Review

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Recent Advances in Selenium-Mediated Redox Functional Group Interconversions

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Abstract: The conversion of a functional group into another represents the core of organic synthesis. Within the arena of functional group interconversions, oxidative and reductive transformations occupy a privileged position and the development of new sustainable, selective, and general methodologies continue to attract significant interest. Owing to the versatility of their chemistry, selenium compounds offer significant opportunities to achieve both oxidation and reduction of a wide range of functional groups. Additionally, the possibility to generate *in situ* the active oxidant or reducing selenium species from suitable inert precursors enables the development of catalytic processes. In this review, recent advances in selenium-mediated oxidative and reductive functional group interconversions, with particular emphasis on cutting-edge researches bringing about new insights into the comprehension of their mechanistic aspects, will be discussed.

Keywords: Selenides, Diselenides, Oxidations, Reductions, Catalysis, Green Chemistry

1. Introduction

The range of oxidation states of selenium (from −2 to +6) and their relatively facile interchange can be exploited to accomplish a variety of valuable oxidative and reductive transformations. While highly oxidised selenium species (*i.e.*, seleninic acids, selenonic acids and their peroxides) can be efficiently employed in oxidation processes, reduced selenium species (*i.e*, selenide anions, hydrogen selenide, selenols) enable the reduction of different functional groups. Oxidised and reduced selenium species can also be formed *in situ* upon reaction of suitable precursors with convenient final oxidising or reducing agents; this feature enables the use of selenium and selenium-containing compounds in a catalytic fashion. Notably, the development of catalytic processes bring about the mitigation of concerns related to the toxicity, cost, and environmental impact of selenium species.

In this scenario, practical and convenient selenium-mediated oxidative functional group interconversions have been developed over the past decades; owing to their central importance in organic synthesis, biology, and material science, review articles and book chapters have been dedicated to selenium-catalysed oxidation processes.[1–3]

Nonetheless, significant advances have been recently achieved within this research area and novel methodologies have been unveiled. Particular emphasis has been placed on mechanistic aspects as well as on the development of sustainable protocols.

Because of their privileged position in organic synthesis, the development of novel efficient, selective, and sustainable protocols to accomplish reductive functional group interconversions is highly sought after.[4] In this context, considerable research efforts are obviously devoted to the study of chemoselective and, especially, enantioselctive methodologies such as – for example – enantioselective reductions of ketones,[5] imines,[6] and alkenes.[7]

Within this research arena, while selenium(IV) or (VI) species can be employed to conduct oxidation reactions, lower oxidation states of this element can be harnessed to achieve a

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variety of synthetically useful reductions. However, while selenium-mediated oxidations have been widely investigated and an array of valuable protocols for the oxidation of organic functional groups have been established, selenium-mediated reductions have been far less explored. Indeed, in spite of their importance and potential versatility, only a limited number of methodologies for the reduction of suitably substituted alkenes and alkynes, ketones, and nitrogen-containing compounds have been described.[3]

Selenium-mediated reductions have been demonstrated to offer new interesting perspectives in the development of sustainable and scalable procedures. Additionally, the reactivity of *mild* selenium-based reducing agents (*i.e.*, Se^{2-} or HSe^{-} anions) also offers a certain leeway to address chemoselectivity issues related to the reduction of labile moieties often occurring when performing reductive functional group interconversions with *classical* reducing agents.[8]

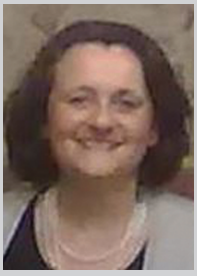
This review covers recently emerged researches focusing on selenium-mediated oxidative and reductive functional group interconversions. Emphasis will be given to the mechanistic aspects of these transformations, with particular attention to new advances achieved in the elucidation of selenium species involved in the different reaction pathways.

As mentioned above, oxidation processes have also been treated in book chapters and review articles.[1–3] Thus, attention will be mainly devoted to the discussion of the literature published in the last ten years, with older reports being referenced only if they are closely related to the articles discussed in this review. On the other hand, as comprehensive reviews on selenium-mediated reduction lack in the literature, a wider overview of these processes will be given.

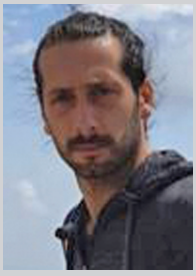
2. Selenium-Mediated Oxidative Functional Group Interconversions

A broad array of selenium compounds can be efficiently used as oxidants in different functional group transformations. Selenium(IV) oxide (**1**), selenoxides (**2**), areneseleninic acids (**3**) and their anhydrides (**4**) are arguably the most commonly employed selenium oxidants (Figure 1). These species, as well as cyclic selenamides (**5**), cyclic seleninates esters (**6**), organic selenides (**7**) and diselenides (**8**) can also be employed under catalytic conditions in the presence of suitable primary oxidants (*i.e*, hydrogen peroxide, *tert*-butyl hydroperoxide, iodoxybenzene, atmospheric oxygen) capable to convert selenium catalysts into active oxidant species (Figure 1).[1c,2,3]

The possibility to oxidise organoselenium compounds with H_2O_2 and organic hydroperoxides under very mild conditions represents an attractive feature to develop selenium-mediated oxidation routes. Indeed, the main drawback in using hydrogen peroxide is that most of the oxygen-transfer reactions involving H_2O_2 are limited by their kinetic; the use of promoters or catalysts enables the circumvention of this limitation. The H_2O_2 activation by organoselenium compounds relies on the formation of selenium oxidised species



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 career 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 and the synthesis of chalcogenated organic derivatives mediated by organosilanes, and the study of their properties as novel antioxidant systems and enzyme modulators.



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 lecturer in Organic Chemistry at the University of Florence. In 2021 he received a positive evaluation to become Associate Professor in the Italian higher education system. His research interests currently centre on organic synthesis, ranging from the development of novel sustainable methodologies towards synthetic intermediates and bioactive molecules to the study of chalcogen-catalysed transformations, with particular attention to oxidative and reductive functional group interconversions, and molecular chirality. D. Tanini is Editorial Board Member and reviewer of several journals in the chemical and biochemical areas.

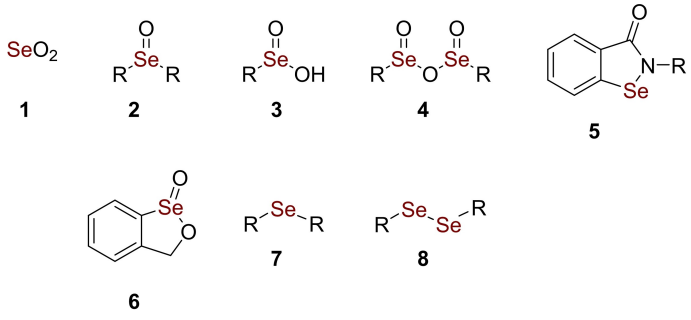


Figure 1. Classes of selenium compounds used as oxidants or catalysts in oxidative functional group interconversions.

(*i.e.*, peroxyseleninic acid, peroxyselenonic acid, and related anhydrides) which transfer an oxygen atom to the substrate. On these basis, selenium compounds have been widely employed as catalysts or promoters to accomplish a broad range of oxidative functional group interconversions. A number of selenium-mediated methodologies for the oxidation – among others – of alkenes, carbonyl compounds, thiols, and amines have been described.[1–3] Selenium-catalysed bromination methodologies[9] and oxiselenocyclisation reactions,[10] which will not be covered by this review, have also been described.

Selenium-based oxidation methodologies represent a valuable tool in organic synthesis and have found significant application in the preparation of natural products. For example, approaches relying on selenium-based oxidation for the total synthesis of natural diaromatic ergosterol derivatives **9**[11] as well as natural occurring butenolides **10** and **11**[12] have been reported (Figure 2).

In this section, recent advances in the development of selenium-mediated oxidative functional group interconversions, as well as new achievements in the comprehension of their reaction mechanism, will be discussed.

2.1. Selenium-Mediated Oxidation of Alkenes and Alkynes

2.1.1. Oxidation of Alkenes

The role of selenides and seleninic acids in the epoxidation of alkenes has been well established since the pioneering and seminal works of Grieco,[13] Kametani,[14] Reich,[15] and Sharpless.[16] Various methodologies for the selenium catalysed epoxidation of alkenes with hydrogen peroxide have been reported over the past four decades. Benzeneseleninic acid, as well as 2-nitro-, or 2,4-dinitro- substituted analogous have commonly been employed as catalysts; these species can also be *in situ* formed upon oxidation of parent diselenides or selenenic acids. On these basis, diselenide-catalysed oxacyclisation reactions of alkenoic acids and alkenols, with hydrogen peroxide have also been documented by Santi and colleagues.[17]

The mechanism of the Se-catalysed epoxydation has been for a long time believed to proceed exclusively through selenium (IV) active oxidants; seleninic acid-based catalysts **12** have been proposed to be oxidised to the corresponding peroxyseleninic derivatives **13**, which have been considered the active oxidants involved in the catalytic pathway. However, Back and colleagues recently showed that – although peroxybenzeneseleninic acid **13** is indeed generated under the oxidation conditions – in solution the conversion of **12** to the mixed selenonium selenonate **14** is faster than its reaction with the alkene. Therefore, the peroxybenzeneseleninic acid **13** plays only a marginal role in the epoxidation of alkenes. On the other hand, the inert selenonium selenonate salt **14** is reasonably oxidised to the peroxybenzeneselenonic acid **16** which rapidly reacts with the alkene providing the epoxide **17** (Scheme 1).[18]

2.1.2. Oxidation of Alkynes

Different methodologies for the selenium catalysed oxidation and functionalisation of acetylenes have been described,[19,20]

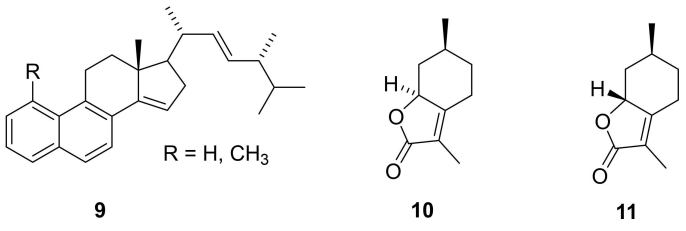
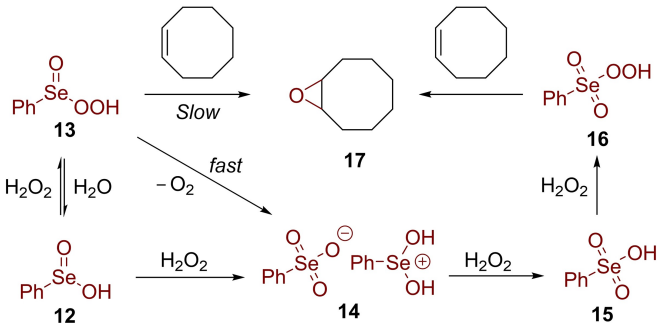


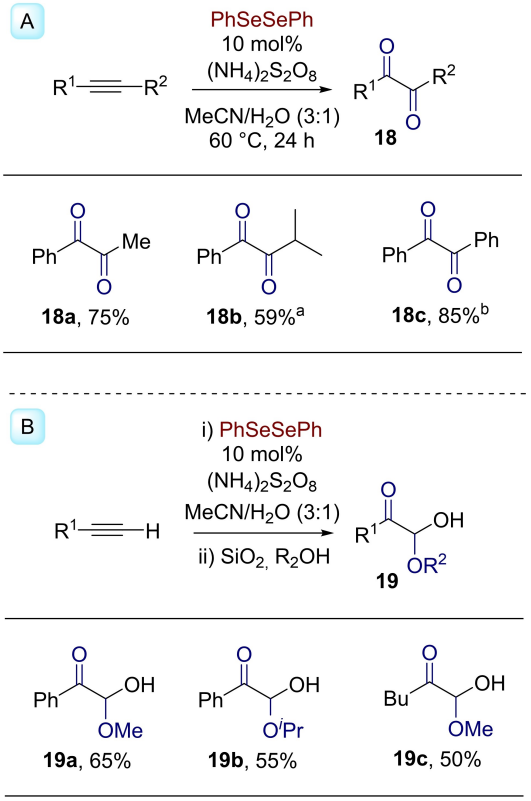
Figure 2. Structures of natural diaromatic ergosterol derivatives **9** and butenolides **10** [(±)-mintlactone] and **11** [(±)-isomintlactone].



Scheme 1. Selenium-containing oxidants involved in the epoxidation of alkenes.

including electrochemical processes.[21] Selenium catalyzed methodologies for the functionalization of alkynes have also been recently reviewed by Liao and Zhao.[20] The selenium dioxide-catalized oxidation of different acetylenes with *t*-butyl hydroperoxide was reported by Sharpless and colleagues;[22] the main oxidation products were propargylic alcohols and diols, alongside with minor amounts of ketones. A diphenyl diselenide (PhSeSePh) catalysed approach for the oxidation of alkynes with ammonium persulfate was reported by Santi and colleagues.[23] Notably, while the application of this protocol to internal alkynes provided the corresponding α-diketones **18**, terminal alkynes in the presence of alcohols gave α-keto hemiacetals **19** (Scheme 2).

The proposed reaction mechanism is depicted in the Scheme 3. The actual catalyst is believed to be the highly electrophilic PhSe-sulfate **20** which, in turn, is formed by the reaction of diphenyl diselenide with ammonium persulfate. In the presence of water, this electrophile reasonably leads to the hydroxyselenenylation on the triple bond, with the formation of the enol **21** that exists in a tautomeric equilibrium with the ketone **22**. The excess of ammonium persulfate activates the phenylselenium moiety (intermediate **23**) to the nucleophilic displacement by a molecule of water, with the consequent formation of **24** which, under the described experimental conditions, is rapidly oxidised to the corresponding 1,2-dicarbonyl derivative **18**.



Scheme 2. Selenium-catalysed oxidation of alkynes with ammonium persulfate (selected examples). A: Conversion of internal alkynes to α-diketones. B: Conversion of terminal alkynes to α-keto hemiacetals. [a]Reaction time 48 h. [b]Reaction time 72 h.

2.2. Selenium-Mediated Oxidative Synthesis of Carboxylic Acids

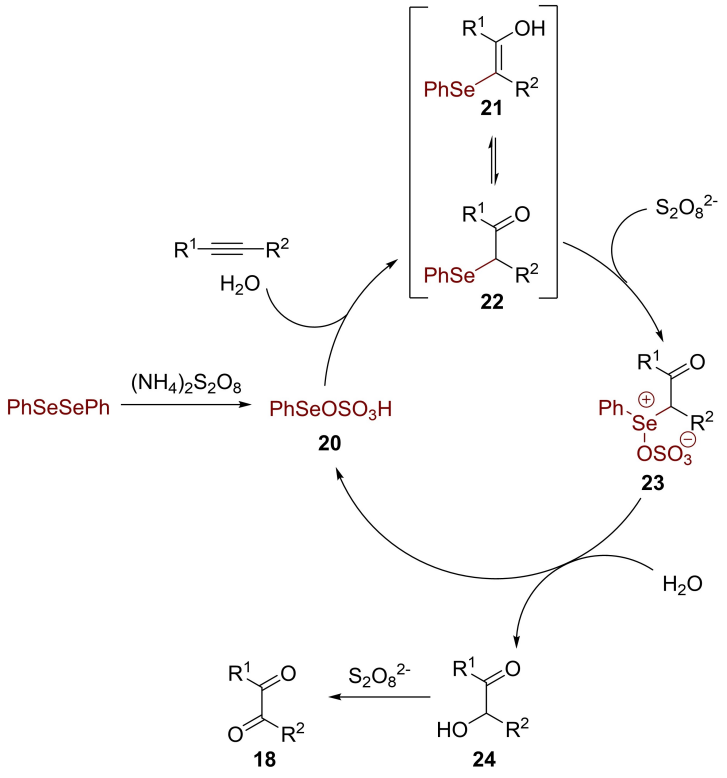
2.2.1. Oxidation of Aldehydes

Nemati and colleagues reported the use of a diselenide stabilized on silica coated Fe_3O_4 magnetic nano particles (**25**) as a novel, efficient and magnetically retrievable heterogeneous catalyst for the oxidation of aldehydes (**26**) to the corresponding carboxylic acids (**27**) with hydrogen peroxide.[24] The reaction was applied to the synthesis of various carboxylic acids (Scheme 4), including differently substituted benzoic acids (**27 a-h**), cinnamic acid **27 i** and alkanoic acid (*i.e.*, butanoic acid **27 j** and hexanoic acid **27 k**). Notably, the magnetic nanoparticles could be efficiently recovered using an external magnetic field and reused up to four times without significant decrease of the catalytic performance.

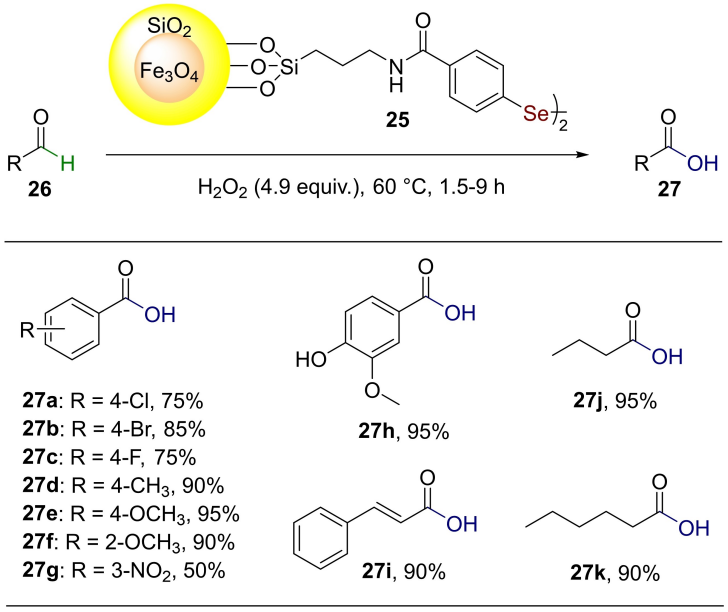
The proposed reaction mechanism (Scheme 5) proceeds through the oxidation of the diselenide **25** to the corresponding seleninic acid **28**, upon reaction with hydrogen peroxide. Further oxidation of **28** with H_2O_2 provides the peroxyseleninic acid **29**, which is believed to be the active oxidant in the proposed mechanism. Indeed, addition of **29** to the aldehyde leads to the intermediate **30** which, after intramolecular rearrangement promoted by the hydrogen bond interaction, yields the carboxylic acid **27** and regenerates the seleninic acid **28**.

A related selenium-mediated protocol for the sustainable synthesis of carboxylic acids and esters upon oxidation of aldehydes with H_2O_2 in water was also reported by Santi and colleagues.[25] Diphenyl diselenide was used to promote the desired oxidation, which was proposed to proceed *via* benzeneseleninic acid as the effective catalyst, according to the mechanism depicted in the Scheme 6 (Part B). The reaction scope proved to be rather broad, and the methodology was successfully applied to a broad range of substrates, including aromatic aldehydes bearing both electron-withdrawing and electron-donating groups, aliphatic, and α,β-unsaturated aldehydes (Scheme 6, Part A).[25]

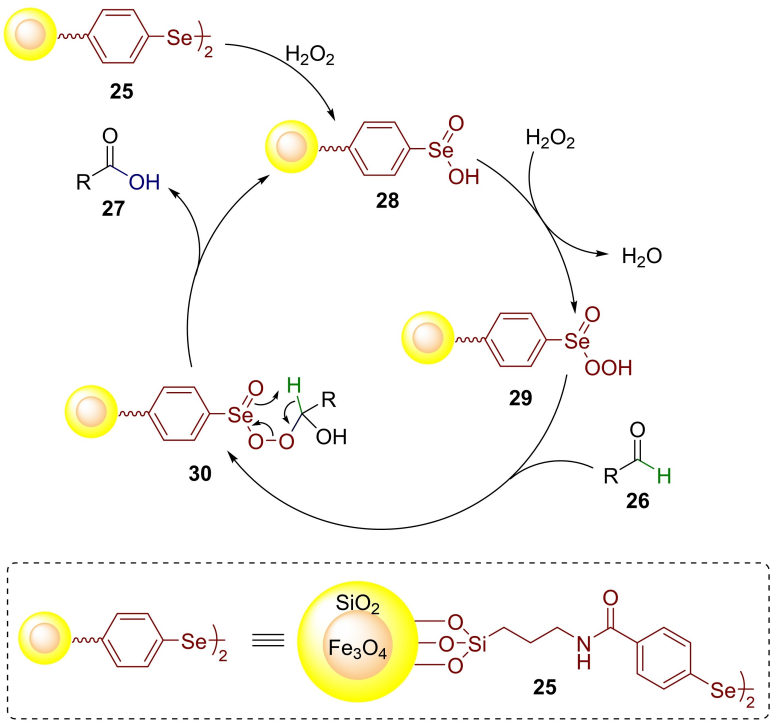
Notably, a slightly modified protocol could also be employed for the synthesis of esters by reacting aldehydes with H_2O_2 in the presence of diphenyl diselenide and alcohols (Scheme 7).



Scheme 3. Proposed mechanism for the selenium-catalysed oxidation of alkynes to α-diketones **18**.



Scheme 4. Selenium-mediated oxidation of aldehydes to carboxylic acids.



Scheme 5. Proposed reaction mechanism for the selenium-mediated oxidation of aldehydes to carboxylic acids.

2.2.2. Oxidation of Benzoin Derivatives

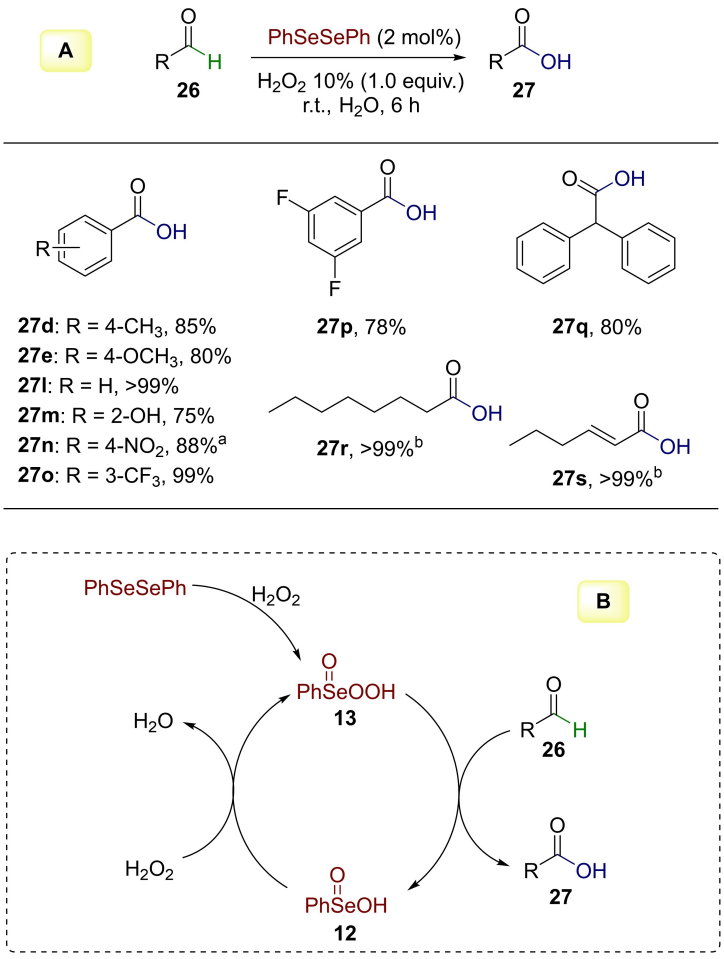
Zhang and colleagues have described a selenium-catalysed oxidative degradation of benzoin derivatives **24** to the corresponding carboxylic acids using hydrogen peroxide.[26] After an initial optimisation study, diphenyl diselenide was selected as the catalyst for this transformation, which could be efficiently applied to the synthesis of differently substituted benzoic acids as well as phenylacetic acid (Scheme 8).

A plausible mechanism for this selenium-catalysed oxidative degradation of benzoin derivatives is reported in the Scheme 9. Peroxybenzeneseleninic acid **13**, formed from the peroxide **34** upon reaction with water, is the active oxidant involved in the mechanism. Evidences of the formation of the peroxide **34** from diphenyl diselenide and hydrogen peroxide were previously provided by ^{77}Se NMR studies.[27] Nucleophilic addition of **13** to the 1,2-dicarbonyl compound **18** – rapidly formed via selenium-catalysed oxidation of **24** – provides the intermediate **35** which, upon C–C cleavage, leads to the anhydride **36** and benzeneseleninic acid **12**. Finally, the carboxylic acid **27** is formed through hydrolysis of **36**. The active oxidant **13** is regenerated by oxidation of benzeneseleninic acid **12** with H_2O_2.[26]

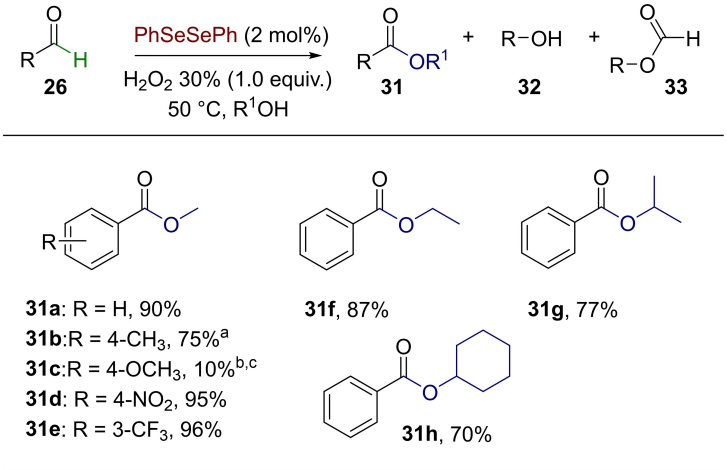
2.3. Selenium-Mediated Oxidative Synthesis of Quinones

A selenium-mediated methodology for the synthesis of quinones **38** has been reported by da Silva J. Júnior and colleagues. During the optimisation of the reaction conditions the authors highlighted that diphenyl diselenide was the more convenient Se-containing catalyst which, using hydrogen peroxide as the oxidant and oxygen (1 atm) as co-oxidant, enabled the conversion of 5-iodo-1-naphthol to the corresponding 5-iodo-1,4-naphthoquinone **38a** in quantitative yield (Scheme 10). The reaction was efficiently applied to the synthesis of differently substituted 1,4-naphthoquinones **38a–h** (yields ranging from 30% to 100%), thus showing a good functional group tolerance (Scheme 10).[28]

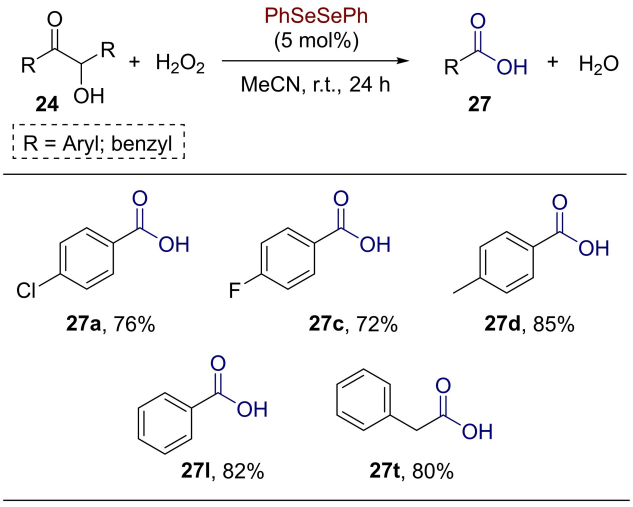
The proposed reaction mechanism involves the formation of peroxybenzeneseleninic acid **13** upon oxidation of diphenyl diselenide with H_2O_2. Peroxybenzeneseleninic acid **13**, which is reasonably formed *via* selenenic and seleninic acid intermediates, is believed to be the active oxidant capable of reacting with the naphthol **37** to yield the epoxide intermediate **39** and to regenerate benzeneseleninic acid **12**. The conversion of the epoxide **39** to the intermediate **40** and its oxidation are the final steps leading to the desired 1,4-naphthoquinone **38** (Scheme 11).[28]



Scheme 6. Selenium-mediated oxidation of aldehydes to carboxylic acids. Selected examples (Part A) and proposed mechanism (Part B).[25] [a]Reaction time 24 h. [a]Reaction time 3 h.



Scheme 7. Selenium-mediated synthesis of esters. Selected examples.[25] [a]15 % of the phenol **32b** was detected. [b]35 % of the phenol **32c** was detected. [c]The related formyl derivative **33** was isolated in 80 % yield when performing the reaction at 0 °C.



Scheme 8. Selenium-catalysed oxidation of benzoin derivatives to carboxylic acids.

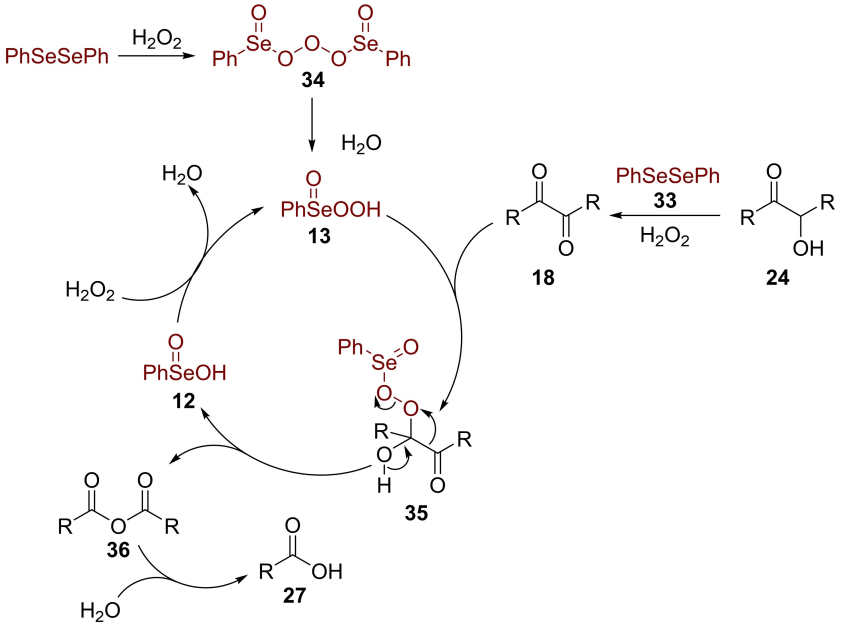
2.4. Oxidation of Nitrogen-Containing Functional Groups

The versatility of selenium-catalysed oxidation reactions has also been exploited for the development of selective procedures for the conversion of anilines to the corresponding nitrosoarenes **41**[29] and azoxyarenes **42**[30,31] (Scheme 12). The synthesis of nitroarenes via oxidation of anilines have also been reported.[32]

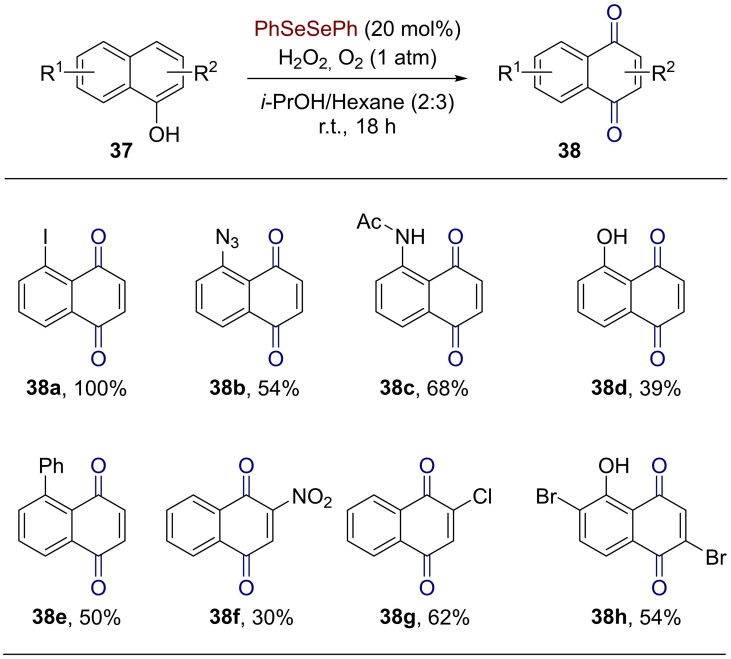
Recently, our group disclosed a selenium-mediated approach for the selective *on water* oxidation of anilines to nitroarenes using hydrogen peroxide.[30] A wide range of differently substituted anilines were smoothly converted into the corresponding nitroarenes **43** upon reaction with H_2O_2 in the presence of diphenyl diselenide or benzeneseleninic acid (Scheme 13). The methodology encompasses a variety of both electron-rich and electron-poor substrates and can be successfully applied to the synthesis of nitroarenes at a gram scale. A preliminary optimisation study conducted on a variety of organoselenium compounds showed that diphenyl diselenide and benzeneseleninic acid gave better results in terms of yield and selectivity. On the other hand, the reaction of aniline with hydrogen peroxide in the presence of selenium dioxide (SeO_2) or sodium selenite (Na_2SeO_3) provided, as already observed under similar conditions using organic solvents,[31] a good yield of the corresponding azoxyarenes.

Control experiments (Scheme 14) and ^{77}Se-NMR studies suggested that the oxidation mechanism probably proceeds through key Se(IV) species. Particularly, neither the starting aniline nor hydroxylamine and nitroso plausible intermediates were converted to the corresponding nitrobenzene upon treatment with H_2O_2 in the presence of Se(VI) catalysts such as benzeneselenonic acid (Scheme 14).

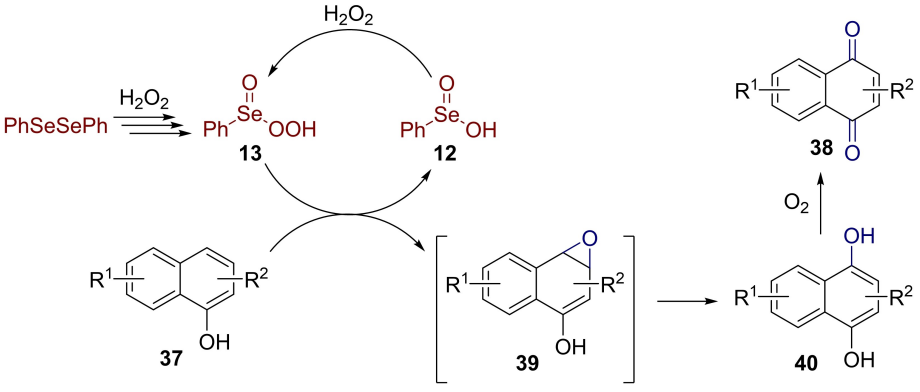
The proposed mechanism is reported in Scheme 15. Diphenyl diselenide behaves as a precatalyst, and the first steps of the reaction mechanism involve its sequential oxidation to benzeneselenenic acid **44** and benzeneseleninic acid **12**. The latter is reasonably the effective catalytic species involved in



Scheme 9. Proposed reaction mechanism for the selenium-catalysed oxidative degradation of benzoin derivatives to carboxylic acids.



Scheme 10. Selenium-mediated synthesis of 1,4-naphthoquinones.

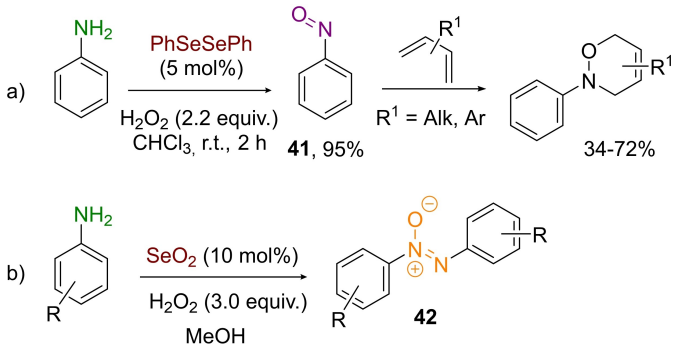


Scheme 11. Proposed mechanism for the selenium-mediated synthesis of 1,4-naphthoquinones.

this oxidation mechanism. Further oxidation of **12** with hydrogen peroxide in water is expected to yield the peroxyselenurane **45**, which can undergo dehydration to afford either peroxyseleninic acid **13** or selenonic acid **16**. The reaction of selenonic acid **16** with seleninic acid **12** might also provide the selenonium salt **14**, which, in aqueous solution, is rapidly reconverted into the parent acids **12** and **16**. Both **13** and **45** are thought to behave as active oxidants. The reaction of aniline with **13** or **45** leads to the formation of the hydroxylamine **46**, which is further oxidised to the dihydroxylamine **47**. Benzeneseleninic acid is regenerated in each of these steps. Next, an acid-mediated dehydration of **47** affords the nitrosoarene **41**, which is finally oxidised by **13** to the nitroarene **43** regenerating benzeneseleninic acid **12**.[30] Interestingly, Se(VI) species (*i.e.*, benzeneselenonic acid) did not catalyse the oxidative conversion of anilines to nitroarenes.

The mechanistic steps leading to the oxidation of anilines to nitroarenes have also been investigated through a combined theoretical (DFT) and experimental approach, when Se(IV) seleninic acid or Se(VI) selenonic acids are used as catalysts and H_2O_2 as the oxidant. The privileged role of "peroxyseleninic" acid as the main active species has been highlighted, supporting an inactivating role of its conversion to Se(VI).

Additionally, the conversion of seleninic to selenonic acid in oxidizing conditions was found to proceed with a higher activation energy than the three substrate oxidations by



Scheme 12. Selenium-catalysed oxidation of anilines to nitroso and azoxy derivatives.

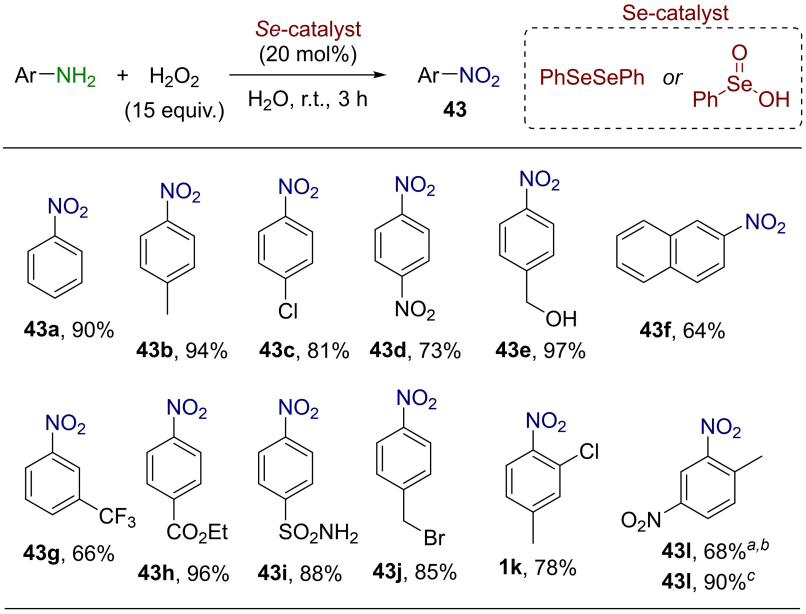
peroxyseleninic acid. The formation of the Se(VI) species is therefore expected only when the substrate is fully converted to the nitroarene.[33]

The use of diselenide-based heterogeneous catalyst **48**, prepared by immobilising diphenyl diselenide on amine-functionalized Santa Barbara Amorphous-15 (SBA-15), in the oxidative conversion of oximes to nitriles has also been documented by Nemati and colleagues.[34] This simple protocol, which relies on the use of hydrogen peroxide as the oxidant, was efficiently employed for the synthesis of differently substituted aryl and heteroaryl nitriles (**49**) by the oxidation of parent aldoximes (Scheme 16). Notably, the catalyst could be reused for up to four consequent cycles with no appreciable decrease of the catalytic activity.

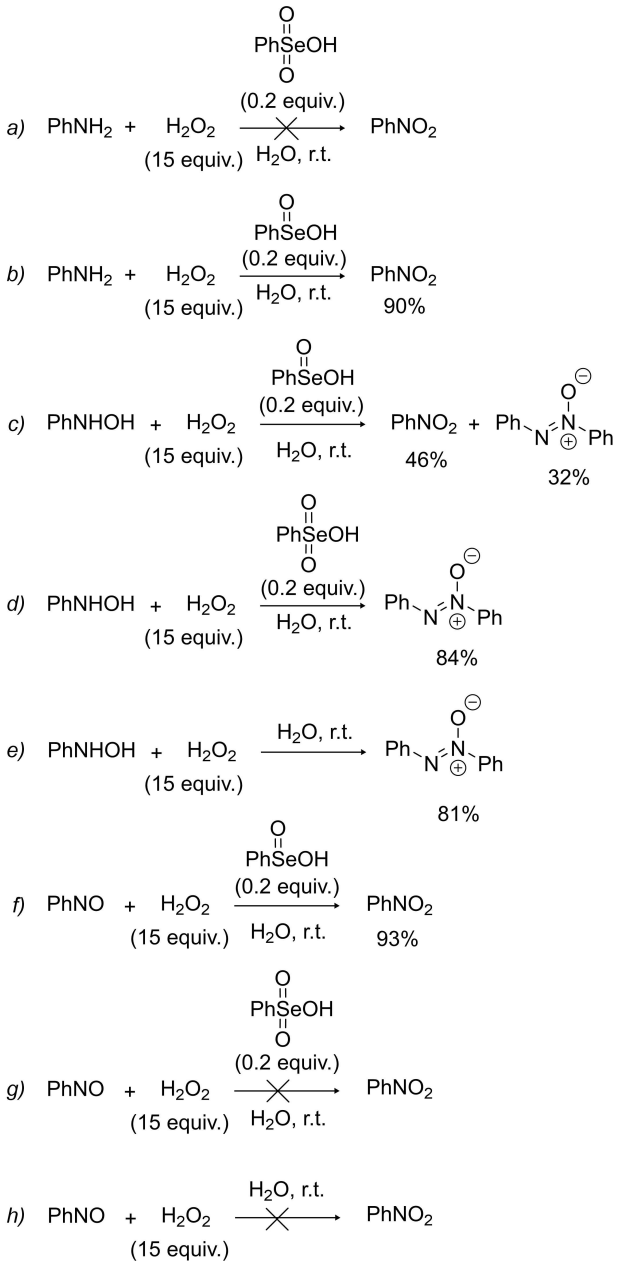
The proposed mechanism is reported in the Scheme 17. Initially, the diselenide-based catalyst **48** is converted into the corresponding selenenic acid upon oxidation with hydrogen peroxide. The selenenic acid can be converted into the anhydride **51**, which undergoes condensation with the aldoxime to afford the intermediate **52**. Rearrangement of **52** to give the intramolecular hydrogen bond-stabilised intermediate **53**, followed by its decomposition *via* selenoxide *syn* elimination, leads to the nitrile **49** and regenerate the key selenenic acid **50**.[34]

2.5. Oxidation of Sulfur-Containing Organic Compounds

A wide variety of selenium-containing compounds have been reported to catalyse the oxidation of thiols to the corresponding disulfides. Owing to their importance in biology, selenium-catalysed thiol-disulfide interconversion reactions have attracted a steadily growing interest amongst organic and medicinal chemists. Indeed, the functioning of glutathione peroxidases (GPxs), a family of selenoenzymes catalysing the reduction of harmful peroxides to non-toxic species and thus providing living cells with endogenous antioxidant defence against oxidative stress, relies on the selenium-catalysed oxidation of glutathione (GSH) to the corresponding disulfide (GSSG). Hydrogen peroxide or organic peroxides are used as oxidant in this reaction.



Scheme 13. Organoselenium-mediated oxidation of anilines to nitroarenes. Similar results were achieved by using diphenyl diselenide or benzeneseleninic acid (selected examples). [a]The reaction was performed at 60 °C; [b]Obtained from 2-methyl-5-nitroaniline; [c]Obtained from 4-methyl-3-nitroaniline.



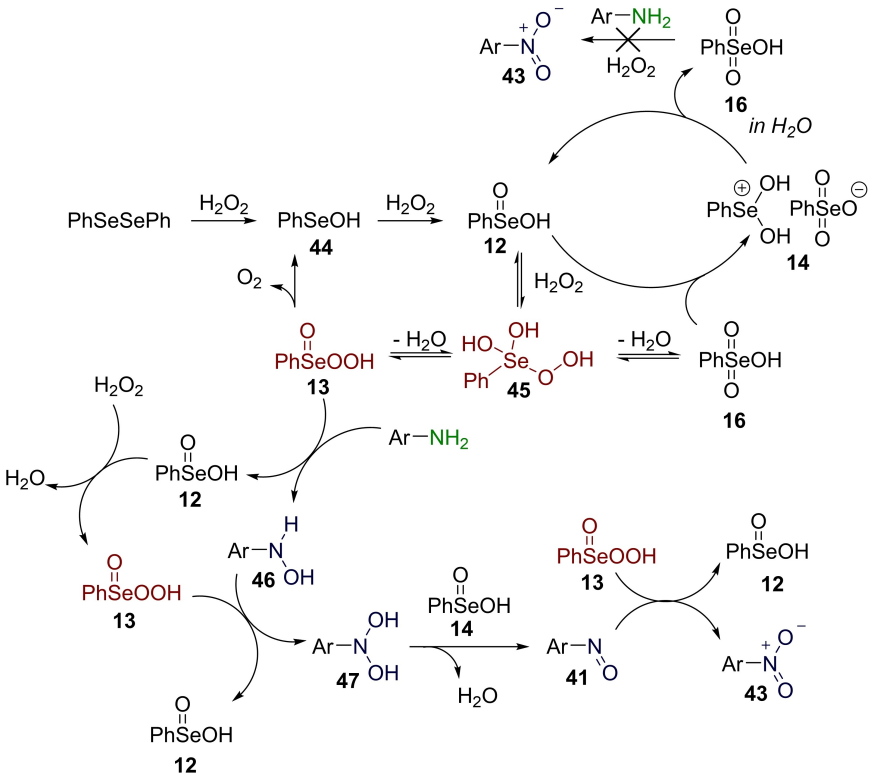
Scheme 14. Mechanistic investigations on the selenium-mediated oxidation of anilines. Control experiments.

Increased concentrations of reactive oxygen species (ROS), and oxidative stress in general, have been correlated with the onset and progression of several pathologies, including for example cancer, neurodegenerative disorders, and cardiovascular disease. In this context, the study and development of novel antioxidants have emerged as a vivacious research arena. The design, synthesis and study of a broad range of structurally diverse selenium-containing GPx-like catalyst have been described in the literature. Exemplificative structures of recently reported thiol-peroxidase-like catalysts are reported in the Figure 3.[35–41] Synthetic and mechanistic aspects of GPx-like compounds have been covered in depth by specific review articles and will be not reviewed herein.[42] Only very recently reported studies focusing on the selenium-catalysed oxidation of sulfur-containing organic compounds will be described in this section.

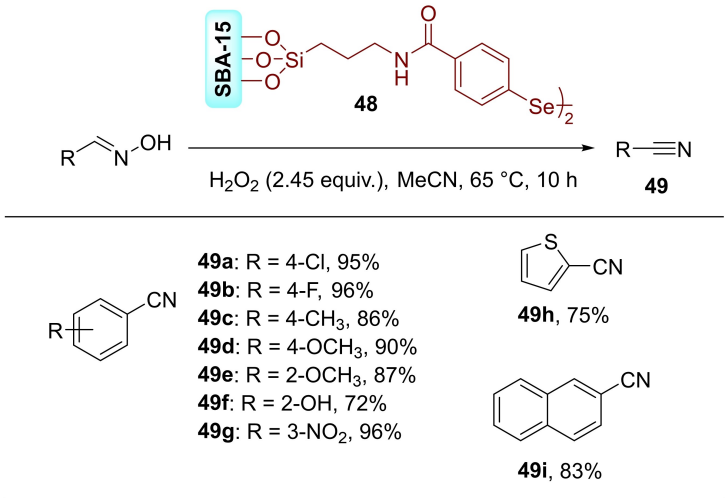
The selenium-catalysed aerial oxidation of thiols to the corresponding disulfides has been recently reported by Kumar and colleagues.[43] An initial optimisation study focusing on the evaluation of the activity of different organoselenium compounds highlighted that the diselenide **54** behaved as the most effective catalyst in promoting the desired transformation. This simple approach was applied to differently substituted thiols, enabling to smoothly achieve a broad range of aryl disulfides bearing electron-withdrawing and electron-donating groups at different position of the aromatic ring (**55a–h**) as well as variously functionalised alkyl and heteroaryl thiols (Scheme 18). Notably, the aerial oxidation of biologically relevant glutathione to the corresponding disulfide **55k** was also efficiently accomplished under the standard conditions (Scheme 18).

The proposed reaction mechanism is reported in the Scheme 19. In the first step of the mechanism, the reaction of the diselenide **54** with a thiol leads to the selenol **56** and the selenenyl sulfide **57**. Then, the selenenyl sulfide **57** may react with another molecule of thiol to afford the disulfide **55** and the selenol **56**. Oxidation of the selenol **56** with oxygen provides hydrogen peroxide and the selone intermediate **58**, which undergoes addition with a thiol to generate the selenenyl sulfide **57** (Scheme 19, Path A). Notably, the selenol **56**, phenylthiyl and hydroperoxyl radicals might also be formed upon reaction of selenenyl sulfide **57** with oxygen. In the path B, which is analogue to the catalytic cycle typically accounting for the thiol-peroxidase like activity of diselenides, the selenol intermediate **56** is oxidised to the corresponding selenenic acid **59** by H_2O_2. Condensation of **59** with a thiol leads to the selenenyl sulfide **57** which, upon reaction with another molecule of thiol, releases the disulfide **55** and regenerates the selenol intermediate **56** (Scheme 19, Path B).[43]

Recently, Santi and colleagues described a simple, selective, and scalable selenium-catalysed procedure for the oxidation of sulfides to the corresponding sulfoxides and sulfones under flow conditions (Scheme 20).[44] Selenous acid, which is generated in situ by the oxidation of selenium (IV) oxide in a diluted aqueous solution of hydrogen peroxide, is the catalyst actually involved in the transformation. The scope of the reaction proved to be rather broad, enabling the conversion of aryl alkyl sulfides, aryl vinyl sulfides, and dialkyl sulfides into



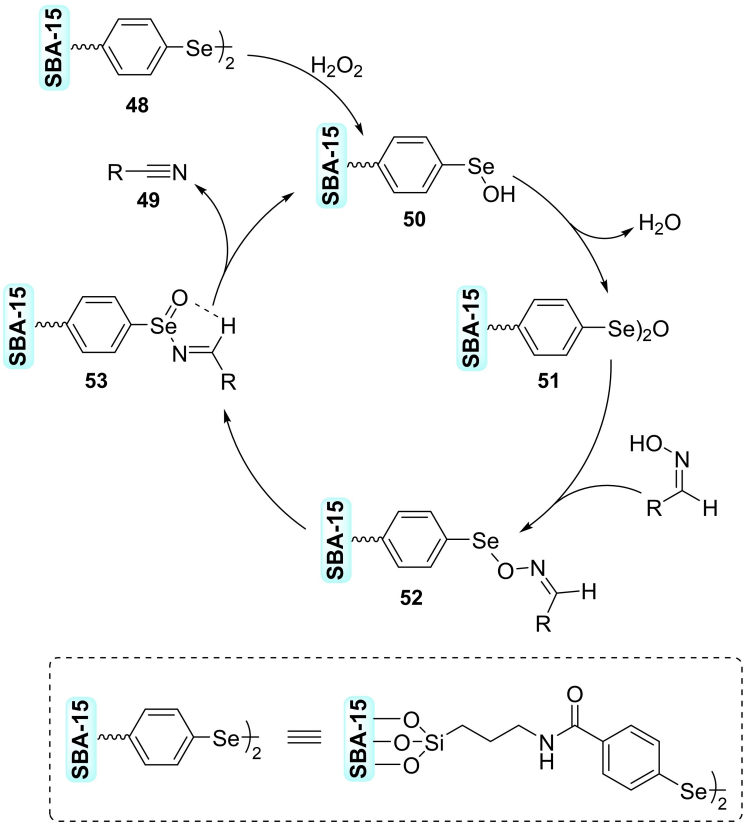
Scheme 15. Proposed mechanism for the organoselenium-promoted oxidation of anilines to nitroarenes.



Scheme 16. Selenium-mediated oxidation of oximes to nitriles. Selected examples.

the corresponding sulfoxides **60** and sulfones **61** in good yield and with excellent selectivity (Scheme 20).

The proposed catalytic cycle is depicted in the Scheme 21. In water, selenium (IV) oxide is in equilibrium with its hydrated form (selenous acid, **62**), which is particularly prone to undergo oxidation with hydrogen peroxide to afford the corresponding peroxyselenous acid **63** as the actual oxidising agent involved in the formation of both the sulfoxide **60** and sulfone **61**, depending on the amount of the oxidant. Thus, while selenous acid **62** behaves as the actual catalyst, selenium (IV) oxide **1** is conveniently used as pre-catalyst.[44]



Scheme 17. Proposed mechanism for the selenium-mediated conversion of oximes to nitriles.

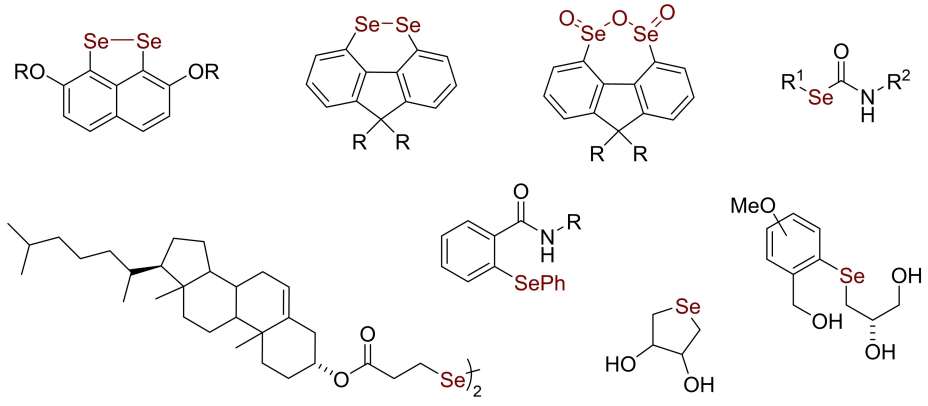
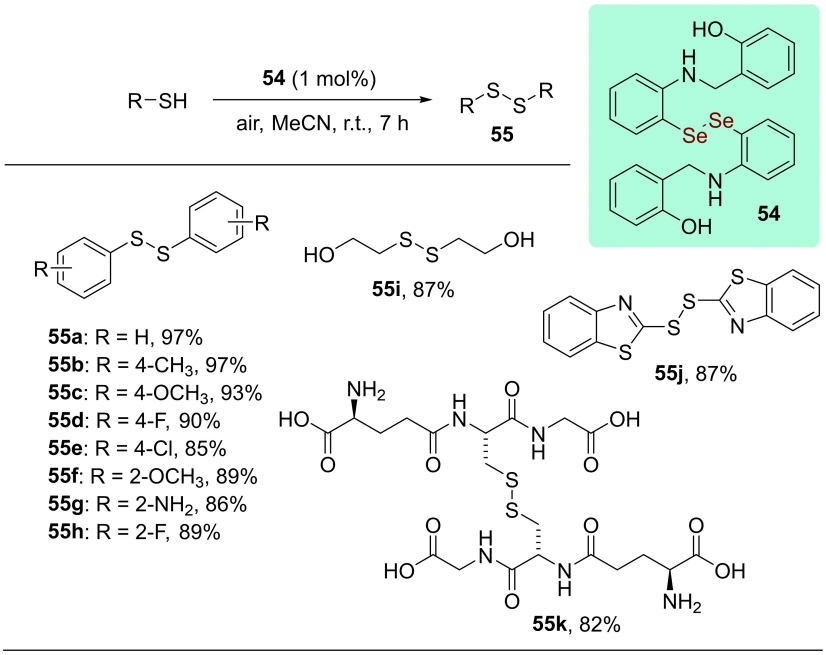


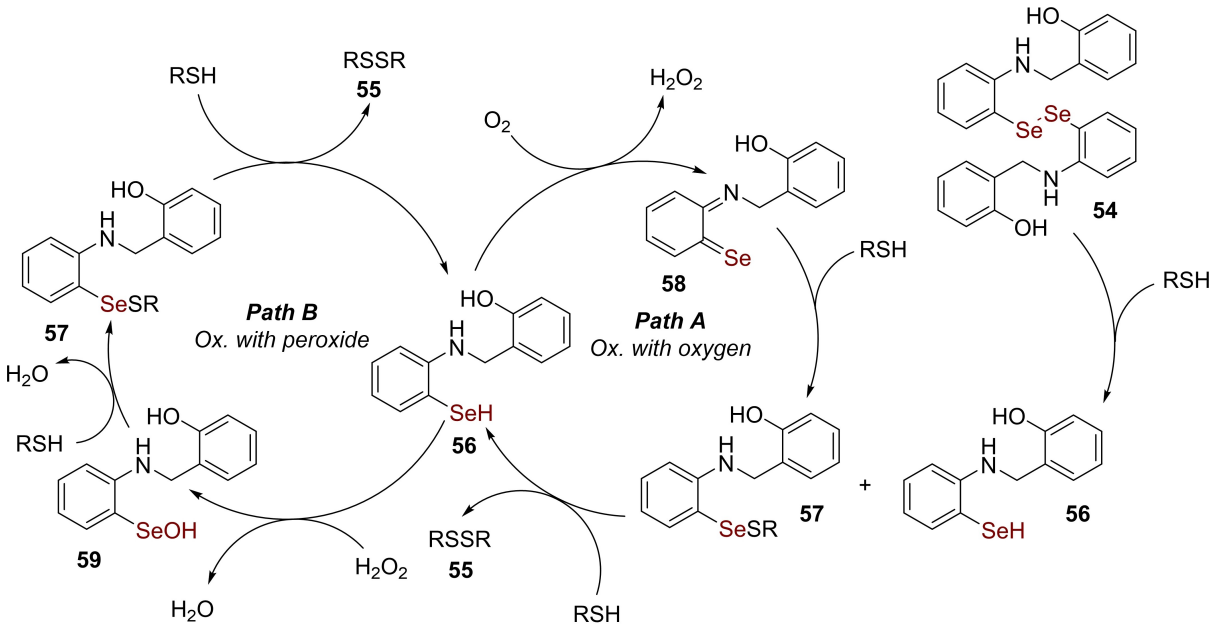
Figure 3. Recently reported thiol-peroxidase-like organoselenium compounds. Selected examples.[35–41]

The selenium-mediated oxidation of disulfides to thiolsulfinates has also been reported by Back and colleagues.[45] Driven by the observation that – in the presence of certain seleninate-ester-based catalysts – the concentration of disulfides formed upon oxidation of thiols with H_2O_2 reached a maximum at ca. 50–60 % completion of the reaction and then decreased in the later stages of the process, the authors envisaged the possibility to develop a selenium-catalysed protocol for the oxidation of disulfides.

Indeed, treatment of disulfides with an equimolar amount of hydrogen peroxide in the presence of the cyclic seleninate **6** enabled the formation of the corresponding thiolsulfinates **64** in rather good yield and with high selectivity over related thiolsulfonates **65**. Optimisation studies indicated that a 95 : 5

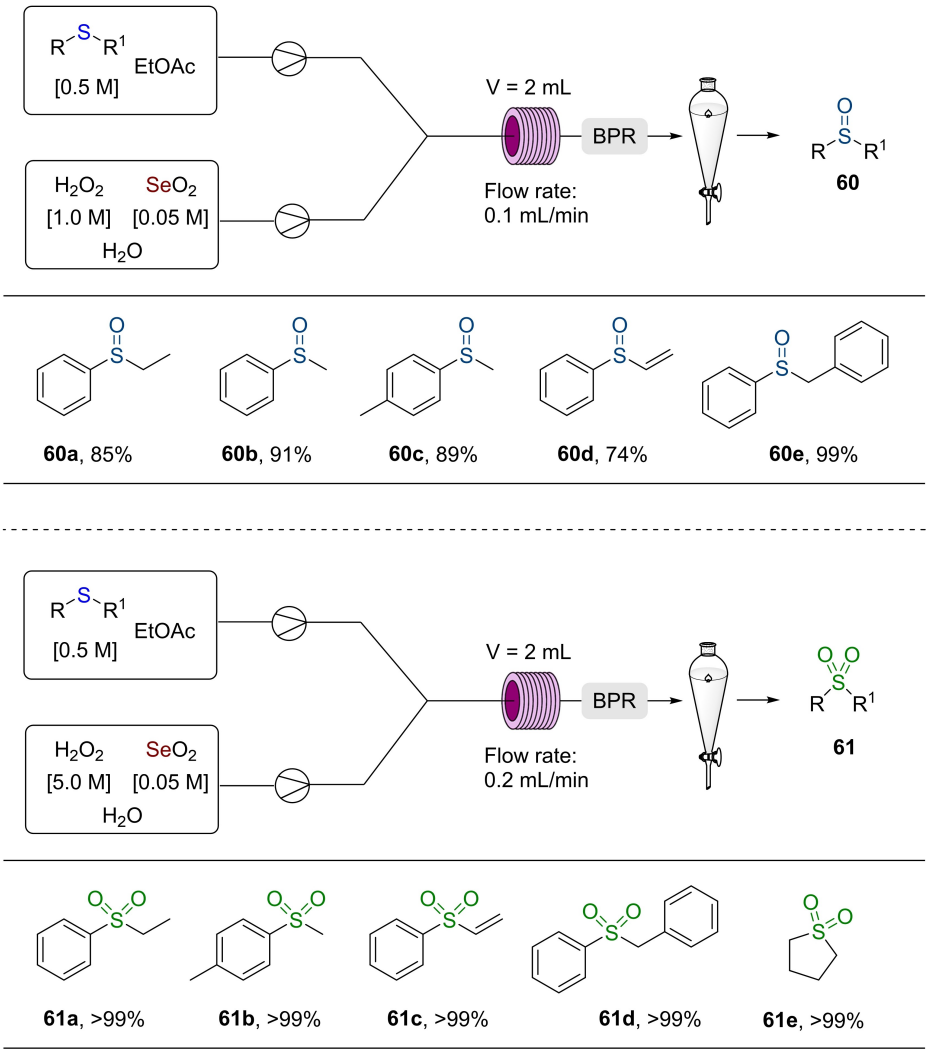


Scheme 18. Selenium-catalysed aerial oxidation of thiols.



Scheme 19. Proposed mechanism for the aerial oxidation of thiols to disulfides catalysed by the diselenide **54**.

mixture of dichloromethane and methanol was capable to improve the conversion of the starting material to the product **64** and to increase the reaction rate. The reaction scope proved to be broad, encompassing aryl- and alkyl-substituted substrates (Scheme 22). In the case of electron-rich aryl derivatives, the formation of the thiolsulfinate was accompanied by significant amount of the corresponding thiolsulfonate (*i.e.*, **65c**); on the other hand, electron-poor substrates (*i.e.*, 4-fluorophenyl derivative) were scarcely reactive and a large amount of unreacted starting material was recovered (Scheme 22, **64b** and **65b**). Notably, a partial decomposition of thiolsulfinates occurred upon their purification by column

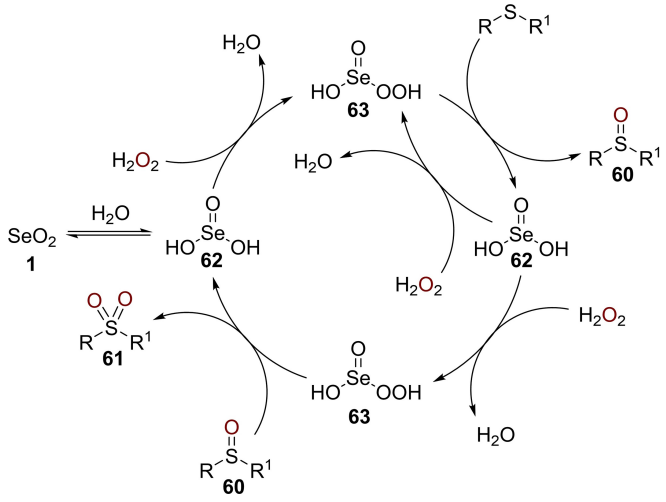


Scheme 20. Selenium-catalysed procedure for the oxidation of sulfides to the corresponding sulfoxides (above) and sulfones (below) under flow conditions. Selected examples.

chromatography on silica gel. Thus, in some cases (*i.e.*, allicin **64i**), relatively modest yields were achieved. The methodology could also be applied to the oxidation of unsymmetrical disulfides, generally providing mixtures of regioisomeric thiolsulfinates and overoxidised products (thiolsulfonates). In the case of aryl-alkyl disulfides, the oxidation preferentially occurred at the alkyl-substituted sulfur atom.[45]

Notably, the protocol was also extended to the oxidation of L-*N*,*N*'-dibenzoylcysteine dimethyl ester, which was converted into a complex mixture of products that could not be separated (Scheme 23). NMR and mass spectra suggested the formation of the diastereoisomeric couple of thiolsulfinates **64j/64k** as well as other unidentified compounds, thus highlighting how the seleninate **6** can promote the oxidation of disulfide linkages of native proteins when used as GPx-like agent *in vivo*.[45]

The proposed reaction mechanism (Scheme 24) is similar to that reported for the catalytic oxidation of sulfides, alkenes, and enamines with H_2O_2 in the presence of **6**[46] and is thought to proceed *via* the initial formation of the peroxyseleninic acid **68** or the peroxyselenurane **67** from **66** and hydrogen peroxide (Scheme 24, a). Such a reaction is enhanced by the protonation of the seleninate **6** by an acid catalyst. The following step involves the oxygen transfer from **67** or **68** to the most electron-rich sulfur atom of the disulfide, leading to the thiol sulfinate **64** and regenerating the catalyst **6** (Scheme 24, b). The formation of anions **69** or **70** upon reaction of the seleninate **6** with hydroxide anions provides explanation for the suppression of the oxidation observed



Scheme 21. Proposed reaction mechanism for the selenium-catalysed oxidation of sulfides to sulfoxides and sulfones.

under basic conditions. Indeed, anions **69** and **70** are unable to react with H_2O_2 to form the active oxidant intermediates **67** and **68** (Scheme 24, c).

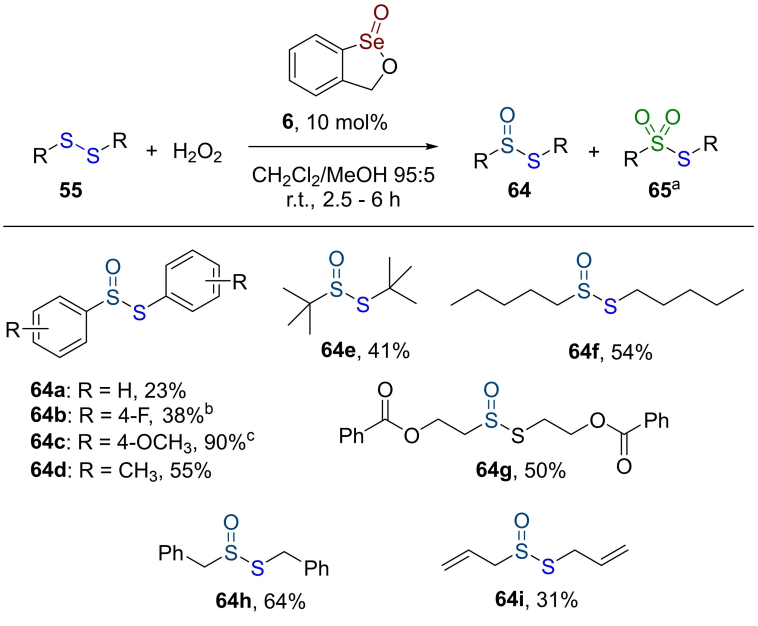
3. Selenium-Mediated Reductive Functional Group Interconvesrions

As stated above, reduced selenium species (*i.e*, selenide anions, hydrogen selenide, selenols) can be employed as reducing agents towards different functional groups. The possibility to generate such species *in situ*, upon reaction of suitable selenium precursors (*i. e.*, elemental selenium, diselenides) with various reducing agents, also enables the development of catalytic procedures. Additionally, selenium compounds can be used as ligands in enantioselective reduction routes. In this arena, selenium-mediated reductions have been demonstrated to offer new interesting opportunities for the development of mild, sustainable, selective and scalable procedures.

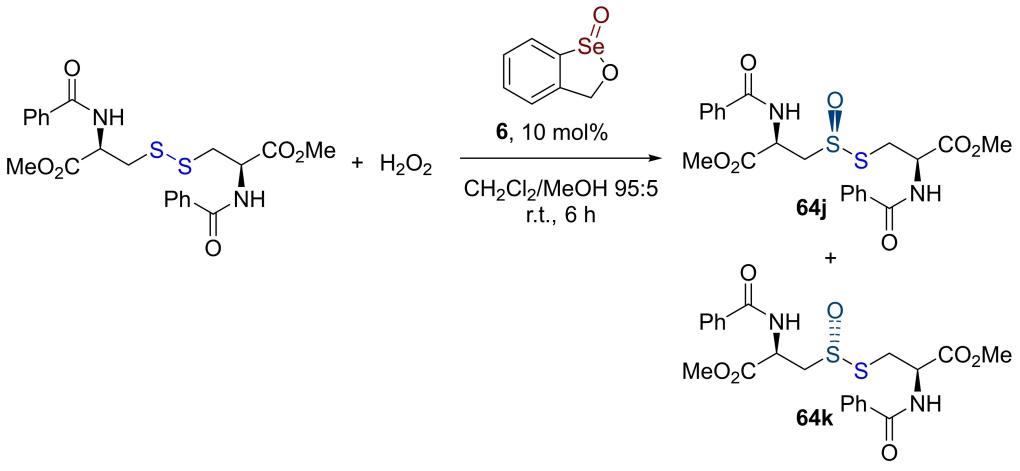
However, although their potential importance, selenium-mediated reductive functional groups interconversion have received far less attention. To the best of our knowledge, only few examples focusing on the reduction of suitably substituted alkenes and alkynes, ketones, and nitrogen-containing compounds have been documented.[3] In this section, the main synthetic and mechanistic aspects of selenium-mediated reductions will be discussed.

3.1. Selenium-Mediated Reduction of Alkenes and Alkynes

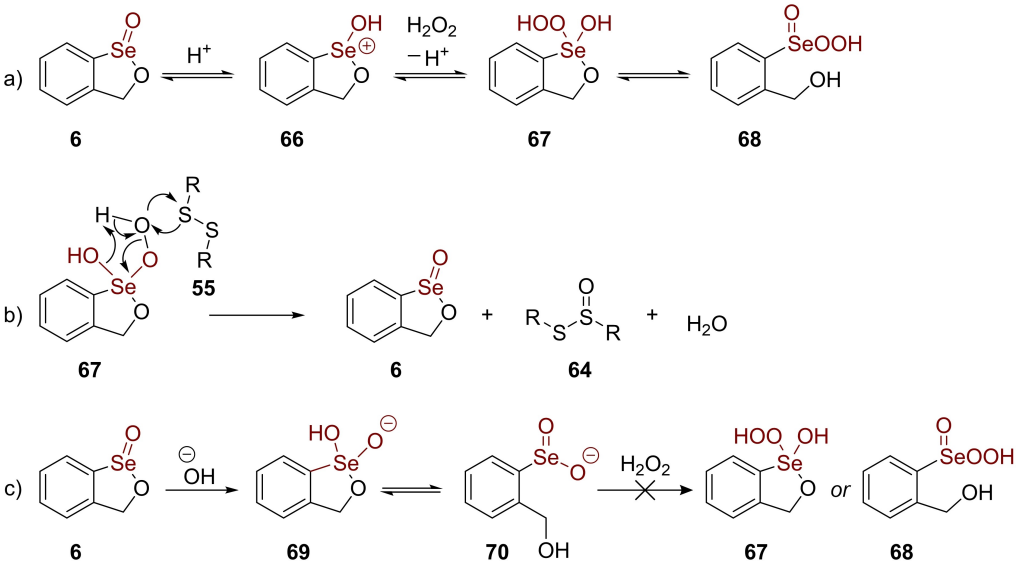
A number of selenium-based procedures for the reduction of α,β-unsaturated ketones to the corresponding alkyl ketones have also been developed.[47,48] Such methodologies rely on the



Scheme 22. Oxidation of disulfides to thiolsulfinates with H_2O_2 catalysed by the cyclic seleninate **6**. Selected examples. [a]Variable amounts (traces-35 %) of corresponding thiolsulfonate were often formed. [b]52 % of starting material remained unreacted. [c]Isolated in a mixture with the corresponding thiolsulfonate.



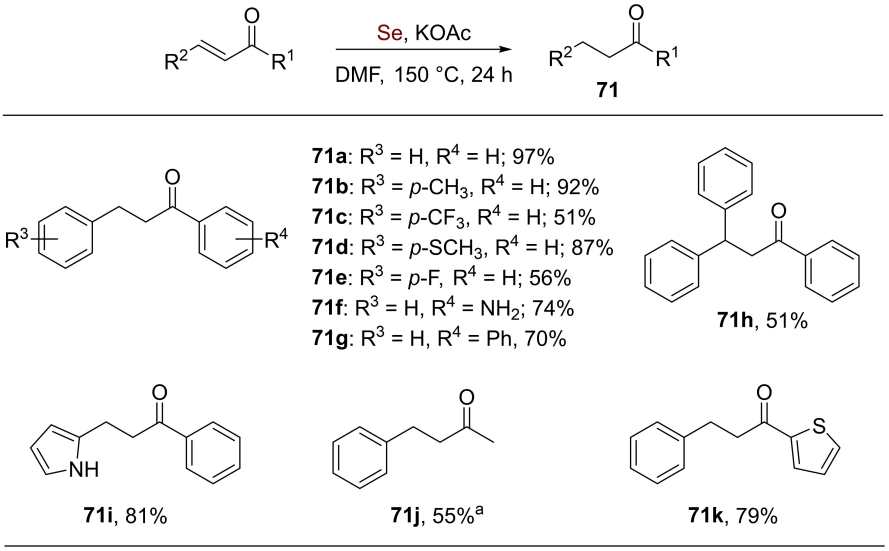
Scheme 23. Oxidation of L-*N*,*N*'-dibenzoylcysteine dimethyl ester with H_2O_2 catalysed by the cyclic seleninate **6**.



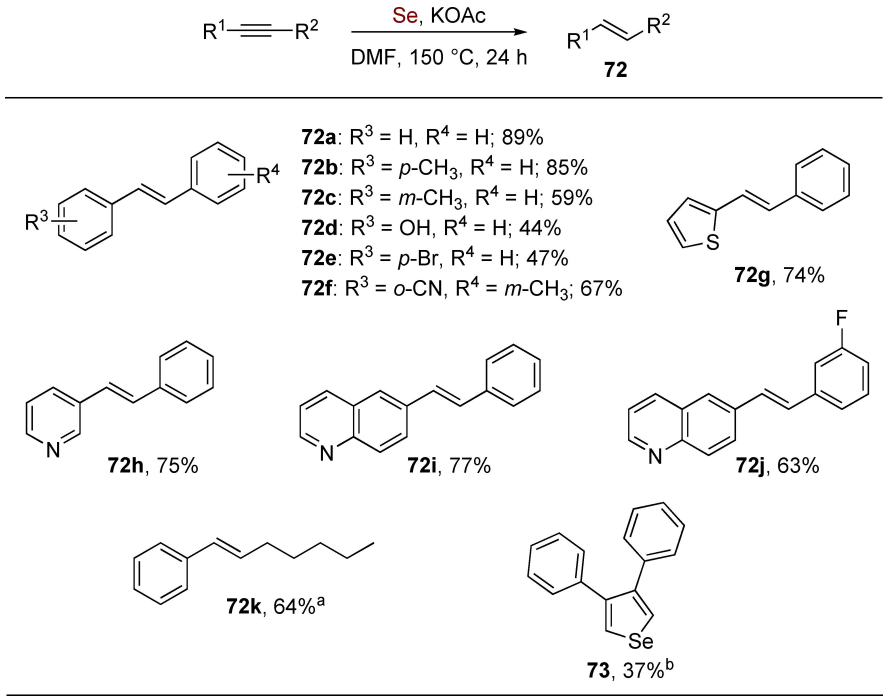
Scheme 24. Mechanistic aspects of the oxidation of disulfides to thiolsulfinates with H_2O_2 catalysed by the cyclic seleninate **6**.

reactivity of carbonyl selenide[47] or MHSe (M=Na or Li),[48] which are generated *in situ* and used as reducing agents. Similarly, the reactivity of *in situ* generated carbonyl selenide under aqueous condition has also been harnessed for the reduction of α- and β- diketones to the corresponding monoketones as well as for the reduction of aryl ketones to the related benzyl derivatives.[49,50]

In this scenario, a transition metal-free selenium-based protocol for the reduction of α,β-unsaturated ketones and alkynes has been recently reported.[51] The methodology relies on the reactivity of H_2Se (or HSe^-) as the reducing agent, and employs water as a safe, inexpensive, hydride surrogate. The reducing agent is *in situ* formed from the Se/DMF/H_2O system. Notably, this approach enables the conversion of α,β-unsaturated ketones to the corresponding saturated analogues with good yield and high selectivity (Scheme 25). Similarly, the protocol could be successfully applied to a series of alkynes, which underwent semihydrogenation to provide the related *E*-alkenes with excellent stereoselectivity (Scheme 26). Alkynes bearing differently substituted aryl and heteroaryl moieties were converted into the corresponding *E*-alkenes in general good yield; lower yields were obtained in the case of substrates bearing hydroxyl and bromo groups (**72d** and **72e**, Scheme 26). The amenability of aryl-alkyl alkynes to this protocol was demonstrated by its application to the synthesis of **72k**, which was obtained in good yield and stereoselectivity



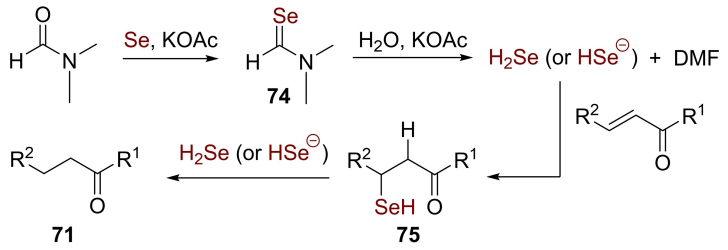
Scheme 25. Reduction of α,β-unsaturated ketones with the Se/DMF/KOAc system in H_2O. Selected examples. [a]$Na_3PO_4{\cdot}12H_2O$ is used as the base.



Scheme 26. Reduction of alkynes with the Se/DMF/KOAc system in H_2O. Selected examples. [a]The product **72 k** was formed alongside 1-phenylheptane (88 : 12 ratio). [b]Obtained upon reaction of phenylacetylene under the standard conditions.

(*E*/*Z* > 20 : 1). Notably, treatment of phenylacetylene under the standard conditions led to the selenophene **73** rather than the expected styrene (Scheme 26).

A series of control reactions, including deuterium-labeling experiments, were accomplished in order to gain insights into the reaction mechanism; H_2O was proposed to behave as the hydride donor in this reduction process. A plausible mechanism for the reduction of α,β-unsaturated ketones is depicted in the Scheme 27. The first step involves the selenylation of DMF to afford the selenoamide intermediate **74**, easily undergoing hydrolysis to provide DMF and H_2Se (or HSe^-), which has been demonstrated to behave as an effective



Scheme 27. Proposed mechanism for the reduction of α,β-unsaturated ketones with the Se/DMF/KOAc system.

reducing agent towards different organic compounds. Conjugate addiction of H_2Se (or HSe^-) to the α,β-unsaturated ketone leads to the corresponding Michael adduct intermediate **75** which, upon reaction with H_2Se (or HSe^-), provides the reduced product **71**. Notably, while the use of weak bases such as KOAc and $KHCO_3$ was demonstrated to promote the reduction, strong bases (*i.e.*, *t*-BuOH, KOH) were detrimental to this reductive protocol. The conversion of HSe^- into Se^{2-} – occurring in the presence of strong bases – could account for the observed results.

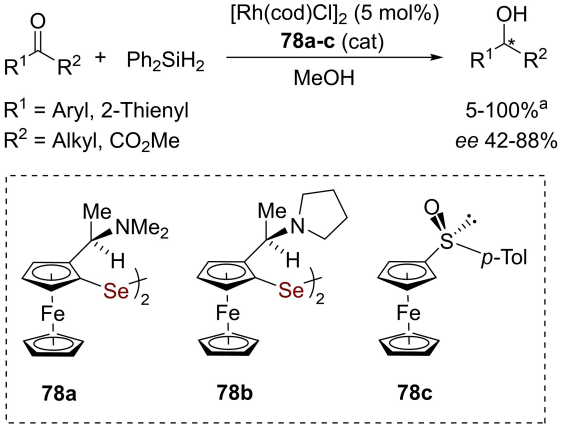
Organic selenols can also be directly employed as reducing agents in reactions with aromatic nitrogen-containing compounds (*i.e.*, nitro-, nitroso-, hydroxylamino-, azoxy-, azo-, and hydrazo- derivatives),[52] benzyl halides,[53] and disulfides.[54,55]

Alkyl- and aryl-substituted selenols can be efficiently used as reducing agents for the conversion of dialkyl dicyanofumarates **76** into the corresponding dicyano succinates **77** (Scheme 28).[56]

3.2. Selenium-Mediated Reduction of Carbonyl Compounds

The enantioselective hydrosilylation and reduction of ketones to the corresponding alcohols in the presence of Rh(I) catalysts and chiral ferrocenyl diselenide-based ligands **78** was disclosed by Uemura and colleagues (Scheme 29).[57–59] Related iridium(I) and ruthenium(II)-catalysed procedures were also studied.[58,59]

A plausible reaction mechanism is reported in the Scheme 30.[58] The first step is the ligand exchange of cyclooctadiene on the Rh(I) complex with the diselenide. Then, the

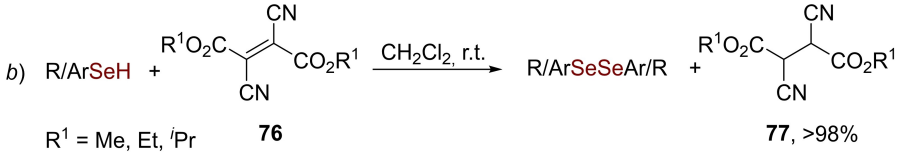


Scheme 29. Rhodium-catalysed asymmetric transfer hydrogenation of ketones using diferrocenyl diselenides as chiral ligands. [a]GLC yield is reported.

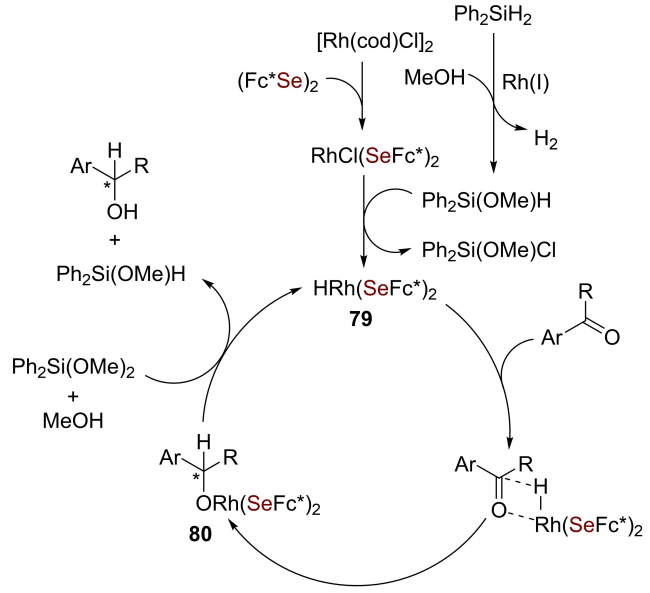
resulting Rh(I)-diselenide complex catalyses the reaction of diphenylsilane with methanol to generate hydrogen and methoxydiphenylsilane. Then, the $RhCl(SeFc^*)_2$ complex is probably converted into the corresponding Rh-hydride **79**, which reasonably reacts with the carbonyl compound in an enantioselective fashion to afford the intermediate **80**. The final step of the mechanism involves the conversion of the intermediate **80** to the corresponding alcohol.

3.3. Selenium-Mediated Reduction of Nitrogen-Containing Functional Groups

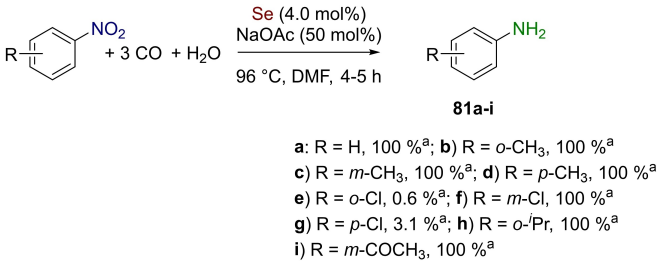
A number of selenium-mediated reduction methodologies relying on the reactivity of carbonyl selenide (Se=C=O) have



Scheme 28. Reduction of dialkyl dicyanofumarates to the corresponding dicyano succinates using selenols.



Scheme 30. Proposed mechanism for the Rhodium-catalysed asymmetric transfer hydrogenation of ketones in the presence of diferrocenyl diselenides as chiral ligands.



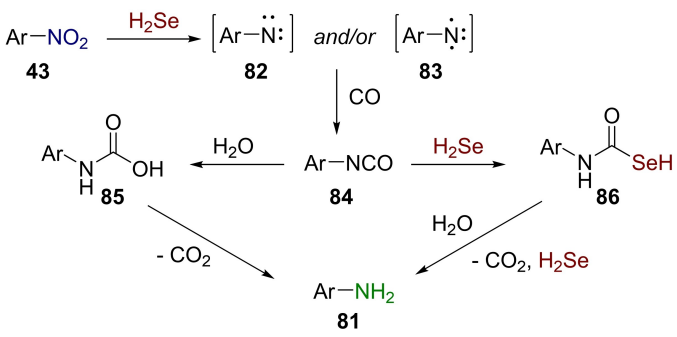
Scheme 31. Selenium-catalysed reduction of nitroarenes to anilines. [a]Conversion is reported.

been reported. Although this compound is a gas at room temperature and it is difficult and dangerous to handle, convenient procedures for its generation and use *in situ* have been described. Generally, carbonyl selenide is hydrolysed in solution to give hydrogen selenide, which is the effective reducing agent involved in such reactions. Carbonyl selenide-based reductions of nitro derivatives have been reported in the past decades.[60,61] These reductions enabled the conversion of nitroarenes into the corresponding anilines which, in the presence of suitable functional groups can be employed to accomplish intramolecular condensation and cyclisation reactions, leading to quinolines, indoles, pyrroles, 3,4-dihydroquinazolin-3-ones, and benzimidazoles.[62–66]

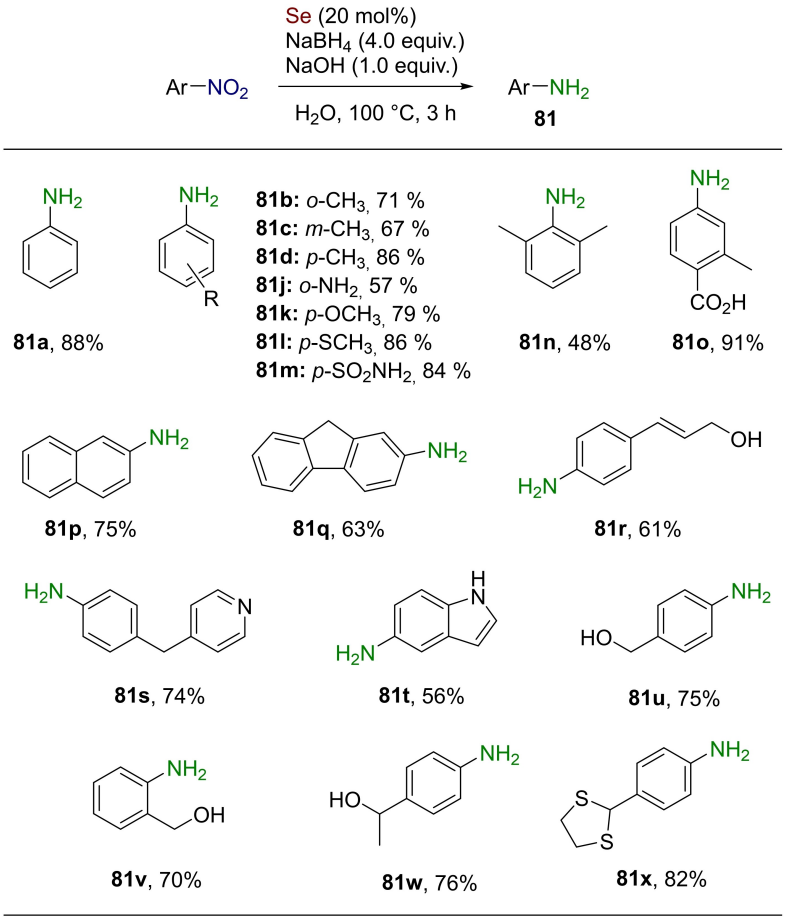
Liu and Lu reported an efficient protocol for the reduction of nitroarenes to anilines with CO/H_2O in the presence of catalytic amounts of selenium under basic conditions and atmospheric pressure (Scheme 31).[67] The reaction is performed using a polar aprotic solvents (*i.e.*, DMF), which favour the formation of carbonyl selenide (SeCO) and promote the nucleophilic attack of water affording H_2Se or its anions. Sodium acetate is used as the co-catalyst. Intriguingly, tertiary amines and strong inorganic bases proved to be detrimental for the reaction. Notably, while organic bases promote the formation of SeCO inorganic mild bases (*i.e.*, NaOAc, Na_2CO_3) are believed to stabilise H_2Se or its anions. In line with these hypotheses, the use of an equimolar amount of Et_3N and NaOAc gave the best results in terms of conversion values. Although the reaction scope seems to be rather broad, the presence of electron-withdrawing groups at *ortho* or *para* position led to a dramatic decrease of conversion values (Scheme 31).

The proposed reaction mechanism (Scheme 32) involves the initial reaction of hydroselenic acid (or its anion) – *in situ* formed upon reduction of selenium with CO in the presence of H_2O and the base – with the nitroarene, which is deoxygenated to provide the corresponding nitrene (**82**) or nitrenoid (**83**) intermediate. Reaction of **82** and/or **83** with CO leads to the isocyanate **84**, which is converted to the carbamic acid or selenocarbamic acids **85** and **86** upon nucleophilic attack of H_2O and H_2Se, respectively. Finally, the formation of the aniline occurs *via* decarboxylation of the carbamic acid **85** or through reaction of the selenocarbamic acid **86** with H_2O and release of CO_2 and H_2Se.[67]

Recently, we also reported a selenium-catalysed methodology for the reduction of nitroarenes to anilines with sodium borohydride in water in the presence of sodium hydroxide (Scheme 33).[8] The methodology relies on the possibility to employ Na_2Se, *in situ* generated upon reaction of selenium with $NaBH_4$, as the reducing agent. The scope of the reaction proved to be broad, encompassing nitroarenes bearing both electron-donating and electron-withdrawing groups at different position of the aromatic ring. Heteroaromatic nitro derivatives



Scheme 32. Proposed mechanism for the reduction of nitroarenes to anilines with CO in the presence of Se.

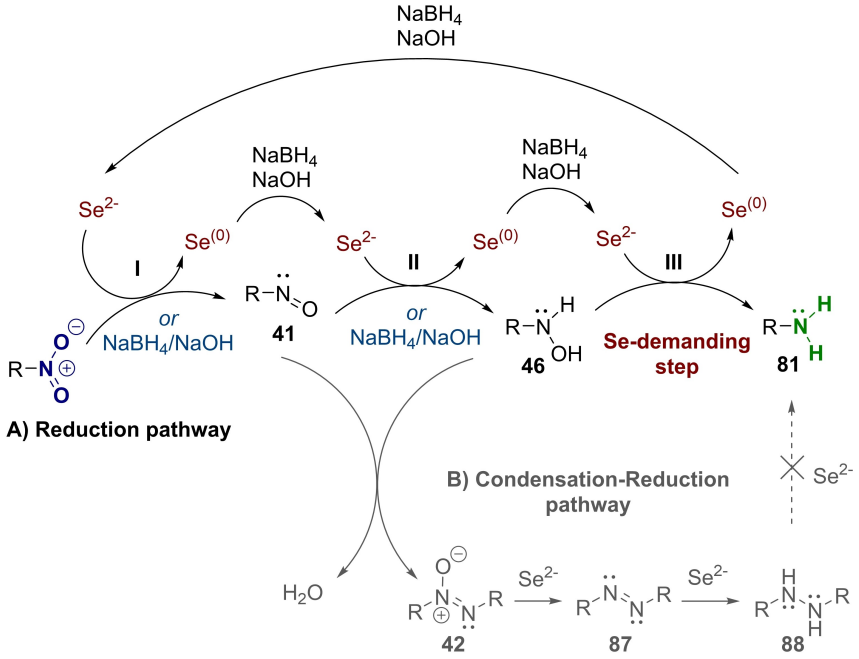


Scheme 33. Selenium-mediated reduction of nitroarenes to anilines with $NaBH_4$ in water. Selected examples. Isolated yields are reported.

were also amenable under these conditions, enabling to achieve the corresponding heteroaromatic amines in good yield (Scheme 33). As expected, in the case of nitrocarbonyl compounds (*i.e.*, 4-nitrobenzaldehyde, 2-nitrobenzaldehyde, 4'-nitroacetophenone) the reduction of the carbonyl group to the corresponding primary or secondary alcohol functionality also occurred, leading to aminobenzyl and amino-α-methylbenzyl alcohols **81v–w**. On the other hand, this Se-mediated protocol well tolerates protected carbonyl groups, enabling its application to the synthesis of aniline derivative **81x**, bearing the aldehyde functionality masked as 1,3-dithiolane (Scheme 33).

A series of control experiments confirmed that Na_2Se is the reducing agent involved in this reaction and highlighted that the mechanism proceeds through a direct reduction pathway (Scheme 34). The reduction of the nitro derivative with Na_2Se – generated *in situ* under reaction of elemental selenium with $NaBH_4$/NaOH in water – affords the nitroso compound **41** and elemental selenium, which is reduced back to Na_2Se by the $NaBH_4$/NaOH reducing system. Although the reduction of nitroarenes to the nitroso derivative **41** might also occur under selenium-free conditions, control experiments highlighted only very low conversion values for the reaction performed in absence of selenium, thus suggesting that the Se-free reduction plays only a marginal role in this step. Subsequently, both Na_2Se and $NaBH_4$ can reduce the nitroso derivative **41** to the corresponding hydroxylamine **46**, which is finally reduced to the aniline **81** by Na_2Se (Scheme 34). Notably, this last reduction step is a selenium-demanding reduction, as the hydroxylamine **46** proved to be completely unreactive under selenium-free $NaBH_4$/NaOH conditions.

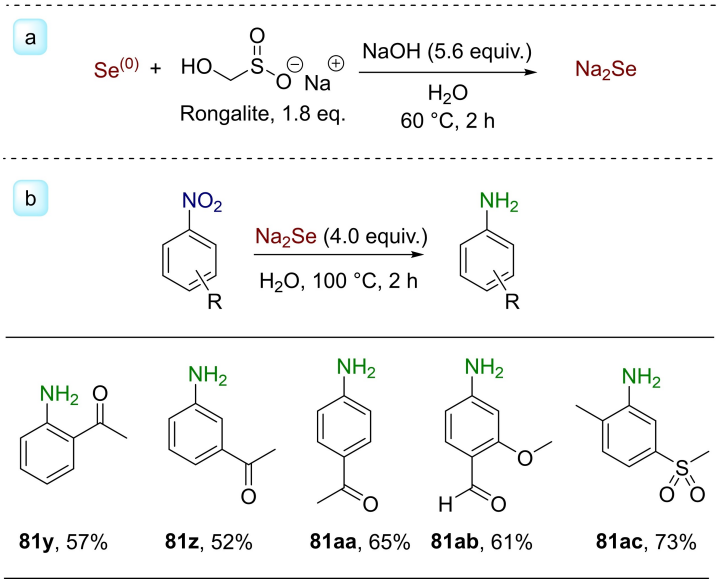
A condensation-reduction pathway – involving the formation of azoxyarene **42** by the reaction of nitrosoarene **41** with hydroxylamine **46** and its further reduction to aniline *via* diazoarene (**87**) and 1,2-diarylhydrazine (**88**) intermediates – was ruled out. Indeed, a series of control experiments highlighted that **42** does not undergo complete selenium-mediated reduction to give **81**, but is only partially reduced to the corresponding hydrazine **88** (Scheme 34). Notably, in absence of selenium **46** is not reduced and undergoes



Scheme 34. Proposed mechanism for the selenium-mediated reduction of nitroarenes to anilines with $NaBH_4$ in water.

condensation with **41** to yield the azoxy-derivative **42**, which is the only product observed under selenium-free conditions.[8]

Remarkably, the possibility to employ Na_2Se as the sole reducing agent – in absence of $NaBH_4$ and NaOH – was exploited to develop a mild protocol for the selective reduction of nitroarenes bearing labile functional groups. Treatment of nitroarenes with Na_2Se – freshly prepared upon reduction of elemental selenium with sodium hydroxymethanesulfinate (rongalite) and NaOH (Scheme 35, reaction a) – enabled to obtain functionalised anilines with excellent chemoselectivity.

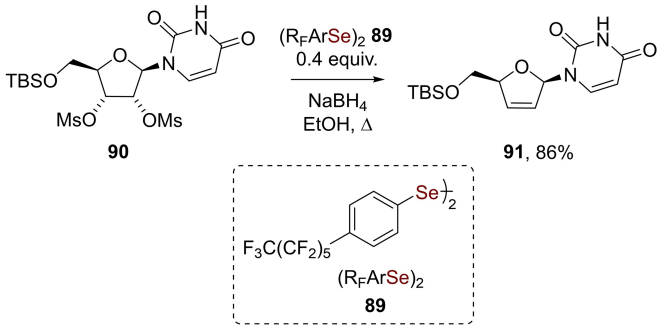


Scheme 35. Preparation of Na_2Se *via* reduction of elemental selenium with rongalite (Reaction a). Reduction of nitroarenes to anilines with Na_2Se in water (Reaction b).

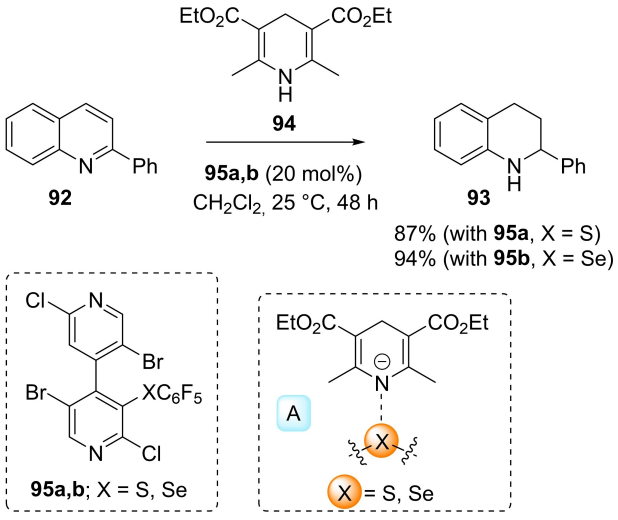
Under these conditions, nitrocarbonyl compounds were efficiently reduced to the corresponding aminocarbonyl derivatives. For example, 2'-, 3'-, and 4'-aminoacetophenones **81 y,z,aa**, and the aminoaldehyde **81 ab** were smoothly prepared upon reduction of the nitro group of the parent nitroacetophenone or nitroaldehyde. Similarly, the amino-derivative **81 ac** – bearing the labile sulfone functionality – was conveniently obtained from the related aromatic nitrosulfone.[8]

3.4. Other Selenium-Mediated Redox Transformations

Selenium mediated reductions of other functional groups have also been reported. For example, conversion of vicinal dibromides and alfa-haloketones into the corresponding alkenes and ketones, respectively was achieved *via* reductive dehalogenation occuring with hydrogen selenide generated upon decomposition of carbonyl selenide in water and *N*-methylpyrrolidine.[68]



Scheme 36. Diselenide-catalysed conversion of vicinal dimesylates alkenes.



Scheme 37. Reduction of 2-phenylquinoline 92 with the Hantzsch esther in the presence of the bipyridyl selenide catalyst 95. Box A: Activation of the Hantzsch esther by the electron-poor bipyridyl selenide 95 *via* chalcogen bonding interaction.

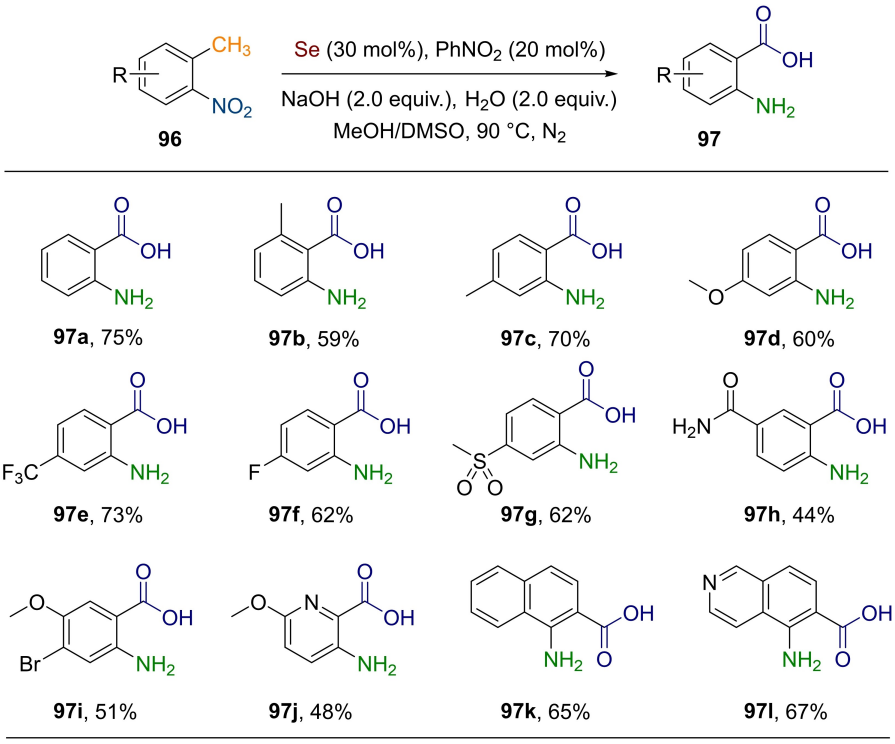
A diselenide-catalysed approach for the conversion of vicinal dimesylates to the corresponding alkene was reported by Crich (Scheme 36).[69] Particularly, the perfluorurated diselenide **89** was employed as the catalyst for the elimination of the vicinal dimesylate moiety of a series of substrates, including the nucleoside **90** which, using $NaBH_4$, was converted to the functionalized alkene **91**.

A selenium-mediated reduction of 2-phenylquinoline **92** to the corresponding tetrahydro derivative **93** was disclosed by Mamane and colleagues (Scheme 37).[70] The methodology proceeds through the activation of Hantzsch esther **94** by the electron-poor bipyridyl selenide catalyst **95** *via* chalcogen bonding interaction (Scheme 37, box A). Notably, although the activity of enantiopure (*P*)-**95 b** catalyst was investigated, an enantioselective version of this reductive approach could not be successfully developed.

The selenium-catalysed intramolecular transformation of *o*-nitrotoluenes into anthranilic acids has also been recently reported (Scheme 38). Selenium, in view of its redox properties, behaves as a catalyst for the oxidation of electron-rich C–H bonds and for the reduction of electron-poor nitro group. The use of an inorganic base was demonstrated to play a crucial role in this reaction. Optimisation studies highlighted that methanol/dimethyl sulfoxide was the best solvent system for this transformation, whose efficiency was further improved by the addition of two equivalents of water and by the use of nitrobenzene (20 mol%). Notably, this route was successfully applied to a series of variously substituted substrates; selected examples are reported in the Scheme 38.

A series of control experiments enabled to hypothesise the mechanism depicted in the Scheme 39, also supported by DFT calculations. In the presence of hydroxide, selenium powder, used as a (pre)catalyst can be dismutated to selenite (SeO_3^{2-}) and polyselenides (Se_n^{2-}). While both selenite and selenide (Se^{2-}) could not catalyze this reaction, polyselenides such as Na_2Se_2, Na_2Se_4, Na_2Se_6, and Na_2Se_8 were demonstrated to be catalytically active.

In the proposed mechanism (Scheme 39), sodium hydroxide first deprotonates one benzylic hydrogen of the *o*-nitrotoluene **96** providing the corresponding dearomatized anionic species **98**, which is then able to abstract a selenium atom from Se_n^{2-} to form Se_{n-1}^{2-} and **99**. Afterwards, a second deprotonation leads to **100** whose rearrangement provides the 5-membered-ring derivative **101**, which undergoes a series of transformations to give the intermediate **103**, formally completing an exchange of O for Se to achieve the mutual redox process. Indeed, in this process two pairs of electrons were formally transferred from the carbon centre to the nitrogen centre. Next, a second O-transfer process occurs; a new 5-membered-ring species (**104**) is formed via an intra-



Scheme 38. Selenium-catalysed conversion of *o*-nitrotoluenes to anthranilic acids. Selected examples.

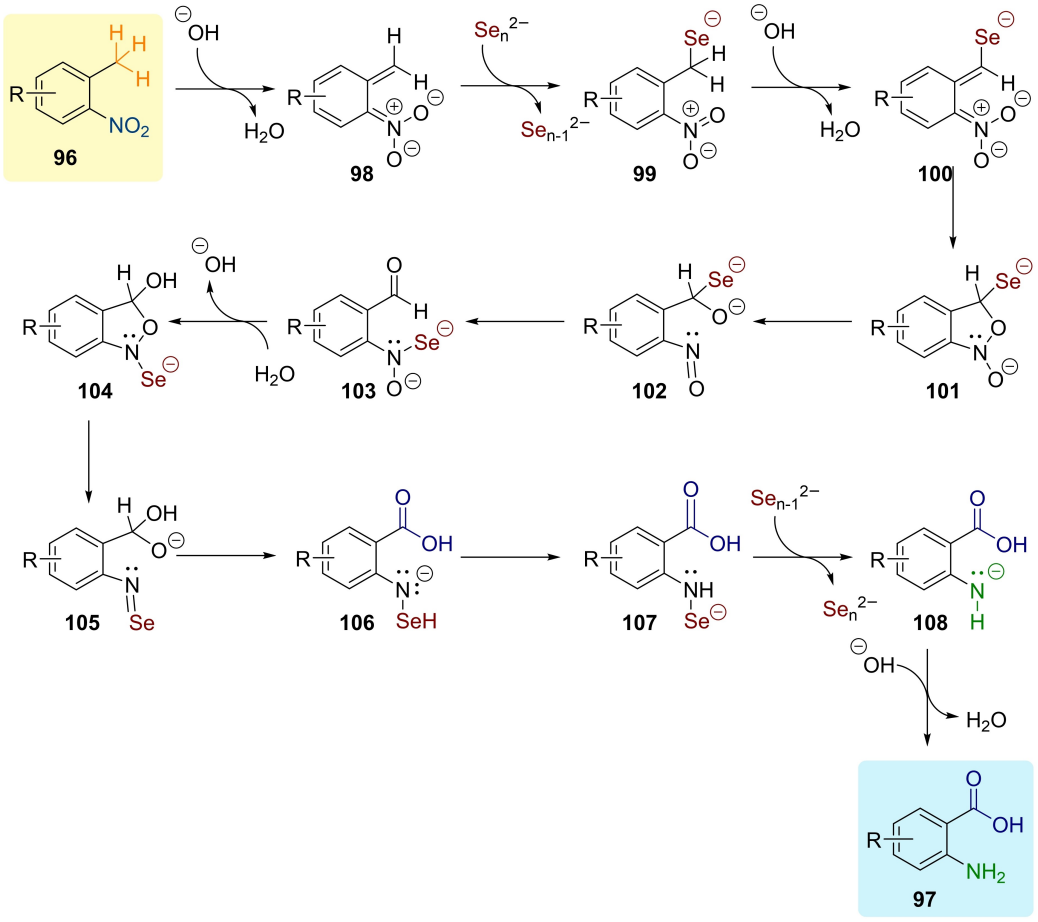
molecular O-nucleophilic attack onto the aldehyde carbon of **103**, followed by a ring N–O bond cleavage providing **105** and then a hydride transfer to give **106** and, after proton migration, **107**. This completes the second O-transfer and the formal transfer of the third pair of electrons. In the final stage, abstraction of a Se atom from **107** by Se_{n-1}^{2-} regenerates the catalyst and affords **108**, which undergoes hydrolysis to yield the anthranilic acid **97**.

4. Conclusions

Owing to their versatile chemistry, selenium compounds can be employed to accomplish a broad range of oxidation and reduction reactions. Because reactive selenium species behaving as oxidising or reducing agents can be generated *in situ* upon oxidation or reduction of suitable inert precursors (*i.e.*, elemental selenium, diselenides, selenides), a number of catalytic approaches have been developed. Particularly, reliable and convenient methodologies for the oxidation – among others – of alkenes, carbonyl compounds, thiols, and amines have been described. Over the past decades, selenium-mediated oxidative and reductive functional group interconversions have therefore become an important tool in organic synthesis and they have been employed in various synthetic sequences, including total syntheses.

Significant advances in the field of selenium-catalysed redox processes have been achieved in recent years and important efforts have been devoted to the development of selective, mild, scalable, and sustainable protocols. Studies on the possibility of recovering and reusing the catalysts have attracted considerable attention, and the number of papers focusing on sustainability have been steadily increasing. Remarkable insights into the mechanism of selenium-catalysed oxidation reactions have been recently reported. New selective selenium-mediated methodologies for the reduction of suitably substituted alkenes and alkynes, ketones, and nitrogen-containing compounds have been developed. For example, the possibility of selectively reducing nitro groups to the corresponding amine in the presence of labile and potentially competing carbonyl moieties have also been documented.

However, although significant advances have been achieved, important challenges remain ahead in the field. As mentioned above, while selenium-catalysed oxidative functional group interconversions have received considerable attention, selenium-mediated reductions have been far less explored albeit their prospective importance. Reduced selenium species (*i.e.*, selenols, selenolates, selenide anions) can behave as mild reducing agents, thus enabling the disclosure of unexpected and selective transformations. For these reasons, new directions in selenium-mediated reductive functional



Scheme 39. Proposed mechanism for the selenium-catalysed conversion of *o*-nitrotoluenes to anthranilic acids.

group interconversions will likely be pursued. Furthermore, enantioselective selenium-based reduction methodologies should be further explored.

Some mechanistic issues also need to be addressed as the nature of selenium species involved in certain catalytic pathways is not completely clear yet. For example, while clear evidences on the role of Se(VI) species in the epoxidation of alkenes and on the role of Se(IV) species in the oxidation of anilines to nitroarenes have been provided, the involvement of Se(VI) and Se(IV) species in the mechanism of other transformations remains to be fully elucidated.

The detailed comprehension of the reaction mechanism – and particularly the elucidation of the nature of active selenium species involved in the redox process – is key to developing chemoselective methodologies as well as to improving the sustainability of the process (*i. e.*, catalyst recoverability and reusability).

For example, the in-depth knowledge of the nature of the oxidant – *i. e.*, Se(VI) *vs* Se(IV) – offers a certain leeway to selectively accomplish oxidative functional group interconversions in the presence of labile moieties. In principle, the selective synthesis of either amino epoxides or nitroalkenes might be possible upon exploiting the different reactivity of Se(VI) and Se(IV) oxidants towards alkenes and anilines. On the other hand, the recycle of the catalyst completely relies on the knowledge of both the catalytic pathway and the fate of selenium species during such a pathway.

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