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Recent Advances in Organoselenium Chemistry

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Dedicated to Professor Alain Krief

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This microreview highlights new developments of organoselenium chemistry and new selenium compounds as versatile reagents in synthesis.

Introduction

Selenium-based methods in organic chemistry have developed rapidly over the past years and organoselenium chemistry is now a very useful tool in the hands of synthetic chemists. A major breakthrough for the development of organoselenium chemistry was the discovery of the selenoxide elimination in the early seventies.[1] But before organoselenium reagents became important reagents it was discovered that electrophilic selenium compounds can add stereospecifically to alkenes.[2] Since that time this reaction has been an important tool in the portfolio of organic chemists and is now routinely used even for the synthesis of complex target compounds. Comprehensive reviews on this chemistry have appeared[3–10] and in recent times, the synthesis of chiral selenium electrophiles and their application in asymmetric synthesis has emerged. This microreview highlights new developments of organoselenium chemistry and new selenium compounds as versatile reagents in synthesis.

New Organoselenium Compounds and Their Applications

In 2003, Braga and co-workers reported a simple and efficient synthesis of chiral amino diselenides and showed their application as catalysts for the enantioselective addition of diethylzinc to aldehydes.[11] The chiral amino diselenides were prepared from the corresponding β-amino alcohols. After Boc-protection and aziridine formation selenium was introduced by regioselective nucleophilic ring opening by attack of Li_2Se_2. For the catalytic addition reactions, 0.5 mol-% of chiral amino diselenide and 2.5 equiv. diethylzinc in toluene at room temperature were used. Overall the chiral secondary alcohols could be obtained in high yields (51% – 93%) and enantiomeric excesses up to 99% (Scheme 1). Similar reactions using enantiomerically pure diselenides have been reported earlier together with detailed mechanistic analysis.[12]

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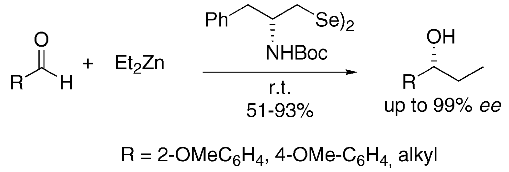
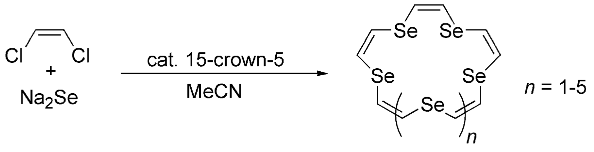
Thomas Wirth (right) received his PhD from the Technical University of Berlin (1992, Prof. S. Blechert). After a postdoctoral stay at Kyoto University as a JSPS fellow (Prof. K. Fuji, 1992/93) he obtained his habilitation on stereoselective oxidation reactions at the University of Basel (Prof. B. Giese, 1999) before taking up the position at Cardiff University in 2000. He was a visiting professor at the University of Toronto (1999), Chuo University in Tokyo (2000), Osaka University (2004) and Osaka Prefecture University (2008). He was awarded the Werner Prize from the New Swiss Chemical Society in 2000.



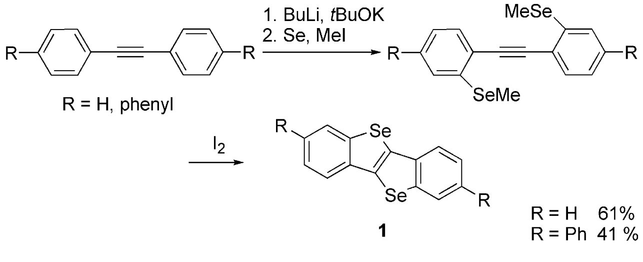
Scheme 1.

Kamigata et al. reported the synthesis and structures of 15- and 18-membered unsaturated selenacrown ethers and their complexation with silver trifluoroacetate.[13] The selenacrown ethers were obtained from an acetonitrile solution containing an excess of *cis*-dichloroethene, sodium selenide and catalytic amounts of 15-crown-5 (Scheme 2); 15- and 18-membered unsaturated selenacrown ethers have been isolated in 2% and 3% yield. The distances from the centres of the two macrocycles to the selenium atoms are 2.77 Å and 3.31 Å. This indicates, that the 18-membered unsaturated selenacrown ether has a slightly larger captivity than its sulfur analogue. Additionally, in a later study 21-, 24- and 27-membered unsaturated selenacrown ethers were isolated.[14] Some saturated selenacrown ethers have been reported earlier.[15]



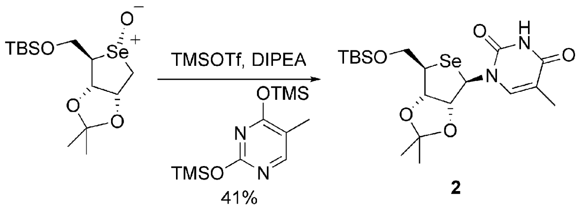
Scheme 2.

Selenophenes and benzoselenophenes attracted some interest in recent years due to their unique electrical and optical properties. Takimiya et al. developed a new benzoselenophene from diphenyl acetylene by sequential treatment with BuLi/*t*BuOK, selenium, methyl iodide and iodine in refluxing chloroform as shown in Scheme 3.[16] The product **1** proved to be a stable organic semiconductor for a high-performance field-effect transistor.



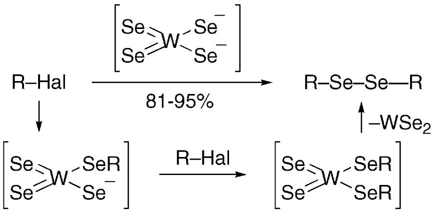
Scheme 3.

In 2008, the groups of Jeong and Pinto published independently the first synthesis of 4′-selenonucleosides such as **2** (Scheme 4).[17] Key step in both syntheses is the Pummerer rearrangement of a selenoxide intermediate.



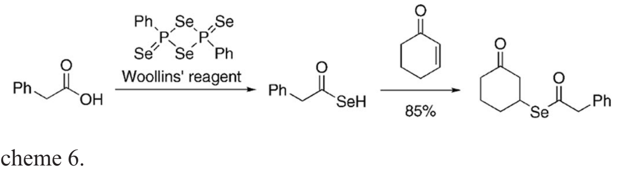
Scheme 4.

An efficient selenium transfer reagent for the chemoselective synthesis of functionalized diselenides, tetraethylammonium tetraselenotungstate, was introduced by Chandrasekaran and co-workers.[18] The reaction of alkyl halides with tetraethylammonium tetraselenotungstate in acetonitrile furnished the corresponding diselenides in high yields (81–95%) as shown in Scheme 5. Easily reducible groups such as cyano-, ester- and keto-functionalities are tolerated under the applied reaction conditions. Additionally, alcohols, activated with dicyclohexylcarbodiimide and a catalytic amount of copper chloride, can be transformed into the corresponding diselenides in good yields using the same tetraselenotungstate reagent. Intramolecular reactions leading to cyclic diselenides have been reported as well.[19]



Scheme 5.

Knapp and co-workers developed a new method[20] to convert carboxylic acids to selenocarboxylates with Woollins' reagent (Scheme 6).[21] In-situ generated selenocarboxylates were used in addition reactions to alkenes, heterocyclic ring-opening reactions, alkylation and amidation reactions in good yields. It is noteworthy that the addition reactions to alkenes are stereoselective without an additional catalyst. Furthermore, the acidity of selenocarboxylates was found to be greater than that of corresponding carboxylic and thiocarboxylic acids, which was exploited in two acid-promoted ring-opening reactions. Their introduction into carbohydrates, peptides, and other frameworks by S_N2 displacement was found to occur under very mild reaction conditions. The chemistry of chalcogenocarboxylic acid derivatives has been reviewed recently.[22]

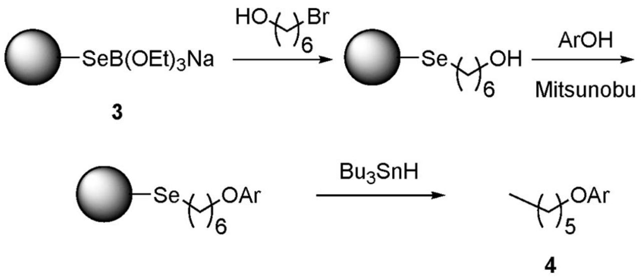


Scheme 6.

Polymer-Supported Selenium Reagents

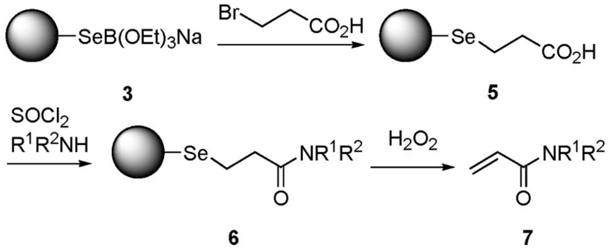
Polymer-supported reagents and catalysts are nowadays frequently used in organic synthesis. Although polymers with selenium functionalities have been known for a long time,[23] there is a high interest in this kind of solid-phase organic chemistry. Selenium-based approaches for solid-phase chemistry have been reported from different research groups[24] and their use in phase tag-assisted synthesis has been reviewed recently together with the corresponding sulfur analogues.[25] Polymer-supported selenium reagents have attracted the interest of synthetic chemists because of their facile handling without the formation of toxic and odorous by-products. New linking strategies with various loading and cleavage protocols now make use of the selenium moiety for further functionalizations of the product molecules.

The polystyrene-bound selenium-containing reagent **3** was applied in the traceless solid-phase synthesis of a library of aryl alkyl ethers by reaction of **3** with 6-bromohexanol, etherification and radical cleavage reaction of **4** from the polymer (Scheme 7).[26]



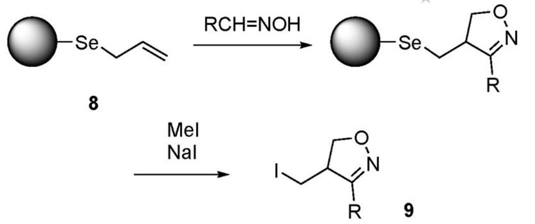
Scheme 7.

But also other research groups used polymer-bound nucleophilic selenium reagents in synthetic transformations.[27,28] Reaction with alkyl bromide derivatives can lead to supported compounds **5** and **8** which have been used for further synthesis. Compound **5** has been transformed into a series of amides **6** which have been cleaved off the polymer-support by oxidation to give the α,β-unsaturated amides **7** in high yields and purities as shown in Scheme 8.[29] The same compound **5** has been used for the combinatorial synthesis of heterocyclic compounds by functionalizing the carboxylic acid moiety.[30]



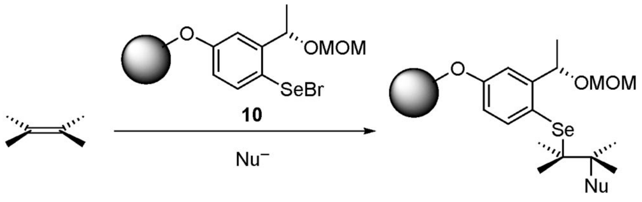
Scheme 8.

Allyl selenide **8** has been used in dipolar cycloadditions and the resulting isoxazoline **9** has been cleaved off the resin by iodomethane and sodium iodide via an intermediate tetravalent selenium derivative.[31] Selenocarbanions have been generated using a similar approach allowing the synthesis of vinylsulfones and vinylphosphonates (Scheme 9).[32]



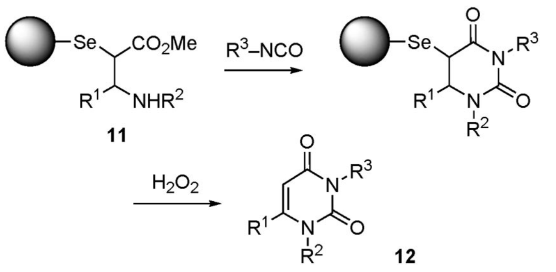
Scheme 9.

The development of chiral selenium electrophiles has already established a very efficient tool for the highly stereoselective synthesis of various molecules.[6,7,9,10,33] We have reported applications of this chemistry to solid-phase synthesis and have developed efficient polymer-bound reagents such as **10** leading to further improvements in selenium-based solid-phase chemistry (Scheme 10).[34]



Scheme 10.

Most recent publications, however, are using polymer-supported selenium reagents for traceless solid-phase synthesis. Electrophilic cyclizations have been performed to deliver dihydrofurane and tetrahydrofurane derivatives in analogy to solution-phase synthesis.[35] Electrophilic addition of polymer-bound selenium derivatives to α,β-unsaturated esters in the presence of nitrogen nucleophiles leads to compounds **11**, which can be used for the synthesis of heterocyclic nucleoside analogues. 1,3,6-Trisubstituted uracils **12** have been prepared in good yields (65–83%) and high purities (88–96%),[36] but also other heterocycles have been successfully made using a similar route (Scheme 11).[37]



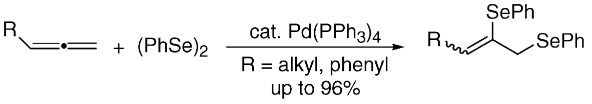
Scheme 11.

Solid-supported selenenyl bromide has also been used as a catalyst in allylic chlorination reactions of polyprenoids, this is discussed in the catalysis part of this review.[136]

Metal-Mediated Syntheses of Organoselenium Compounds

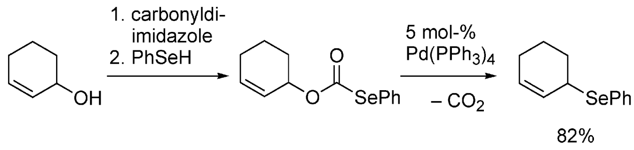
Palladium-Mediated Reactions

Very recently, the transition-metal-catalyzed reactions of organoselenium compounds have been growing. In 2005, Ogawa et al. developed a regioselective bisselenation of allenes with diphenyl diselenide (Scheme 12).[38] Acetonitrile proved to be the best solvent for these reactions as well as tetrakis(triphenylphosphane)palladium as catalyst. Primary and secondary alkyl-substituted allenes undergo regioselective bisselenation with diphenyl diselenide in up to 96% yield. However, tertiary alkyl-substituted allenes do not react and phenyl-substituted allenes give yields up to 81%.



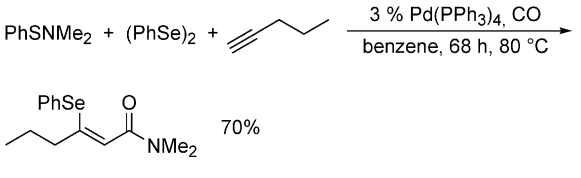
Scheme 12.

In 2008, Tunge and co-workers developed a palladium-catalyzed decarboxylative selenation reaction that affords allyl selenides in up to 99% yield as shown in Scheme 13.[39] The reaction is highly regioselective and provided linear allylation products. Using chiral selenocarbonates like *cis*-allyl selenocarbonate the reaction proceed with retention of configuration. Employing the (*S*,*S*)-naphthyl-Trost ligand in toluene results in kinetic resolutions of the selenocarbonates leading to enantioselectivities between 89% and 99%. Further manipulations (amination, chlorination) mediated by *N*-chlorosuccinimide of the enantioenriched allyl selenides were demonstrated.



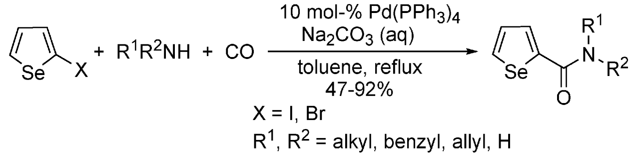
Scheme 13.

A regio- and stereoselective preparation of β-selenyl acrylamides from sulfenamides, terminal aliphatic alkynes and diphenyl diselenide with carbon monoxide and catalytic amounts of $Pd(PPh_3)_4$ was developed by Meyer and co-workers (Scheme 14).[40] The products were obtained after 50–60 h and 85 °C in up to 60% yield with 100% stereoselectivity for the *Z*-isomer. However, phenyl- or hydroxy-substituted alkynes did not react at all.



Scheme 14.

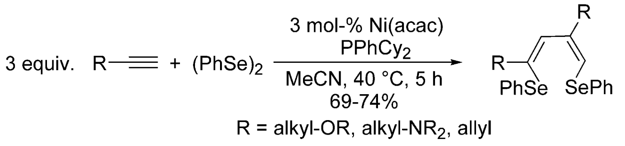
The carbonylation of haloselenophenes with amines catalyzed by 10 mol-% palladium in the presence of sodium carbonate was reported by Zeni et al. to afford selenophenes-2-carboxamides in good yields (Scheme 15).[41] Selenophene-2,5-dicarboxamides and *N*,*N′*-bridged selenophene-2-carboxamides could also be obtained by stoichiometric control of 2-haloselenophene and a diamine.



Scheme 15.

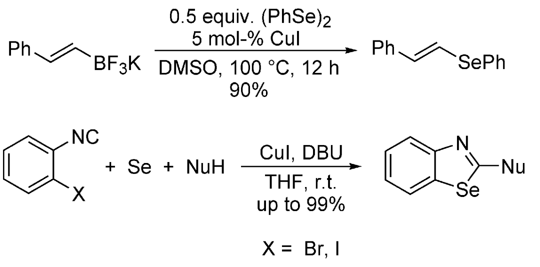
Nickel- and Copper-Mediated Reactions

As shown in Scheme 16, Ananikov, Beletskaya and co-workers published a new stereo-defined nickel-catalyzed synthesis of 1,4-chalcogen-substituted unsymmetrical 1,3-dienes.[42] The products can be obtained from alkynes and diphenyl diselenide after 5 h stirring at 40 °C in acetonitrile with 3 mol-% $Ni(acac)_2$ and 30 mol-% $PPhCy_2$ in good yields and with high selectivity in the multistep diene formation. The developed catalytic system is tolerant to typical functional groups in alkynes and the yields of the symmetrical dienes were less than 26% in all cases.



Scheme 16.

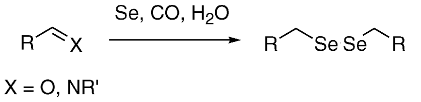
Very recently, two copper-catalyzed syntheses were published. Braga, Stefani and co-workers developed a stereoselective synthesis of (*E*)-vinyl selenides from potassium vinyltrifluoroborates using copper(I) iodide as catalyst (Scheme 17).[43] Utilizing the same catalyst Fujiwara, Kambe et al. reported an efficient synthesis of 1,3-benzoselenazoles with a heteroatom functionality at the 2-position using 2-halophenyl isocyanides and DBU (Scheme 17).[44]



Scheme 17.

Syntheses of Selenides and Diselenides

Although there are many different syntheses available for selenium-containing compounds, different novel procedures have emerged to prepare such derivatives more easily and under milder reaction conditions. Diselenides can be prepared reductively from either aldehydes[45] or imines[46] in the presence of carbon monoxide as shown in Scheme 18.



Scheme 18.

Metal catalysts can be used to activate and cleave diselenides. Indium(I) salts have been proven to be efficient reagents to cleave diselenides and react with aryl halides to yield selenides **13**.[47] But also similar protocols involving ruthenium[48] or copper[49] as catalysts have been published recently. The reaction of aryl halides with selenium dichloride prepared in situ is another alternative for symmetrical diaryl selenides (Scheme 19).[50]

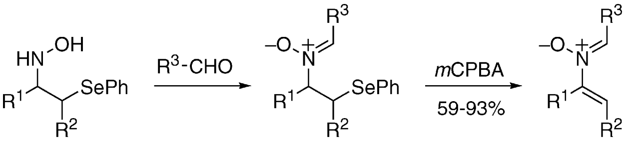
$$\text{R-X} + (\text{PhSe})_2 \xrightarrow[\substack{\text{21 examples}\\ \text{52-97\%}\\ \text{X = Cl, Br. I}}]{\text{In(I)}} \underset{\mathbf{13}}{\text{R–SePh}}$$

Scheme 19.

In addition to these methods, diphenylsulfonium salts have been used for the synthesis of alkyl selenides[51] and phenyl tributylstannyl selenide has been introduced as a reagent to introduce phenylseleno moieties using palladium catalysis.[52]

Oxidation and Rearrangements

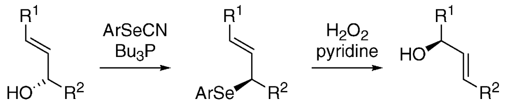
It was not until 1970, when the formation of alkenes by decomposition of selenoxides was found to be a very versatile process proceeding under mild conditions.[1b] Since that time this reaction has attracted chemists and still nowadays, this method is used to introduce double bonds into molecules. The precursors for the selenoxide elimination are selenides, which can be generated by nucleophilic, electrophilic, or radical reactions. A comprehensive review on this subject has been published by Reich and Wollowitz.[53] The oxidation of these selenides is influenced by the substituents on selenium. It has been shown by experiments and by ab initio calculations that electron-withdrawing substituents stabilize selenides towards oxidation, whereas electron-donating substituents accelerate the oxidation process to selenoxides.[54] This process is still applied in synthesis of double bonds, for example in the efficient elimination of selenoglycosides to the corresponding glycals.[55] Access to *N*-vinyl nitrones, a new type of heterodienes, has also been achieved using the selenoxide elimination strategy. β-Seleno hydroxylamines **14** can be easily synthesized by selenolate addition to nitroalkenes and a subsequent reduction. The reaction with an aldehyde forms nitrones **15** which, after treatment with *m*CPBA lead to the formation of *N*-vinyl nitrones **16** in good overall yields (Scheme 20).[56] Addition – elimination sequences to double bonds using only catalytic amounts of selenium-containing reagents have also been reported recently and are described in the section on "catalysis".



14 **15** **16**

Scheme 20.

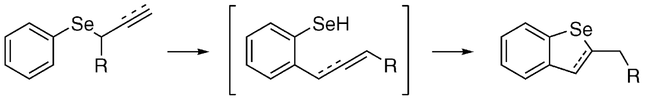
Stereoselective [2,3]-sigmatropic rearrangements of allylic selenoxides have been used to effect a 1,3-transposition of allylic alcohols within natural product synthesis. The reaction of allylic alcohol **21** with a selenocyanate and tributylphosphane led to **22** by activation and substitution under inversion. The subsequent oxidation and [2,3]-sigmatropic rearrangement allows the synthesis of transposed allylic alcohols of type **23** in about 60% overall yield.[57,58] Stereoselective rearrangements by either employing optically active selenoxides or chiral substituents on the selenium have been described (Scheme 21).[59]



21 **22** **23**

Scheme 21.

In contrast to the thio-Claisen rearrangement, the seleno-Claisen rearrangement has received very little attention. It has been shown that allyl or propargyl selenides **24** can undergo a seleno-Claisen rearrangement and the rearranged products react in a subsequent cyclization to selenoheterocycles of type **25** in moderate yields as shown in Scheme 22.[60]



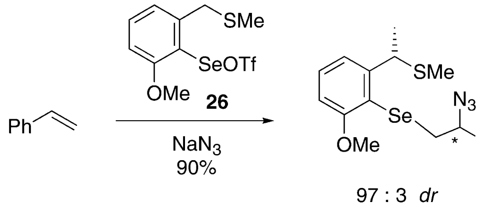
24 **25**

Scheme 22.

The seleno-Pummerer reaction has been used in natural product synthesis[61] and for the preparation of functionalized carbohydrates.[62]

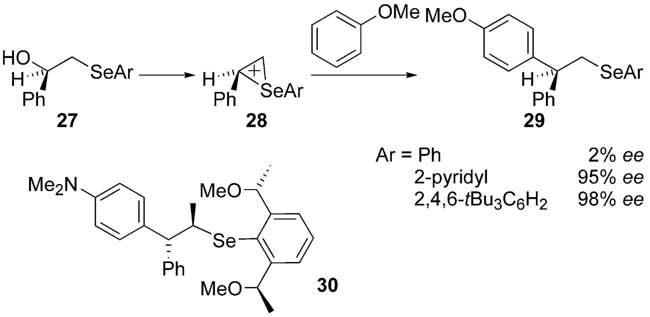
Selenium Electrophiles

Well before the wide use of organoselenium compounds in chemistry it was discovered that electrophilic selenium compounds of the type RSeX add stereospecifically to alkenes.[2] Since that time this reaction has been an important tool in the portfolio of organic chemists and been used even for the construction of complex molecules. Diselenides are usually used as versatile precursors for the synthesis of different electrophilic selenium reagents, as they can be easily transformed into selenenyl halides or into selenenyl compounds with non-halide counterions. These electrophilic reagents can react with a variety of carbon or heteroatom nucleophiles to produce a wide range of different selenenylated compounds. For instance, they can be used for the α-selenenylation of carbonyl compounds.[63,64] Oxidation of selenides to the corresponding selenoxides and subsequent elimination for the synthesis of α,β-unsaturated carbonyl compounds as outlined in another chapter of this microreview is still a current topic and has been used successfully in many natural product synthesis.[65,66] Substitution or reductive deselenenylation and involvement in radical coupling processes make organoselenium electrophiles most invaluable among other electrophiles. The reaction of selenium electrophiles with alkenes is a stereospecific *anti* addition. It involves the initial formation of seleniranium intermediates, which are immediately opened in the presence of nucleophiles. Internal nucleophiles will lead to cyclized products as described later. Reactivity of selenium electrophiles also depend on the counterion X and different methods have been developed to exchange these counterions. Recently, also addition reactions to alkynes have been studied in detail. Poleschner et al. found a strong indication for the existence of selenirenium ions with a distinct steric influence of the alkyne substituent on the addition of PhSeF to alkynes. Reaction of RSeX reagents with alkynes at low temperatures produce selenirenium ions, which have been detected by ^{77}Se and ^{13}C NMR spectroscopy.[67] The synthesis of chiral, non-racemic aryl selenium electrophiles has been investigated by several research groups and was recently reviewed.[10] A convenient route for the synthesis of optically active alkyl selenium electrophiles from *p*-menthane, carane and pinane and their asymmetric methoxyselenenylation of styrene with, however, low selectivities has been published,[68] in contrast to the successful camphor-derived derivatives prepared by Back et al.[69] Tiecco et al. discovered asymmetric azido selenenylations with the addition of nitrogen nucleophiles to carbon–carbon double bonds. It is remarkable that this reaction occurs with a very high level of facial selectivity with Markownikoff orientation. Chiral, non-racemic electrophilic selenium reagents such as **26** have been used for a subsequent synthesis of optically active aziridines and triazoles (Scheme 23).[70]



Scheme 23.

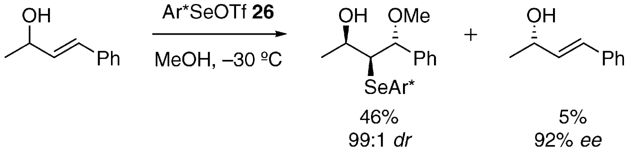
When aromatic compounds such as anisole are employed as carbon nucleophiles, selenophilic attack is rarely observed irrespective of the nature of aryl group on the selenium atom. For example, starting with optically active β-hydroxy selenides **27**, available by ring-opening reactions of enantiomerically pure epoxides with selenium nucleophiles, addition products type **29**, can be obtained by selective generation of seleniranium ions of type **28**. In order to obtain high stereoselectivities in the addition reactions, bulky substituents are introduced to the *ortho*-position of the aryl group attached to the selenium atom. Alternatively, electron-deficient aryl groups attached to the selenium such as 2-pyridyl must be employed in these reactions. Their use is essential to prevent racemization during the reaction. The stereospecificity of these reactions has been found to also depend on a large extent on the aromatic nucleophiles involved as shown in Scheme 24.[71] The aromatic nucleophile attacks selectively on the most substituted carbon atom of the seleniranium ion (Markovnikov addition product).



Scheme 24.

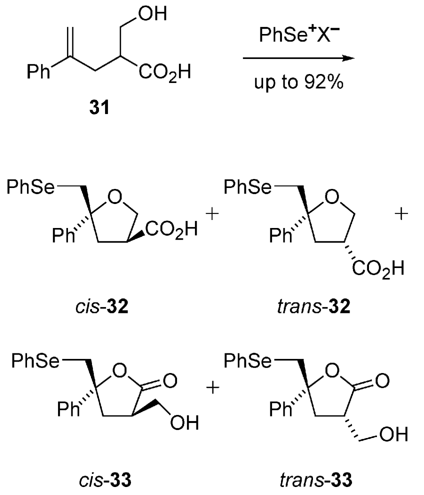
Good yields and high diastereoselectivities can also be obtained by carboselenenylation of β-methyl styrene using enantiomerically pure selenium electrophiles employing a range of aromatic compounds as nucleophiles. This method is convenient for the preparation of chiral hydrocarbons. Not only heteroaromatic compounds, but also electron-rich benzene derivatives such as *N*,*N*-dimethylaniline can be used as nucleophile in the synthesis of **30**. Selectivities of up to 90% *de* have been obtained.[72]

Kinetic resolutions of racemic allylic alcohols can be performed with enantiomerically pure electrophilic selenium reagents. The regiospecific formation of the corresponding addition products with a very high facial selectivity from 95:5 to 98:2 *dr* was observed as the selenium electrophile is able to coordinate to the allylic alcohol moiety. The unreacted alcohols can be recovered in an optically enriched form from 90 to 94% *ee* (Scheme 25).[73]



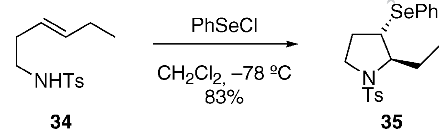
Scheme 25.

The structure of the selenium electrophile, its counterion, solvents, and external additives coordinating to the electrophilic species are influencing the course of cyclizations.[74–76] This has recently been demonstrated by the selective cyclization of substrate **31**, with a hydroxy and a carboxylic acid functionality as internal nucleophiles. 5-*exo*-Cyclizations of alkene **31** can lead, depending on the cyclizing nucleophile to two different heterocycles: tetrahydrofurans **32** or lactones **33**. The different interactions with selenium electrophiles can be used to influence the cyclization of **31** either towards tetrahydrofurans **32** or towards lactones **33** as shown in Scheme 26.[77,78] The selenium moiety of hydroxyalkyl phenyl selenides, obtained by epoxide-opening with selenolates, can be substituted by an allyl group by treatment with allyltributyltin and AIBN. The reaction of these allylic derivatives with electrophilic selenium reagents afforded the corresponding tetrahydrofurans as the result of a stereospecific 5-*exo*-trig cyclization.[79] Denmark et al. have performed detailed studies of selenolactonizations[80] while Iwaoka and Tomoda have investigated the effect of substituents towards the reactivity of selenium electrophiles.[81]



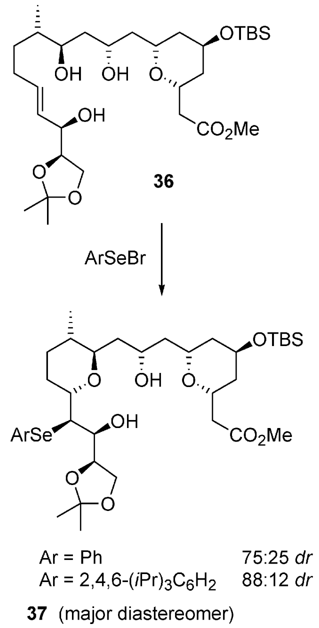
Scheme 26.

Electrophilic selenium-induced cyclizations followed by oxidative deselenenylations have been used successfully as key steps in natural product synthesis.[82] Selenocyclization of homoallylic sulfonamides such as **34** using phenyl selenenyl halides lead exclusively to β-selanyl pyrrolidines **35** by a 5-*endo-trig* pathway, but with considerable variations in the stereochemical outcome, depending upon the substituents and the reaction condition employed (Scheme 27). Subsequent oxidative eliminations lead smoothly to the corresponding 3-pyrrolines and polyhydroxylated pyrrolidines.[83] Several enantiomerically pure substituted pyrrolidines were synthesized from enantiopure amino alcohols using organoselenium reagents. The key step is a substrate-controlled cyclization of *N*-Boc protected δ-alkenylamines by *N*-(phenylseleno)phthalimide. The reaction of these allylic derivatives with phenylselenium electrophiles affords pyrrolidines as the result from the 5-*exo-trig*-cyclizations. Moreover, the selenides were converted into the selenones, which easily gave substitution with different nucleophiles. Enantiopure 2,5-disubstituted pyrrolidines containing azido, methylthio, cyano and iodo groups were obtained.[84]



Scheme 27.

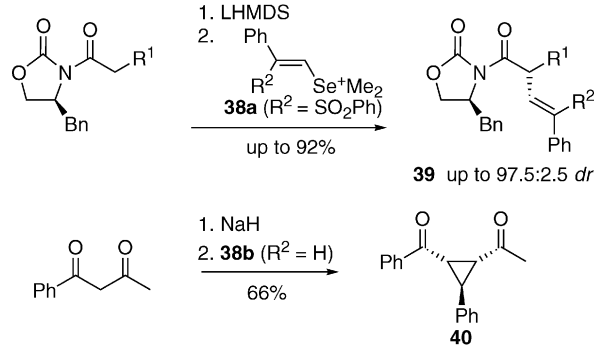
A number of 2-(α-selenoalkyl)pyrrolidines were synthesized by a similar selenocyclization. Asymmetric induction by stereocentres in the substrate or double asymmetric induction by additional chiral selenenyl bromides resulted in diastereoselectivities up to 84:16.[85] 2,4,6-Triisopropylphenylselenenyl bromide has been reported by Lipshutz to give improved selectivities in electrophile-mediated cyclizations of homoallylic alcohols to tetrahydrofurans as compared to phenylselenyl chloride.[86] The use of this reagent gave the best results when applied to the cyclization of **36**, leading to selenide **37** in 74% yield with a diastereomeric ratio of 88:12 (Scheme 28).[87]



Scheme 28.

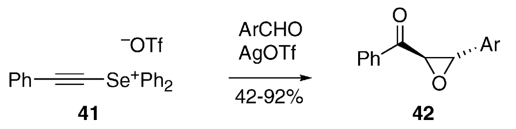
Selenonium Salts

Alkenyl or alkynyl selenonium compounds can be used in various syntheses. Kataoka et al. investigated the reaction of chiral enolates with alkenyl selenonium salts reacting as electrophiles. The diastereoselectivity of this reaction is dependant on the nature of the selenonium salts, with dimethylalkenyl selenonium salt **38** exclusively the *Z*-isomer **39** was obtained in high yield.[88] Reaction with 1,3-dicarbonyl compounds afford cyclopropane derivatives **40** via a novel Michael Favorskii type reaction (Scheme 29).[89]



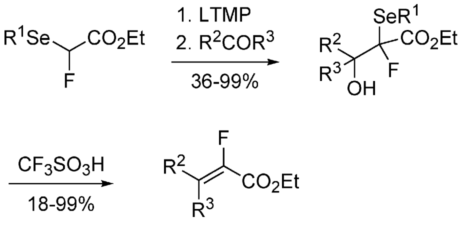
Scheme 29.

Alkynyl selenonium salts **41** can react with aldehydes to form epoxides **42**.[90] Only *trans*-oxiranyl ketones **42** are obtained in good yields as shown in Scheme 30, whereas benzoyl aziridine derivatives are the products from the reaction with sodium *p*-toluenesulfonamide instead of a hydroxide ion.



Scheme 30.

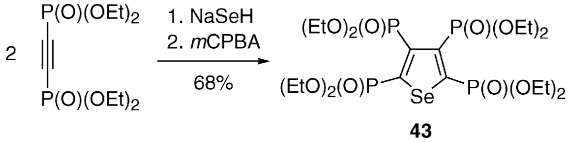
Selenium-stabilized carbanions play an important role in organic synthesis and have been used in the synthesis of complex natural products such as halichlorine[91] as well as in syntheses of β-keto esters.[92] Recently, a new method has been developed for the direct conversion of aldehydes into α-hydroxy stannanes via α-(phenylseleno)stannanes, which upon treatment with BuLi affords selenium-stabilized carbanions by Sn/Li exchange.[93] The *Z*-selective formation of α,β-unsaturated esters was achieved by deselenenylation of the *syn*- or *anti*-organoselanylacetates with trifluoromethylsulfonic acid as shown in Scheme 31. In contrast, 3-alkyl-substituted propanoates stereospecifically underwent alkenylation to give *E*- or *Z*-unsaturated esters in a one-pot sequence (Scheme 31).[94]



Scheme 31.

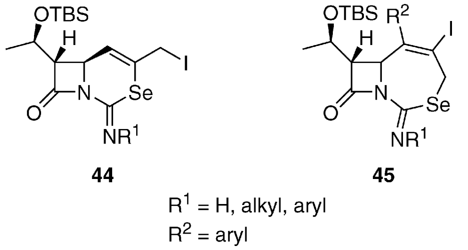
Selenium Nucleophiles

In 2007, Yoshifuji reported an interesting synthesis of selenophenes by the reaction of bis(diethoxyphosphoryl)acetylene with sodium hydroselenide to obtain tetraphosphorylselenophene **43** after cyclisation and oxidation with *m*CPBA in 68% yield.[95] Substituted β-chloroacrylonitriles can react with sodium selenide and bromonitromethane to yield selenophenes in a one-pot procedure (Scheme 32).[96]



Scheme 32.

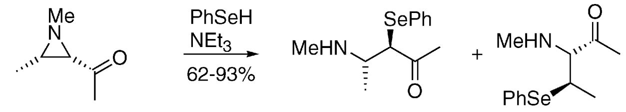
The biological and medicinal properties of selenium-containing compounds are increasingly appreciated.[97] The β-lactam skeleton is a key structural element of antibacterial agents. Koketsu et al. published the syntheses of the selenium-containing heterocycles 3-selena-1-dethiacephems **44** and selenazepines **45** by a regioselective iodocyclization reaction (Scheme 33).[98]



Scheme 33.

Alkynylselenium compounds can be highly valuable intermediates in organic synthesis due to their potential for transformation into substituted olefins.[99] Recently, some alkynylseleno alcohols were synthesized in good yield by lithiation of phenylacetylene followed by addition of elemental selenium and 3-bromopropanol.[100]

In 2005, ring-opening reactions of aziridine derivatives and *meso* epoxides with selenium nucleophiles as shown in Scheme 34 were published.[101] Ring-opening reactions of aziridine-2-carboxylic acid derivatives with selenium nucleophiles afforded α-seleno-β-aminoacid-containing peptides with a site-selective backbone. Furthermore, high enantioselectivities in the epoxide ring-opening process were achieved by the utilisation of a Ti-Ga-Salen catalyst system.



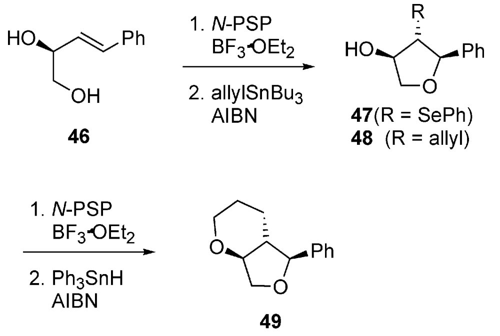
Scheme 34.

Movassagh reported an efficient synthesis of β-seleno carbonyl compounds by a Zn/RuCl$_3$ catalyzed cleavage of diselenides, epoxide ring opening by Zn/AlCl$_3$ and synthesis of unsymmetrical selenides through zinc-mediated cleavage of diselenides.[102] Synthesis of diorganyl selenides from tertiary alkyl halides, selenols and selenolates from diselenides in the presence of zinc was published by Krief et al.[103]

Most recently, the preparation of selenols by a zinc-mediated reduction of diselenides and air-stable selenolates have been synthesized from phenylselenenyl halides and elemental zinc by Santi et al.[104]

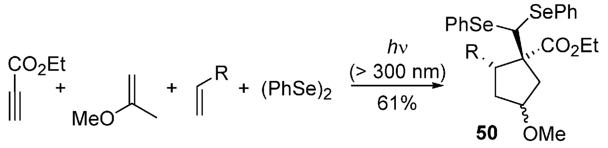
Free Radical Reactions

Tiecco and co-workers converted alkene **46** into the enantiomerically pure tetrahydrofurane **47** using *N*-phenylselenophthalimide (*N*-PSP) as selenenylating reagent.[105] Further functionalisation was achieved by treatment with allyltributyltin and AIBN. Additionally, a similar sequence applied on **48** afforded perhydrofuro[3,4-*b*]pyran as single diastereomer in 75% yield.[106] The bicyclic compound **49** was obtained in 80% yield after deselenenylation (Scheme 35).



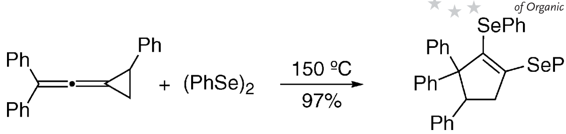
Scheme 35.

Ogawa et al. developed a photochemically initiated, solvent-free four-component coupling reaction with diphenyl diselenide, ethylpropiolate, *tert*-butyl acrylate and 2-methoxypropene, which afforded cyclopentane derivative **50** (81:19 *dr*) through a radical 5-*exo* cyclization process (Scheme 36).[107]



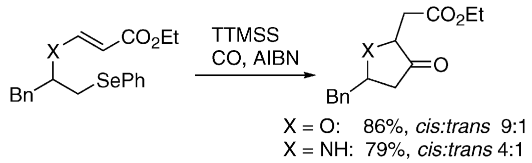
Scheme 36.

Zard and co-workers reported a method to generate acyl radicals from the corresponding acyl triphenylmethyldiazo derivatives, produced by in-situ oxidation of hydrazide precursors with phenylseleninic acid.[108] Further treatment of the acyl radicals with diphenyl diselenide provided cyclic ketones in 64–74% yield. Shi and co-workers established ring-opening reactions with diphenyl diselenide in good yields.[109] Arylvinylidene cyclopropanes are converted into 1,2-diaryl cyclopentenes with this method as shown in Scheme 37 and methylenecyclopropanes can be used for the synthesis of dihydrofuranes after subsequent oxidative cyclization with hydrogen peroxide. Palladium-catalyzed reactions of allenes with diphenyl diselenide have already been mentioned above (Scheme 12).



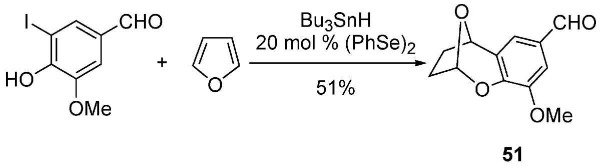
Scheme 37.

Tetrahydrofuran-3-ones and pyrrolidin-3-ones were obtained with a new methodology by Engman from readily available starting materials in good yields and with a radical carbonylation/reductive cyclization process using tris(trimethylsilyl)silane (TTMSS) in the key step (Scheme 38).[110] The required radical precursors were obtained either from epoxides/aziridines by regioselective benzeneselenolate ring-opening and *O*/*N*-vinylation.



Scheme 38.

Crich and co-workers reported the synthesis of 2-aryl-2,3-dihydrofurans in a single step by a selenol-catalyzed aryl radical addition to furane.[111] The products **51** were obtained with 20 mol-% diphenyl diselenide in moderate yields (32–51%) with 2-aryl-2,5-dihydrofurans as major side products (Scheme 39). It was also found that an analogous chemistry is found with thiophene, although the 2-aryl-2,5-dihydrothiophene is preferred over the 2,3-dihydro isomer.

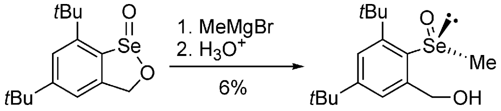


Scheme 39.

Selenium at Higher Oxidation Stages

Selenoxides

Kamigata et al. reported the synthesis and isolation of cyclic optical active seleninate esters and their transformation into a chiral selenoxide.[112] The selinate esters were prepared from bromobenzyl alcohol derivatives or 2-(chloroseleno)benzoyl chloride via selenides in yields from 43% to 59%. The separation of these compounds was achieved with HPLC on a preparative scale. However, the racemization of the selenate esters depend on the alkyl substituents at the benzyl position or the *ortho*-position of the aromatic ring. Reaction of sulfinate esters with methylmagnesium bromide afforded the selenoxides in up to 6% yield and with 97% *ee* (Scheme 40). Interestingly the reaction proceeds with retention of configuration. In further studies, Shimizu and co-workers showed the stabilizing effect of intramolecular Lewis bases toward racemization of optically active selenoxides.[113]

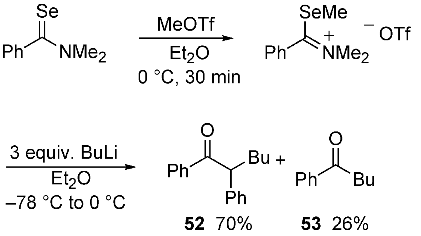


Scheme 40.

In 2007, Shimizu et al. additionally reported the synthesis and optical resolution of selenonium imides bearing an 8-dimethylamino-1-naphthyl group.[114] The selenonium imides were obtained by reaction of the corresponding selenoxides with *p*-toluenesulfonamide or trifluoromethanesulfonamide. The stable products were isolated in 19% to 53% yield and separated by HPLC.

Applications of Selenoamides

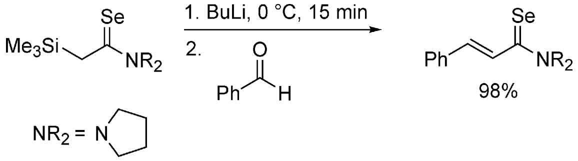
Selenoamides are useful synthetic intermediates in many synthetic transformations. In 2003, several publications by Murai and co-workers, Takido et al. and Huang's group showed a range of reactions with selenoamides as starting material. A variety of stable acyclic selenoiminium salts were obtained by reacting the corresponding selenoamides with methyl triflate in yields 80% to 99%.[115] According to X-ray molecular structure analysis and ^{13}C NMR spectra of these selenoiminium salts suggested that the electrons on the selenium atom of the salts are delocalized with respect to the iminium group. An aromatic selenoiminium salt was treated with butyllithium to afford the two ketones **52** and **53** in 70% and 26% yield (Scheme 41).



Scheme 41.

Similar investigations were done by Takido et al., who synthesised 1-benzylselenophenylmethaniminium bromide and treated it with organic halides to obtain asymmetrical benzyl selenides in 59% to 94% yield.[116]

The Peterson olefination of aromatic aldehydes with α-silyl selenoacetamides, developed by Murai and co-workers, was reported with the selective formation of *E*-isomers and moderate to good yields (44%–99%).[117] α-Silyl selenoacetamides are synthesised by successive treatment of (trimethylsilyl)acetylene with butyllithium, selenium, amine and water. The unsaturated selenoamides were obtained upon treatment of α-silyl selenoacetamides with butyllithium and an aldehyde as shown in Scheme 42. Reactions with aromatic aldehydes bearing various functional groups, such as cyano, nitro, methoxy, halogen and dimethylamino groups proceeded smoothly.



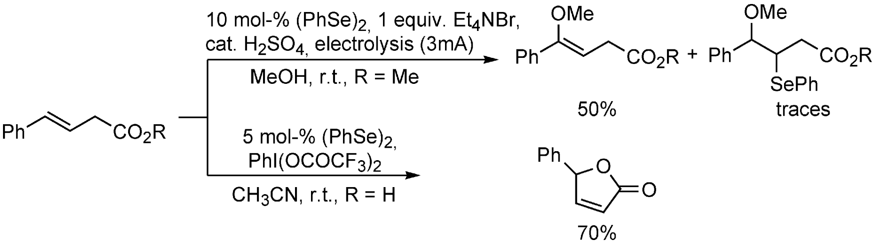
Scheme 42.

Organoselenium Compounds as Catalysts or Ligands

Recent advances of catalytic reactions using selenium electrophiles, organoselenium compounds in carbonylation reactions and oxidative reactions as well as the use of organoselenium compounds as chiral ligands for a palladium-catalyzed asymmetric allylic alkylation process are highlighted in this chapter.

Catalytic Use of Selenium Electrophiles

Recently several applications of the catalytic use of organoselenium electrophiles were published.[118] The use of catalytic amounts of several diphenyl diselenides in electrochemical alkoxyselenenylation-deselenenylation sequences was described. Typically, 10 mol-% diselenide, one equivalent tetraethylammonium bromide, and traces of sulfuric acid in methanol at room temperature were employed. Tetraethylammonium bromide acts as redox catalyst and electrolyte in these reactions. Up to 66% *ee* could be obtained with a chiral sulfur-containing diselenide. Additionally, a convenient way to cyclise a range of β,γ-butenoic acids to the corresponding butenolides with catalytic amounts of selenium reagents was developed. The method utilizes 5 mol-% diphenyl diselenide and [bis(trifluoroacetoxy)iodo]ben-



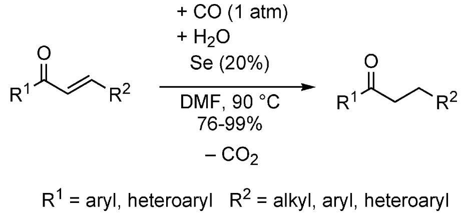
Scheme 43.

zene as stoichiometric oxidant in acetonitrile with good yields (49%–96%). However, 5 mol-% of the catalyst is critical because lower catalytic loadings resulted in a side product (Scheme 43).

Selenium-Catalyzed Carbonylation Reactions

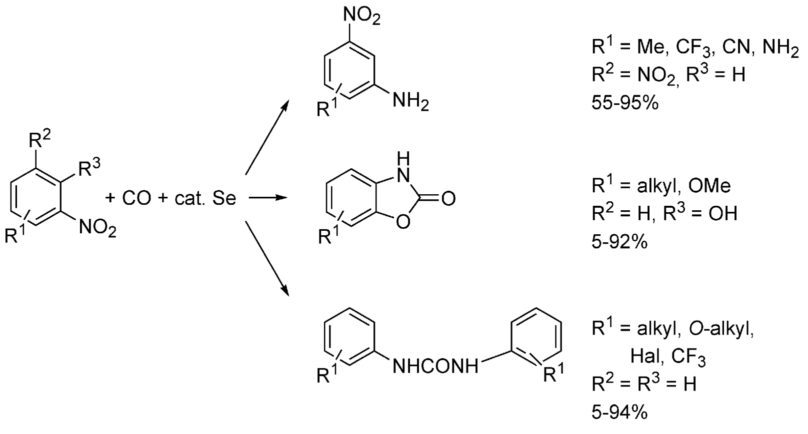
Selenium-catalyzed carbonylation reactions have been intensively studied because of their cheap and easily available catalysts, mild reaction conditions and their phase-transfer-like properties. Studies in this field were done by Sonoda et al.[119] and further developed by Lu et al. These groups developed several selenium-catalyzed carbonylation reactions with nitroarenes, 2-aminoethanol derivatives and α,β-unsaturated carbonyl compounds. Lu et al. reported the monoreduction of dinitroaromatic compounds with catalytic amounts of elemental selenium (4 mol-%), carbon monoxide and water using sodium acetate as a base in DMF under atmospheric pressure to give the corresponding nitroaniline.[120] The reactions proceed with good yields (55%–95%) and selectivities with *m*-dinitrobenzene and homologous substituted *m*-dinitrobenzenes (Scheme 44). The catalyst and base can be recovered and reused with no loss of catalytic activity over at least three cycles. However, *o*- and *p*-dinitrobenzenes cannot be reduced under these conditions due to their electron deficiency. 1,3-Diaryl ureas and analogous can be obtained from nitroarenes with KOH as base under similar reaction conditions.[121] The conversion rate of the reactions depends on the substitution on the phenyl rings. Electron-donating substituents in the 4-position made the nitro group more reactive, resulting in a faster conversion. However, halogen-substituted nitrobenzenes require sodium acetate as base to avoid nucleophilic substitutions. In 2006, Lu et al. additionally reported the same reaction under solvent-free conditions in high yields.[122] The selenium-catalyzed reductive carbonylation of 2-nitrophenols with 8 mol-% of selenium in the presence of organic or inorganic bases depending on solvent produces 2-benzoxazolones in good yields (Scheme 44).[123]

The selective reduction of α,β-unsaturated carbonyl compounds was achieved with catalytic amounts of selenium (20 mol-%) with carbon monoxide and water in dimethylformamide, as shown in Scheme 45.[124] The reducing agent hydrogen selenide (HSe^-) is formed in situ and able to reduce the α,β-unsaturated carbonyl compounds in high yields (76%–99%). However, aromatic aldehydes can be reduced and selenated to symmetrical diselenides. The authors found implications that isolated carbon–carbon double bonds are unreactive under these conditions.

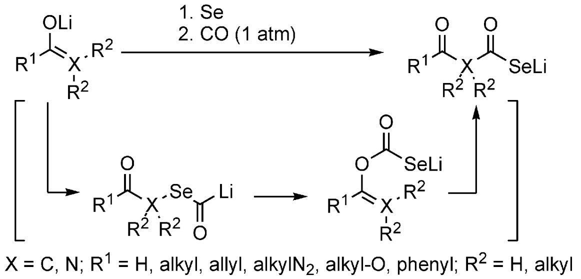


Scheme 45.

Fujiwara and co-workers published the first introduction of carbon monoxide into lithium enolates mediated by selenium.[125] 1,3-Dioxoalkanes were obtained in reasonable to good yields (41–87%) from lithium enolates of ketones upon treatment with selenium and carbon monoxide. The proposed carbonylation mechanism proceeds by a sigmatropic rearrangement or a stepwise elimination of carbonyl selenide (SeCO) followed by nucleophilic attack of the enolate oxygen at the carbon atom of SeCO as shown in Scheme 46. Further studies revealed that the carbonylation of lithium enolates of esters, amides and acylsilane are likewise successful.[126] In 2007, their studies were extended to *N*-carbonylation of lithium azaenolates of amides, formamides, ureas and carbamates (Scheme 46).[127] Typically one equivalent of selenium and three equivalents of HMPA are used with atmospheric pressure of CO in THF to form the carbamoselenoates from amides in up to 88% yield. Carbonylation of ureas and carbamates proceeded well without HMPA, although addition of three equivalents enhanced the yields.



Scheme 44.

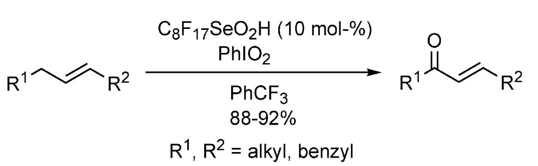


Scheme 46.

Selenium-Catalyzed Oxidative Reactions

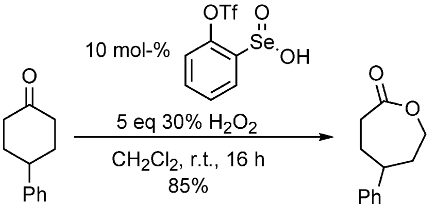
Several selenium compounds are efficient reagents for the oxidation of organic molecules. For example, selenium dioxide, SeO_2, is widely used as an oxidising reagent for alkenes, ketones and other substrates. Seleninic acids and peroxyseleninic acids have proved to be useful reagents in a range of oxidation reactions. For example, peroxyseleninic acid ($RSeO_3H$) was revealed to be an effective reagent for the epoxidation of alkenes.

In 1999, Knochel and co-workers already described an efficient selenium-catalyzed epoxidation of alkenes in a fluorous biphasic system, where the selenium catalyst is immobilized in perfluorinated solvents.[128] Crich et al. developed a new fluorous seleninic acid catalyst for catalytic allylic oxidations.[129] The highly electron-deficient seleninic acid is easy to handle and an effective catalyst when used in conjunction with a hypervalent iodine-based oxidant. A typical catalytic reaction with 5 mol-% seleninic acid and three equivalents iodoxybenzene in trifluoromethylbenzene is shown in Scheme 47. The products were obtained in high yields (88% and 92%). The fluorous seleninic acid can be synthesised in two steps from perfluorooctyl iodide and dibutyl diselenides to afford perfluoro-octylbutyl selenide, which oxidises after treatment with hydrogen peroxide to perfluorooctylseleninic acid.



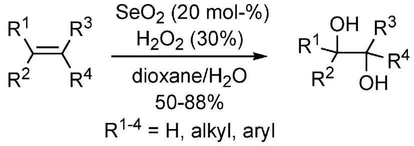
Scheme 47.

Ichikawa and co-workers reported the utilisation of a novel organoselenium compound that catalyzes the Baeyer–Villiger oxidation with 30% hydrogen peroxide in dichloromethane in moderate to good yields.[130] Oxidant in this reaction is a new peroxyseleninic acid, in situ generated from the corresponding diselenide with two equivalents of hydrogen peroxide. Additionally the synthesis of three new diselenides from phenol was achieved. A typical catalytic reaction with 5 mol-% diselenide is shown in Scheme 48. Detty et al. have used various selenoxides as catalysts for epoxidations and Baeyer–Villiger Reactions using hydrogen peroxide as stoichiometric oxidant.[131] Also cyclic selenoamides have been found to catalyse oxidation reactions of aldehydes to carboxylic acids.[132]



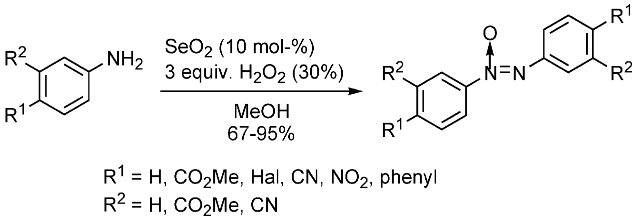
Scheme 48.

A new transition-metal-free catalytic system for *trans* dihydroxylations of olefins with selenium dioxide and hydrogen peroxide was published in 2007 by Gogoi and Konwar.[133] In a typical reaction, seleninic acid, formed from selenium dioxide (20 mol-%) and hydrogen peroxide (2 equiv.), oxidises the olefins in good yields (50–88%) (Scheme 49). The oxidation does not affect other functionalities (alcohol, ester, alkyl, ether, halogens) in the substrate. However, aliphatic olefins exhibited better results in comparison to aromatic olefins and sterically hindered double bonds that showed poor yields compared to less hindered ones. Arylidenemalononitriles, with two electron-withdrawing groups, were oxidised to their corresponding carbonyls under the reaction conditions.



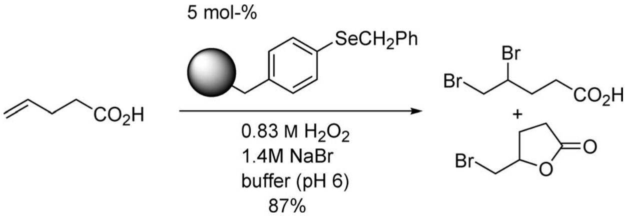
Scheme 49.

For the oxidation of anilines a similar reagent mixture was utilised.[134] As shown in Scheme 50, 10 mol-% selenium dioxide and three equivalents of 30% hydrogen peroxide in methanol at room temperature provide a simple and efficient method for the preparation of azoxyarenes in high yields. 4-Alkoxy-*N*-(4-nitrophenyl)anilines can be obtained under the same reaction conditions in reasonable yields. By using nonpolar solvents (*n*-heptane) and establishing heterogeneous reaction conditions the formation of nitrosoarenes is favoured (up to 95% yield).



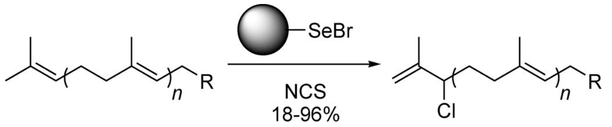
Scheme 50.

In 2008, Detty and co-workers reported the development of a Xerogel-sequestered selenoxide catalyst for brominations.[135] The selenoxide catalyst is synthesised from 4-bromobenzyl alcohol by protection of the alcohol functionality, lithiation and reaction with selenium powder and benzyl bromide. Connection to the Xerogel was accomplished after deprotection and oxidation to the selenoxide. Bromination of several examples was achieved after 24 h with 5 mol-% of the selenoxide catalyst, 1.4 м NaBr and 0.25 м H_2O_2 in water or aqueous dioxane as solvent (Scheme 51). The reaction with the Xerogel-sequestered selenoxide is 23 times faster in comparison to the homogeneous reaction and the catalyst can be recovered and recycled without apparent loss of activity for at least four cycles.



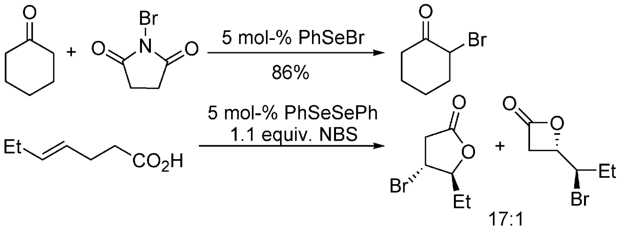
Scheme 51.

Barrero et al. reported highly regioselective functionalisations toward the terminal double bond of a series of easily available terpenoids with catalytic amounts of polymer-supported selenenyl bromide and *N*-bromosuccinimide.[136] The methodology is compatible with the presence of different functional groups and led to moderate to high yields (18%-96%) as shown in Scheme 52.



Scheme 52.

On the basis of results obtained from selective selenocatalytic allylic chlorination reactions, Tunge and co-workers developed a selenium-catalyzed oxidative halogenation with catalyst-bound halogen sources.[137] A reagent-controlled selectivity in selenium-mediated halolactonisations, α-halogenations of ketones and allylic halogenations could be obtained. The halolactonisations proceed with 5 mol-% diphenyl diselenide and 1.1 equiv. *N*-bromosuccinimide (NBS) with good yields and regioselectivities. The authors suggest an activation of NBS through nucleophilic attack by diphenyl diselenide. Regioselectivities of α-halogenations of ketones, using NBS and phenylselenium bromide, are dependent on the solvent. Tunge and co-workers speculate that in this case the activation of NBS proceeds by oxidative addition to PhSeBr to form a Se^{IV} intermediate. The mechanism of allylic chlorination with phenylselenium chloride and NBS is examined in detail and they showed that the rate-limiting step for these reactions is the elimination (Scheme 53).

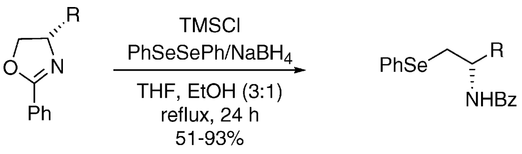


Scheme 53.

In 2003, Back et al. reported that allyl selenides are good catalysts for the oxidation of benzyl thioalcohol with *tert*-butyl hydroperoxide (TBHP), a mimetic for the enzyme glutathione peroxidase.[138] 3-Hydroxypropyl allyl selenide proved to be exceptional in this reaction. It was found that this selenide is a procatalyst which undergoes a series of rapid oxidation and [2,3]sigmatropic rearrangement steps to form a cyclic seleninate ester, the true catalyst. The cyclic seleninate esters represent the first reported unsubstituted examples of these structures (Scheme 54). Subsequently spiroselenuranes have been reported to act as efficient glutathione peroxidase mimetics.[139]

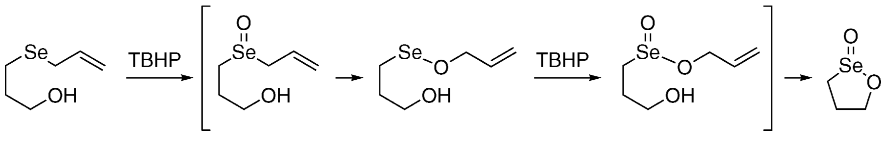
Organoselenium Compounds as Chiral Ligands

A highly efficient preparation of chiral β-selenium, -sulfur, and -tellurium amides by ring-opening reactions of 2-oxazolines in high yields was reported by Vargas and Braga.[140] In these reactions the chalcogenide was generated in situ in the presence of sodium borohydride, THF/ethanol (3:1) as the solvent and one equivalent of TMSCl as shown in Scheme 55. Additionally, all compounds were evaluated as chiral ligands for the palladium-catalyzed asymmetric allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate with malonates. The best results were obtained with a chiral β-selenium amide, which demonstrates the higher ability of selenium to complex with palladium compared to other chalcogenes.



R = alkyl, benzyl, CH_2OR', CO_2Me, $(CH_2)_2SMe$

Scheme 55.



Scheme 54.

Various important aspects of organoselenium chemistry are summarized in this microreview and major developments during the last years are highlighted. Improved and new selenium-containing reagents will surely be developed in the future to gain further profit from the usually very mild conditions in these reactions. This will lead to enhanced stereoselectivities in known reactions, to new selenium-based transformations and methods as well as to new applications of this chemistry. It should allow the reader to identify future research directions and should also enable the non-specialist reader to understand the significant advantages of organoselenium chemistry.

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