Diaryl diselenides and benzisoselenazol-3(2*H*)-ones as oxygen-transfer agents

Jacek Młochowski,* Monika Brząszcz, Magdalena Chojnacka, Mirosław Giurg, and Halina Wójtowicz

Institute of Organic Chemistry, Biochemistry and Biotechnology, Wroclaw University of Technology, PL 50-370 Wrocław, Poland
E-mail: jacek.mlochowski@kchf.ch.pwr.wroc.pl

Dedicated to Prof. Mieczysław Mąkosza on the occasion of his 70th birthday
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Abstract
Diaryl diselenides and related benzisoselenazol-3(2H)-ones are presented as the catalyst for hydogen peroxide and *t*-butylhydroperoxide oxidation of various types of organic substrates. Most of the reactions studied in our laboratory have a practical value. The aromatic aldehydes and ketones are oxidized to arenecarboxylic acids or converted to the phenols while cycloalkanones gave cycloalkanecarboxylic acids with ring contraction. From the azomethine compounds, depending on their structure, nitriles, parent carbonyl compounds, carboxylic acids or their esters are produced. Primary benzylamines gave nitriles, while the secondary are oxidized to nitrones. Alkylarenes are oxidized to the alkylaryl ketones and alkenes to epoxides. By oxidation of 1,4-dimethoxysubstituted and some polycondensed arenes the quinones are produced. The postulated mechanisms are discussed and the methods for synthesis of the title compounds are described.

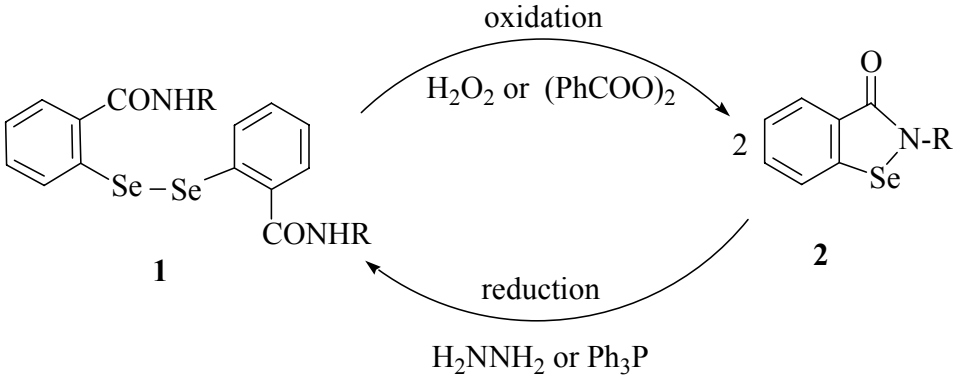
Keywords: Benzisoselenazolones, catalysis, diselenides, hydroperoxides, oxidation

Contents

Introduction

During the last four decades it has been reported that selenium, its dioxide and some organoselenium compounds can be used as stoichiometric oxidants or oxidation catalysts.[1-4] Diaryl diselenides and benzisoselenazol-3(2H)-ones have been in the centre of our interest, because in many cases they can act more efficiently and selectively as oxygen-transfer catalysts then other selenium compounds and they are particularly useful for hydrogen peroxide and *t*-butyl hydroperoxide (TBHP) oxidation of variety organic compounds. Use of hydrogen peroxide and TBHP as the oxidants corresponds to modern trends in organic synthesis since both of these reagents are environmentally friendly, easily available and can be used in a large scale synthesis. Nevertheless, both of them are low or only moderately active toward most organic substrates, thus various activators or catalysts, among them selenium compounds, must be used. This brief review covers our contribution to the knowledge of the synthetic approach, properties and application of organoselenium compounds as the promotors of hydroperoxide oxidation of various groups of organic compounds. Our particular interest is focused on the title compounds – diaryl diselenides and benzisolenazolon-3(2H)-ones because of their usefulness in organic synthesis.

There is a close relation between diselenides substituted in the *ortho* position with the carbamoyl group (**1**) and benzisoselenazol-3(2H)-ones (**2**) because the oxidation of **1** gives **2.** Conversely, when **2** is treated with reducing reagents the C-N bond is cleaved and diselenides **1** are produced as it is shown in Scheme 1.



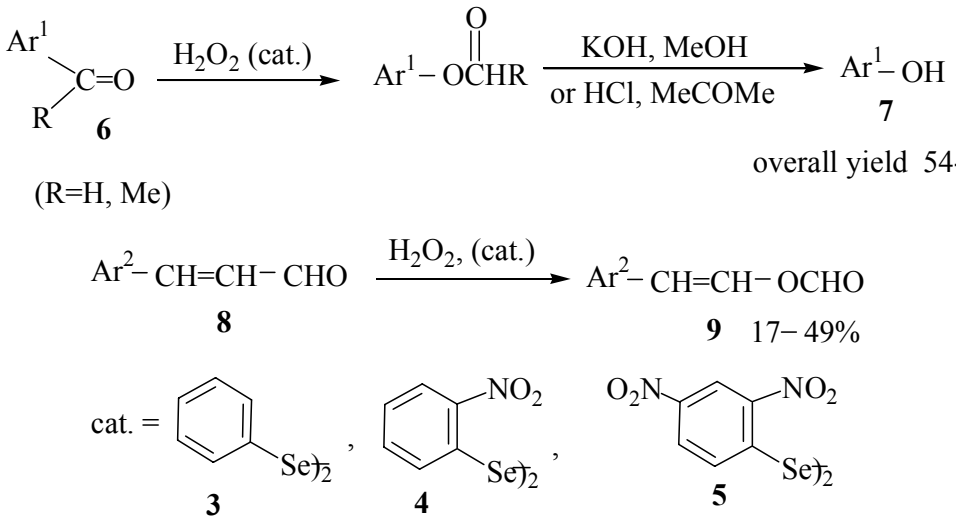
Scheme 1

It should be mentioned that although it is commonly thought that organoselenium compounds are malodorous and toxic the compounds mentioned in this article are odourless and according to known rules their toxicity should be low.[5-7] For example, 2-phenylbenzisoselenazol-3(2H)-one (ebselen) is practically nontoxic (LD_{50}= 6.8 g/kg).[7]

1. The reactions catalyzed with diaryl diselenides and benzisoselenazol-3(2*H*)-ones and their mechanisms

1.1. Oxidation of carbonyl compounds

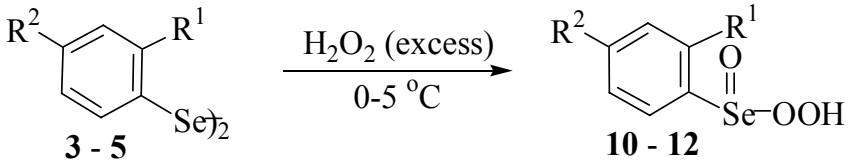
In late eightees Ludwik Syper of our laboratory discovered that diselenides: diphenyl (**3**), di(2-nitrophenyl) (**4**) and di(2,4-dinitrophenyl) (**5**) effectively catalyzed Baeyer-Villiger oxidation of aromatic aldehydes and ketones **6** with hydrogen peroxide (Scheme 2). As a result a convenient and cheap method for transformation of aromatic aldehydes having polycondensed ring systems or electron-donating substituents, and polymethoxy derivatives of acetophenone into phenols **7** was elaborated.[8] In a similar reaction α,β-unsaturated aldehydes **8** gave the vinyl compounds **9** accompanied by the products of their subsequent transformations.[9] In all these reaction use of the areneseleninic acids, instead of their precursors diaryl diselenides, gave similar results.



Scheme 2

We postulated that the active oxygen donor should be areneperoxyseleninic acid, formed *in situ*,. Since peroxyseleninic acids remained unknown we showed that benzeneperoxyseleninic acid (**10**) could be obtained in 85 % yield through oxidation of diselenide **3** with excess of 30 % aq. H_2O_2 at 0-5°C. In a similar way 2-nitrobenzeneperoxyseleninic acid (**11**) and its 2,4-dinitro analogue (**12**) were obtained from corresponding diselenides **4** and **5** by their treatment with 90 % hydrogen peroxide (Scheme 3). Investigation of the reactivity of areneperoxyseleninic acids has shown that the use of the compound **11** as a stoichiometric reagent for Bayer-Villiger

oxidation gave results similar to those when hydrogen peroxide in the presence of a catalytic amount of its precursor diselenide **4** was an oxidant.[10]

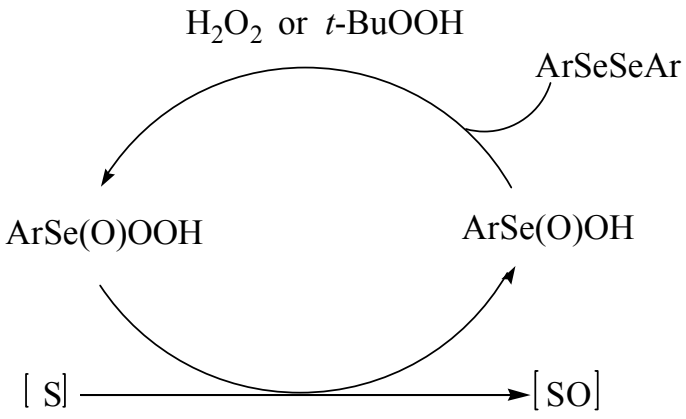


3 - 5 **10 - 12**

$R^1 = R^2 = H$ (**3**, **10**); $R^1 = NO_2$, $R^2 = H$ (**4**, **11**); $R^1 = R^2 = NO_2$ (**5**, **12**)

Scheme 3

These results support the postulated mechanism of hydrogen peroxide oxidation, catalyzed by diaryl diselenide or areneseleninic acid, presented in Scheme 4.



[S] = substrate

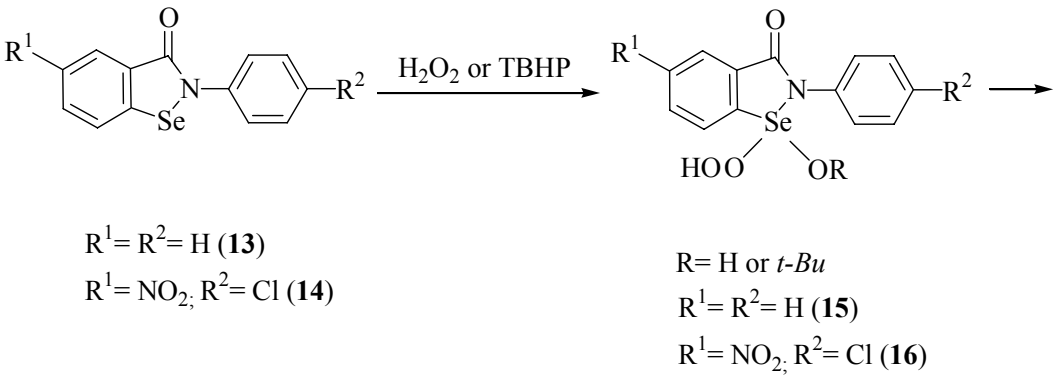
[SO] = oxidation product

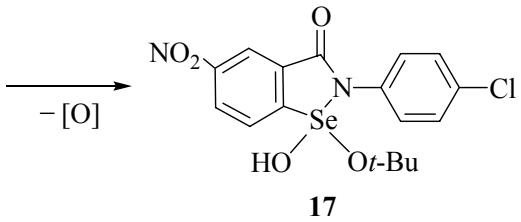
Scheme 4

Most recently it has been found that aromatic aldehydes having in the *ortho* or *para* position an electron-donating substituent, such as a methoxy group, can be oxidized with hydrogen peroxide in the presence of selenium dioxide as catalyst to give a mixture of carboxylic acids and phenols or just phenols. In other cases oxidation of aliphatic, aromatic and heteroaromatic aldehydes led to carboxylic acids almost exclusively.[11] When 2-phenylbenzisoselenazol-3(2H)-one (**13**), named ebselen, was used as a catalyst and TBHP was an oxidant even electron-rich aromatic aldehydes were exclusively oxidized to carboxylic acids.[12]

The role of ebselen as an oxygen transfer agent remained ambiguous. By analogy to benzeneperoxyseleninic acid (**10**) having a hydroperoxide group, it seemed to be possible that hydroperoxyselenurane **15** would be an active intermediate. When ebselen (**13**) was treated with hydrogen peroxide an unstable crystalline compound, most probably **9a** (R=H)**,** was produced but could not be identified because upon isolation, it immediately fragmented to ebselen

selenoxide, water and molecular oxygen. More stable hydroperoxyselenurane **16** (R=H) was obtained when ebselen analog **14** was treated with hydrogen peroxide. Another hydroperoxyselenurane **16** (R=*t*-Bu) was also obtained but it quickly lost oxygen, producing **17** (Scheme 5). Nevertheless, the identification of **16** and **17** provides strong support for the hypothesis that in the TBHP-ebselen system the active oxidant is the hydroperoxyselenurane **15**.[12]





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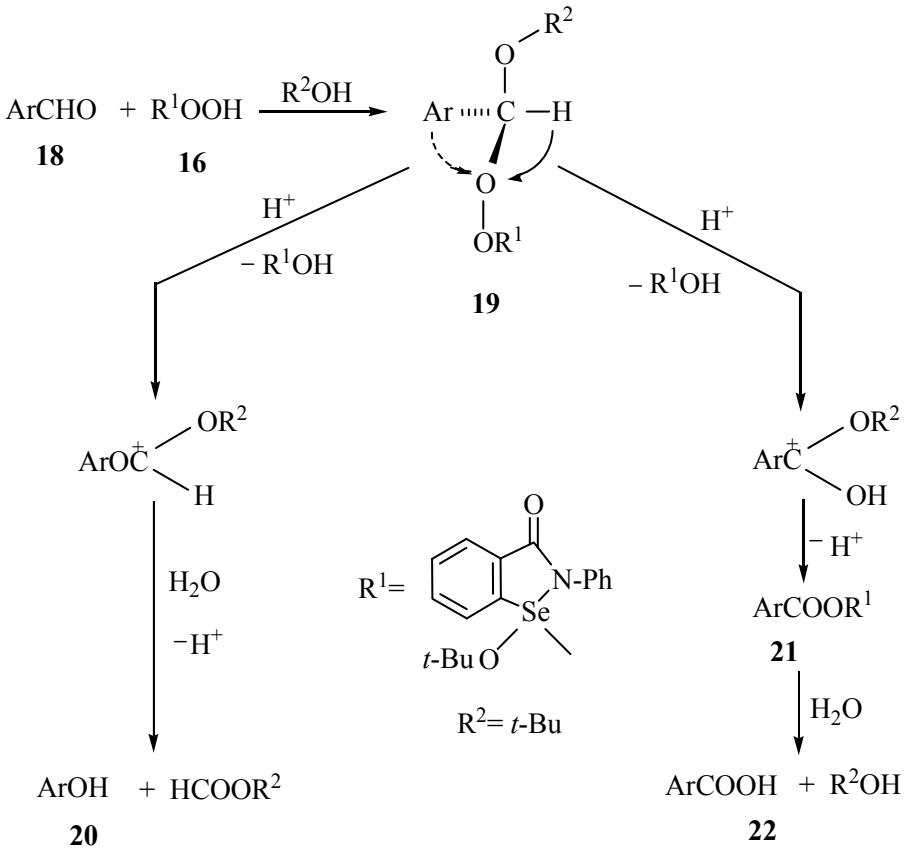
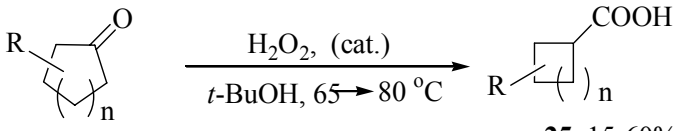
Scheme 5

The results presented above explain the role of TBHP and ebselen in the chemoselective oxidation of aromatic aldehydes to arenecarboxylic acids. Consistent with the widely accepted mechanism for reaction of carbonyl compounds with peroxyacids, the first step is addition of hydroperoxyselenurane **15** to the carbonyl compound **18** to form a tetrahedral intermediate **19** (Scheme 6). The subsequent step of the Baeyer-Villiger rearrangement, which is rate-determining, should be migration of the aryl group to the electrophilic oxygen atom of the peroxide bridge and simultaneously, cleavage of the O-O bond along with release of hydroxyselenurane R^1OH. The phenol **20** should be the final product. Nevertheless, two bulky groups R^1 and R^2 in the vicinity of the electrophilic oxygen atom in the peroxy bridge hinder aryl migration and competitive hydride ion migration predominates. This pathway leads to ester **21**, and finally to the acid **22**.



Scheme 6

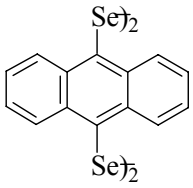
It is known that cycloalkanones (**23**), oxidized with hydrogen peroxide in the presence of selenium dioxide, undergo Favorski-type rearrangement involving ring contraction and formation of cycloalkanecarboxylic acids (**25**).[13, 14] Although yields of the acids were low and did not exceed 37 %, this method was applied to the synthesis of some natural products.[15] We reinvestigated this reaction using different selenium compounds as the potential catalysts. Among them poly(bis-9,10-anthracenylene) diselenide, named PADS (**24**), was found as the most effective one (Scheme 7).[16] For example, cyclohexanone oxidized in the presence of **24** was converted into cyclopentanecarboxylic acid in 78 % yield (GC analysis) and isolated in 60 % yield. Since the cycloalkanones are cheap and easily available substrates this method is suitable for synthesis of acids **25**, particularly those having five, six and seven-membered rings. Thus, H_2O_2-PADS can be regarded as a potential reagent for obtaining of bicyclo[4,3,0]nonanes the intermediates in total synthesis of homocarbaprostacyclins.



23 **25** 15-60%

n= 1-4, 8; R= H, Me, *t*-Bu, Ph

cat. =



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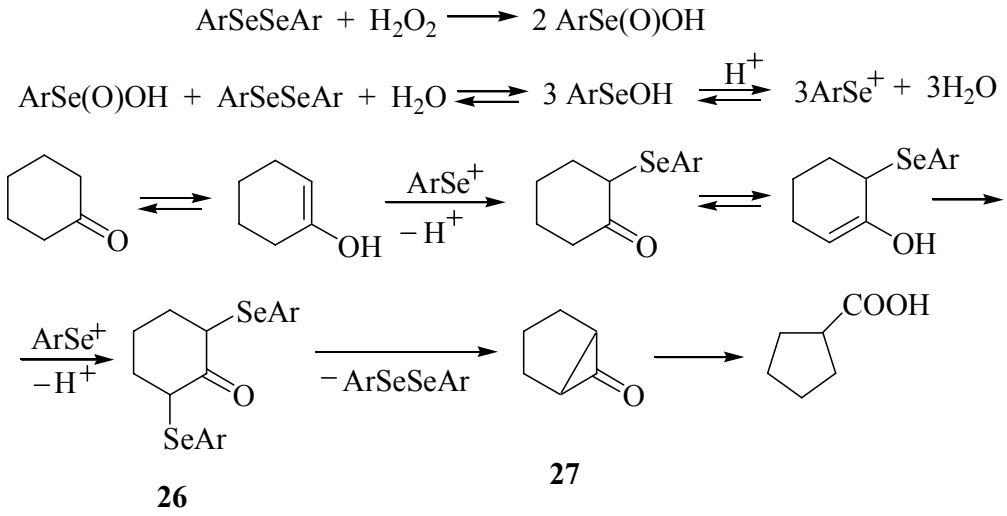
Scheme 7

The results of more detailed studies on the chemo- and stereoselectivity of this reaction support the mechanism, presented for oxidation of cyclohexanone in Scheme 8. Most probably it involves addition of two bulky arylselenium cations to both α-positions of the ketone, elimination of diaryl diselenide from the adduct **26,** and finally the rearragement of intermediate **27** into the cyclopentanecarboxylic acid.[17]



26 **27**

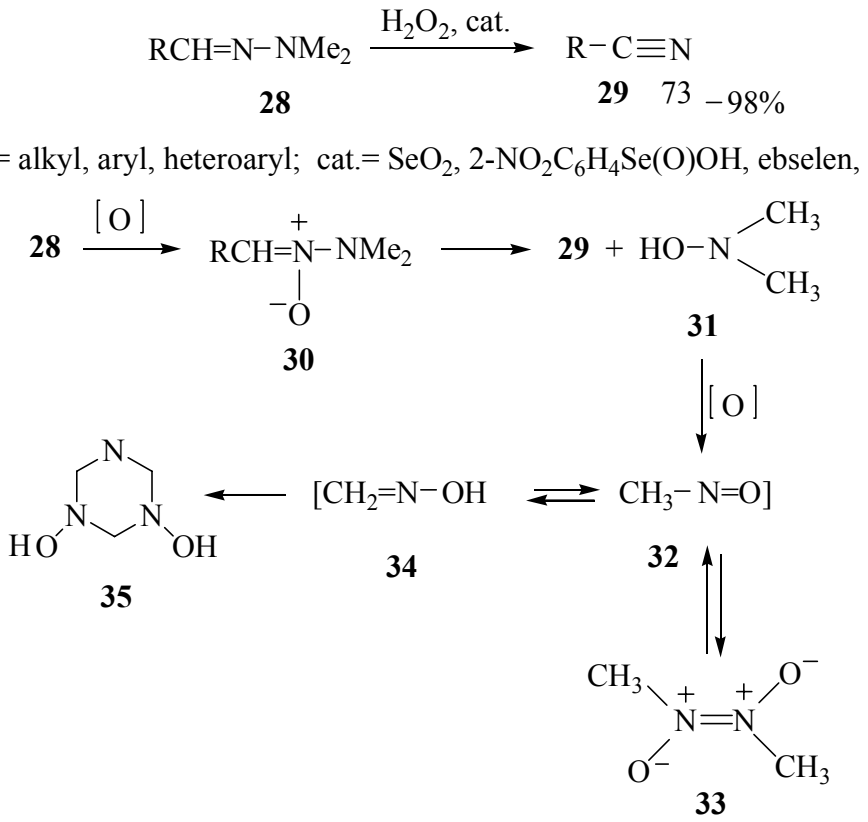
Scheme 8

1.2. Oxidation of azomethine compounds

Oxidation of azomethine-containing compounds is more complex than oxidation of carbonyl compounds and some unexpected results have been found. The azomethine C=N group occurs in many organic molecules of fundamental importance. It is in many respects, intermediate between the C=C and C=O groups, and certain analogies and differences are observed. Both these groups have two electrons in binding π-orbitals and this accounts for some of their most characteristic properties. While carbon atoms present in these groups have no lone pair of electrons, the

nitrogen and oxygen atoms possess it; this explains the distinctive properties of azomethine and carbonyl group. For these purposes oxidation of azomethine compounds drew our attention, even more than oxidation of carbonyl compounds, and various types of these compounds, such as aldimines, ketimines, oximes, hydrazones and azines, have been taken as the model substrates.[18]

It was known that hydrogen peroxide oxidation of N,N-dimethylhydrazones (**28**) gave nitriles (**29**) accompanied by substantial amounts of the parent aldehydes and aldazines but the reaction was limited to N,N-dimethylhydrazones derived from benzaldehyde and its analogues having electron-donating substituents in the aromatic ring.[19] We found that the reaction proceeded with high chemoselectivity giving aromatic nitriles in fair yields when selenium dioxide, 2-nitrobenzeneseleninic acid or ebselen was used as the catalyst.[20,21] The reaction involved N-oxidation of dimethylhydrazones **28** and Cope reaction of N-oxide **30** to nitrile **29**. Although dimethylhydroxylamine (**31**) itself never was isolated as a product of this reaction, we identified products of its oxidation such as nitrosomethane (**32**), its dimer **33** and 1,3,5-trihydroxyhexahydro-1,3,5-triazine (**35**) being a product of formaldoxime (**34**) trimerization (Scheme 9).[2]

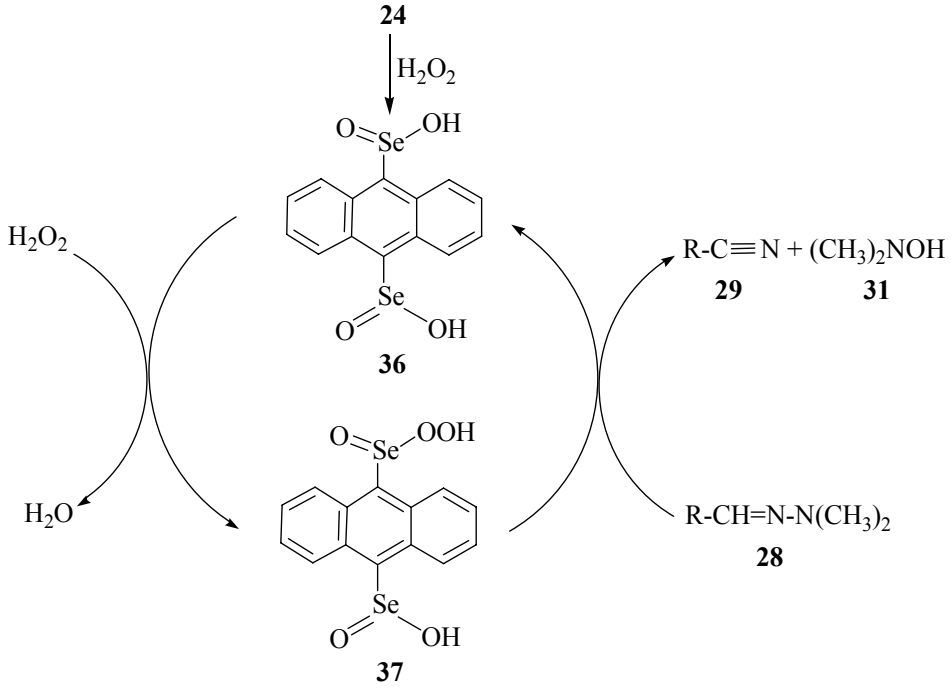


Scheme 9

Most recently we have extended this method to the conversion of aromatic, heteroaromatic, and aliphatic N,N-dimethylhydrazones to nitriles, and we have found PADS (**24**) more versatile as the catalyst. The oxidant was 30 % hydrogen peroxide. The catalyst was used in a 5 % mol

amount (related to the substrate) and the reaction carried out in *tert*-butanol in 55 ^{o}C for a period 2.5-8 h to give nitriles in good to excellent yield.[22]

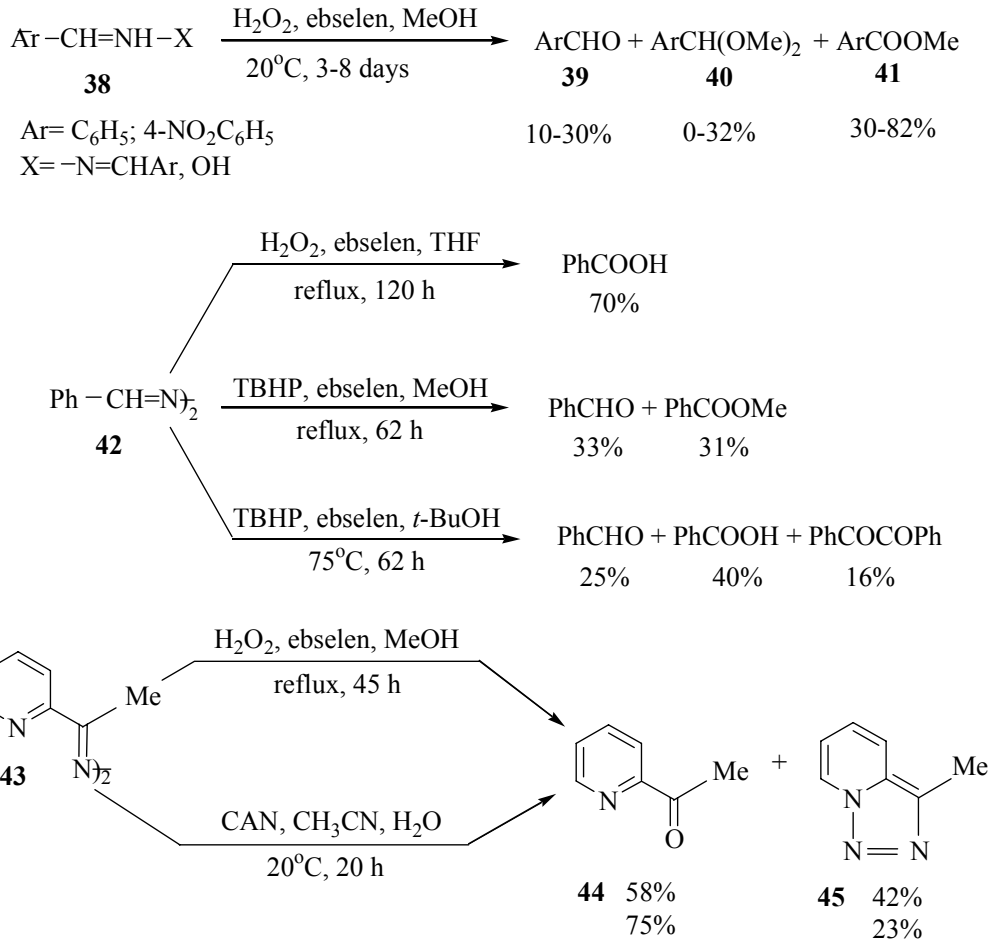
The oxidation with the H_2O_2–PADS system can be explained according to the mechanism postulated earlier for other diaryl diselenides.[2,23] In this case the compound **24,** oxidized with hydrogen peroxide, underwent depolymerization to produce areneseleninic acid **36** which was subsequently converted into peroxyseleninic acid **37 (**Scheme 10). The similar catalyst, poly(bis-1,2-phenylene) diselenide *o*-$[SeC_6H_4Se]_n$ named PPDS was aplied to hydrogen peroxide oxidation of aromatic aldazines, aldoximes and tosylhydrazones having an alkyl group, electron withdrawing or 3-methoxy, and 3-phenoxy substituents attached to arenecarboxylic acids. Exceptionally, oxidation of the azomethine compounds derived from 1-naphthaldehyde lead to (1-oxo-1,3-dihydroisobenzofuran-1-yl)acetic acid resulted from oxidative transformation of the formed *in situ* 1-naphthol.[24]



Scheme 10

In other work, we provided evidence that hydrogen peroxide and TBHP in the presence of a catalytical amount of ebselen might be used as a reagent for oxidation of azomethine groups in azines and oximes.[25] Azines and oximes **38** derived from benzaldehydes oxidized with hydrogen peroxide in methanol gave parent aldehydes **39**, their dimethylacetals **40** and methyl benzoates **41**. The oximes gave esters **41** as the main products. The extended experiments carried out on the azine **42** shows that the result of the reaction depended on the oxidant used and on the reaction conditions, particularly on the solvent since methanol could participate in the reaction. The results are shown in Scheme 11.

Ketazines were oxidized with H_2O_2-ebselen system exclusively to parent ketones, while oxidation of azine **43** derived from 2-acetylpyridine gave the mixture of expected ketone **44** and condensed triazole **45**. The same compounds were produced when cerium(IV) ammonium nitrate (CAN) was an oxidant. Since CAN is well known one-electron oxidant generating free radical, it seems possible that a free radical mechanism is involved in the hydroperoxide oxidation of azines catalyzed by ebselen.

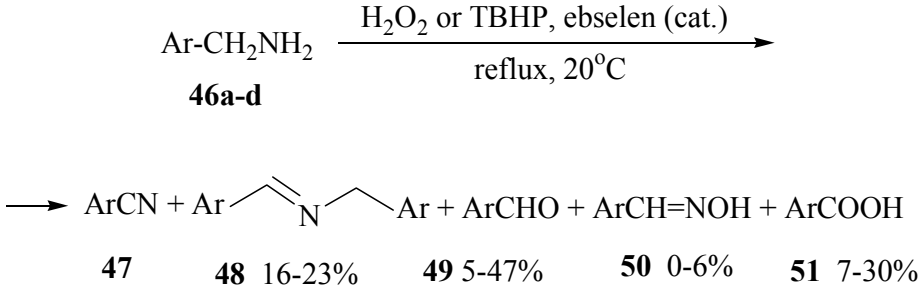


Scheme 11

1.3 Oxidation of benzylamines

Oxidation of amines is an useful way for synthesis of variety nitrogen-containing organic compounds. The reaction leads to different products depending on the nature of the oxidizing agents and a type of amine.[26] In our work selenium compounds were used as the catalysts for hydroperoxide oxidation of primary and secondary benzylamines. Four primary benzylamines **46a-d** and three N-substituted benzylamines: N-methylbenzylamine (**46e**), dibenzylamine (**46f**) 1,2,3,4-tetrahydroisoquinoline (**46g**), were taken as the model substrates. Among different selenium compounds tested as catalysts PPDS and particularly ebselen had appreciable activity.

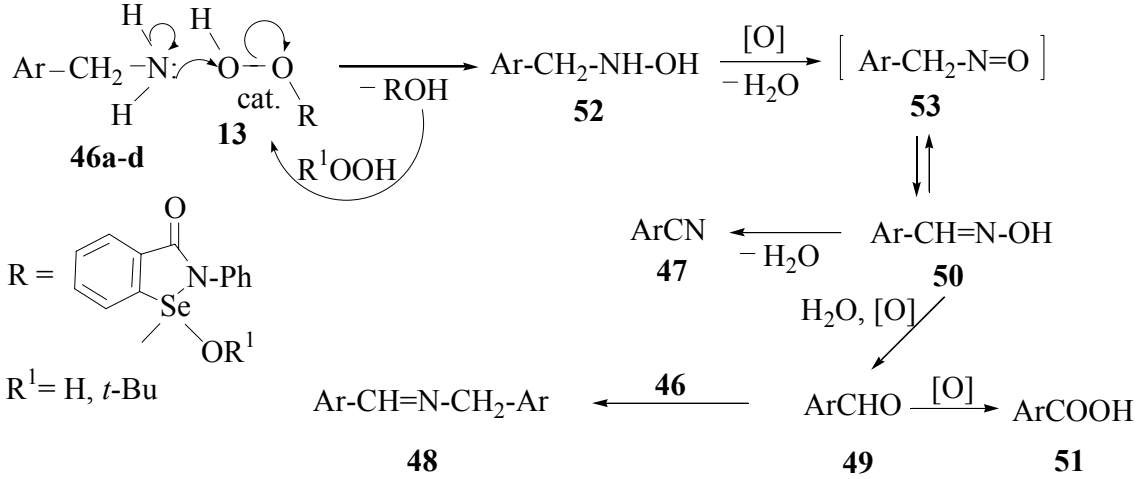
They were used in 5 % mol while the stoichiometric oxidants were 30% hydrogen peroxide and 80 % TBHP. Although the results, presesented in Scheme 12, varied depending on the substrate, oxidant and catalyst used they provided evidence that the most effective and selective catalyst was ebselen and from primary amines **46a-d** corresponding nitriles **47** can be obtained in satisfactory to high preparative yields 66-82 % thus the elaborated method has a practical value.[27]



Scheme 12

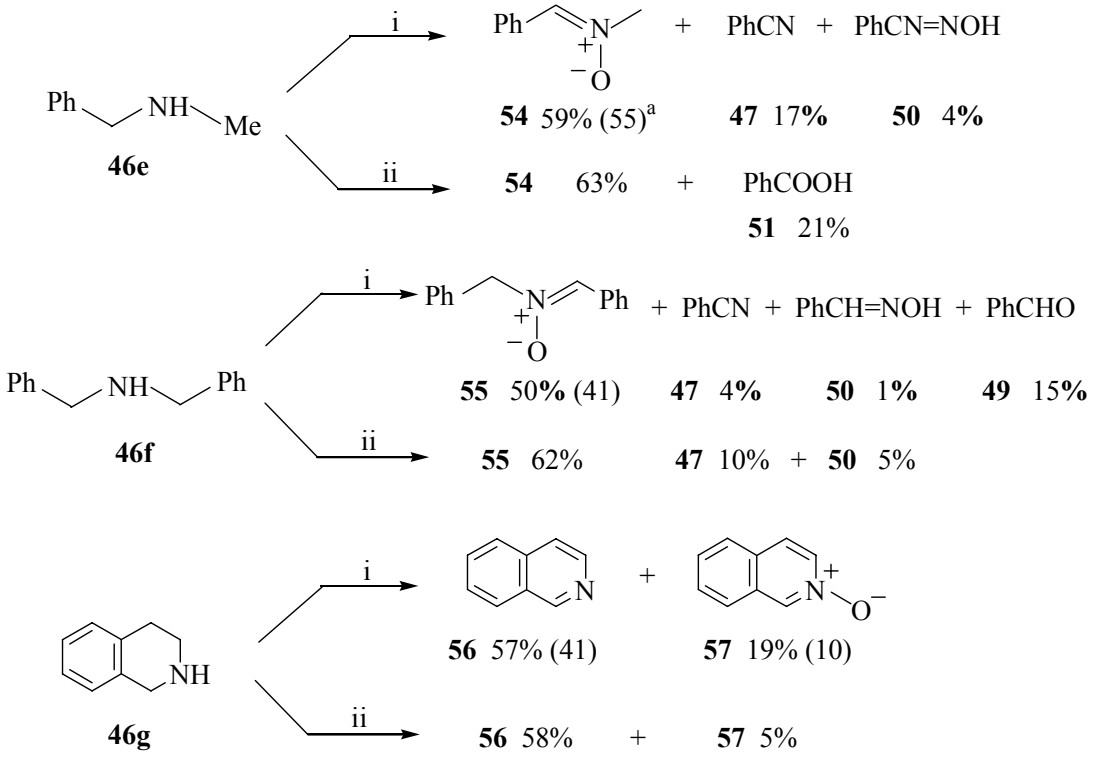
The possible mechanism of the oxidation of primary amines with hydroperoxides in the presence of ebselen, shown in Scheme 13, involves formation of hydroperoxyselenurane **15** as an active intermediate.

The first step of the reaction leads to the oxime **50** *via* highly reactive hydroxylamine **52** and nitroso compound **53,** analogously as it has been postulated when benzylamines were oxidized with hydrogen peroxide in the presence of sodium wolframate,[28] peroxotungstophosphate[29] or methyl trioxorhenium.[30] According to known reactions the oximes **50** can be subsequently dehydrated to the nitriles **47** or oxidized to arenecarboxylic acids **51** *via* aldehyde **49** as an itermediate. In some cases condensation of **49** with starting amine **46** to aldimine **41** takes place.



Scheme 13

Results of the oxidation of N-substituted benzylamines with hydrogen peroxide or TBHP in the presence of ebselen are presented in Scheme 14.



i = TBHP, ebselen (cat), *t*-BuOH, reflux, 20 h; ii = H_2O_2, ebselen (cat), *t*-BuOH, reflux, 20 h

[a] Data in parentheses are referred to isolated yields.

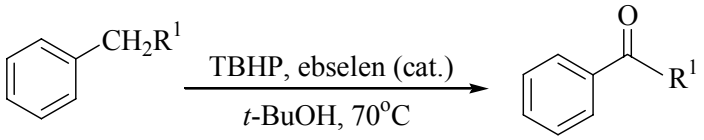
Scheme 14

N-Methylbenzylamine (**46e**) and dibenzylamine (**46f**) gave nitrones **54** and **55** as the major products similarly as it was observed earlier when secondary amines were oxidized with H_2O_2-SeO_2.[31,32] Most probably the reaction proceeds *via* dehydrogenation of the amine and subsequent N-oxidation of intermediated imine. The main reaction is accompanied by cleavage of the C-N bond resulting in formation of the nitrile **47**, aldehyde **49**, benzaldoxime **50** and carboxylic acid **51** in a similar manner to that described earlier for primary benzylamines. Tetrahydroisoquinoline **46g** was dehydrogenated to isoquinoline **56** accompanied by N-oxide **57,** in contrast to hydroxyalkyflavine-catalyzed oxidation with hydrogen peroxide where 3,4-dihydroisoquinoline N-oxide is a product.[33] To our knowledge it is the first example of aromatization of tetrahydroisoquinoline by hydroperoxides.

1.4 Oxidation of alkylarenes and other substituted arenes

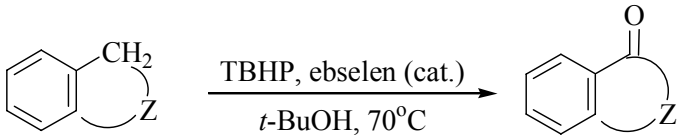
Toluene (**57a**) and five other alkylarenes **57b-f** were oxidized with TBHP in the presence of ebselen to benzaldehyde (**58a**) and ketones (**58b-f**) respectively (Scheme 15). Although the

methyl group in toluene remained resistant toward oxidation and benzaldehyde was formed only in low yield, the benzylic methylene group in alkylarenes **57b-f** was oxidized to a carbonyl group more efficiently. The experiments with ethylbenzene (**5fb**) have shown that although during long period conversion of the substrate increased, side reaction took place and selectivity of the main reaction decreased. A similar effect was observed when the oxidant was used in a large excess. No reaction was observed when catalysts such as titanosilicate TS-1, selenium(IV) oxide or ebselen were used for hydrogen peroxide oxidation of toluene.[25]



57a-c **58a-c**

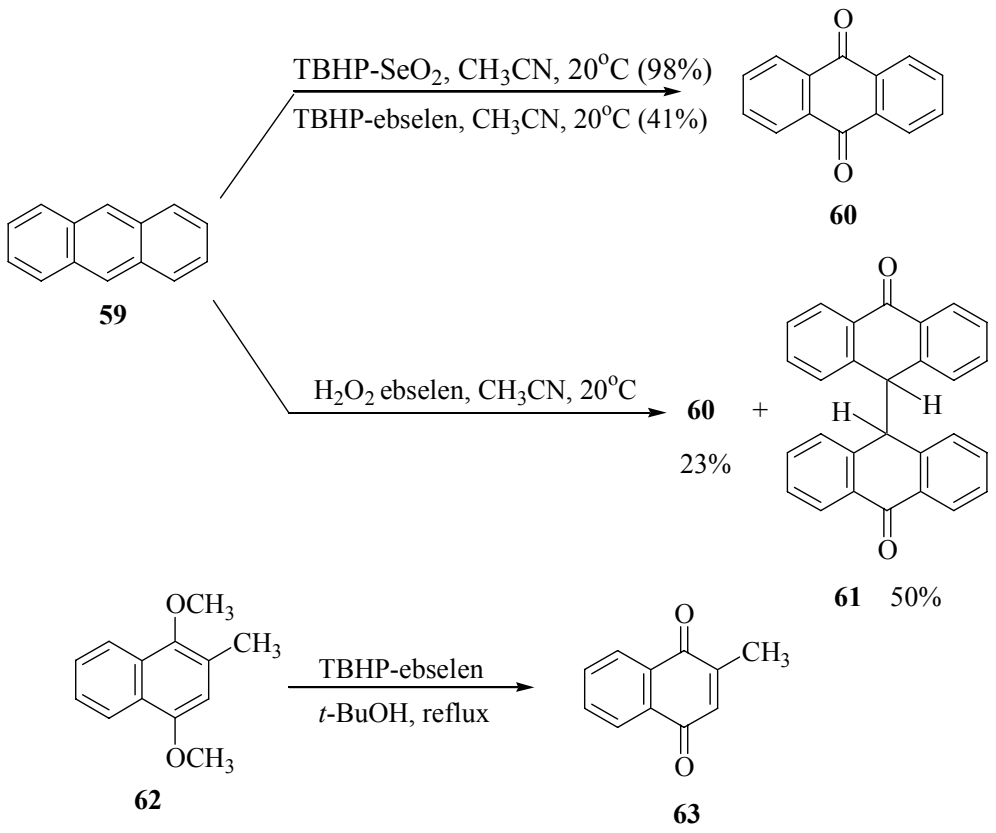
R= H (**a**) 10%; Me (**b**) 55%; Ph (**c**) 48%



Z =  (**d**) 91%; -CH_2CH_2- (**e**) 35%; -$CH_2CH_2CH_2$- (**f**) 25%

Scheme 15

Anthracene **59** was oxidized with TBHP-SeO_2 to anthraquinone **60** in almost quantitative yield. In a similar reaction when TBHP-ebselen was an oxidant the quinone **52** was produced only in 41 % and the rest of substrate **59** remained unreacted. Oxidation of **59** with H_2O_2-ebselen gave quinone **60** only in 23 % yield while the major product was a dimer **61** formed in 50 % yield. Other arenes such as 2-methylnaphthalene, phenanthrene and acenaphthylene were oxidized to corresponding quinones in the yields below 21 %. Electron-donating substituents such as hydroxy or methoxy group made the aromatic ring more susceptible towards oxidation with hydroperoxides. For example, 2-methylnaphthalene treated with TBHP-ebselen was converted into the products only in 15 % and suspected menadione (**63**) was formed only in a trace amount (ca. 3 %) while 2-methyl-1,4-dimethoxynaphthalene (**52**), oxidized with the same reagent, gave **63** in 60 % yield (Scheme 16).[34] The result was similar to that one when the reagent was a one-electron oxidant such as Ce(IV) or Ag(II) cation.[35] It suggests that the reaction proceeds *via* radical or cation-radical intermediates.

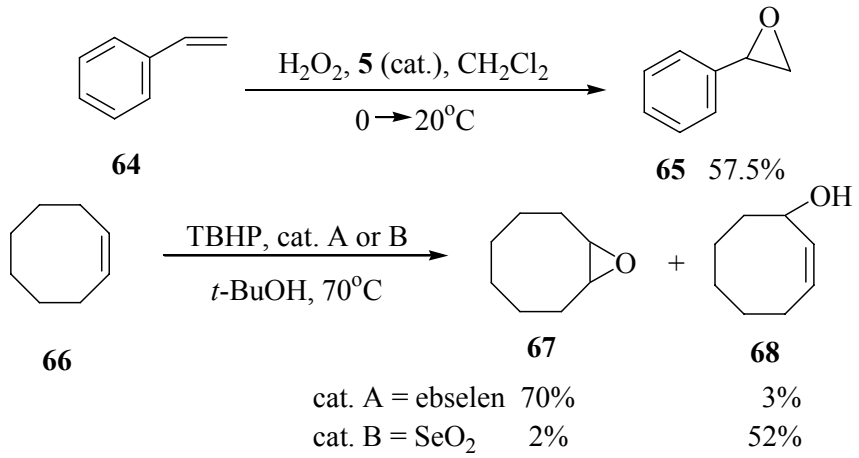


Scheme 16

1.5. Epoxidation of alkenes

Alkenes can be epoxidized with any of a number of peroxyacids. Nevertheless, the method is cheaper and more covenient when, instead of 3-chloroperoxybenzoic or other peroxycarboxylic acid used in a stoichiomeric amount, an oxidant is generated *in situ* and recyclized with peroxyseleninic acid. It has been found that, styrene (**64),** resistant toward epoxidation, can be converted into epoxide **65** in 57.5 % preparative yield on treatment with hydrogen peroxide in the presence of anhydrous magnesium sulfate and bis(2,4-dinitrophenyl) diselenide (5) as a catalyst (other organoselenium compounds and selenium(IV) oxide were less active). The unreacted styrene can be recovered in 35.5 % yield and reused. Other differently substituted vinylbenzenes were epoxidized in the same way.[36]

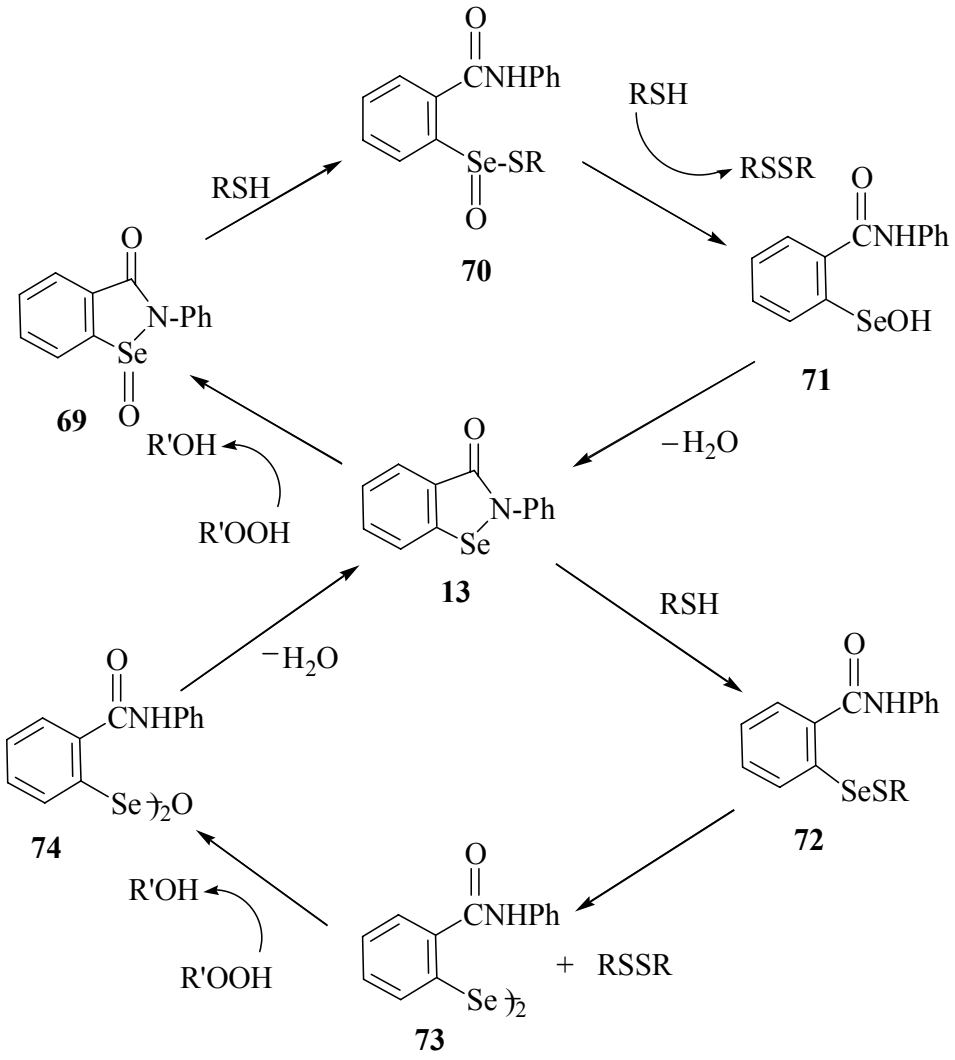
Result of the oxidation of alkenes strongly depends on the catalyst used. We found that cyclooctene (**66**) oxidized with TBHP-ebselen gave the epoxide **67** accompanied with trace of 3-hydroxycyclooctene (**68**) being a product of α-hydroxylation.[37] On the contrary, the same reaction catalyzed by selenium(IV) oxide afforded **68** as the major product (Scheme 17).[37,38]



Scheme 17

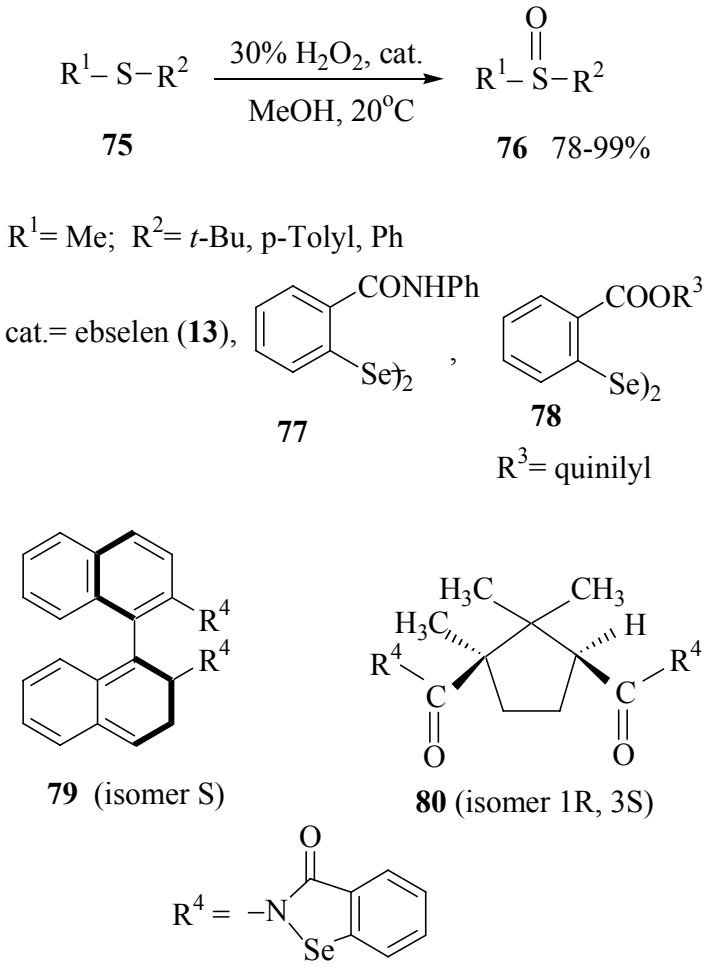
1.6. Oxidation of organosulfur compounds

Near two decades ago it was found that ebselen could act against oxidative stress in a similar way as common selenoenzyme – glutathione peroxidase (GSH-Px).[7,39,40] Some years later it was found that other 2-substituted bezisoselenazol-3(2H)-ones, cyclic selenenamides, and bis(2-carbamoyl)phenyl diselenides are able to deactivate oxygen species present in the living cell such as peroxides, hydroperoxides, hydroxyl radical and superoxide anion.[6] The mode of the biological action of ebselen and its analogues has been postulated to be similar to that observed for GSH-Px and results in dehydrogenation of thiols to disulfides while hydrogen peroxide is reduced to water.[7,41] Later it was found that ebselen did not promote hydrogen peroxide oxidation of thiols such as N-acetylcysteine, butanethiol and octanethiol in nonenzymic conditions.[42] Nevertheless, the selenenamide derived from camphor effectively catalyzed oxidation of phenylmethanethiol to the disulfide.[43] The postulated mechanism of the enzyme-like action of ebselen is presented in Scheme 18.[7,41,43,44] When concentration of hydroperoxide is high, ebselen (**13**) is oxidized to selenoxide **69** which reacting with one molecule of the thiol gives selenosulfide **70**. The intermediate **70** and the second molecule of thiol produce disulfide while the selenenic acid **71** is converted back to the ebselen. In the biological systems, where concentration of hydroperoxide is low, ebselen and thiol give the selenosulfide **72** which disproportionates to the disulfide and diselenide **73** is subsequently oxidized to selenenic anhydride **74** and finally to ebselen (**13**).



Scheme 18

A broad spectrum of selenium compounds, among them diaryl diselenides and benziso-selenazol-3(2*H*)-ones has been tested as the catalysts for hydrogen peroxide and *tert*-butylhydroperoxide oxidation of sulfides (**75**) into sulfoxides (**76**). When ebselen (**13**) or its open-chain analogue bis(2-carbamoylphenyl)phenyl diselenide (**77**) was employed as a catalyst the reaction was highly chemoselective and sulfoxides (**76**) were formed exclusively or were accompanied only with minute amounts of sulfones (Scheme 19).[21,45]



Scheme 19

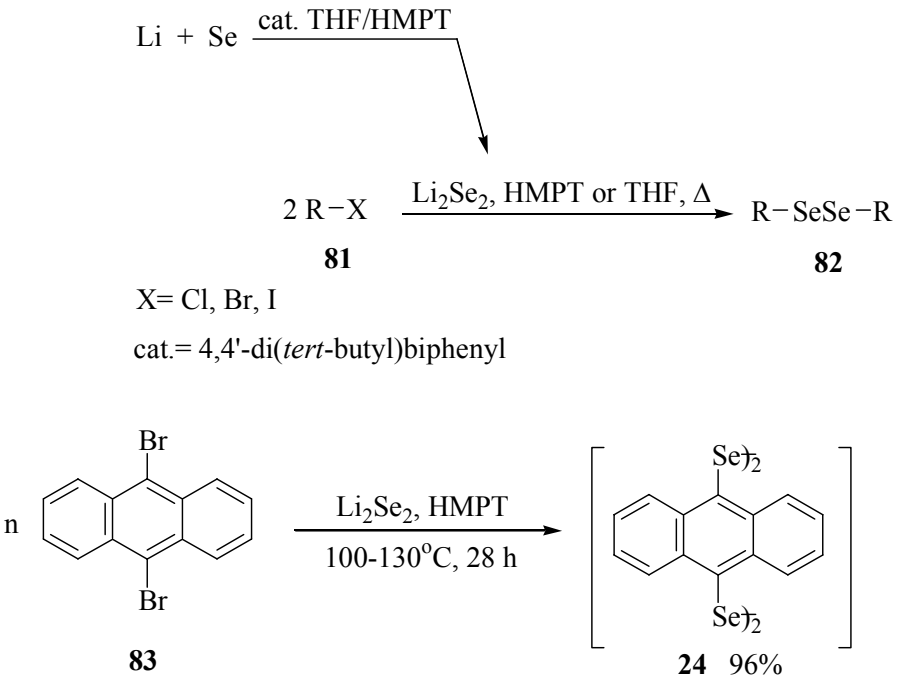
We expected that new chiral aryl diselenides such as 2,2'-diselenobisbenzoate (**78**), 1,1'-binaphthalene 2,2'-disubstituted with benzisoselenazol-3(2H)-onyl groups (**79**) and derivative of (1R,3S)-(+)-camphoric acid (**80**) should be catalysts for stereoselective oxidation of prochiral sulfides. Unfortunately, none of stereochemical effect was observed and only racemic selenoxides were produced in high yields.[45,46]

2. Synthesis of diaryl diselenides and benzisoselenazol-3(2*H*)-ones

2.1. Synthesis of diaryl diselenides

In the late eightees we developed a convenient method for practical synthesis of dialkyl and diaryl diselenides (**82**) by selenenylation of corresponding halides (**81**), lactones, oxiranes and tosylates with dilithium diselenide in aprotic medium (THF or HMPT). Dilithium diselenide was generated *in situ* from elemental lithium and selenium in the presence of diphenylacetylene, or later of 4,4'-di(*t*-butyl)biphenyl, as a catalyst. The method has a general value, competitive formation of selenides is avoided, yields of diselenides are high, also PPDS and PADS (**24**) were

obtained in this manner.[16,24,47,48] The synthesis of diselenide **24** from 9,10-dibromoanthracene (**83**) presented in Scheme 20 is an example.

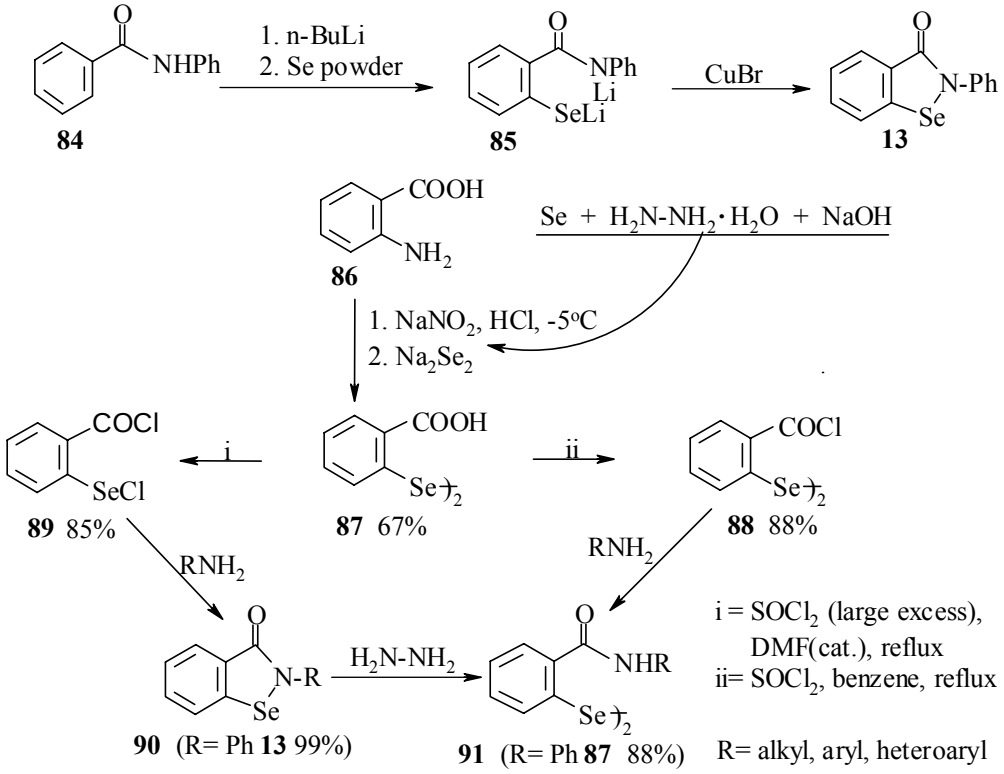


Scheme 20

2.2. Synthesis of ebselen and other benzisoselenazol-3(2*H*)-ones

There are alternative ways to synthesize ebselen (**13**) and other 2-substituted benzisoselenazol-3(2H)-ones (**90**). The first of them starts from benzanilide (**84**) which is selenenylated to intermediate **85** and subsequently cyclized to ebselen (**13**) by treatment with copper(I) bromide.[49] A more general method for the synthesis of ebselen and other 2-substituted benzisoselenazol-3(2H)-ones (**90**) as well as for synthesis of 2-carbamoylphenyl diselenides (**83**), presented in Scheme 21, was elaborated in our laboratory as a modification of the old procedure reported by Lesser and Weiss.[48, 50, 51] The first two steps of the synthesis involve diazotization of anthranilic acid (**86**) and repleacement of the diazonium group by the diselenide group by treatment of a diazonium salt with disodium diselenide, generated in situ from elemental selenium and hydrazine hydrate in the presence of sodium hydroxide. The formed 2,2'-diselenobisbenzoic acid (**87**), treated with an excess of thionyl chloride in the presence of catalytical amounts of DMF, gives 2-(chloroseleno)benzoyl chloride (**89**), or when thionyl chloride is used a stoichiometric amount 2,2'-diselenobis benzoyl chloride (**88**) is produced. The dichloride **87** is a reagent for tandem acylation-selenylation of primary amino groups giving a variety of 2-substituted benzisoselenazol-3(2H)-ones (**90**), among them ebselen (**13**). The Se-N bond in the heterocyclic ring of **90** can easily be cleavaged by reducing agents such as hydrazine or triphenylphosphine and 2-carbamoylphenyl diselenides (**91**), among them close analogues of ebselen (**77**), are formed. The same diselenides **91** can be obtained directly in the reaction of chloride **88** with

primary amines. Their oxidation lead to benzisoselenazol-3(2*H*)-ones (**90**) as shown in Scheme 1.



Scheme 21

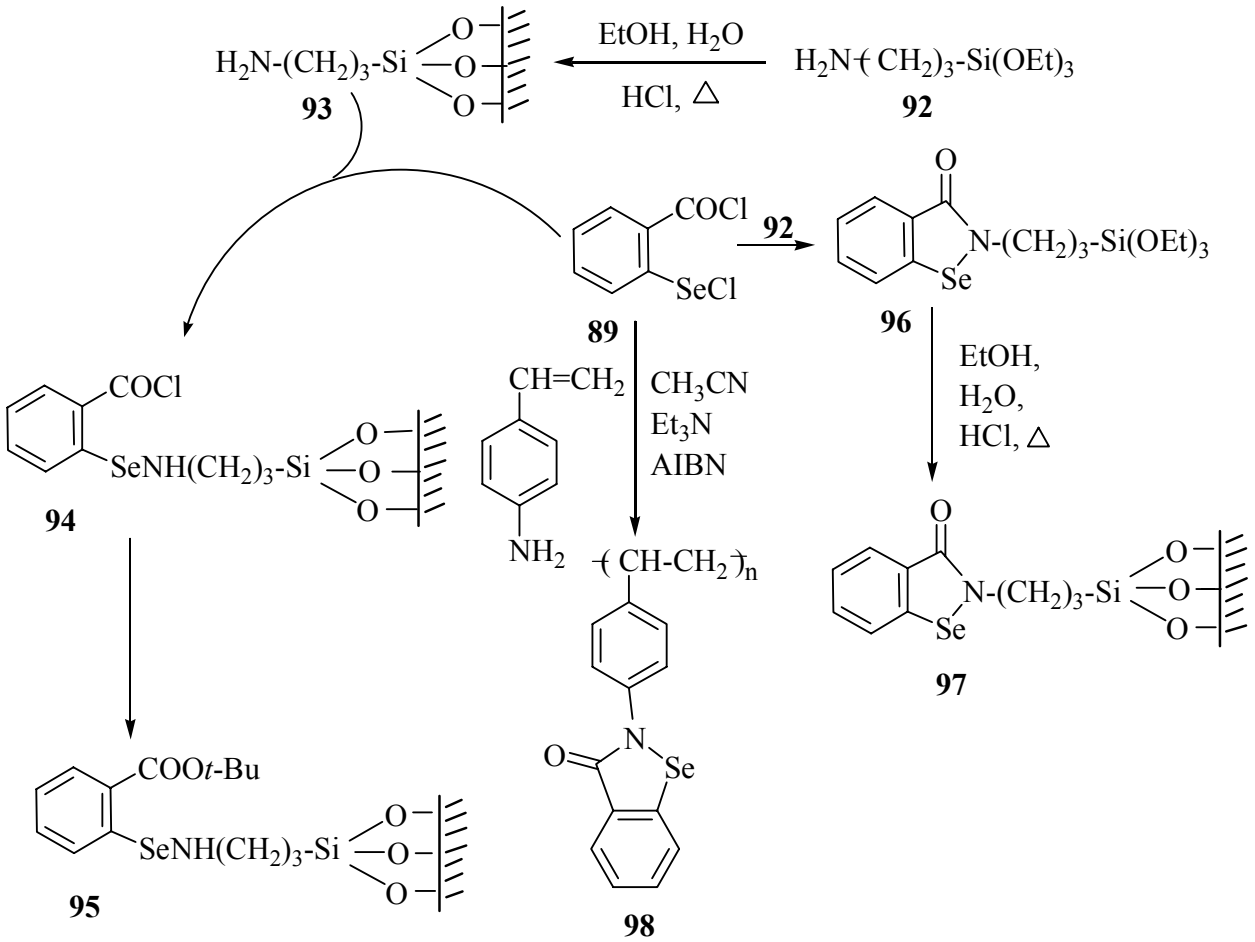
2.3. Synthesis organoselenium compounds immobilized on solid supports

In modern organic synthesis covalent immobilization of homogenous catalysts to insoluble polymer support has received considerable attention in recent years.[52-55] The covalent binding of catalyst with polymeric support offers a number of advantages over traditional solution-phase chemistry. In an ideal case, the supported catalysts can be recovered from reaction mixtures by simple filtration, they do not contaminate the product solution, they may be recycled, and they can help increase selectivity. Moreover, the immobilization of homogenous catalysts potentially allows their adaptation to continuous flow type processes. The use of polymeric supports in organic synthesis has become common practice. Starting with the introduction of solid-phase peptide synthesis by Merrifield, insoluble supports have been implemented in a wide range of synthetic methodologies.[56-58] Athough a variety of selenium compounds have been used during the last three decades as stoichiometric oxidants or oxygen transfer catalysts[59] to our knowledge only one of them (polyester resin containing oxyselenium groups) has been used as an oxidant for conversion of benzyl, allyl and active alkyl bromides to aldehydes [60] and a second one (polystyrene-supported benzeneseleninic acid) as a catalyst for TBHP oxidation of benzyl and allyl alcohols to aldehydes and phenols to quinones.[61]

In our work 2-(chloroseleno)benzoyl chloride (**89**) was used as a key substrate for synthesis of silica-supported selenenamide MONICAT A (**95**) and benzisoselenazol-3(2H)-one HALICAT (**97**) (Scheme 22).

The first of them was obtained from 3-aminopropylsilicate (**93**) prepared by hydrolysis of 3-aminopropyltriethoxysilane (**92**) and dichloride (**89**). Since selenenylation of amino group proceeded easier then acylation 2-(aminoseleno)benzoyl chloride (**94**) was formed initially and then treated with TBHP in *t*-butanol gave **95**. This compound was successfully used as a catalyst for TBHP oxidation of aldehydes to carboxylic acids, ethers to esters, and benzylamines to nitriles.[62]

Another silica-supported catalyst HALICAT (**97**) was obtained in the reaction of 3-aminopropyltriethoxysilane (**92**) with dichloride (**89**) and subsequent hydrolysis of formed by-product (**96**). This catalyst exhibited appreciable activity in TBHP oxidation of sulfides to sulfoxides and alkylarenes to alkylaryl ketones.[63] 4-Aminostyrene treated with dichloride (**89**) in the presence of a polymerization catalyst α,α'-azo-bis-isobutyronitrile (AIBN) gave ebselen covalently immobilized on a polyethylene chain MONICAT B (**98**).



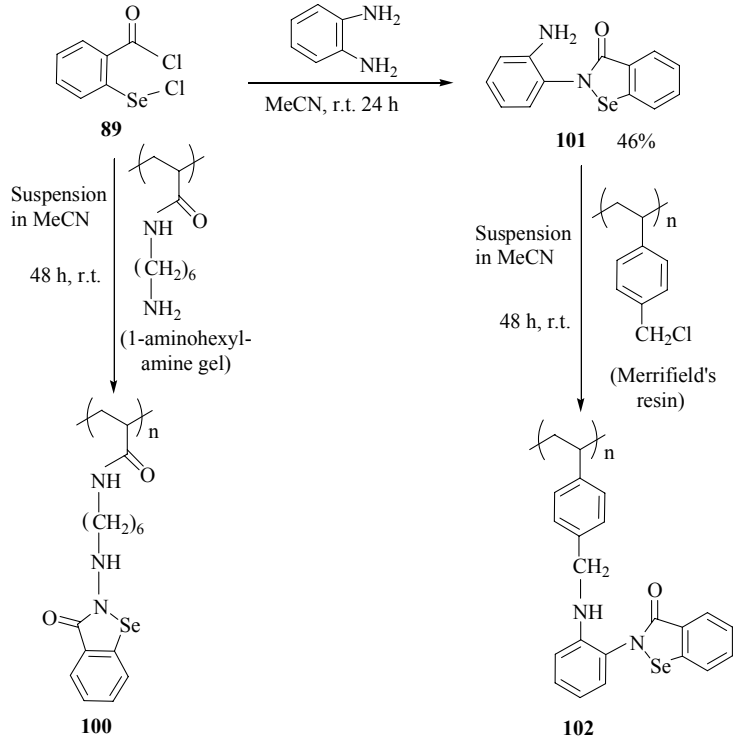
Scheme 22

Other polymer-supported benzisoselenazol-3(2H)-one is MONICAT C (**100**) obtained by acylation-selenenylation of primary amino groups in 1-aminohexylamine gel with dichloride (**89**) while the aminoebselen (**101**) was a substrate for synthesis of benzisoselenazol-3(2H)-one supported on Merrifield resin MONICAT D (**102**) as shown in Scheme 23.[62] The studies on the catalytical properties of silica- and polymer-supported selenium catalysts are in progress.

3. Conclusions

In conclusion we wish to say that diaryl diselenides, among them polyaryldiselenides, and 2-substituted benzisoselenazol-3(2H)-ones, particularly ebselen, are effective catalysts for hydrogen peroxide and *tert*-butyl hydroperoxide oxidation of organic compounds such as sulfides, amines, azomethine compounds, aldehydes, cycloalkanones, alkenes and alkylarenes. Most of these reactions have a synthetic value because of their selectivity and high yields of the products. Diselenides act via peroxyseleninic acids as active intermediates while in the case of benzisoselenazol-3(2H)-ones selenahydroperoxides (hydroperoxyselenuranes) are active oxygen donors. These intermediates are involved in an ionic mechanism although *tert*-butyl hydroperoxide oxidation of alkylarenes and some other reactions known as one-electron processes suggests that free-radical mechanisms are also possible.

A new generation of polymer and silica-supported organoselenium compounds has been designed as recyclizable oxygen-transfer catalysts and synthesized. Preliminary results show their appreciable catalytical activity.



Scheme 23

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