Selenium-Promoted Oxidation of Organic Compounds: Reactions and Mechanisms

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Oxidation reactions are fundamental processes widely applied in organic synthesis. Elemental selenium and more often its compounds have been successfully used as stoichiometric reagents and catalysts for oxidation of different organic substrates. Selenium(IV) oxide, areneseleninic acids and their anhydrides are widely used as stoichiometric oxidants or as oxygen-transfer agents for oxygen donors, particularly hydrogen peroxide and *tert*-butyl hydroperoxide. Organic diselenides (the precursors of seleninic acids) have been used as oxidation catalysts while dimethyl and diphenyl selenoxides are stoichiometric oxidants. Selenenamides, such as 2-phenyl-1,2-benzisoselenazol-3(2*H*)-one (ebselen) and its analogues, known as glutathione peroxidase mimics acting via active hydroperoxide intermediates, are efficient and selective oxidation catalysts. Selenium(IV) oxide and some organoselenium compounds have been successfully applied for various oxidations useful in practical organic syntheses such as epoxidation, 1,2-dihydroxylation, and α-oxyfunctionalization of alkenes as well as for ring contraction of cycloalkanones, conversion of halomethyl, hydroxymethyl, or active methylene groups into formyl groups, oxidation of aldehydes into carboxylic acids, sulfides into sulfoxides, and secondary amines into nitrones, regeneration of parent carbonyl compounds from their azomethine derivatives and for other reactions. The oxidation mechanisms depend on the substrate and oxidant or catalyst used. The electrophilic center localized on the selenium atom or the nucleophilic center localized on the oxygen atom of the selenahydroperoxide group are involved in the reaction mechanism. In both cases the selenium-containing moiety is a good leaving group. Exceptionally oxidation can proceed via free radical selenium species.

1. Introduction

The very rapid development of synthetic methodology is based mainly on the introduction of a great variety of heteroorganic derivatives as reagents and catalysts. Among them an important role is played by selenium compounds.[1] Moreover, owing to the synthetic utility of the oxidative conversion of a broad spectrum of organic substrates, oxidation is one of the fundamental processes very often applied in contemporary organic synthesis in both research and industry. Particularly important among the oxidants are hydrogen peroxide and *tert*-butyl hydroperoxide (TBHP) as commercially available and cheap reagents of low molecular weight.[2,3] They contain a high proportion of active oxygen and are environmentally friendly, because their reduction products are water or *tert*-butanol. Since they are only moderately active toward most organic substrates, many promoters are used, among them selenium compounds. In most reactions these function as catalysts, transferring oxygen atoms from stoichiometric oxygen donor to oxidized substrate.

It should be noted that selenium compounds are generally regarded as toxic. It is important to realize that elemental selenium is nontoxic in contrast to the highly toxic hydrogen selenide. Thus experiments in which hydrogen selenide is used as the reagent or is evolved during the reaction should be avoided, or should be done with precautions. The volatile alkyl selenides and selenols, although malodorous, are less toxic than hydrogen selenide. Selenium compounds of low volatility such as selenium(IV) oxide, selenic(IV) and selenic(VI) acids, diphenyl diselenide, areneseleninic acids, their anhydrides, and related compounds are odorless but may be moderately toxic when absorbed. They may also cause skin irritation. The toxicity of most organoselenium compounds remains unknown but according to known rules their toxicity should be low.[4] For example, ebselen is practically nontoxic (LD_{50} = 6.8 g·kg^{-1}).[4d]

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MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

Selenium is relatively cheap in comparison to other modern catalysts used for hydroperoxide oxidation (Se: US $ 0.03 per mol, MTO: US $ 35 per mmol). Moreover, some of the selenium reagents and catalysts can be recovered.[4e,5]

In this Microreview we present the developments in the application of selenium compounds as oxidants and oxygen-transfer catalysts useful in contemporary organic synthesis. The mechanisms of their action in oxidation processes are discussed.

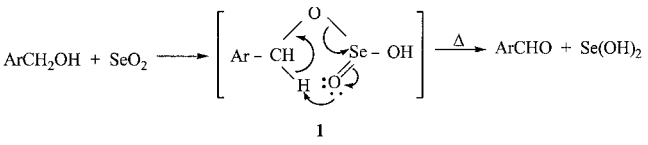
2. Selenium and Its Inorganic Compounds

2.1 Selenium

Elemental selenium has been used for aromatization of unsaturated homo and heterocyclic rings. All these reactions, carried out at elevated temperature (ca. 300 °C), are of minor importance because of low selectivity and hydrogen selenide elimination. For example, the alkyl groups in 2-ethyl-3,5-dimethylpyridine are oxidized into carboxylic groups by heating with concentrated sulfuric acid in the presence of catalytic amounts of selenium at 300 °C. The active oxidant is, most probably, selenium(IV) oxide formed in situ.[6] The only reaction with a synthetic utility is generation of diimine by oxidation of hydrazine with elemental selenium in the presence of oxygen.[7]

2.2. Selenium(IV) Oxide, Selenic(IV) Acid and Its Derivatives

The most common selenium compound, widely used in organic synthesis as stoichiometric oxidant or as the catalyst, is the cheap and easily available selenium(IV) oxide.[1a,1b,1d,1f,1h,3d,8] It has an electrophilic center localized on the selenium atom. In water or water-containing solvents it exists as selenic(IV) acid $(HO)_2SeO$. In alcohols selenic(IV) esters are formed in situ, e.g. dimethyl selenate(IV) postulated for the reaction carried in methanol.[9] Although this ester was never isolated, the stable diethyl analogue was successfully used for oxidation of some organophosphorus compounds and fenacyl halides.[1e]



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Scheme 1. Oxidation of benzyl alcohol with selenium(IV) oxide

Sharpless and co-workers reported selenium(IV) oxide as an efficient and selective reagent for α-hydroxylation of alkenes and alkynes.[10] This reaction, carried out in methanol, was applied for α-hydroxylation of natural 1,6-dienes (among them linalol and its acetate) and 15-*O*-acetylisocupressone. Other solvents such as dioxane and formic acid were also used but in the second case formates of the corresponding allyl alcohols were produced.[9,11]

A widely used reagent for α-hydroxylation of various alkenes and alkynes is a mixture of selenium(IV) oxide and *tert*-butyl hydroperoxide (TBHP).[6,11f,12] Using this reagent, long-chain alkanols are obtained from alkenes and hydroxy acids from unsaturated fatty acids.[13] When an α-methylene group is oxidized, the selenium(IV) oxide may be used in catalytic amounts under mild reaction conditions.[14] In dif-

Jacek Młochowski (top, left) was born in Warsaw, Poland, in 1937. He studied chemistry at Wrocław University of Technology and completed his PhD thesis on the chemistry of naphthalene and its sulfur analogues derived from coal tar under the supervision of Prof. B. Roga in 1967. In 1975 he completed his habilitation on the synthesis, structure and reactivity of phenanthrolines. In 1983 he was nominated as a full professor. The main emphasis of his research lies in the development of new synthetic methods; in the last decade the synthesis of organoselenium compounds as new enzyme mimics, biological response modifiers, and oxygen transfer agents has been the major interest. His work also involves mechanistic studies of the oxidation processes and applications of hydroperoxides in practical organic synthesis. More recent research topics include selenenylation of carbon and heteroatoms synthesis of selenium- and nitrogen-containing heterocycles and hydroperoxide oxidation of organic substrates catalyzed by diselenides and selenenamides.

Monika Brząszcz (top, right) was born in Jastrzębie, Poland, in 1975. She studied chemistry at Wrocław University of Technology. In 1999 she completed her Diploma and now she is completing her PhD studies working on the selective oxidation of aldehydes, amines, and ethers with hydroperoxides in the presence of selenium compounds as catalysts.

Mirosław Giurg (middle, left) was born in Strzelin, Poland, in 1965. He studied Chemistry at Wrocław University of Technology and completed his PhD thesis on the oxidation of heteroorganic compounds in 2000, under the supervision of Prof. L. Syper. Then he spent half a year in the research group of Prof. Manfred Schlosser (Lausanne University, Switzerland) as a post-doctoral fellow. Now he is working in the research group of Professor Jacek Młochowski on the oxidative heterocyclization of oxygen and nitrogen compounds.

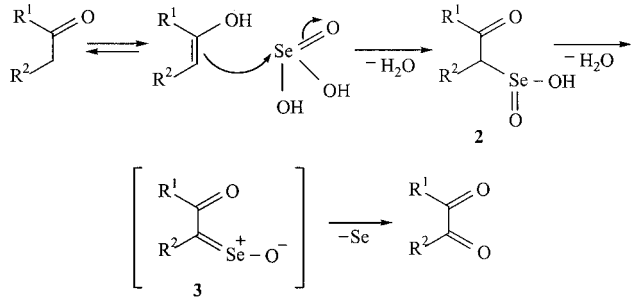
Jerzy Palus (bottom, right) was born in Wrocław, Poland, in 1960. He studied bioorganic chemistry at Wrocław University of Technology and completed his PhD thesis on synthetic low-molecular-weight immunomodulators and cytostatics under the supervision of Prof. J. Młochowski in 1993. His major scientific interest is focused on the synthesis and evaluation of organoselenium compounds designed as biological response modifiers and on the mechanisms of their action in the living cells.

Halina Wójtowicz (bottom, left) obtained her first degree in Chemistry at Wrocław University of Technology in 1972 and completed her PhD studies in 1976 in the Institute of Organic and Physical Chemistry at the same University. In 1993 she moved to the Antwerpen University to take up a postdoctoral position with Prof. Achiel Haemers. From there she works in the organic research group headed by Prof. Jacek Młochowski in the Institute of Organic Chemistry, Biochemistry, and Biotechnology at Wrocław University of Technology. Her scientific interest is concentrated on the chemistry of heterocyclic compounds with nitrogen, oxygen, and sulfur atoms in the heterocyclic ring, especially the design, synthesis and properties of new organoselenium compounds, which have been found to be catalysts for electron- and oxygen-transfer processes, and useful in organic syntheses for chemo- and stereoselective oxidation of various organic substrates. The second area of her research interests is the design and study of synthetic methods for low-molecular-weight heteroorganic mimics of glutathione peroxidase.

ferent alkenes the order of susceptibility of α-carbon atoms toward hydroxylation is $CH_2 > CH_3 > CH$. Cycloalkenes with alkyl substituents in the allylic position are preferentially hydroxylated on the ring α-carbon atom. Oxidation of terminal alkenes results in C=C bond migration, and primary allyl alcohols are produced.[14a]

When an alkene is oxidized with TBHP/SeO_2 used in excess under more severe conditions, the final product is an α,β-unsaturated aldehyde or ketone.[15] Most probably the initially formed allyl alcohol is oxidized according to a mechanism similar to that proposed for aromatic alcohols, illustrated in Scheme 1, where the reaction proceeds via a selenic(IV) ester (**1**), which spontaneously decomposes to a carbonyl compound.[16]

Silica-gel-supported SeO_2 with TBHP has been used for selective oxidation of primary allyl alcohols into α,β-unsaturated aldehydes while secondary allyl or benzyl alcohols and saturated alkanols remain unreactive.[17] Under microwave irradiation a methyl allyl group is also oxidized into a formyl group.[13f] Oxidation of an activated methyl or methylene group with selenium(IV) oxide is a general, convenient way to introduce a new carbonyl group into the α-position of enolizable aldehydes or ketones.[6,18] According to the mechanism presented in Scheme 2 the reaction proceeds via adduct **2** and subsequent elimination of selenium from intermediate **3**.[6,18,19]

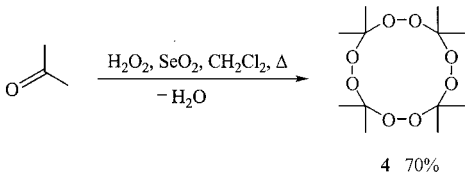


Scheme 2. The mechanism of oxidation of active methylene group in enolizable carbonyl compounds

Competitive coupling of α-methylene carbons was observed when ferrocenyl ketones $FcCH_2COR$ were oxidized. The major products were 1,4-butandiones RCOCH(Fc)−CH(Fc)COR instead of the expected diketones FcCOCOR.[20]

The oxidation of methyl groups attached to a pyridine ring into formyl groups by heating their dioxane solutions with selenium(IV) dioxide or selenic(IV) acid is the best method for synthesis of pyridine aldehydes and their quinoline, isoquinoline and phenanthroline analogues.[21]

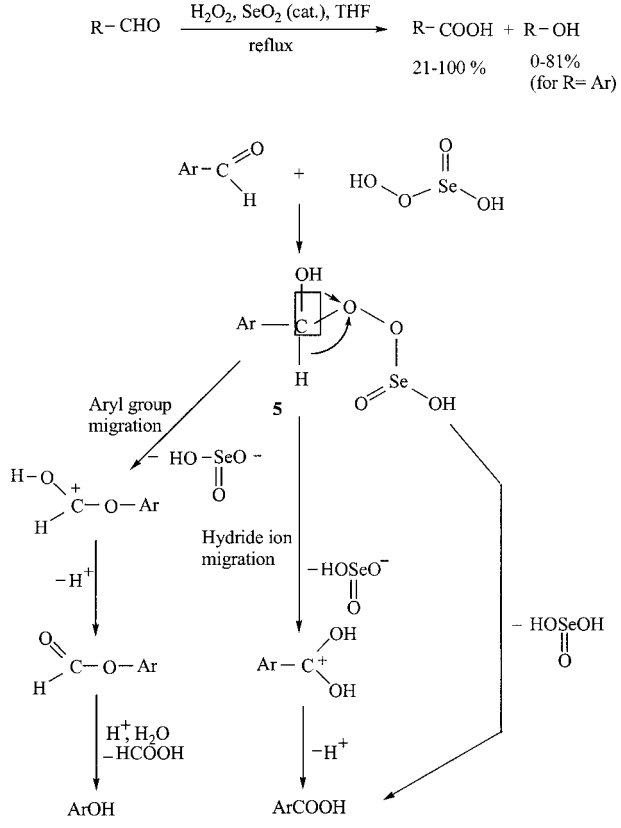
A variety of organic compounds has been oxidized with a mixture of hydrogen peroxide and catalytic amounts of selenium(IV) oxide, where an active oxidant was peroxyselenic(IV) acid HOSe(O)OOH, formed in situ.[3a,8,22] Alkenes and cycloalkenes were epoxidized and 1,2-dihydroxylated. Enolizable ketones were hydroxylated or underwent the



Scheme 3. Oxidation of acetone into tetrameric peroxide (**4**)

Bayer−Villiger reaction. Alkanones and cycloalkanones were converted into carboxylic acids with a rearrangement of the carbon chain or ring. Oxidation of acetone gave propionic acid but when water was removed azeotropically during the reaction, the tetrameric acetone peroxide (**4**) (Scheme 3) was produced in 70% yield.[23,24]

Hydrogen peroxide oxidation of aldehydes into aliphatic, aromatic, and heteroaromatic carboxylic acids, catalyzed by selenium(IV) oxide, has a general synthetic value since in most cases yields are high to excellent. The method is attractive because other oxidizing agents such as potassium permanganate, chromic acid, bromine, fuming nitric acid, and Jones' reagent do not meet environmental restrictions. Exceptionally, when the starting aromatic aldehyde has an electron-donating substituent, such as a methoxy group, in the *ortho* or *para* position, phenols are produced in substantial amounts or even as the major products. This phenomenon can be explained by the mechanism presented in Scheme 4. The initial step of the reaction is addition of peroxyselenic(IV) acid to the carbonyl group of the alde-



Scheme 4. Hydrogen peroxide oxidation of aldehydes catalyzed by SeO_2

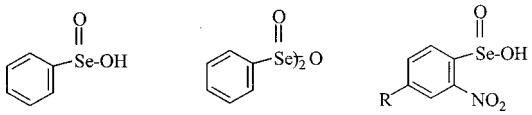
hyde. Selenic(IV) acid is eliminated from adduct **5** and the process can be characterized as an addition−elimination. The alternative pathway involves intramolecular hydride ion migration, and then elimination of a selenic(IV) anion and deprotonation of an intermediate carbocation. When the aromatic ring is substituted with an electron-donating group, aryl migration to the electrophilic oxygen atom takes place instead of hydride ion migration. From the formed carbocation a proton is abstracted and the formate produced undergoes hydrolysis into phenol.[25]

Oxidation of secondary amines with H_2O_2/SeO_2 is a convenient way of synthesizing nitrones.[26] The ethylene group in enolactams and the azomethine group in hydrazones or oximes are oxidized with the same reagent into a carbonyl group.[22a,27] Other azomethine compounds such as semicarbazones treated with SeO_2 are oxidatively cyclized into 1,2,3-selenodiazoles.[28]

3. Organoselenium Compounds

3.1. Benzeneseleninic Acids, their Derivatives and Precursors

In the 1970s and 1980s Barton, Ley and Back recognized the synthetic utility of benzeneseleninic acid (**6**) and anhydride (**7**) as oxidants, or catalysts of hydrogen peroxide oxidation.[1a,1h,29] A couple of years later, 2-nitro- and 2,4-dinitrobenzeneseleninic acid (**8**, **9**) (Scheme 5) were also successfully employed as catalysts for hydrogen peroxide oxidation of various organic compounds.[30] These acids and anhydride **7** are easily prepared by oxidation of the corresponding diselenide with ozone, *tert*-butyl hydroperoxide, hydrogen peroxide, or by other, less frequently used, methods. Compounds **6**−**9** are otherwise stable although anhydride **7** is easily hydrolyzed into acid **6** upon exposure to moisture. They show some similarity to selenium(IV) oxide in their behavior, but often react more cleanly making isolation of the products less troublesome. Moreover, the formation of evil-smelling by-products is minimized and formation of red selenium is generally avoided.

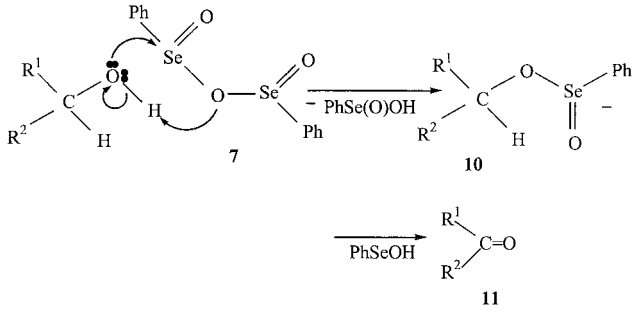


6 **7** **8** R = H, **9** R = NO_2

Scheme 5. Benzeneseleninic acids **6**, **8**, **9**, and anhydride **7**

Polystyrene-supported benzeneseleninic acid has been employed as catalyst for TBHP oxidation of benzyl and allyl alcohols into aldehydes and phenols into quinones.[31] The oxidation of phenols with acid **6** provides an useful route to 1,4-quinones, while the use of anhydride **7** affords chiefly the corresponding 1,2-quinones. A recent application of the phenol to 1,2-quinone conversion with **7** to the synthesis of carbazoquinocins has been reported.[1h,32] When the reaction is carried out in the presence of hexamethyldisilazane, selenoimides are produced. Their reduction gives *ortho*-hydroxyanilines or their derivatives, and is a useful, general way of synthesizing these important compounds.[32c−32e]

Alkyl groups in alkylarenes and alkylheteroarenes are oxidized by **7** into carbonyl groups.[33] Benzyl and aliphatic alcohols give aldehydes or ketones **11** via postulated ester **10** according to the mechanism presented in Scheme 6.[34]

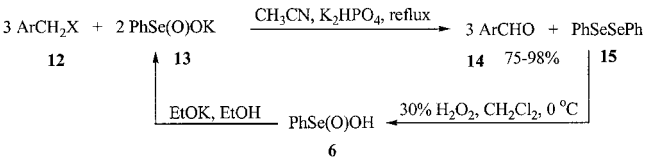


Scheme 6. Oxidation of alcohol with benzeneselenic anhydride (**7**)

A variety of dehydrogenations of carbonyl compounds into corresponding α,β-unsaturated derivatives with anhydride **7** has been reported. This reagent is particularly effective for dehydrogenation of biologically important cholestenones.[1i,34a,35] When iodylbenzene ($PhIO_2$) or 3-iodylbenzoic acid is a stoichiometric oxidant, anhydride **7** or its precursor, diphenyl diselenide, can be employed in a catalytic amount.[36] Anhydride **7** can also be used as a reagent for α,β-dehydrogenation of lactones and lactams but in some cases the lactams are oxidized into imides.[34b,37]

Acid **6**, and more often anhydride **7**, are employed for oxidation of sulfides, thioketones and thioacetals, and for oxidation of nitrogen compounds such as hydrazines, hydrazides, amines, imines, hydroxylamines, and enamides. Oxidation of indolines affords the corresponding indoles, and applications of this method include key steps in the synthesis of the ergot alkaloids.[1h,37a] Pentaflurobenzeneseleninic acid and 2-(*N*-oxide)pyridineseleninic anhydride have been proposed as reagents for oxyfunctionalization of the allylic position in alkenes and oxidation of hydroxymethyl groups into formyl groups.[38]

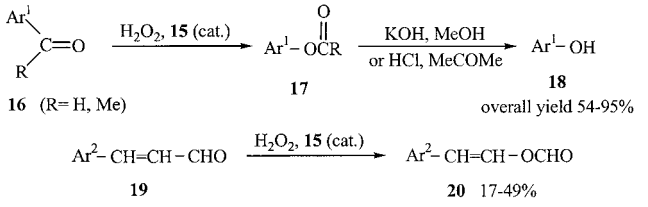
Potassium benzeneselenoate (**13**), a stable nonhygroscopic solid, has been employed for the oxidation of halomethylarenes **12** into aldehydes **14** (Scheme 7). Diphenyl diselenide (**15**) resulting from this reaction can be quantitatively converted into salt **13** and reused.[5a] A broad spectrum of substituted aromatic aldehydes, precursors of oxir-



Scheme 7. Oxidation of halomethylarenes with potassium benzeneselenoate (**13**)

anylquinones, expected to be bioactivated alkylation agents, was obtained in this way.[39]

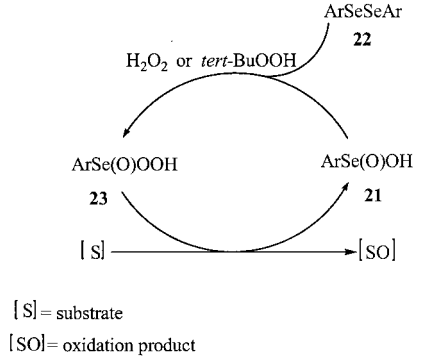
2-Nitro- and 2,4-dinitrobenzeneseleninic acids (**8** and **9**) and related diselenides have been applied as catalysts for hydrogen peroxide and TBHP oxidation of different groups of organic compounds.[1j,3d,17,40] Oxidation of aldehydes and aryl methyl ketones (**16**) into phenol formates or acetates (**17**), which in one-pot procedures are subsequently hydrolyzed to phenols (**18**), is a useful way of synthesizing phenols with electron-donating substituents or polycondensed ring systems.[40c] In a similar reaction, α,β-unsaturated aldehydes (**19**) give vinyl formates (**20**), accompanied by the products of their subsequent transformations (Scheme 8).[40d]



Scheme 8. Oxidation of aromatic aldehydes and ketones (**16**), and α,β-unsaturated aldehydes (**19**)

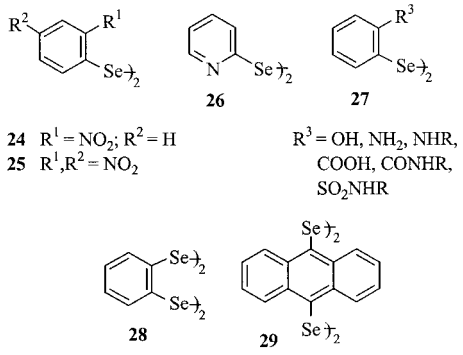
Epoxidation of styrene and its analogues with hydrogen peroxide catalyzed by acid **8** also has synthetic value.[40b] The same reagent can be used for practical conversion of *N*,*N*-dimethylhydrazones into nitriles[40e] while aldoximes in the presence of primary or secondary alcohols produce carboxy esters.[40f]

Most probably the areneseleninic acids (**21**), or their precursor diaryl diselenides (**22**), are oxidized in situ with hydrogen peroxide into areneperoxyseleninic acids (**23**), which are the active oxygen donors. Benzeneperoxyseleninic acid and its 2-nitro and 2,4-dinitro analogues are obtained by hydrogen peroxide oxidation of the corresponding diaryl diselenides and have been fully characterized. Oxidation of carbonyl compounds with 2-nitrobenzeneperoxyseleninic acid, used as a stoichiometric oxidant, gave results similar to these, presented in Scheme 8, when 2-nitrobenzeneseleninic acid (**8**) or the related diselenide (**24**) was used as a catalyst.[41] These results support the general mechanism presented in Scheme 9 for the hydroperoxide oxidation of an organic substrate catalyzed by diaryl diselenide or areneseleninic acid.



Scheme 9. The mechanism of hydroperoxide oxidation of organic substrate catalyzed by diaryl deselenide (**22**) or areneselenic acid (**21**)

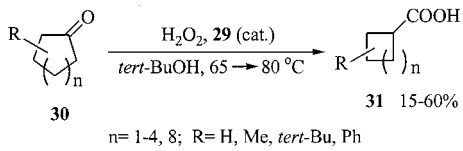
In the last decade diselenides have been used more frequently than seleninic acids. They act as catalysts for the oxidation of different organic compounds with hydrogen peroxide, TBHP, and other oxygen donors.[1d,1h,1j,3d] They are easily available in the reaction of alkyl, aryl, and heteroaryl halides with dilithium diselenide formed in situ from elemental lithium and selenium in aprotic media.[42] Apart from diselenides **15**, **24**, and **25**, other compounds of this class, such as **26**–**29** (Scheme 10), are also synthetically valuable oxidation catalysts.



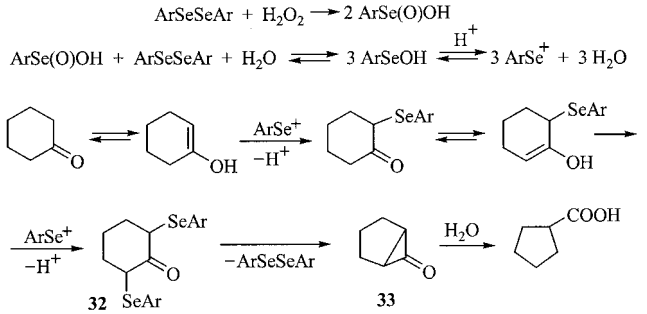
Scheme 10. Diselenides used as the oxygen-transfer catalysts

It has been observed that the catalytic effectiveness of selenium catalysts strongly depends on the substrate used. While the *ortho*-substituted diphenyl diselenides are the best catalysts for hydrogen peroxide oxidation of sulfides into sulfoxides and of ketazines into their parent ketones,[43] the poly(bis-1,2-phenylene) diselenide **28** was selected for preparative oxidation of various aromatic aldazines, aldoximes, and tosylhydrazones into arenecarboxylic acids.[42b] In the presence of poly(bis-9,10-anthracenylene) diselenide (**29**) a broad spectrum of aliphatic, unsaturated and aromatic nitriles was obtained, in excellent preparative yields, by oxidation of the corresponding *N*,*N*-dimethylhydrazones.[44]

The same diselenide **29** was the catalyst of choice for oxidative conversion of cycloalkanones (**30**) into cycloalkanecarboxylic acids (**31**) (Scheme 11).[45] Although preparative yields of the acids did not exceeded 60% they were substantially higher than those obtained when selenium(IV) oxide was the catalyst. Since the cycloalkanones are cheap and easily available substrates the elaborated method is suitable for the synthesis of acids **31**, particularly those having five-, six- and seven-membered rings. Thus the H_2O_2/**29** system can be regarded as a potential reagent for obtaining bicyclo[4.3.0] nonanes, intermediates in the total synthesis of homocarbaprostacyclins.[46]



Scheme 11. Oxidative conversion of cycloalkanones into cycloalkanecarboxylic acids



Scheme 12. The mechanism of the oxidation of cycloalkanones into cycloalkanecarboxylic acids catalyzed by diaryl diselenide

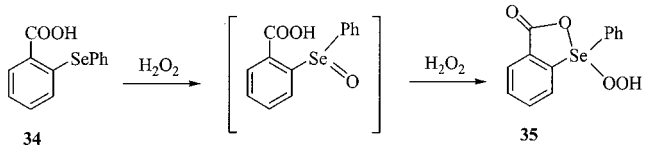
The results of more detailed studies on the chemo- and stereoselectivity of this reaction support the mechanism presented in Scheme 12. Most probably it involves addition of two bulky arylselenium cations in both α-positions of the ketone, elimination of diaryl diselenide from adduct **32** and finally the Favorski-like rearrangement of intermediate **33** to the acid form.[47]

Recently it was found that bis[3,5-bis(trifluoromethyl)-phenyl] diselenide is significantly more active than other previously described selenium catalysts for epoxidation and Bayer−Villiger oxidation of carbonyl compounds with hydrogen peroxide.[4e,48]The active intermediates, with an electrophilic center localized on the selenium atom, are generated from diselenides using oxidants such as ammonium peroxysulfate $(NH_4)_2S_2O_8$,[1c,49,50] the sodium salt of chloramine-T ($4\text{-}ClC_6H_4SO_2NClNa$)[51] and iodylbenzene.[52] In the first reaction, applied for conversion of β,γ-unsaturated carboxy esters, amides, and nitriles into allyl ethers, the anion $PhSeOSO_3^-$ is an active selenium intermediate.[1c,49] The reaction is stereospecific when the catalyst diphenyl diselenide is replaced by dicamphoryl diselenide.[50] *N*-(arylseleno)-4-chlorobenzenosulfonamide ($ArSeNHSO_2C_6H_4Cl$), formed in the second reaction, oxidizes secondary alcohols into ketones.[51] 2,2′-Dipyridyl diselenide promotes iodylbenzene oxidation of allylic carbons and dehydrogenation of cycloalkanones into enones and dienones.[35a,52]

When diphenyl diselenide and benzenesulfonic acid are treated with hydrogen peroxide, dihydroxyphenylselenonium benzenesulfonate $PhSe(OH)_2{}^+PhSO_3^-$ (or tosylate) is formed. These salts are active intermediates or can be isolated and used as stoichiometric reagents for oxidation of arenes into quinones.[53]

3.2. Selenides and Selenoxides

Synthetic applications of selenides as catalysts are limited to only a few cases. Oxidation of sulfides into sulfoxides and/or sulfones is effected using hydrogen peroxide and 2-carboxyphenyl phenyl selenide (**34**). The hydroperoxyselenuran **35** has been postulated as an active intermediate (Scheme 13).[54] Another catalyst, 3,5-bis(perfluorooctyl)-phenyl butyl selenide, was used in fluorinated solvents under mono-, bi-, or triphasic conditions for epoxidation of alkenes by 60% hydrogen peroxide.[55]



Scheme 13. Hydrogen peroxide oxidation of selenide **34** into hydroperoxyselenurane **35**

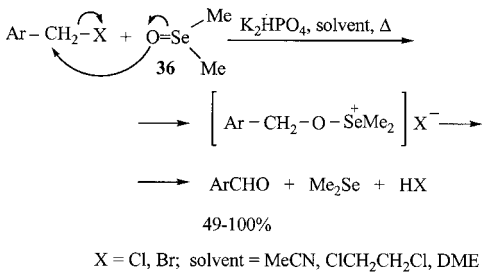
The selenoxides $R^1Se(O)R^2$, particularly diphenyl, bis(*p*-methoxyphenyl), and dimethyl selenoxide, are known as mild reagents for oxidation of various organic compounds − olefins, thiols, sulfides, phosphanes, hydrazides, amines, catechols, benzyl alcohols, and halomethylarenes.[56] Although their properties are generally similar to these of analogous sulfoxides, the selenoxides are more reactive. Dimethyl selenoxide is a stronger base and softer nucleophile than dimethyl sulfoxide. The Se−O bond is weaker than the S−O bond and its cleavage proceeds more smoothly.

Diphenyl selenoxide (or its precursor diphenyldichloroselenuran) has been employed for oxidation of hydrazides into 1,2-diacetylhydrazides and aromatic amines into azo compounds.[56a−56c] Oxidation of tertiary amines into N-oxides as well as conversion of thiones, and thio- and selenophosphorus compounds with both of these reagents, can also be accomplished in this way.[56d−56g]

Dimethyl selenoxide (**36**) was found to be an excellent oxidizing agent which converts P(III) compounds, thio- and selenophosphoryl compounds, and thiocarbonyl compounds into their phosphoryl or carbonyl analogues under very mild conditions. For this reason it is the reagent of choice for selective modification of the thiocarbonyl compounds such as thiouracils and the corresponding thionucleosides and thionucleotides.[56f]

The facile synthesis of dimethyl selenoxide[57] prompted us to elaborate a simple and efficient method for preparation of aldehydes from halomethyl or hydroxymethylarenes and allyl or saturated aliphatic alcohols, using this reagent as an oxidant.[5a] The first step of the reaction is nucleophilic attack of the oxygen atom on the electrophilic carbon of the halide, as shown in Scheme 14, or electrophilic attack of selenium on the oxygen atom of the alcohol. Finally, cleavage of the Se−O bond takes place and the products are formed in very high yields.

The less reactive bis(*p*-methoxyphenyl) selenoxide was used for the oxidation of aromatic alcohols in combination



Scheme 14. Oxidation of halomethylarenes with diemethyl selenoxide (**36**)

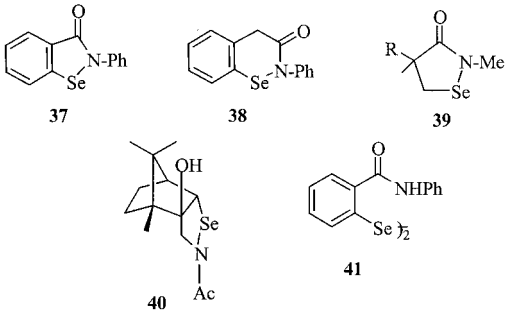
with catalytic amounts of selenium(IV) oxide or elemental selenium.[56j] For hydroxylation of the olefins with diphenyl selenoxide, osmium(VIII) oxide was employed as the catalyst. In this case the oxyanion $OsO_4(OH)_2^{2-}$, formed in situ by oxidation of OsO_4 by diphenyl selenoxide in aqueous medium, is an active intermediate.[56i]

Another group of oxidants based on selenoxides is their adducts with sulfonic acids. An adduct formed from dimenthyl selenoxide and 2,2,2-trifluoroethanesulfonic acid can be used for oxidation of sulfides into sulfoxides. The recovered selenide can be converted into selenoxide and reused.[5b,58]

Diphenyl selenoxide treated with trifluoroacetic anhydride in dry ethylene glycol dimethyl ether (DME) produces diphenylselenium bis(trifluoroacetate), a hygroscopic solid, which can be isolated in an inert atmosphere or generated in situ without isolation. It serves as a mild two-electron oxidant for phenols, catechols, amines, and amino acids.[59]

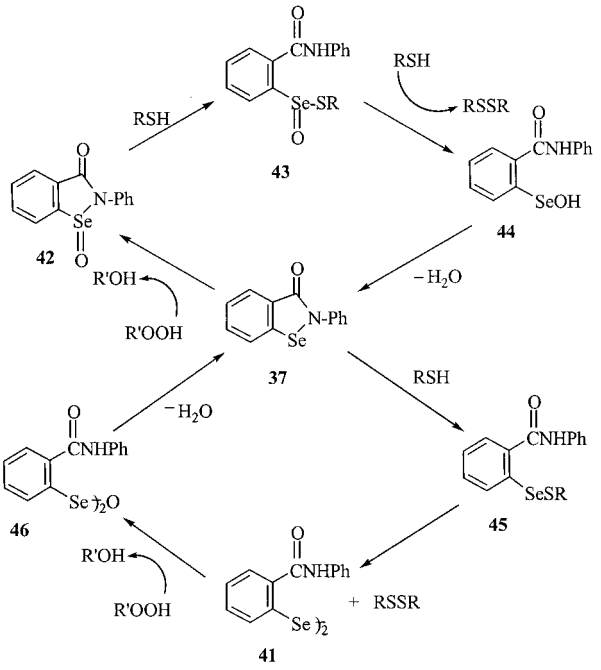
3.3. Selenenamides

Almost two decades ago it was revealed that a simple, synthetically available cyclic selenenamide − 2-phenyl-1,2-benzisoselenazol-3(2*H*)-one (**37**) named ebselen could act against oxidative stress in a similar way to the common selenoenzyme glutathione peroxidase (GSH-Px).[60] Later it was found that other 2-substituted-1,2-benzisoselenazol-3(2*H*)-ones, cyclic selenenamides (**38**−**40**) and their open-chain analogues, among them bis[(2-carbamoylphenyl)-phenyl] diselenide (**41**) (Scheme 15) are able to deactivate active oxygen species present in the living cell, such as peroxides, hydroperoxides, hydroxyl radical and superoxide anion.[61]



Scheme 15. The cyclic selenamides **37**−**40** and related bis[(2-carbamoylphenyl)phenyl] diselenide (**41**)

The mode of the biological action of compounds **37**−**41** has been postulated to be similar to that observed for GSH-Px, and results in dehydrogenation of thiols into disulfides while hydrogen peroxide is reduced to water.[60c,61] Surprisingly, it has been found that ebselen (**37**) and the related diselenide (**41**) did not promote hydrogen peroxide oxidation of the thiols such as *N*-acetylcysteine, butanethiol, and octanethiol.[62] Nevertheless, the selenenamide derived from camphor (**40**) effectively catalyzed oxidation of phenylmethanethiol into the disulfide.[63] The postulated mechanism of the enzyme-like action of ebselen and other



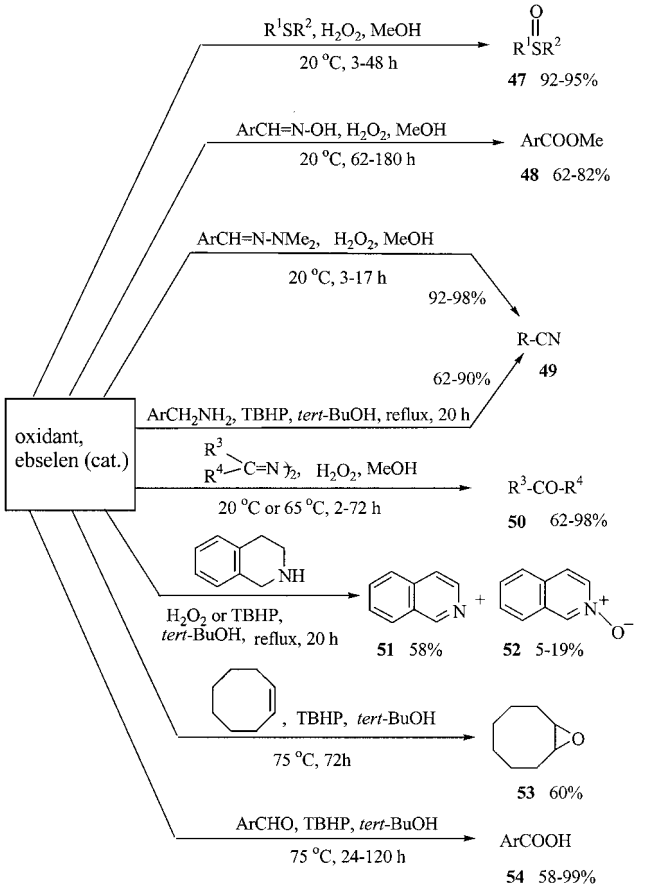
Scheme 16. The mode of action of ebselen (**37**) in the hydroperoxide oxidation of thiols into disulfides

selenenamides is presented in Scheme 16.[60c,61b,63,64] When the concentration of hydroperoxide is high, ebselen (**37**) is oxidized into selenoxide **42** which reacts with one molecule of the thiol to give selenoxysulfide **43**. Intermediate **43** and the second molecule of thiol produce disulfide while formed selenenic acid **44** is converted back to ebselen. In biological systems, where the concentration of hydroperoxide is low, ebselen and the thiol give selenosulfide **45** which disproportionates into the disulfide and diselenide **41**, subsequently oxidized into selenenic anhydride **46** and finally into ebselen.

It seemed possible that ebselen and related selenenamides could promote hydroperoxide oxidation of various organic compounds other than thiols. Experiments in our laboratory, where 5 mol% of ebselen was used while the stoichiometric oxidant was 30% hydrogen peroxide or 80% TBHP, strongly support this hypothesis and some of the reactions have a synthetic value.[43a,65] Examples are presented in Scheme 17.

Sulfides are exclusively oxidized into sulfoxides (**47**).[43a] Aromatic aldoximes oxidized in methanol gave carboxymethyl esters (**48**).[65b] Nitriles (**49**) are produced from *N*,*N*-dimethylhydrazones by oxidation with hydrogen peroxide[43a] or from benzylamines oxidized with TBHP.[65b] Hydrogen peroxide oxidation of ketazines give the parent ketones **50**.[43a]1,2,3,4-Tetrahydroisoquinoline is dehydrogenated to isoquinoline (**51**) which undergoes subsequent oxidation into the *N*-oxide **52**.[65a] To the best of our knowledge this is the first example of aromatization of a hydropyridine ring by hydroperoxide.

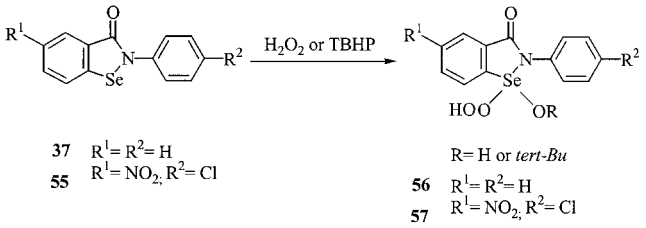
Cyclooctene treated with TBHP gives epoxide **53** accompanied with trace amounts of 3-hydroxycyclooctene resulting from α-hydroxylation.[65c] In contrast, oxidation cat-



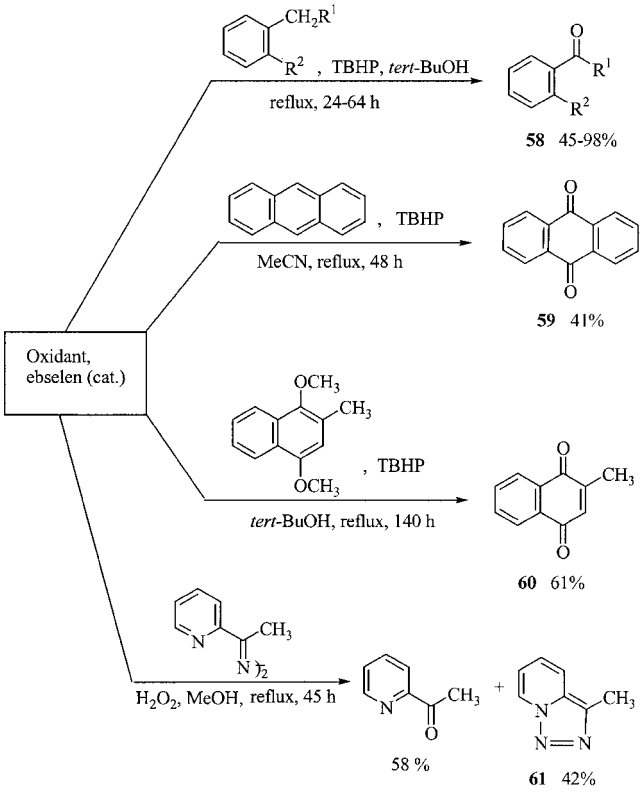
Scheme 17. Oxidation of the organic compounds catalyzed by ebselen

alyzed by selenium(IV) oxide affords 3-hydroxycyclooctene as a major product while epoxidation is not observed.[14b,65c]

As mentioned earlier (Section 2.1., Scheme 4), some aromatic aldehydes with electron-donating substituents, when oxidized with hydrogen peroxide in the presence of selenium(IV) oxide, gave mixtures of arenecarboxylic acids and phenols, or even phenols as the sole products.[25] More recently we found that oxidation of these aldehydes with TBHP in the presence of ebselen led almost exclusively to the acids **54** while no phenols, or only small amounts, were produced. This raised a question about the role of the oxidant and catalyst in this reaction. When ebselen (**37**) was treated with hydrogen peroxide, selenoxide **42** and finally an unstable crystalline compound, most probably **56**, was produced. A more stable and fully characterized analogue (**57**) was obtained by oxidation of compound **55** with hydrogen peroxide or with TBHP (Scheme 18). This provided evidence that ebselen can act as an oxygen-transfer agent via an active intermediate − hydroperoxyselenuran **56**. The postulated mechanism is similar to that in which peroxyseleninic or peroxyselenic(IV) acid is an active oxidant (Schemes 4 and 9) and quite different from the enzymic mechanism (Scheme 16).[55] The observed difference between the catalytic actions of selenium(IV) oxide and ebselen can be explained by assuming that in the peroxyselenic(IV) acid [HOSe(O)OOH] the active centers interacting with the molecule of substrate are less hindered than in the hydroperoxyselenuran **56** and that the nucleophilicity of the hydroperoxy groups is different in the two intermediates.



Scheme 18. Oxidation of benzisoselenazol-3(2*H*)-ones (**37**, **55**) into hydroperoxyselenuranes **56**, **57**

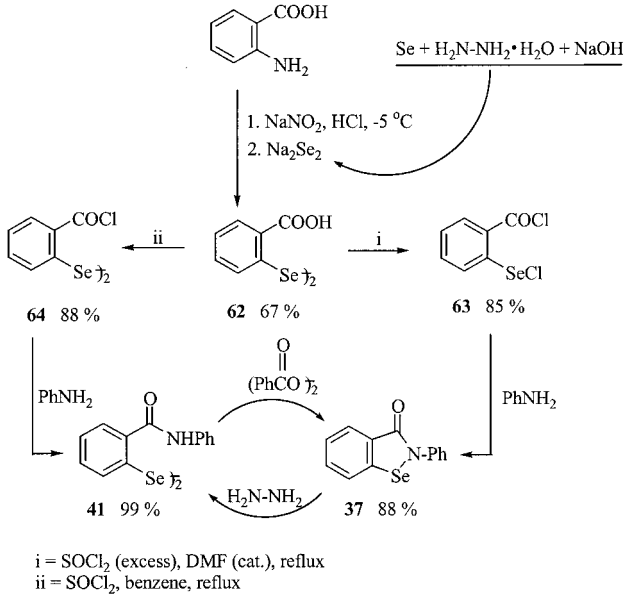


Scheme 19. Hydroperoxide oxidation of the orgainc substrates catalyzed by ebselen with probably free-radical mechanisms

The results of the reactions presented in Scheme 19 lead us to suppose that oxidation of the organic substrates with hydroperoxides in the presence of ebselen can also proceed via a free-radical mechanism. Oxidation of methyl and benzylic methylene groups in alkylarenes into carbonyl groups results in the formation of ketones **58**[65b] and oxidation of anthracene into anthraquinone (**59**) supports this hypothesis.[65e] Moreover, it was observed that the results of oxidation of 1,4-dimethoxy-2-methylnaphthalene into menadione (**60**)[65f] and conversion of azine derived from 2-acetylpyridine to triazene (**61**) are very similar to those when cerium(IV) ammonium nitrate (CAN) was a reagent. Since

CAN is a well-known one-electron oxidant generating free radicals[66], it seems possible that a free-radical mechanism is involved in all these reactions. The role of ebselen is evident, because no reaction was observed when the substrates listed in Scheme 19 were treated with hydrogen peroxide or TBHP without this catalyst. To the best of our knowledge, examples of free-radical oxidation promoted by organoselenium compounds are rare.

Finally it should be noted that ebselen (**37**) and related diselenide **41** can be simply synthesized from anthranilic acid via bis(2-carboxyphenyl) diselenide (**62**) and corresponding acyl chlorides **63** and **64** in the way presented in Scheme 20. The method has a more general value because by using various amines and other compounds with primary amino groups, different benzisoselenazol-3(2*H*)-ones and 2-substituted diphenyl diselenides can be obtained.[67]



Scheme 20. Synthesis of ebselen (**37**) and bis[(2-carbamoylphenyl)-phenyl] diselenide (**41**)

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