Synthesis of diselenols **3a** and **4** from 1,3-dibromopropane and 1,3-dibromo-2-propanol. [a]Formation of minor amount of selenodiselenol $HSe(CH_2)_3Se(CH_2)_3SeH$ was also observed [^{77}Se NMR ($CDCl_3$): δ = -14.49, 150.85 ppm; **3a**, ^{77}Se NMR ($CDCl_3$): δ = -18.22 ppm]. Significant decomposition was observed when purification of **3a** by distillation was attempted.

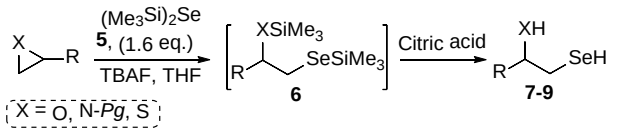
Song and co-workers reported a simple synthesis of diselenols **3a** and **4** by the reaction of 1,3-dibromopropane and 1,3-dibromo-2-propanol with sodium hydrogen selenide followed by acidification of the resulting solution with HCl and chloroform extraction. (Scheme 3).[26,27] Notably, 1,3-

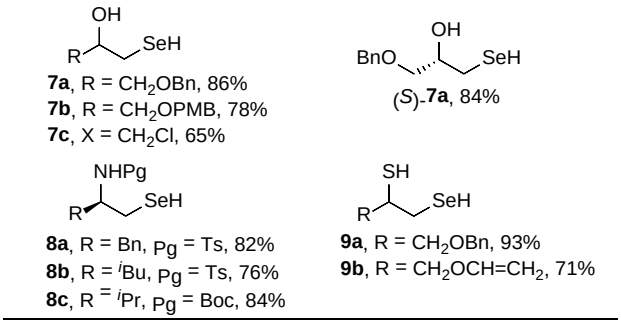
[1] Calculated [HSe^-]>99%; calculated [Se^{2-}]<0.5%. See reference [24]

propanediselenol **3a** was further employed for the preparation of new linear and macrocyclic (diphosphine)Ni-bridged butterfly Fe/Se cluster complexes.[27] However, in spite of their operational simplicity, methods relying on the NaHSe-acidification reaction sequence suffer from the drawback related to the formation of dangerous hydrogen selenide.

2.1.2. Selenols *via* nucleophilic ring-opening-reaction (NROR) of strained heterocycles

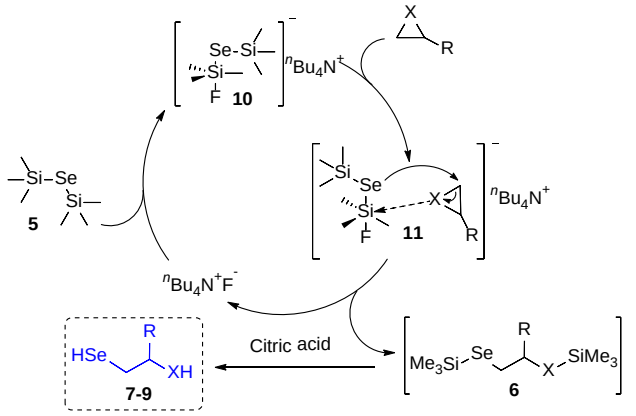
Besides alkyl halides, three-membered heterocycles have also been employed as electrophiles capable of reacting with selenylating reagents to provide the corresponding ring-opening-reaction products. A straightforward route for the synthesis of β-functionalised alkyl selenols through the reactivity of epoxides, aziridines, and thiiranes with bis(trimethylsilyl)selenide [$(Me_3Si)_2Se$, HMDSS] **5** has been recently reported. Under fluoride ion catalysis, differently substituted strained heterocycles smoothly react with HMDSS leading to the corresponding bis-silyl derivatives **6**, whose *in situ* citric acid-induced protodesilylation provides access to selenols **7-9** (Scheme 4). Notably, the NROR is highly regioselective and the nucleophilic attack of the selenosilane occurs at the less hindered carbon of monosubstituted epoxides, aziridines, and thiiranes. The mild reaction conditions and the broad functional group tolerance allow this methodology to be applied to the synthesis of a wide variety of alkyl-selenols bearing hydroxy-, amino-, or mercapto-functionalities. Chiral non racemic selenols could also be easily prepared upon ring-opening reaction of enantioenriched substrates. Bidentate selenols can also be employed for the synthesis of selenium-containing heterocycles.[28-30]





Scheme 4. Synthesis of β-functionalised selenols by nucleophilic ring-opening-reaction of strained heterocycles with bis(trimethylsilyl)selenide.

A plausible reaction mechanism involves the formation of silicon hypervalent species (Scheme 5). The silicon atom of the pentacoordinate species **10**, formed in the first step by coordination of the fluoride ion with the silicon atom of $(Me_3Si)_2Se$, interacts with the heteroatom of the strained heterocycle to generate the hexacoordinate complex **11**. Regioselective nucleophilic attack of the selenium atom provides the key bis-silyl intermediate **6** which, upon protodesilylation, is converted into the corresponding bidentate selenol. TBAF is released in the step leading to **6**, therefore providing explanation for the catalytic role played in this protocol.[28,31,32] The synthesis of few examples of β-hydroxyselenols through NROR of epoxides with hydrogen selenide (H_2Se) was also reported; however, the significant toxicity of the used selenylating agent represents the main drawback of such a route.[33]



Scheme 5. Proposed mechanism for the fluoride-induced silicon-mediated synthesis of selenols from strained heterocycles.

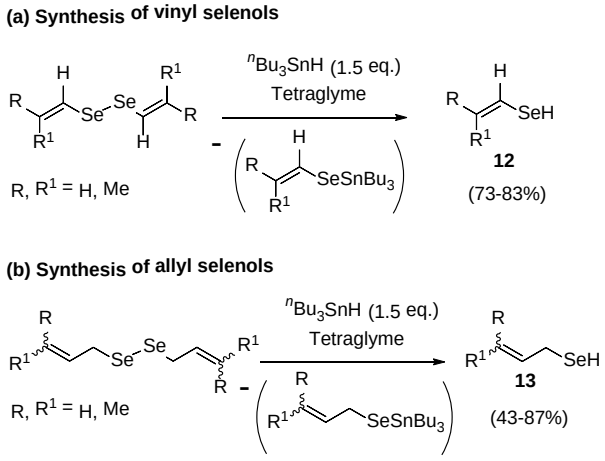
2.1.3. Selenols *via* reductive cleavage of diselenides and selenocyanates

As stated above, selenols can be prepared by reductive cleavage of diselenides or selenocyanates with a variety of reagents. Sodium borohydride is a reducing agent commonly employed for the conversion of diselenides (or selenocyanate) into the corresponding selenolates; subsequent treatment with an acid affords the selenol. Notably, this approach has also been used for the synthesis of selenocysteine through the reduction of the corresponding protected diselenide (*N*-Boc selenocystine *t*-butyl ester) followed by trifluoroacetic acid-promoted cleavage of both protecting groups.[34] The use of dithiothreitol (DTT) as an effective reducing agent for the conversion of diselenides into selenols has also been described.[35]

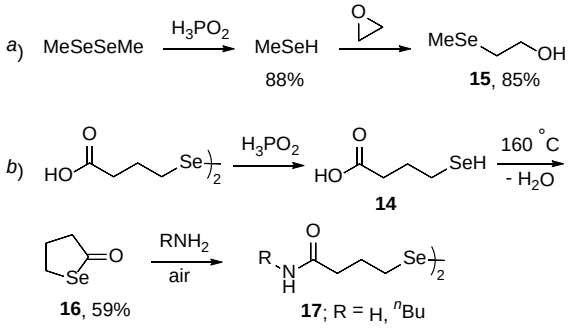
Bu_3SnH can be used as an effective reducing agent for the reduction of diselenides; However, the application of tributyltin hydride-based procedures to the synthesis of selenols is hampered by the quick reaction of the ─SeH moiety with the tin hydride, to

give the corresponding selenostannane. Guillemin and co-workers addressed this issue by continuously distilling *in vacuo* the formed selenols, before their reaction with the tin hydride. This procedure was applied to the synthesis of kinetically unstable vinyl selenols **12** *via* Bu_3SnH reduction of the corresponding diselenides (Scheme 6, *part a*).[36] Subsequently, this route was also extended to the synthesis of a number of alkenyl and alkynyl selenols, including allylic derivatives **13** (Scheme 6, *part b*).[37]

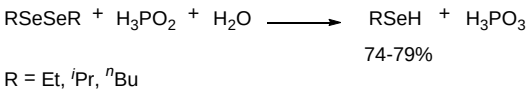
Hypophosphorous acid (H_3PO_2) has also been employed as a reducing agent to convert diselenides into the corresponding selenols. Back in 1966, Günther reported the synthesis of methylselenol (Scheme 7, *part a*) and 4-selenolbutyric acid **14** (Scheme 7, *part b*) by treating dimethyl diselenide or 4,4-diselenobutyric acid with H_3PO_2. The functionalisation of the selenol function enabled the synthesis of other selenium-containing small molecules, including 2-methylselenoethanol **15**, γ-selenolbutyrolactone **16**, and amides **17** (Scheme 7).[38] A related H_3PO_2-based approach was exploited by Schmidt and Block for the synthesis of ethyl-, isopropyl-, and butyl-selenols from the corresponding dialkyl diselenides (Scheme 8).[39]



Scheme 6. Synthesis of selenols *via* Bu_3SnH reduction of diselenides.

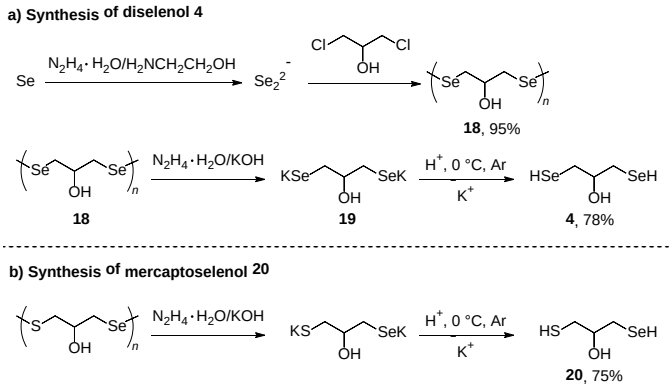


Scheme 7. H_3PO_2-based reduction of diselenides and functionalisation of the corresponding selenols.



Scheme 8. Reduction of diselenides with H_3PO_2.

As aforementioned, the reduction of diselenides represents one of the most commonly employed routes to access selenols. Levanova *et al*. reported the synthesis of diselenols through the hydrazine-mediated reduction of selenium-containing polymers and olygomers, obtained from suitable dihaloalkanes upon treatment with elemental selenium in hydrazine hydrate-alkali and hydrazine hydrate-amine systems.[40,41] For example, this strategy has been applied to the synthesis of selenium-containing isosteres of glycerol. The diselenol **4** was achieved upon acidification of the solution of the potassium diselenolate **19**, obtained by reducing the selenium-containing polymer **18** with the hydrazine hydrate/KOH system (Scheme 9, *part a*).[42] A related reduction-acidification sequence was exploited for the synthesis of **20**, bearing a mercapto-, an hydroxy-, and a selenol- moiety onto the same skeleton (Scheme 9, *part b*).[43]

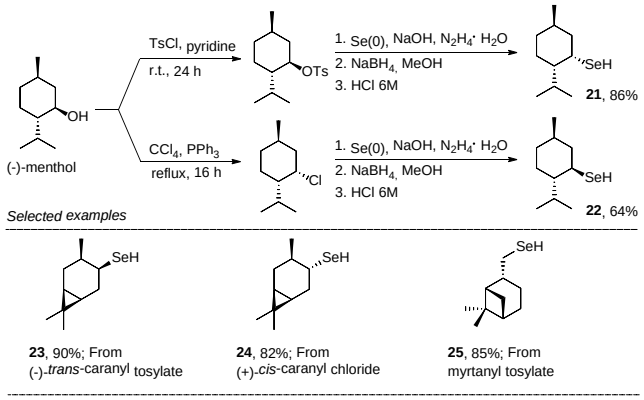


Scheme 9. Hydrazine-mediated synthesis of hydroxy-substituted diselenol **4** and mercaptoselenol **20**.

As highlighted above, Song and co-workers reported an alternative procedure for the synthesis of hydroxy-diselenol **4** by the reaction of 1,3-dibromo-2-propanol with sodium hydrogen selenide followed by acidification of the resulting solution with HCl and chloroform extraction. Although is simpler, such a method suffers from lower yield with respect to the reported procedure and leads to the formation of dangerous hydrogen selenide (Scheme 3).[26]

Scianowski and co-workers employed the hydrazine hydrate-alkali system to access terpene diselenides from elemental selenium and terpene chlorides or tosylates. Diselenide precursors were subjected to reduction with $NaBH_4$ and the resulting selenolates were subsequently treated with HCl to afford monoterpene-derived selenols.[44] Notably,

enantioenriched terpene alcohols were employed for the synthesis of two different stereoisomers of the corresponding selenols through a simple stereodivergent approach. Indeed, while the tosylation of the hydroxyl moiety occurs with retention of configuration, the Appel reaction leading to terpene chlorides proceeds with inversion of configuration (Scheme 10, upper). A variety of optically active selenols derived from monoterpenes have been achieved by using this procedure (Scheme 10, lower).

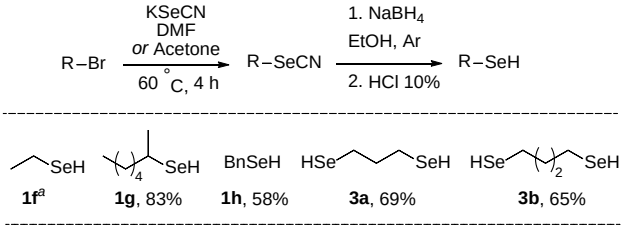


Scheme 10. Stereodivergent synthesis of menthol-derived selenols (upper) and selected examples of optically active monoterpene-derived selenols (lower).

Besides diselenides, selenocyanates also represent valuable precursors of selenols. Alkyl and alkenyl esters of selenocyanic acid are readily prepared upon treatment of the corresponding bromides or tosylates with potassium selenocyanate. On the other hand, vinyl selenocyanates can be synthesised from cyanogen bromide and suitable vinyl selenolates.[37]

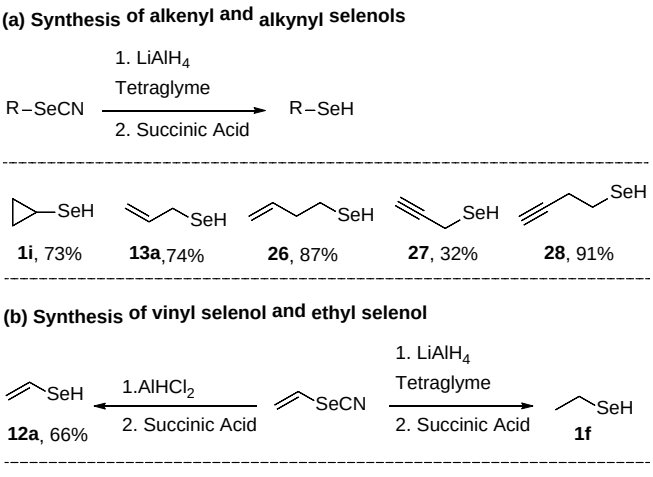
Krief *et al*. reported the synthesis of alkyl-substituted selenols through the reduction of the corresponding selenocyanates with $NaBH_4$ (Scheme 11). Such selenols, as well as benzeneselenol prepared by selenylation of phenylmagnesium bromide, were employed for the synthesis of a wide variety of valuable selenoacetals upon reaction with carbonyl compounds in the presence of Lewis acids such as $TiCl_4$, $ZnCl_2$ or BF_3•Et_2O.[45,46]

Reduction of selenocyanates with metal-hydrides and subsequent treatment of the so formed selenolates with succinic acid provides the corresponding selenols in good yield. This strategy has been employed by Guillemin and co-workers for the synthesis of cyclopropaneselenol,[47,48] alkenyl-[49] and alkynyl-[50] selenols, including allyl-[51] and propargyl-[52] selenols (Scheme 12). Notably, while the use of the lithium aluminium hydride-based procedure enables the conversion of a variety of selenocyanates into the corresponding selenols **1i, 13a, 26-28** (Scheme 12, *part a*), its application to the synthesis of conjugated selenols is hampered by the reduction of the double C=C bond of the starting selenocyanate, readily occurring in the presence of $LiAlH_4$ and leading to the formation of saturated systems (*i.e*. **1f**). However, the use of dichloroalane allows the selective reduction of the selenocyanate moiety, enabling to achieve α,β-unsaturated selenols, such as etheneselenol **12a** (Scheme 12, *part b*).[49] A related procedure was also employed to access allenyl selenols from the corresponding selenocyanates.[53]



Scheme 11. Synthesis of alkyl selenols and diselenols from selenocyanates, selected examples from Krief *et al*. [a]ethereal solutions of volatile selenols (*i.e*. ethaneselenol, *n*-butaneselenol and 2-propane-selenol) were used.

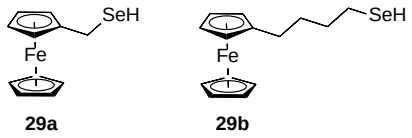
The conformational properties of such small-molecules have been extensively investigated through photoelectron spectroscopy, microwave spectroscopy and quantum chemical studies. Experimental and theoretical data revealed that weak intramolecular hydrogen bonding interactions, involving the SeH moiety and the π electrons of the multiple carbon-carbon bonds, play a significant role in stabilising these classes of unsaturated selenols.[49,52] The extent of conjugative interactions and hyperconjugative effects in alkynyl- and allenyl-derivatives have also been studied.[53]



Scheme 12. Synthesis of selenols *via* reduction of selenocyanates.

The reduction of selenocyanates with $NaBH_4$ was also harnessed by Henderson *et al*. to generate ferrocenylalkyl selenols **29a** and **29b** (Figure 1),

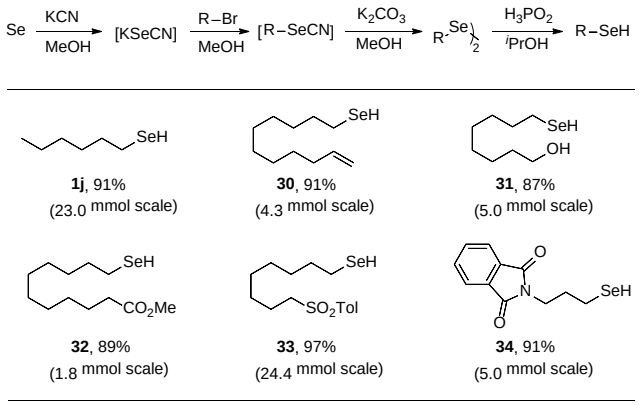
which were shown to be substantially air-sensitive and were always isolated together with significant amount of the related diselenides and selenides. Using ferrocenylalkyl diselenides as selenols precursors proved to be less effective with respect to the use of selenocyanates, leading to the formation of selenols only in traces. The air oxidation of **29b** was monitored by IR and NMR studies. Additionally, control experiments conducted using benzeneselenol showed that the ferrocenyl moiety cannot provide kinetic stabilisation towards the oxidation of the SeH functionality, rather being related to an increased selenol oxidation rate.[54]



29a **29b**

Figure 1. Ferrocenylalkyl selenols.

Recently, a four step telescoped process for the synthesis of 1,2-dialkyldiselenides and 1-alkaneselenols has also been reported.[55] Simple reactions requiring an easy and fast work-up were selected in order to address the issues related with the poor stability of selenols and the strong pungent odour of low-molecular-weight organoselenium derivatives. The optimised stepwise process (Scheme 13) involves the treatment of alkyl halides (or tosylates) with KSeCN, *in situ* generated from potassium cyanide and elemental selenium. The resulting selenocyanates are then converted into the corresponding diselenides, which are finally reduced to 1-alkaneselenols by using H_3PO_2 as reducing agent. Notably, the first three steps of the process were telescoped; all reactions were performed in methanol leading to the formation of diselenides without the isolation of any intermediate. Diselenides can be purified *via* distillation prior the reduction with H_3PO_2 or they can be directly reduced to selenols without distillation. In both cases, similar yield and purity of synthesised selenols were achieved.



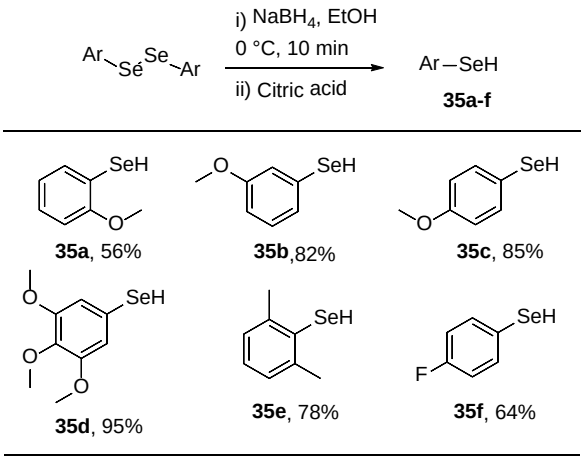
Scheme 13. Stepwise synthesis of 1-alkaneselenols.

2.2. Synthesis of aromatic selenols

Similarly to their alkyl analogues, aryl selenols are commonly synthesised by reduction of the corresponding diselenides or selenocyanates. Preparation of aryl selenols through the insertion of a selenium atom into carbon-lithium or carbon-magnesium bonds of organolithium and Grignard reagents has also been widely exploited. Furthermore, benzeneselenol can also be achieved upon reaction of (phenylseleno)silanes with hydrogen chloride gas bubbled into acetonitrile.[56]

2.2.1. Selenols *via* reductive cleavage of diselenides and selenocyanates

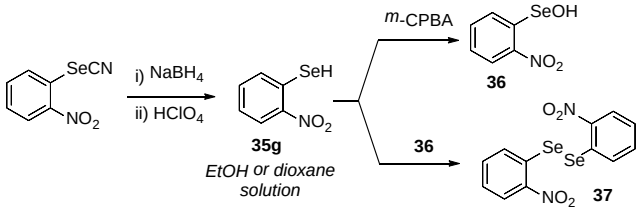
Differently substituted aryl selenols **35a-f** were easily prepared by reduction of the corresponding diselenides with $NaBH_4$ and subsequent treatment with citric acid as the proton source (Scheme 14). Notably, citric acid proved to be the more effective proton source amongst different inorganic and organic acids tested during the optimisation of the reaction conditions.[57]



Scheme 14. Synthesis of aryl selenols by reduction of diaryl diselenides. Selected examples.

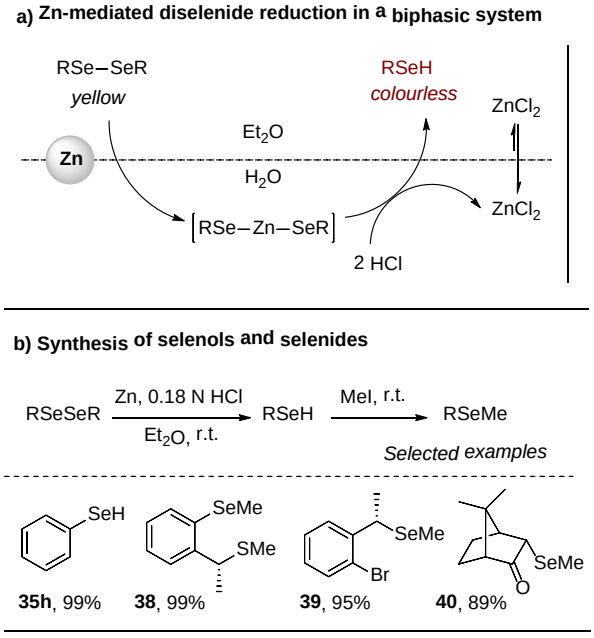
A related approach using $HClO_4$ as the proton source was also described. The preparation of *o*-nitrobenzeneselenol **35g** and the measurement of the rate constants for its oxidation into the corresponding diselenide and selenenic acid were reported by Kice and Chiou (Scheme 15).[58] Because the sensitivity of the selenol moiety to air oxidation hampered the isolation of *o*-nitrobenzeneselenol, the kinetic experiments were performed by studying the oxidation of solutions of *o*-nitrobenzeneselenol with *m*-chloroperoxybenzoic acid and *o*-nitrobenzeneselenenic acid **36**. Solutions of *o*-

nitrobenzeneselenol were prepared by treating *o*-nitrophenyl selenolate, achieved by reduction of the corresponding selenocyanate with sodium borohydride, with an excess of perchloric acid in the suitable solvent (ethanol or dioxane).



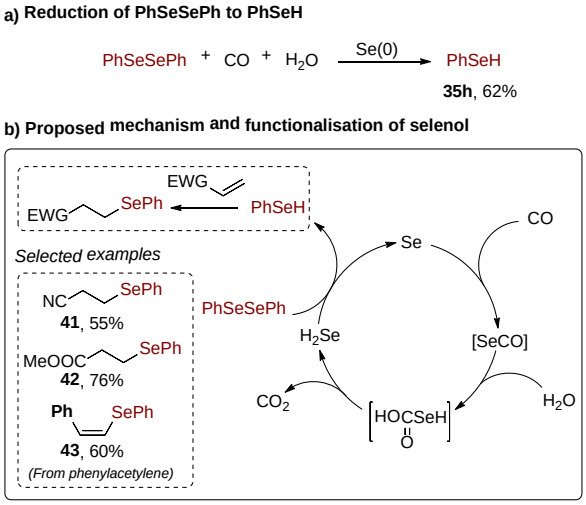
Scheme 15. Synthesis of *o*-nitrobenzeneselenol **35g** and its oxidation to *o*-nitrobenzeneselenenic acid **36** and dislenide **37**.

Santi and co-workers developed a zinc-mediated procedure to convert diselenides into the corresponding selenols in a biphasic system (H_2O/Et_2O) under acidic conditions (Scheme 16, *part a*). Selenols obtained through this methodology were either isolated or reacted *in situ* with electrophiles to afford the corresponding selenides **38-40** (Scheme 16, *part b*).[59]



Scheme 16. Zinc-mediated reduction of diselenides and its application to the synthesis of selenols and selenides.

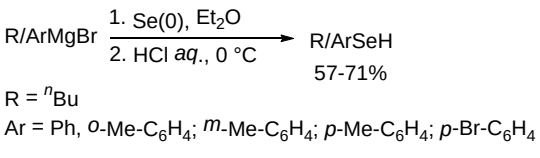
Selenium, carbon monoxide and water were also employed as an alternative reduction system to convert diphenyl diselenide into benzeneselenol **35h**. The so obtained selenol can be isolated (Scheme 17, *part a*) or *in situ* functionalised with activated olefins to afford the corresponding unsymmetrical selenides **41-43** (Scheme 17, *part b*). A possible mechanism of the diselenide reduction (Scheme 17, *part b*), involves the formation of carbonyl selenide (COSe) as precursor of hydrogen selenide (H_2Se), which likely reacts with a selenium atom of the diselenide leading to the formation of the corresponding selenol.[60]



Scheme 17. Reduction of diselenides using selenium, carbon monoxide and water. Synthesis and functionalisation of benzeneselenol.

2.2.2. Selenols from Grignard reagents and organolithium compounds

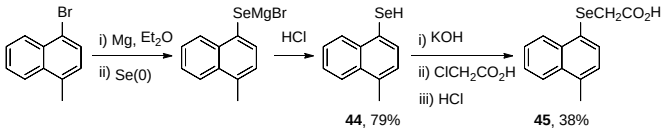
Selenols can also be achieved upon treatment of Grignard reagents with elemental selenium followed by treatment with acids. Foster reported the synthesis of benzeneselenol, selenocresols, *p*-bromoselenophenol, and butyl selenol by using this methodology (Scheme 18).[61]



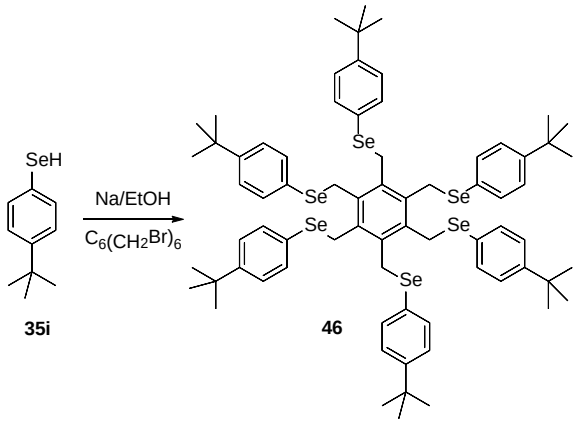
Scheme 18. Synthesis of selenols from Grignard reagents.

Foster's methodology was also employed by Yıldırır and co-workers to access 4-methyl-1-naphthylselenol **44**, which was further functionalised with chloroacetic acid to afford the corresponding Se-alkylated derivative **45** (Scheme 19).[62] Hardy *et al*. applied a related Grignard-based approach to prepare 4-(*tert*-butyl)benzeneselenol **35i**, a key intermediate for the synthesis of the hexasubstituted benzene **46** (Scheme 20) which, upon recrystallisation from different solvents, provided different inclusion compounds.[63]

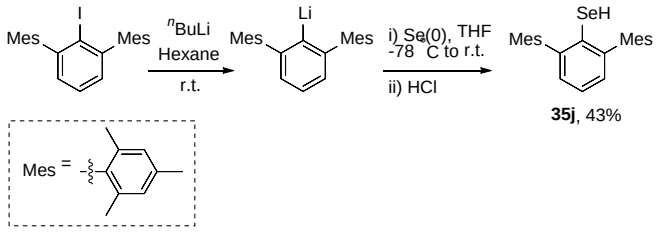
Selenols can also be accessed from organolithium compounds through the insertion of selenium atoms into the C-Li bond and subsequent reduction of the resulting polyselenides with $LiAlH_4$. Beckmann *et al*. employed this approach to prepare the selenol **35j**, bearing the 2,6-dimesitylphenyl moiety (Scheme 21), which was used as precursor of the corresponding diselenide to afford the thermally stable radical cation $[(2,6\text{-}Mes_2C_6H_3Se)_2]^{\bullet+}$, isolated as $[SbF_6]^-$ salt.[64]



Scheme 19. Synthesis and alkylation of 4-methyl-1-naphthylselenol.



Scheme 20. 4-(*tert*-butyl)Benzeneselenol **35i** and hexakis (*p-tert*-butyl-phenylselenomehtyl)benzene **46**.

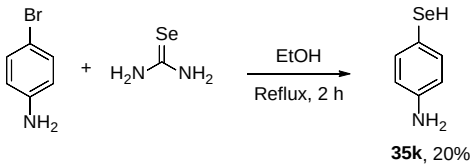


Scheme 21. Synthesis of selenol **35j** by insertion of selenium atoms into the C-Li bond.

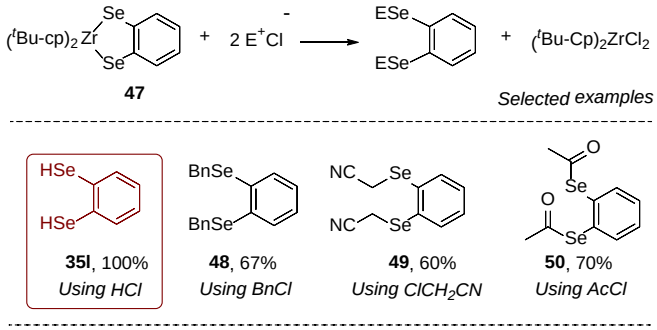
2.2.3. Other methodologies for the synthesis of aromatic selenols

Sanmartín *et al*.reported an alternative route for the synthesis of 4-aminobenzeneselenol **35k**, which was achieved in moderate yield by refluxing a 1:1.1 mixture of 4-bromoaniline and selenourea in ethanol (Scheme 22).[65]

Benzene *o*-diselenol **35l** was prepared by electrophilic cleavage of the complex **47**, synthesised from selenium and ^{t}Bu-zirconocene diphenyl, with HCl (Scheme 23). Notably, the reactivity of the complex **47** with other electrophiles was also exploited to access differently Se,Se'-disubstituted derivatives, including selenides and selenolesters (Scheme 23).[66]



Scheme 22. Synthesis of 4-aminobenzeneselenol **35k** from 4-bromoaniline and selenourea.

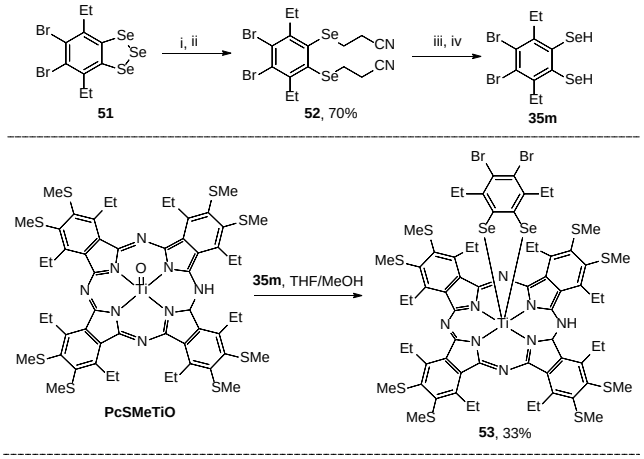


Scheme 23. Cleavage of Zr-Se bonds of complex **47** with electrophiles.

Kimura and co-workers reported the preparation of the benzenediselenol **35m** from the corresponding cyanoethyl selenide **52** through the CsOH-promoted cleavage of the C-Se bond, followed by treatment with HCl. Bis(aryl-alkyl)selenide **52** could be efficiently achieved by reduction and alkylation of the benzotriselenole **51** (Scheme 24). Although diselenol **35m** was not isolated and characterised, its methanolic solution was efficiently employed for the synthesis of a new phthalocyanine-derived complex. The synthesis of octakis(methylthio)octaethylphthalocyaninato titanium (IV) benzenediselenolate **53** from Octakis(methylthio)octaethylphthalocyaninato titanium (IV) oxide (**PcSMeTiO**) is reported in the Scheme 24.[67]

The formation of selenols (RSeH) is sometimes accompanied by variable amounts of related diselenides (RSeSeR) or selenides (RSeR). In this context, ^{77}Se NMR spectroscopy is a valuable diagnostic tool in order to clearly discriminate among these derivatives; the resonance frequency of the selenium atom of selenols is indeed significantly shielded with respect to that of related selenides and diselenides. ^{77}Se NMR chemical shift values are

strongly influenced by the nature of substituent close to the selenium atom. Typical ^{77}Se NMR chemical shift values of selenols are generally observed in the range δ_{Se} −100 ppm (aliphatic selenols) and δ_{Se} 200 ppm (aromatic selenols). Similarly, the resonance frequency of the SeH proton is generally shifted upfield with respect to protons attached to other heteroatom (*i.e.* O, S, N). Although significant differences can be observed, ^{1}H NMR chemical shift values of the SeH group are typically comprised in the range δ_{H} −0.95 ppm (aliphatic selenols) and δ_{H} 1.80 ppm (aromatic selenols).[28,32,57,68-71]



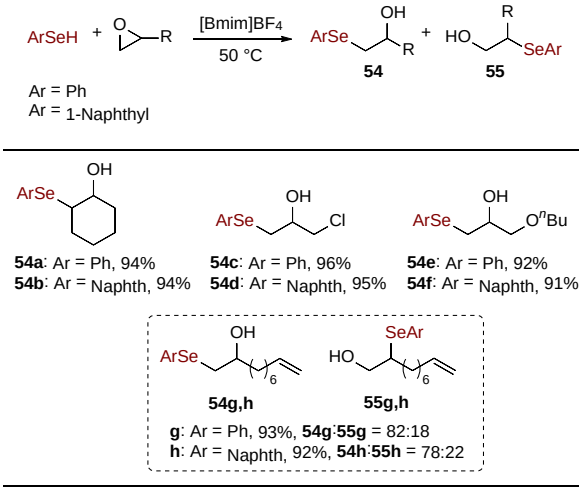
Scheme 24. Synthesis of diselenol **35m** and complex **53**. Reagents and conditions: i) $NaBH_4$, K_2CO_3, THF/MeOH; ii) $BrCH_2CH_2CN$; iii) CsOH, THF/MeOH; iv) HCl.

3. Synthetic applications of selenols

Owing to the acidity of the SeH moiety (pK_a of benzeneselenol = 5.9; pK_a of benzenethiol = 6.62), selenols can be easily deprotonated by weak bases providing nucleophilic selenolate anions under mild reaction conditions. This feature, coupled with the exquisite nucleophilicity of the SeH group, enables selenols to be successfully employed in a variety of reactions involving a diverse array of electrophilic partners. The redox chemistry of selenols, and particularly the properties of the selenol-diselenides couple, have been harnessed to accomplish reductive functional group transformations. Selenol-catalysed reactions, including redox transformations and interchange reactions of dithiols and disulfides, have also been investigated.[35] Furthermore, owing to the electronic and steric features of selenium, the chemistry of selenols has been widely exploited for the synthesis of polymers, metal complexes, and selenolated metal nanoclusters.

3.1. Synthesis of selenium-containing small molecules

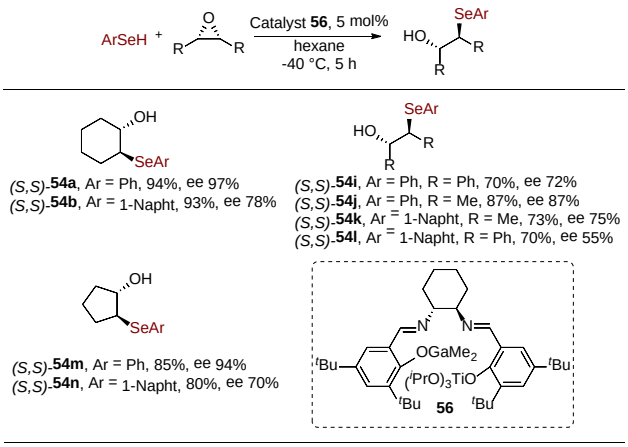
Taking advantage of the nucleophilicity of selenols, a broad array of methodologies for the synthesis of functionalised selenium-containing small molecules have been reported over the past years. Yang and co-workers reported the preparation of β-hydroxy selenides through the $[Bmim]BF_4$ regioselective ring-opening-reaction of epoxides with aryl selenols. Benzeneselenol and naphthalene-1-selenol were employed as effective nucleophiles with different epoxides enabling the efficient synthesis of the corresponding β-arylseleno alcohols **54a-h**, arising from the attack of the selenium atom on the less hindered carbon of the three-membered heterocycle. In the case of the ring-opening of 1,2-epoxy-9-decene, **54g** and **54h** were achieved in a regioisomeric mixture with compounds **55g** and **55h** formed by nucleophilic attack of the selenol on the more substituted carbon of the epoxide (Scheme 25).[72]
The reactivity of selenols with strained heterocycles has also been exploited for the enantioselective desymmetrisation of *meso*-epoxides. Zhu and co-workers reported an heterobimetallic gallium-titanium-salen complex-catalysed asymmetric ring-opening reaction of *meso*-epoxides with aryl selenols. The reaction proceeds with good yield and high enantioselectivity enabling the synthesis of a enantioenriched β-hydroxy selenides (*S,S*)-**54** (Scheme 26).[73,74] A scandium-bipyridine-catalysed enantioselective NROR of aryl-substituted *meso*-epoxides was also developed by Schneider *et al*. Notably, a related sequential *one-pot* ring-opening-reduction protocol allowed the conversion of aryl *meso*-epoxides into enantioenrched 1,2-diaryl carbinols **57** *via* deselenylation of β-hydroxy selenide intermediates (*R,R*)-**54** (Scheme 27).[75]



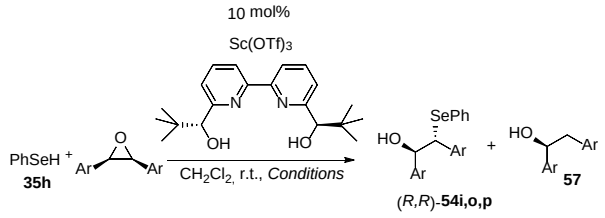
Scheme 25. Ring-opening reaction of epoxides with selenols in $[Bmim]BF_4$. Selected examples from Yang and co-workers.

Kreft *et al*. reported the use of benzeneselenol in the ring-opening reaction of donor-acceptor cyclobutanes bearing two geminal ester groups as acceptors. $AlCl_3$–promoted reaction of **58** with benzeneselenol

enabled the synthesis of the γ-phenylseleno-substituted diester **59** in good yield (Scheme 28).[76]
As stated above, selenols can be easily deprotonated by to generate nucleophilic selenolate anions. Reaction of such selenolates with electrophiles represents an attractive route to form new selenium-carbon bonds. Salvatore and colleagues reported the synthesis of unsymmetrical phenyl-alkyl selenides through the CsOH-promoted alkylation of benzeneselenol with different alkyl halides or mesylates. Although the study is limited to benzeneselenol, such a procedure – which was also carried out on solid support – represents an efficient and direct route towards unsymmetrical organoselenides.[77]



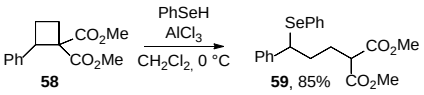
Scheme 26. Heterobimetallic gallium-titanium-salen complex-catalysed asymmetric ring-opening reaction of *meso*-epoxides with aryl selenols.



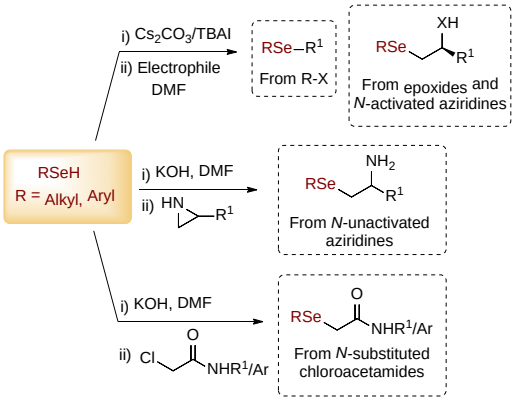
Entry	Ar	Conditions	(*R*,*R*)-**54** (%)	**57** (%)
1	Ph	A	77 (93% *ee*)	<5 (92% *ee*)
2	4-F-C_6H_4	A	51 (93% *ee*)	16 (80% *ee*)
3	3-Me-C_6H_4	A	51 (94% *ee*)	18 (82% *ee*)
4	Ph	B	7 (94% *ee*)	63 (90% *ee*)
5	4-F-C_6H_4	B	6 (93% *ee*)	60 (75% *ee*)
6	Ph	B	<5 (94% *ee*)	64 (92% *ee*)

Scheme 27. Schneider and co-workers' enantioselective scandium-bipyridine catalysed reaction of selenols with aromatic *meso*-epoxides. *Conditions A*: reaction in the dark with degassed solvent; addition of 1.5 eq. of PhSeH at the start of the reaction, followed by the addition of 3 x 0.5 eq. of PhSeH over 8 h. *Conditions B*: reaction under daylight, addition of 2.0 eq. of PhSeH at the start of the reaction, followed by the addition of other 2.0 eq. after 24 h.

A weak base such as Cs_2CO_3 can be employed to generate selenolates under mild conditions. The use of TBAI (tetrabutylammonium iodide) as the phase transfer catalyst (PTC) was found to improve the rate of the deprotonation reaction. Selective Se-alkylation was achieved upon treatment of the so generated selenolates with alkyl halides or strained heterocycles (Scheme 29).[28,78] Epoxides and *N*-protected aziridines were also employed as electrophiles, leading to the formation of functionalised unsymmetrical dialkyl selenides through a regioselective nucleophilic ring-opening path. Unactivated *N*-unsubstituted aziridines were also converted into the corresponding unsymmetrical amino-substituted selenides by NROR with selenolate anions, *in situ* generated from selenols and KOH (Scheme 29). A related approach was employed for the synthesis of differently substituted seleno-acetamides through Se-alkylation of selenols with 2-chloroacetamides (Scheme 29). These Se-alkylation routes were also harnessed to access biologically valuable selenium-containing carbonic anhydrases inhibitors **60**[79,80] and activators **61**[81] (Figure 2).



Scheme 28. Ring-opening reaction of donor-acceptor cyclobutane **58** with benzeneselenol.



Scheme 29. Functionalisation of selenols with electrophiles.

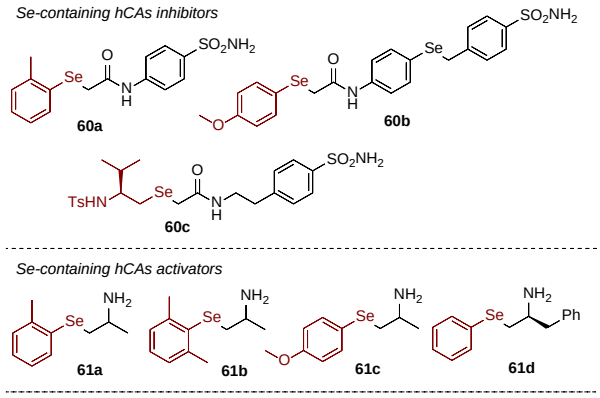
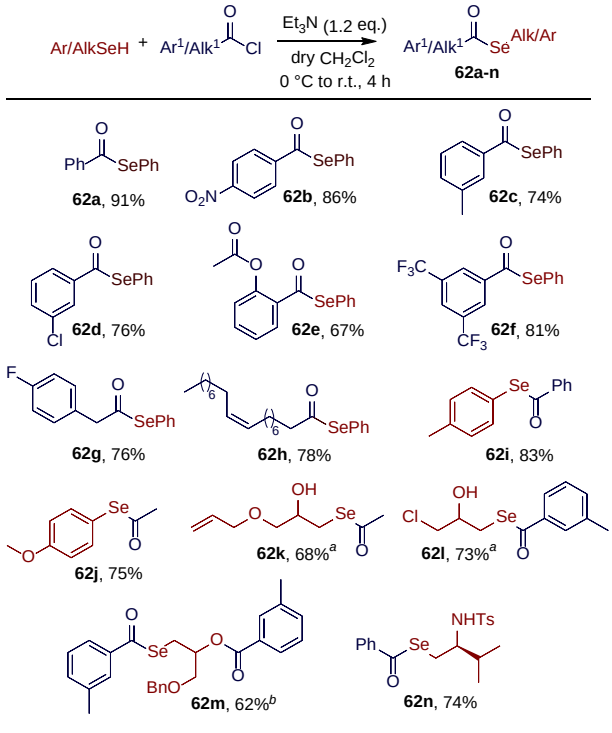


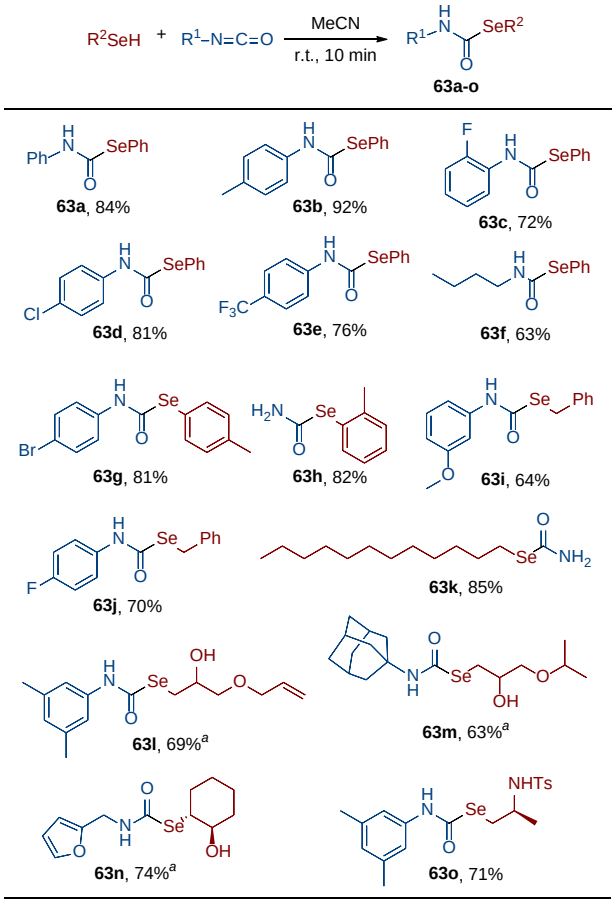
Figure 2. Selenium-containing human carbonic anhydrases (hCA) inhibitors and activators synthesised from selenols.

Selenols can be easily converted into selenolesters upon reaction with acyl chlorides in the presence of Et_3N. Owing to the acidity of the SeH group, selenols readily undergo Et_3N-promoted deprotonation to afford the corresponding selenolates, whose *in situ* Se-acylation with acyl chlorides provides a mild entry to selenolesters **62**. This approach is amenable to aromatic and aliphatic selenols, including systems bearing hydroxy- and amino- functionalities (Scheme 30).[82] Notably, selenolesters can be employed as potential prodrugs capable of releasing biologically active selenols.[83] For example, the carbonic anhydrase-mediated hydrolysis of the selenolester moiety enables the releasing of selenol fragments acting as effective CA inhibitors. Through this mechanism, compounds reported in the Scheme 30 were demonstrated to behave as novel prodrug inhibitors with potential pharmacological applications.[82]



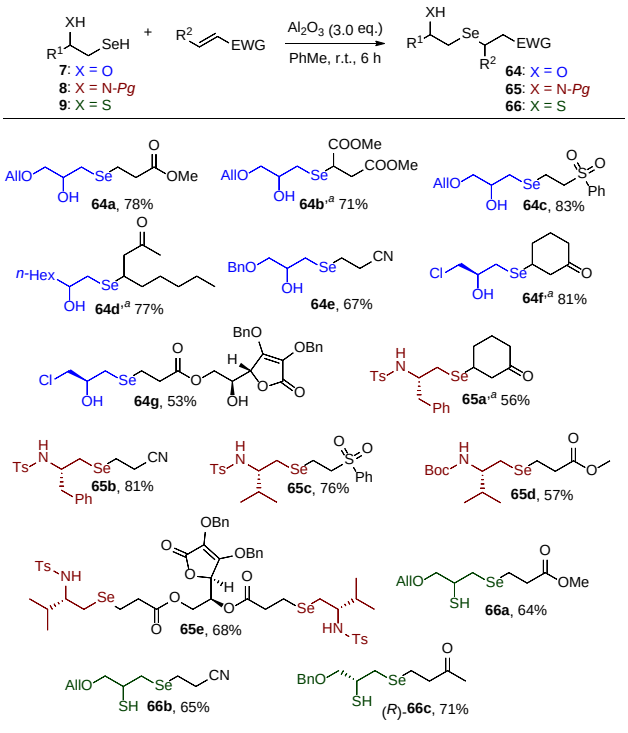
Scheme 30. Synthesis of selenolesters from selenols and acyl chlorides. Selected examples. [a]0.8 equiv. of acyl chloride were used. [b]2.5 equiv. of acyl chloride were used.

Isocyanates have also been efficiently employed as electrophilic partners in reactions with selenols. Notably, isocyanates exhibited a remarkable selenophilicity which, coupled with the reactivity of selenols, was exploited for the development of a click catalyst-free route to selenocarbamates **63** (Scheme 31). Both aromatic and aliphatic selenols smoothly react with a variety of differently substituted isocyanates providing rapid access to the corresponding coupling products. Owing to the mild reaction conditions, the methodology demonstrated broad functional group tolerance and high selectivity, thus enabling the synthesis of polyfunctionalised systems. Notably, selenocarbamates bearing hydroxy- and amino- functionalities **63l-o** were efficiently obtained through the selective carbamoylation of the SeH group (Scheme 31).[84] Selenocarbamates exhibit remarkable thiol-peroxidase-like catalytic properties. Studies on the reaction mechanism suggested an unprecedented path involving a peroxide-driven transcarbamoylation reaction engendering catalytically active selenolate anions. Therefore, because of the reactivity of their selenium-carbon bond, selenocarbamates act as unconventional equivalents of selenolate anions.[84]



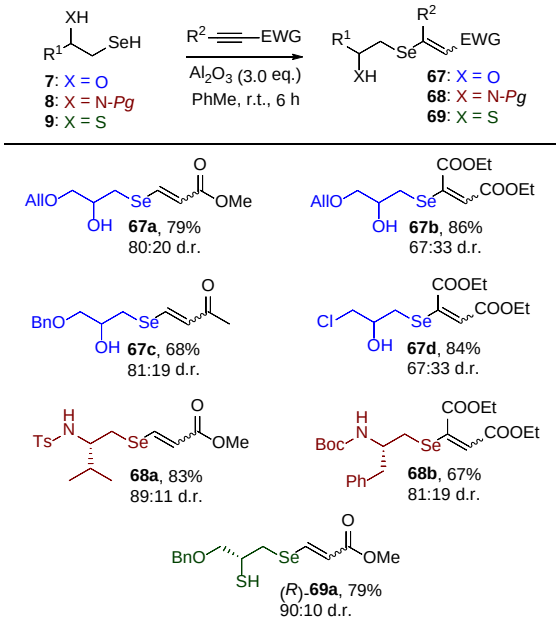
Scheme 31. Click reaction of selenols with isocyanates to afford selenocarbamates. Selected examples. [a]Racemic.

Selenols efficiently react with electron-poor alkenes providing access to the corresponding seleno-Michael adducts. Owing to the nucleophilicity of the selenol moiety such a conjugate addition can be performed under mild conditions, thus enabling the selective Se-functionalisation of substrates bearing potentially competing nucleophiles. A wide variety of polyfunctionalised unsymmetrical selenides **64-66** were smoothly achieved upon reaction of differently substituted β-hydroxy-, β-amino-, and β-mercapto-selenols **7-9** with electron-deficient alkenes. The reaction exhibited broad functional group tolerance, demonstrated over a range of selenols and Michael acceptors. The methodology is indeed amenable to α,β-unsaturated alkenes bearing ester, keto, sulfone, cyano functionalities. Useful but labile moieties such as a chlorinated chain and the L-ascorbic acid core can be introduced through this conjugate addition by using suitably substituted partners. Enantioenriched unsymmetrical selenides can be easily prepared by using the corresponding enantioenriched selenols (Scheme 32). Although both Al_2O_3 and Et_3N could be employed to promote the seleno-Michael addition, the use of Al_2O_3 generally led to higher selectivity, especially when challenging mercapto-selenols or highly labile substrates were employed.[85] Such functionalised unsymmetrical selenides can be efficiently transferred onto the L-ascorbic acid core through a biocatalysed approach, thus enabling the mild synthesis of new vitamin C-derived semisynthetic hybrids with remarkable antioxidant properties.[86]

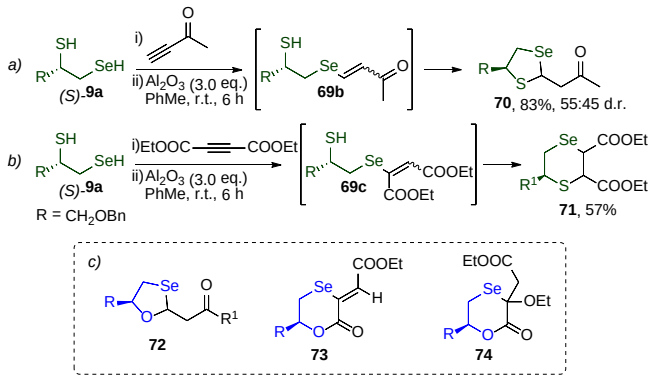


Scheme 32. Seleno-Michael addition of selenols to electron-poor alkenes. Selected examples. [a]Mixture of diastereoisomers.

The scope of this Al_2O_3-promoted conjugate addition was also extended to electron-deficient alkynes, providing access to variously substituted alkyl-vinyl selenides **67-69** bearing hydroxy-, amino-, and mercapto- functionalities (Scheme 33). Notably, substituted S,Se-containing heterocycles such as 1,3-thiaselenolanes **70** and 1,4-thiaselenanes **71** were easily obtained from β-mercapto selenols and electron-poor alkynes. Mercapto-substituted vinyl selenides **69b,c** smoothly undergo intramolecular thia-Michael addition affording the corresponding five- or six-membered heteroatom-containing ring system (Scheme 34, *part a* and *b*). Additionally, hydroxy-functionalised polysubstituted selenoalkenes can be employed as valuable precursors of O,Se-containing heterocycles of various ring size (**72-74**) *via* intramolecular lactonisation or conjugate addition reactions (Scheme 34, *part c*).[85]

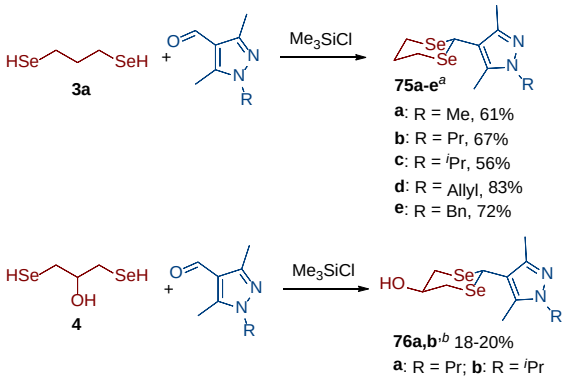


Scheme 33. Seleno-Michael addition of selenols to electron-poor alkynes.



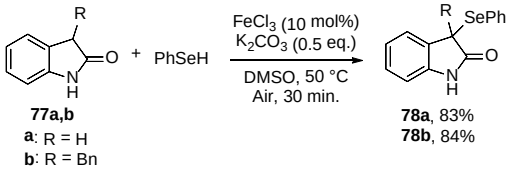
Scheme 34. Synthesis of Se-containing heterocycles using selenols.

Regarding the synthesis of selenium-containing heterocycles, bidentate ligands such as diselenols **3a-4** (*vide supra*) could be easily employed for the synthesis of 1,3-diselenanes upon reaction with aldehydes. 1,3-propanediselenol **3a** and its related 2-hydroxy-substituted derivative **4** were treated with formylpyrazoles in the presence of trimethylchlorosilane to afford the corresponding 2-(pyrazol-4-yl)-1,3-diselenanes **75a-e** and **76a,b**, respectively. Notably, the lower yields observed for 5-hydroxy-1,3-diselenanes **76** are reasonably due to both competitive oxidation of diselenol **4** to the corresponding 1,2-diselenolane and electronic effects induced by the hydroxyl moiety in **4**. Indeed, stabilizing the conformer bearing adjacent SeH functionalities, the presence of the hydroxyl group favours the formation of 1,2-diselenolan-4-ol at the expense of the desired diselenanes **76a,b**.[87]



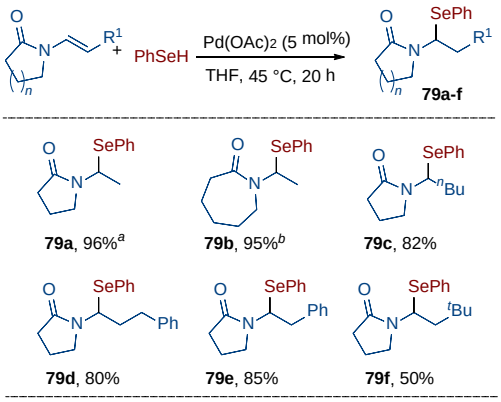
Scheme 35. Synthesis of 2-(pyrazol-4-yl)-1,3-diselenanes **75** and **76** from diselenols and aldehydes. [a]Up to 10% of 1,2-diselenolane arising from oxidation of **3a** was formed. [b]15-20% of 1,2-diselenolan-4-ol arising from oxidation of **4** was formed.

The synthesis of phenylseleno-substituted oxindoles **78** through the iron-catalysed cross-dehydrogenative coupling of oxindoles **77** with benzeneselenol was described by Huang *et al*. The reaction enables the direct and efficient formation of new C(sp^3)-Se bond under mild conditions (Scheme 36). The reaction reasonably proceeds through a SET mechanism and involves the formation of key indolin-2-one radical intermediates.[88]

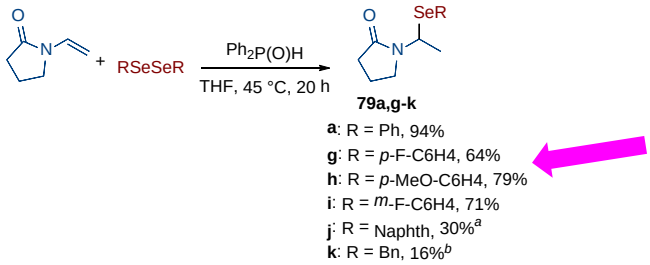


Scheme 36. Synthesis of phenylseleno-substituted oxindoles **78a,b** through the iron-catalysed cross-dehydrogenative coupling of oxindoles **77** with benzeneselenol.

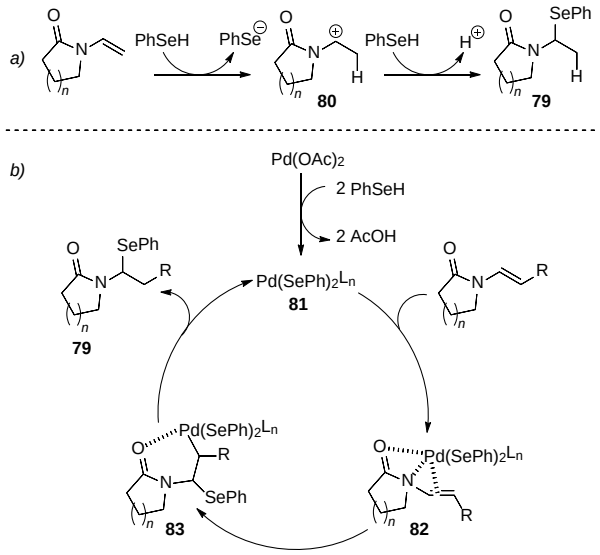
Ogawa and co-workers reported the synthesis of *N,Se*-acetals through the Markovnikov-selective hydroselenation of *N*-vinyl lactams with selenols. Owing to the acidity of the SeH moiety, terminal vinyl lactams react efficiently with selenols providing the corresponding *N,Se*-acetals as Markovnikov adducts **79a,b** in absence of any catalyst. On the other hand, palladium acetate is required in order to promote the hydroselenation of internal *N*-vinyl lactams **79c-f** with selenols (Scheme 37). Selenols could also be generated *in situ* from the corresponding diselenides upon reduction with diphenylphosphine oxide. *N*-Vinylpyrrolidone could be regioselectively converted into a variety of Markovnikov hydroselenation products **79a,g-k** (Scheme 38). In absence of catalysts, the first step of the reaction mechanism reasonably involves the protonation of the terminal *N*-vinyl lactam by the selenol. The cation **80**, stabilised by electron donation from the nitrogen atom, reacts with the selenol to afford the Markovnikov-type hydroselenation product **79** (Scheme 39, *part a*). On the other hand, when the reaction is performed in the presence of the palladium catalyst, the coordination of the *N*-vinyl lactam with the palladium-selenide-complex **81** – arising from the reaction of the selenol with $Pd(OAc)_2$ – leads to the formation of a palladium-selenide-alkene complex **82**. The complex **82** is stabilised by coordination of heteroatoms to the palladium atom. Regioselective selenopalladation affords the intermediate **83**, which undergoes protonation with the selenol providing the Markovnikov-type adduct **79** and regenerating the palladium-selenide complex **81** (Scheme 39, *part b*).[89]



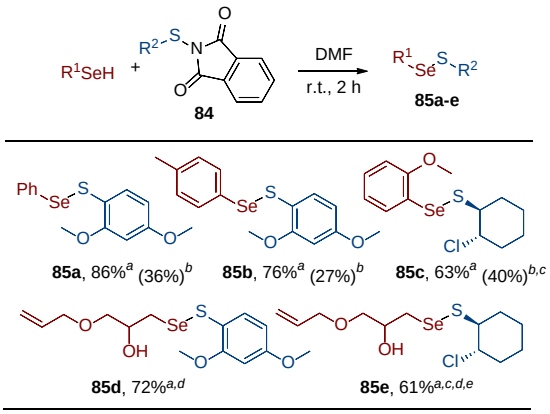
Scheme 37. Hydroselenation of *N*-vinyl lactams with benzeneselenol. [a]**79a** was achieved in 93% yield without $Pd(OAc)_2$; [b]**79b** was achieved in 57% yield without $Pd(OAc)_2$.



Scheme 38. Hydroselenation of terminal *N*-vinyl lactams with in situ generated selenols. [a]**79j** was achieved in 81% yield in the presence of $Pd(OAc)_2$; [b]**79k** was achieved in 78% yield in the presence of $Pd(OAc)_2$.



Scheme 39. Proposed mechanism for the hydroselenation of *N*-vinyl lactams with selenols in the absence of Pd-catalyst (*part a*) and in the presence of Pd-catalyst (*part b*).



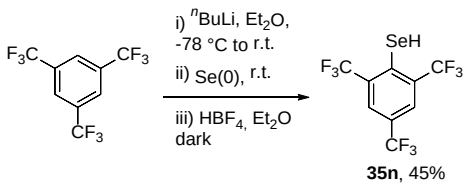
Scheme 40. Catalyst-free synthesis of selenenyl sulfides from selenols and *N*-thiophthalimides. Selected examples. [a]Conversion of selenol and *N*-thiophthalimide into the corresponding selenenylsulfide **85** is given. [b]Values in parentheses refer to isolated yields. [c]Racemic. [d]Complete transformation of the selenenyl sulfide into the corresponding diselenide and disulfide occurred during purification on silica gel. [e]Reaction performed in the presence of the Cs_2CO_3/TBAI system.

Besides their versatility in carbon-selenium bond forming reactions, selenols also behave as convenient reagents for the formation of selenium-heteroatom bonds. In this context, compounds bearing a selenium-sulfur bond (*i.e.* selenenyl sulfides)[90] are particularly important in biology. Indeed, the key intermediate involved in the biochemical mechanism of the GPx is postulated to be a selenenyl sulfide. Therefore, selenium-sulfur bond forming reactions represent a valuable tool in order to gain insight into the catalytic mechanism of GPx, elucidating the reactivity of selenenyl sulfides. We recently developed a catalyst-free mild route towards selenenyl sulfides by using selenols and *N*-thiophthalimides **84** as sulfur-centered electrophiles. This procedure is amenable to differently substituted selenols and *N*-thiophthalimides, enabling the formation of variously functionalised selenenyl sulfides **85a-e** (Scheme 40). Notably, although the scope of the reaction was found to be broad, partial or complete decomposition leading to disulfides and diselenides occurred during the purification on silica gel of most of the obtained selenenyl sulfides.[91] The synthesis of selenenyl sulfides upon reaction of selenols with thiols in the presence of chloramines has also been described.[92]

3.2. Synthesis of polymers and metal complexes

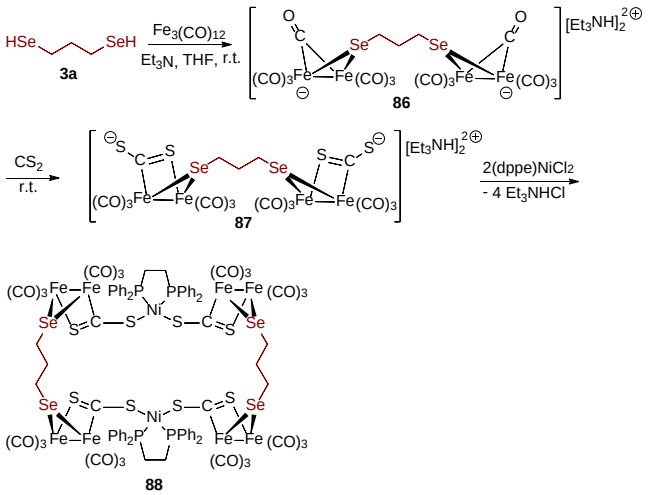
Schlecht *et al.* described the use of homoleptic lead(II) bis-(2,4,6-trifluoromethylphenylselenolate) $Pb[SeC_6H_2(CF_3)_3]_2$, prepared from the corresponding selenol **35n**, as single source precursor for the thermolytic formation of lead(II) selenide (PbSe). Polymer films of polyethylene oxide (PEO) or

poly(L-lactide) (PLLA) containing such a single-source precursor of PbSe were employed to prepare films of nanoparticles of these thermoelectric materials. The key selenol **35n** was prepared through lithiation-selenylation of 2,4,6-tris(trifluoromethyl)benzene, followed by treatment with tetrafluoroboric acid (Scheme 41).[93]

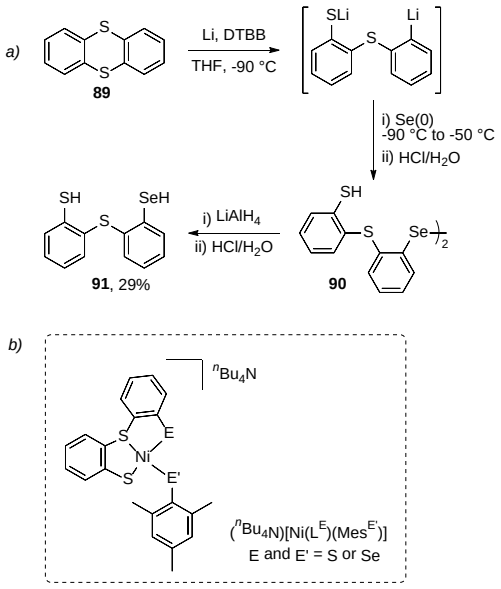


Scheme 41. Synthesis of selenol **35n** as single source precursor for the thermolytic formation PbSe.

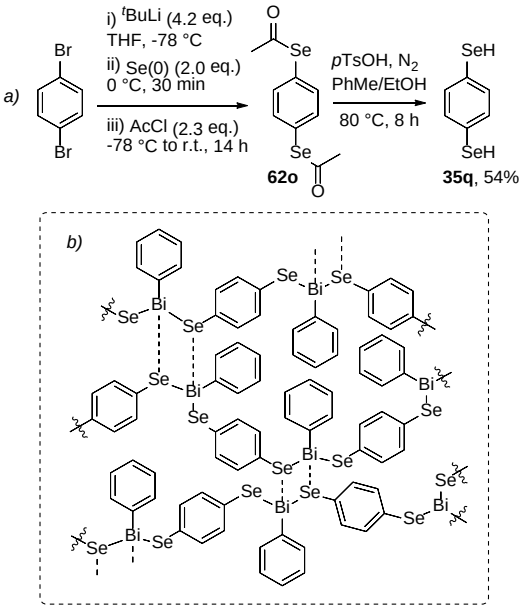
De Clerck *et al*. reported the synthesis of degradable diselenide-cross-linked nanofibers by aqueous electrospinning of *in situ* generated selenol-functionalised poly(2-oxazoline)s. The ring-opening reaction of γ-butyroselenolactone with the secondary amine functionalities of partially hydrolysed poly(2-ethyl-2-oxazoline-)-ω-ethylenimine was employed to prepare the key selenol-containing polymers. Interestingly, the morphology and the diameter of such diselenide-cross-linked nanofibers could be controlled by tuning the selenol group content.[94]
The reactivity of selenol intermediates, *in situ* generated through the aminolysis of styrene-derived diselenocarbonate-end capped polymers, was also harnessed for the synthesis of reactive oxygen species-responsive amphiphilic diblock copolymers. Sequential organoselenium-mediated reversible addition fragmentation chain transfer polymerization (Se-RAFT) was used to access diselenocarbonate polymer precursors. Aminolysis and Se-Michael addition reaction of selenol intermediates with poly(ethylene glycol) methyl ether methacrylate (PEGMA) enabled to accomplish suitable polymer chain end modifications for the development of new potential platform for drug delivery.[95] Notably, a variety of macromonomers could be synthesised through this approach, relying on the generation of selenol-ended polymers *via* Se-RAFT polymerisation-aminolysis sequence and further nucleophilic functionalisation.[96]
Benzeneselenol, butaneselenol and diselenol **3a** (*vide supra*) were employed for the preparation of new linear and macrocyclic (diphosphine)Ni-bridged butterfly Fe/Se cluster complexes.[27] For example, the quadruple butterfly **88** could be achieved through the one pot sequential reactions of the diselenol **3a** with $Fe_3(CO)_{12}$ and Et_3N followed by treatment of the corresponding dianion **86** with CS_2 and dichloro(1,2-bis(diphenylphosphino)ethane)nickel. As the procedure used for the synthesis of **3a** led also to the formation of selenodiselenol $HSe(CH_2)_3Se(CH_2)_3SeH$, the latter was also employed for the synthesis of [1+1] type of double butterfly macrocyclic complexes. Explanation for the formation of the two different types of macrocycles is proposed considering the length influence of the organic chain between the two μ-Se atoms of dianions (*i.e.* **87** in the synthesis of **88**). Notably, different diphosphine-chelated $NiCl_2$ species could be used for the preparation of different macrocyclic Ni-bridged quadruple- and double-butterfly clusters.[27]
Wombwell and Reisner employed the mercapto-substituted selenol **91** as a tridentate mixed donor ligand for the synthesis of structural models of the Ni site of reduced [NiFeSe] hydrogenases (Scheme 43, *part b*). The key selenol **91** was prepared from thianthrene **89** as reported in the Scheme 43 (*part a*). A catalytic amount of 4,4'-di-*tert*-butylbiphenyl and two equivalents of lithium gave a radical anion strong enough to cleave a C-S bond of **89**. Insertion of selenium into the C-Li bond, followed by acidic workup, provided the diselenide **90**, which was reduced to **91** by using $LiAlH_4$.[97]
Selenols **35o** and **35p**, prepared from the corresponding arylmagnesium bromides and elemental selenium (*vide infra*), were employed for the synthesis of selenium-containing metal complexes. Zhou *et al*. used **35o** as key precursor of a suitable hydridonickel complex which, upon insertion with alkynes provided vinylnickel and nickelacyclopropane complexes containing a chelate [P,Se] ligand **92** (Scheme 44, *part a*).[98] Davidson *et al*. reported the synthesis of new selenium-complexes exploiting the reactivity of derivatives of pentafluorobenzeneselenol **35p** with monocyclopentadienyl complexes of molybdenum and tungsten. An example of a molybdenum selenolate complex is reported in the Scheme 44 (*part b*, compound **93**).[99]



Scheme 42. Example of synthesis of a Ni/Fe/E (E = S, Se) cluster complex from diselenol **3a**. ^{77}Se NMR ($CDCl_3$): δ = 395.53 ppm.

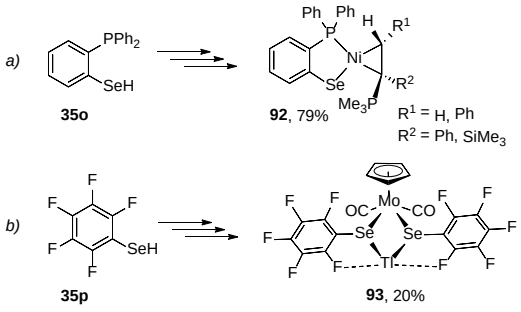


Scheme 43. Synthetic route towards mercaptoselenol **91** from thianthrene **89** (*part a*). Structure of a model of the Ni-site in [NiFeSe] hydrogenases (*part b*). DTBB: 4,4'-di-*tert*-butylbiphenyl (*part b*).



Scheme 45. Synthesis of diselenol **35q** (*part a*) and selenium-containing reversibly thermochromic bismuth-based inorganic-organic hybrid material (*part b*).

Zhang et al. described the preparation of reversibly thermochromic bismuth-based inorganic-organic hybrid materials (Scheme 45, *part b*) *via* a one-step condensation reaction between triphenylbismuth and the diselenol **35q**. Owing to their properties, such materials could find applications for the development of reversible smart windows, camouflage coatings, color filters and display, as well as in temperature sensing and photocatalysis. The synthesis of the diselenol **35q** was pursued by *p*-TsOH-promoted cleavage of the diselenolester **62o**, achieved from 1,4-dibromobenzene through a lithiation-selenium insertion-esterification sequence (Scheme 45, *part a*). All these reactions required strictly controlled reaction conditions in terms of temperature and inert atmosphere.[100]



Scheme 44. Selenol **35o** as precursor of nickelacyclopropane complexes **92** containing a chelate [P,Se] ligand (*part a*). Pentafluorobenzeneselenol **35p** and a monocyclopentadienyl complex of molybdenum with $Tl(SeC_6F_6)$ **93** (*part b*).

The chemistry of selenols has also been exploited for the synthesis of selenolated metal nanoclusters which, owing to the electronic and steric features of selenium that significantly differ from those of sulfur, are characterised by different chemical and physical properties with respect to their thiolated analogues. In comparison with sulfur, the electronegativity and the atomic radius of selenium are closer to those of gold. Au─Se bonds exhibit a more covalent character with respect to Au─S bonds and, therefore, nanoclusters stabilised by selenol ligands are expected to be more stable than their sulfur-containing analogues.[101] For example, the bond stability of selenol-based self-assembled monolayers (SAMs) on Au{111} is higher than that of the related thiol-based SAMs.[101-104] In this context, the synthesis, structure determination and investigation of selenolated metal nanoclusters have attracted considerable attention over the past decades. Amongst the methods available for the synthesis of selenol-stabilised superatomic nanoclusters, ligand exchange approaches often represent a rewarding strategy widely employed for biolabeling, functionalisation of nanoparticles and the processing of semiconductor colloids for solar cell applications. This fundamental reaction has been applied to the synthesis of a number of selenol-based gold[105-109] and silver[110] nanoclusters. The replacement of thiolate ligands on the metal surface with selenolates may offer the great possibility of making new stable functional nanomaterials with potential applications ranging from molecular electronics, biomimetic devices, nanosensors, and corrosion protection. Both aromatic[105-110] and aliphatic[103,104] selenols have been successfully employed. The synthesis and the physicochemical properties of alkaneselenol-[111,112] and benzeneselenol-[113] derived SAMs on Cu(100)

surfaces, as well as the stability of *n*-dodecanethiol SAMs on Cu in the presence of competing *n*-dodecaneselenol,[114] have also been investigated.

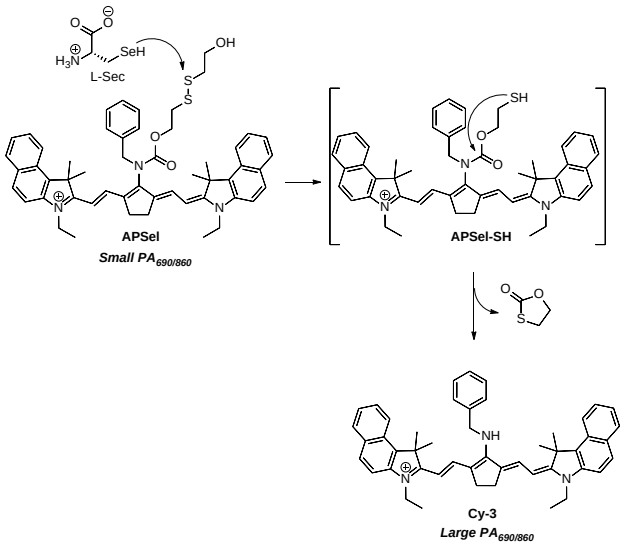
Synthetic strategies involving the reactivity of *in situ* generated selenols with electrophilic metal-compounds have also been described. Bhabak and Bhowmick reported the synthesis of gold(I)-selenolates from *ortho*-substituted diaryl diselenides and thiols. Diselenides react with thiols to afford a selenenyl sulfide and a selenol, which reacts with electrophilic Au(I) compounds to afford the corresponding selenolate-based complex. This route has been successfully applied to the synthesis of Au(I)-selenolates from electrophilic anti-arthritic gold(I) compounds.[115] A similar approach, relying on the reactivity of diselenides with thiols, was also exploited to investigate the response of a gold nanoparticle-based near-infrared fluorescent nanosensor (Cy5.5-peptide-AuNPs). Selenocysteine was generated upon reaction of selenocystine with cysteine. Notably, such a probe was successfully employed for monitoring the changes of selenocysteine in HepG2 cells during Na_2SeO_3-induced apoptosis and for *in vivo* imaging of selenols H22 tumor-bearing mice injected with the nanosensor and Na_2SeO_3.[116]

As selenocysteine plays essential functions in biological systems, the development of rapid and reliable tools for its detection represents a critical point in order to elucidate the roles of Sec-containing derivatives involved in the functioning of living cells and in pathological processes. In this context, Wang *et al*. recently reported the development of a fluorescent Au-NPs-based probe for the selective detection of Sec in living cells and food. Such a **GSH-NB@AuNPS**, consisting of glutathione and Nile blue (NB) assembled on AuNPs, harnesses the aforementioned higher stability of Au-Se bonds with respect to Au-S bonds. The functioning of the probe relies on a nucleophilic substitution occurring at the GSH-functionalised AuNPs surface in the presence of Sec. The selenol-promoted cleavage of Au-S bonds engenders the free fluorophore leading to an increase in fluorescence intensity.[117]

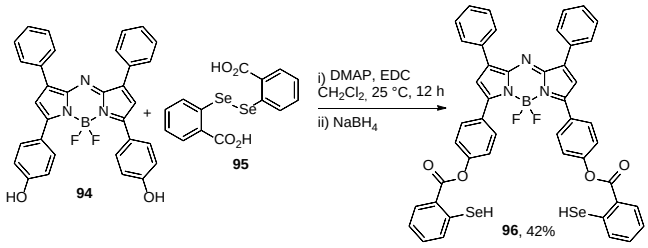
The reactivity of a selenol-modified peptide chain with gold nanoparticles (AuNPs) was also exploited for the synthesis of an Au-Se-bond-based nanoprobe for fluorescence imaging of tumor marker matrix metalloproteinases 2 (MMP-2). Notably, Au-Se-based probes exhibited significant advantages with respect to related Au-S probes. Such improved features include i) the high thermal stability; ii) a significant anti-interference ability towards glutathione; iii) the high-fidelity fluorescent signal towards MMP-2.[118] A gold nanorod fluorescent sensor with antibacterial activity, capable to selectively recognise *Escherichia coli* was also developed exploiting the reactivity of sulfamide bonds of the probe with the selenol moieties of bacterial selenoproteins.[119]

A selenol-responsive photoacustic (PA) imaging probe for the visual monitoring of pathological progression of autoimmune hepatitis (AIH) was very recently developed by Zhang *et al*.[120] The functioning of such a probe exploits the nucleophilicity of selenols (*i.e.* Sec, or its corresponding selenolate anion) and the rapid response of bis(2-hydroxyethyl)disulfide to selenols, with high specificity for Sec and GSeH (selenoglutathione). The near-infrared cyanine dye was employed as the scaffold to design the PA probe with minimised background interferences. Upon reaction with Sec, the responsive group of **APSel** undergoes selenol-thiol exchange to afford a Sec-derived selenenyl sulfide and APSel-SH, which releases Cy-3 and resulting in a blue shift of the photoacoustic spectrum peak from 860 nm to 690 nm (Scheme 46). The ratio of the PA signal intensity at 860 nm to 690 nm (PA_{690}/PA_{860}) was employed to quantify the selenol concentration, thus enabling the ratiometric PA imaging. AIH-specific antibodies, such as those against soluble liver antigen (SLA) and liver pancreas antigen (LP), are commonly used as diagnostic markers and are also among the most important Sec synthases. In this context, a probe for monitoring the selenols concentration may provide new tools to study the progression of AIH.[120]

On the other hand, selenol chemistry can also be exploited for the detection of sulfur-containing systems. Gao *et al*. developed a new selenium-containing near-infrared fluorescent probe for imaging of sulfane sulfur changes under hypoxic stress in cells and *in vivo*. Such a probe **96**, bearing a NIR azo-BODIPY pluorophore and a strong nucleophilic selenol moiety, was synthesised through the EDC-mediated esterification of the hydroxyl functions of the BODIPY platform **94** with the carboxylic groups of the diselenide **95**, followed by reduction of the Se-Se bond with sodium borohydride (Scheme 47). The unique features and the exquisite nucleophilicity of the SeH moiety positively influences the selectivity, sensitivity and kinetics of the probe for sulfane sulfur detection. When exposed to sulfane sulfur, the selenol function of **96** captures a sulfur atom to afford a reactive intermediate (bearing two SeSH groups) which undergoes intramolecular nucleophilic attack onto the C=O releasing the azo-BODIPY fluorophore.[121] Other selenium-containing probes for the detection of glutathione and hydrogen polysulfides have also been synthesised by exploiting the reactivity of a selenol with suitable substrates.[122]



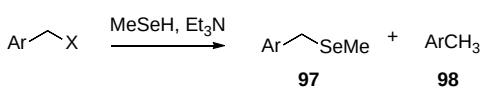
Scheme 46. Reaction of the probe **APSel** with Sec. At physiological pH, selenols mainly exist in their deprotonated form.



Scheme 47. Synthesis of selenol **96**.

3.3. Selenols as reducing agents

Selenols have also been employed as reducing agents towards aromatic nitrogen-containing compounds. Such reactions reasonably proceed through a SET mechanism. Oae and co-workers reported a study on the reactivity of benzeneselenol with aromatic nitro-, nitroso-, hydroxylamino-, azoxy-, azo-, and hydrazo-derivatives. Different reduction products, such as anilines, hydrazobenzenes, and hydroxylamines could be achieved from different organic nitrogen compounds. Furthermore, the reaction temperature and the use of DABCO as a base catalyst proved to play a key role in the selective formation of the above mentioned reduced derivatives.[123]



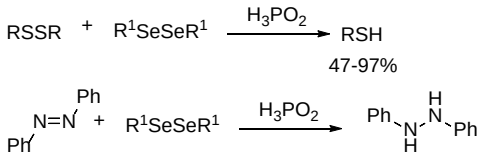
a: X = I, Ar = Ph, 87%; **97a**:**98a** = 82:18
b: X = Br, Ar = 4-NO_2-C_6H_4, 89%; **97b**:**98b** = 57:43
c: X = I, Ar = 4-NO_2-C_6H_4, 97%; **97b**:**98b** = 20:80
d: X = I, Ar = 2,4-NO_2-C_6H_3, 75%; **97c**:**98c** = 0:100

Scheme 48. Reaction of benzyl halides with methaneselenol: competitive reduction and nucleophilic substitution.

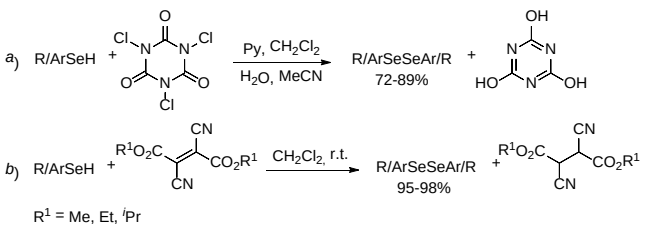
The reducing character of selenols was also highlighted by Hevesi, who reported a study on the competing reduction occurring upon treatment of benzyl halides with selenols. Indeed, both selenides **97** and methylarenes **98** can be formed depending on the nature of the starting material (Scheme 48). The proposed reaction mechanism proceeds *via* stabilised carbanions or through a radical anion-free radical chain process.[124]

Selenols were also employed as reducing agents to convert disulfides into thiols and azobenzene into hydrazobenzene through a diselenide-catalysed reaction (Scheme 49). Selenols – generated *in situ* from diselenides and H_3PO_2 – react effectively with disulfides to yield thiols and diselenides, which are readily reduced back to selenols upon reaction with H_3PO_2.[38] In this context, the selenol-catalysed reduction of diselenides using sodium borohydride or dithiothreitol as reducing agents has also been studied.[125]

Similarly to thiols-disulfides interconversion, oxidation of selenols to the corresponding diselenides has important implications in biological processes. Such a simple organic transformation has been deeply investigated and synthetic methodologies for the selective conversion of selenols into diselenides have been developed. Diaryl and dialkyl diselenides can be easily prepared in good yield by oxidation of selenols with trichloroisocyanuric acid (Scheme 50, *part a*).[126] Recently, dialkyl dicyanofumarates have been employed as mild and efficient oxidising agents for the conversion of thiols and selenols into the corresponding disulfides and diselenides (Scheme 50, *part b*).[127] The use of sodium perborate as an oxidant for the synthesis of diselenides from the corresponding selenols was also reported.[128]



Scheme 49. Reduction of disulfides and azobenzene using selenols as reducing agents.



Scheme 50. Oxidation of selenols with trichloroisocyanuric acid (*reaction a*) and dialkyl dicyanofumarates (*reaction b*).

4. Selenols in biology: modelling and investigation of selenoenzymes

The study of the reactivity of selenols is of paramount importance in order to elucidate the mechanism of the reactions involved in the chemistry of seleno-enzymes. Indeed, the essential activity of natural mammalian selenium-containing enzymes, such as glutathione peroxidase (GPx), iodothyronine deiodinase (ID) and thioredoxin reductase (TrxR), relies on the chemistry of the selenol moiety of the selenocysteine amino acid.[129] On the other hand, also because of the increased availability of reliable routes for their synthesis, the investigation of the biological properties of selenols have attracted growing attention over the last years. For example a number of aryl- and alkyl-substituted selenols (Schemes 4 and 14) have been demonstrated to possess interesting carbonic anhydrase inhibitor activity.[57,130] The antitumor activity of 4-methoxybenzeneselenol **35c** has also been reported.[131,132] Additionally, selenol-containing formulations for cancer treatment and prevention have been described.[133]

As stated above, the chemistry of selenols is of central importance in the catalytic mechanism of glutathione peroxidase (GPx). Selenol species have also been demonstrated to play a key role in the mechanism accounting for the GPx-like activity of ebselen. Engman *et al*. investigated the molecular basis of such a catalytic mechanism by studying the reactivity of the intermediates formed upon reaction of ebselen with glutathione. Such intermediates, namely ebselen-glutathione selenenyl sulfide **99**, ebelen selenol **100**, and ebselen diselenide **101** (Figure 3) were synthesised and their reactivity with hydrogen peroxide was studied. In this regard, the selenol species exhibited remarkable activity. The study revealed that the selenol **100** is the predominant species responsible of the glutathione-dependent peroxidase properties of ebselen under typical peroxidase assay conditions. The rate constants of reactions of **99**, **100**, **101** with H_2O_2 were also measured. Notably, the oxidation of **100** to the corresponding ebselen-derived seleninic acid was found to be the fastest path, thus demonstrating the high reactivity of **100** towards hydrogen peroxide.[134]

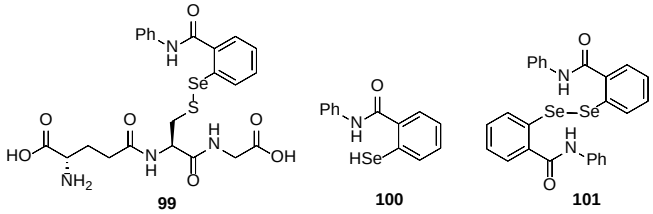


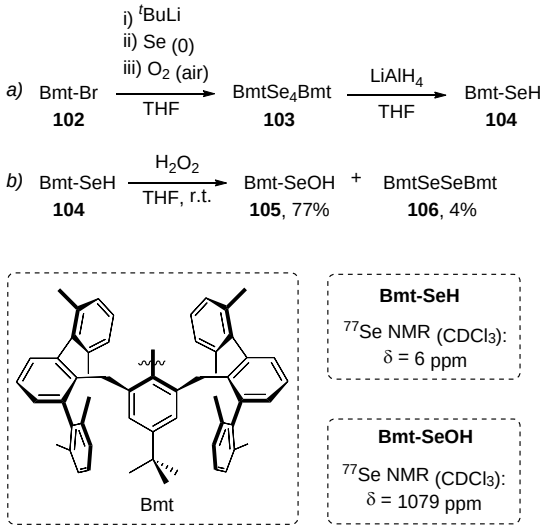
Figure 3. Structures of ebselen-glutathione selenenyl sulfide **99**, ebelen selenol **100**, and ebselen diselenide **101**.

Density functional theory studies elucidated the reaction energetics of oxidation of species **99**, **100**, and **101** with hydrogen peroxide. The selenol **100** exhibited the lower barrier to oxidation, largely because of entropic effects in the reactant complex. In agreement with experimental data, the results of such a study highlighted the key role of ebselen-selenol in the GPx-like catalytic cycle.[135] A computational kinetic and thermodynamic study of the glutathione peroxidase-like mechanism of a zwitterionic selenol was also performed by means of density functional theory and solvent-assisted proton exchange methods. The study suggests that the reduction of the selenenyl sulfide represents the rate-determining-step of the process. The selenol arising from such a reduction is confirmed to be a key catalytically active species in the mechanism of action of GPx mimics.[136] Similarly, selenols play a central role in the mechanism of the diselenides-catalysed reduction of peroxides with thiols. In this regard, Mugesh *et al*. performed a detailed ^{77}Se NMR study in order to characterise the intermediates involved in the GPx-like catalytic mechanism of a series of diselenides, which was demonstrated to proceed *via* selenol, selenenic acid, and selenenyl sulfide intermediates. Furthermore, the GPx-like properties of amino-substituted diselenides proved to be strongly influenced by intramolecular Se···N interactions which, rendering the selenenyl sulfide prone to undergo nucleophilic attack by the thiol, hamper the formation of the key selenol species that would drive the GPx-like mechanism.[137]

The synthesis and the study of the chemical behaviour of suitably substituted molecular models bearing a stabilised SeH functionality attracted a great deal of interest. Indeed, the study of the reactivity of such systems is of particularly important in order to investigate the reaction mechanism of complex selenoenzymes with essential biological functions.

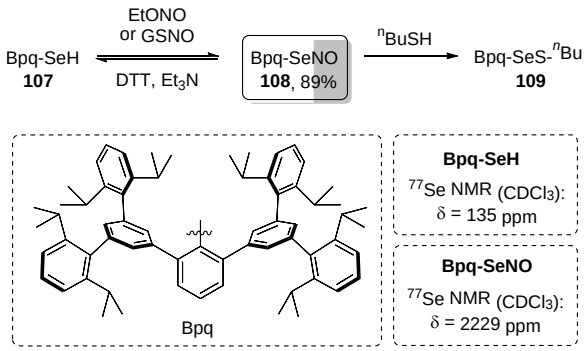
In this *scenario*, Goto *et al*. reported the synthesis and the oxidation reaction of a stabilised selenol bearing a suitable bowel-type substituent. The Bmt-substituted selenol **104** was synthesised as reported in the Scheme 51, reaction *a*. Lithiation of bromide **102** with ^{t}BuLi followed by treatment with elemental selenium provided tetraselenide **103** which, upon reduction with $LiAlH_4$, was easily converted into the corresponding selenol **104**. Oxidation of **104** with a stoichiometric amount of hydrogen peroxide led directly to selenenic acid **105** as the main reaction product, only a small amount of the diselenide **106** being formed (Scheme 51, reaction *b*). The hindered bowel-shaped framework reasonably hampers the formation of **106** through the reaction of the selenol **104** with the selenenic acid **105** which, therefore, proved to be rather stable. Notably, the reaction of **105** with 1,4-dithiols affords selenenyl sulfides which,

in turn, can be easily reduced to the parent selenol upon treatment with tertiary amines. Therefore, using the bowel-type selenol **104** as the model, the study provides experimental evidence of three processes involved in the catalytic cycle of the glutathione peroxidase.[138]



Scheme 51. Synthesis of the bowel-type-substituted selenol **104** (reaction *a*) and its oxidation to provide the selenenic acid **105** (reaction *b*).

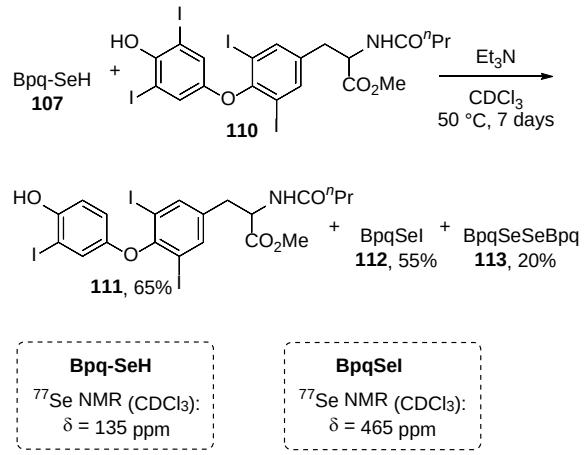
Goto *et al*. also studied the synthesis and the nitrosation reaction of the selenol **107**, bearing an hindered dendrimer-type substituent. Similarly to the approach used for the synthesis of **104**, Bpq-substituted selenol **107** was prepared in 86% yield from the corresponding iodide following a lithiation-selenium insertion-reduction sequence. Reaction of **107** with ethyl nitrite or *S*-nitrosoglutathione afforded the corresponding *Se*-nitrososelenol **108** which, upon treatment with butanethiol, was quantitatively converted into the selenenyl sulfide **109**. Furthermore, reduction of **108** to the parent selenol **107** easily occurred with dithiothreitol (DTT) in the presence of Et_3N (Scheme 52). Interestingly, the study provides a model for the investigation of the mechanism involved in the reaction of the selenocysteine residue of selenoproteins *(i.e.* glutathione peroxidase) with exogenously administered and endogenously produced reactive nitrogen species such as NO.[139]



Scheme 52. Synthesis and reactivity of nitrososelenol **108**.

The hindered Bpq-substituted selenol **107** was also used as a model compound to investigate the mechanism of the iodothyronine deiodinase-catalysed 5'-deiodination of thyroxine. The reaction of **107** with the thyroxine derivative *N*-butyrylthyroxine methyl ester **110** afforded the monodeiodinated compound **111** in 65% yield alongside with the selenenyl iodide **112**, formed from **107** in 55% yield. The formation of a minor amount of the diselenide **113** was also detected (Scheme 53). Notably, the deiodination only occurred at the outer phenol ring of compound **110**; reactions involving the iodine atoms of the inner ring were not observed (Scheme 53). Furthermore, conversion of **110** into **111** did not proceed when the selenol **107** was replaced with the related Bpq-substituted thiol. By using cavity shaped molecules, the study modelled the 5'-deiodination of thyroxine by iodothyronine deiodinase and demonstrated the key role played by the selenol function, corroborating the involvement of a selenenyl iodide intermediate in the catalytic cycle.[140]

The biologically important selenol-mediated tyrosyl ring deiodination reaction was also investigated by Mugesh *et al*.[141] A series of differently substituted naphthyl-based diselenols **114a-g** (Figure 4), freshly generated *in situ* by reducing the corresponding diselenides with $NaBH_4$, were employed for the deiodination of thyroid hormones (TH_S) and their decarboxylated metabolites iodothyronamines (TAMs). The activity of such synthetic mimics of iodothyronine deiodinase, investigated following the deiodination of THs and their decarboxylated TAMs by HPLC, proved to be influenced by the nature of the group placed in the close proximity to one of the selenium atom. Compounds **114b-f**, bearing secondary amine, primary alcohol or thioacetal moieties next to the selenol group, exhibited higher activity with respect to the unsubstituted naphthalene-1,8-diselenol **114a**. Interestingly, the different deiodinase activity of the studied compounds can be explained on the basis of the strength of Se···X (X = O, N, S) intramolecular chalcogen bonding interactions. Additionally, the deiodinase activity was also found to be dependent on the nature of the iodinated substrate and on the strength of Se···I halogen bonding.[141]



Scheme 53. Deiodination reaction of the thyroxine derivative **110** by BpqSeH.

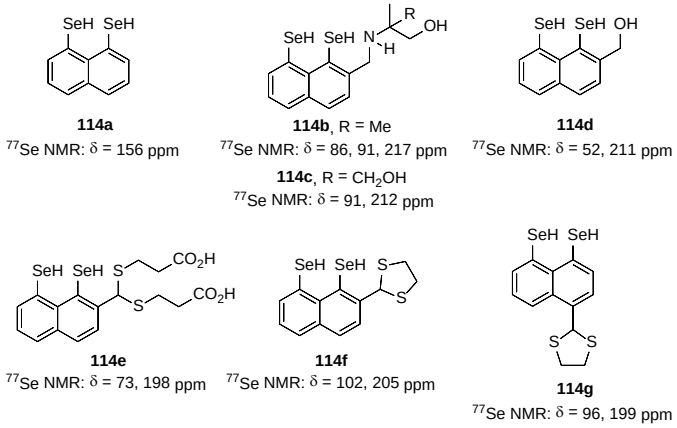
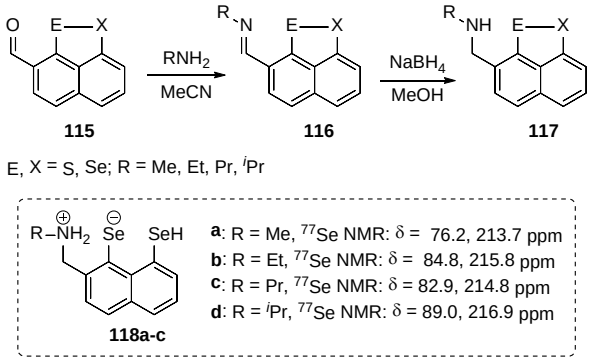
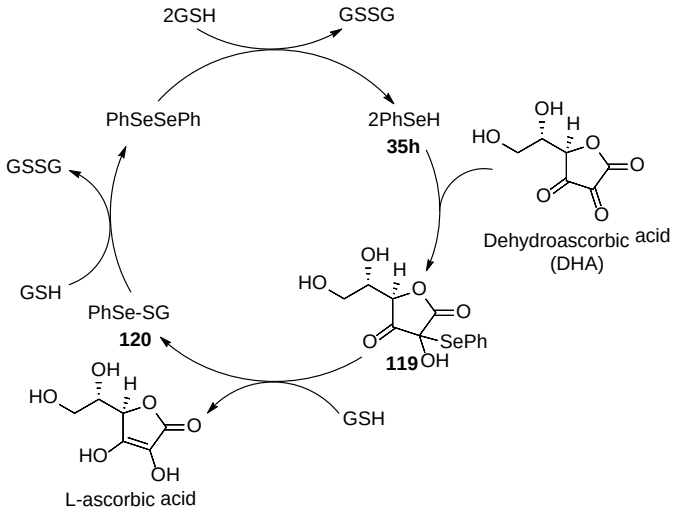


Figure 4. Structure and ^{77}Se NMR chemical shift of diselenols **114a-g**. ^{77}Se NMR spectra were recorded in a mixture of 1:1 chloroform and methanol.

Manna and Mugesh also investigated the deiodinase activity of a series of *peri*-substituted naphthalenes bearing different amino groups. Aldehydes **115**, prepared through formylation of the corresponding dichalcogenides with $POCl_3$/DMF under Vilsmeier-Haack conditions, were treated with primary amines to afford the Schiff bases **116**. Secondary amine-based dichalcogenides **117** were achieved by reduction of **116** with $NaBH_4$. Further reduction of **117** using $NaBH_4$ provided the desired naphthalene-derived chalcogenols (Scheme 54). Notably, the ^{77}Se NMR chemical shift of the selenium atom adjacent to the secondary amino group of compounds **118** is significantly shifted upfield, indicating that the amino group abstracts the proton from the selenol moiety and increases its nucleophilicity. Conversely, the deshielding effect observed on the ^{77}Se NMR chemical shift of the other selenol moiety suggests that the deprotonation of one SeH functionality by the adjacent amino group may decrease the nucleophilicity of the other selenol function (Scheme 54). Within the studied series of naphthyl-based iodothyronine deiodinase mimics, compounds having two selenols in the *peri*-positions displayed higher deiodinase properties with respect to those bearing two thiols or a thiol−selenol pair. Furthermore, amino-substituted systems **118a-d** proved to be more active than the unsubstituted naphthalene-1,8-diselenol **114** (*vide supra*). Interestingly, the deiodination reaction regioselectively occurs at the inner ring of thyroxine (T4) and 3,5,3'-triiodothyronine (T3) which are converted into 3,3',5'-triiodothyronine (rT3) and 3,3'-diiodothyronine (3,3'-T2), respectively.[142]



Scheme 54. Synthesis of Secondary amine-based dichalcogenides **117** and selected examples of iodothyronine deiodinase mimics with related ^{77}Se NMR chemical shift from Mugesh *et al.*



Scheme 55. Mechanism for the DHA reductase-like activity of diphenyl diselenide.

Thiol-promoted diselenide-selenol interconversion reactions also account for the dehydroascorbate reductase-like activity of diphenyl diselenide. The proposed mechanism foresees the generation of benzeneselenol **35h** upon reaction of glutathione with diphenyl diselenide which, therefore, exhibits glutathione S-transferase activity. The so generated

benzeneselenol reduces dehydroascorbic acid into L-ascorbic acid, reasonably *via* the key phenylseleno-hemiketal intermediate **119**. In the final step of the catalytic cycle, the selenenyl sulfide **120** provides diphenyl diselenide by reacting with GSH (Scheme 55).[143]

5. Conclusions and outlook

Selenol are a class of versatile organic molecules that can be easily functionalised under mild reaction conditions providing direct access to a broad range of functionalised selenium-containing organic molecules. The presence of the Se-H bond renders selenols stronger acids and nucleophiles with respect to related thiols. On the other hand, selenols are significantly more prone than thiols to undergo oxidation, rapidly affording the corresponding diselenides upon exposure to mild oxidative conditions (*i.e*. oxidation with air). Because of their poor stability, selenol chemistry has been for long time overlapped with selenolate chemistry. Understanding the central role of the selenol moiety of selenocysteine in the mechanism of selenoproteins prompted researchers to investigate further the synthesis and the reactivity of selenols. Therefore, over the past years several routes for the synthesis of selenols have been described. Such advances led to a deeper investigation of the chemical behaviour of selenols, enabling to explore new frontiers of selenium chemistry and biochemistry. As such, selenols can be efficiently employed in a range of highly selective reactions that would be hardly feasible using diselenides as precursors of nucleophilic selenolate anions. From the synthetic perspective, the mild conditions of selenylation reactions with selenols enable to enlarge their scope to include substrates bearing labile functionalities. Additionally, the use of selenols offers significant advantages in terms of chemo-, regio- and stereo-selectivity compared to related transformations performed with selenolates.

As stated above, a number of approaches for the synthesis of variously functionalised selenols have been described over the last years. Broad though these routes are, access to complex systems with certain structural motives remains challenging. In terms of functional group compatibility, the development of general synthetic methodologies to access selenols bearing valuable functionalities (*i.e.* aldehydes, boronic esters, boronic acids, phosphorus functional groups) would be highly desirable. Furthermore, while the synthesis of complex thiols including chiral tertiary derivatives has been explored, significant effort is still needed to access related selenols through asymmetric syntheses.

The development of new synthetic procedures for the preparation of complex, chiral, densely functionalised selenols would lead to the exploration of new directions in organic synthesis, medicinal chemistry, and biology. For example, the catalytic application of selenols in redox transformations remains a promising, yet scarcely explored, field. On the other hand, the study of the biological activity of synthetic and semisynthetic selenols could enable the development of novel potential drug candidates. Furthermore, considering the relevance of the selenol functionality in biochemistry, the investigation of the chemical behaviour of functionalised synthetic selenols could help one to map out the biological role of selenoproteins and to elucidate their mechanism.

Safety measures

Selenols, bis(trimethylsilyl)selenide, selenocyanates, and hydrogen selenide are malodorous and potentially toxic compounds. All reactions and handling should be carried out in a well-ventilated fume hood.

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