1
Electrophilic Selenium

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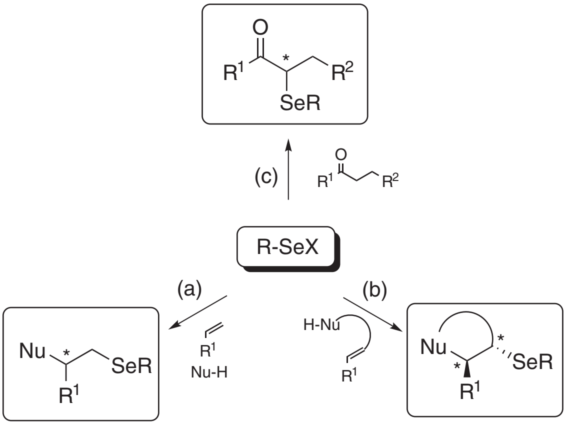
1.1
General Introduction

During the last few decades, organoselenium compounds have emerged as important reagents and intermediates in organic synthesis.

Selenium can be introduced as an electrophile, as a nucleophile, or as a radical and generally it combines chemo-, regio-, and stereoselectivity with mild experimental conditions. Once incorporated, it can be directly converted into different functional groups or it can be employed for further manipulation of the molecule.

Since the discovery in the late 1950s that species of type RSeX add stereospecifically to simple alkenes [1], electrophilic organoselenium compounds provided the synthetic chemist with useful and powerful reagents and the selenofunctionalization of olefins represents an important method for the rapid introduction of vicinal functional groups, often with concomitant formation of rings and stereocenters (Scheme 1.1a and b).

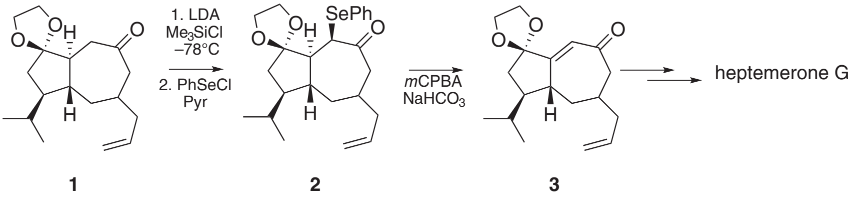


Scheme 1.1 The reactivity of electrophilic selenium reagents.

Organoselenium Chemistry: Synthesis and Reactions, First Edition. Edited by Thomas Wirth.

In addition, electrophilic selenium reagents can be also used for the α-selenenylation of carbonyl compounds (Scheme 1.1c) affording useful intermediates for the synthesis of α,β-unsaturated [2] derivatives or 1,2-diketones through a seleno-Pummerer reaction [3].

Oxidation of selenides to the corresponding selenoxide for the synthesis of α,β-unsaturated compounds represents a current topic in organic chemistry and has been used successfully also in structurally complex product synthesis. An example has been very recently reported in which the electrophilic selenenylation followed by an oxidative elimination represent a crucial step in the total synthesis of heptemerone G, a diterpenoid fungi-derived with interesting antibacterial activity (Scheme 1.2) [4].

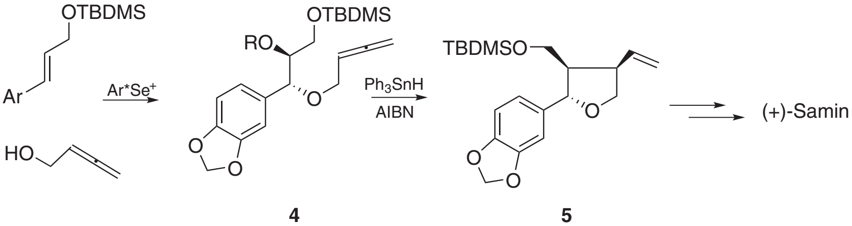


Scheme 1.2 Electrophilic selenium reagent in the total synthesis of heptemerone G.

The kinetic lithium enolate **1**, trapped as trimethysilyl derivatives, reacts with PhSeCl affording the selenide **2** that, after oxidation with metachloroperbenzoic acid, is converted into the enone **3** from which the heptemerone G can be prepared in some additional steps.

The treatment of selenides with tin hydrides, in the presence of AIBN, produces the homolytic cleavage of the carbon–selenium bond generating a carbon radical and opening the way for interesting radical reactions.

An elegant application was reported for the total synthesis of (+)-Samin (Scheme 1.3). The selenide **4** was subjected to radical deselenenylation conditions affording the tetrahydrofurane derivative **5** following a *5-exo-trig* radical cyclization mechanism. From **5**, (+)-Samin was obtained through a few classical steps [5].



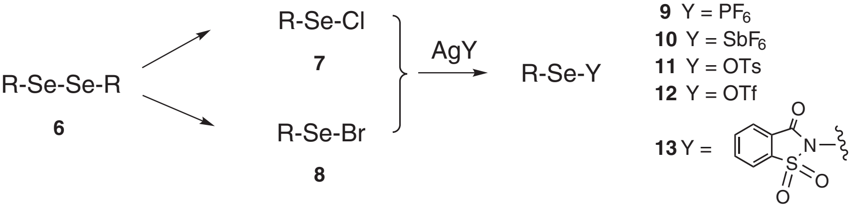
Scheme 1.3 Electrophilic selenium reagent in the total synthesis of (+)-Samin.

The main aspects of organoselenium chemistry have been described in a series of books [6] and review articles and, in recent times, the synthesis of chiral selenium electrophiles as well as their applications in asymmetric synthesis represents a very interesting field of interests for many research groups [7].

In this chapter, we take in consideration some general aspects of the chemistry promoted by electrophilic selenium reagents by reporting selected examples and some more recent and innovative applications.

1.1.1
Synthesis of Electrophilic Selenium Reagents

Some phenylselenenyl derivatives such as chloride, bromide, and *N*-phenylselenophthalimide [8] are nowadays commercially available and represent the most common electrophilic reagents used to introduce selenium into organic molecules. Otherwise, in a more general procedure, very versatile precursors for the preparation of various electrophilic selenium species are the corresponding diselenides **6**. They can be easily converted into selenenyl halides **7**, **8** by treatment with sulfuryl chloride or chlorine in hexane and bromine in tetrahydrofuran, respectively (Scheme 1.4).



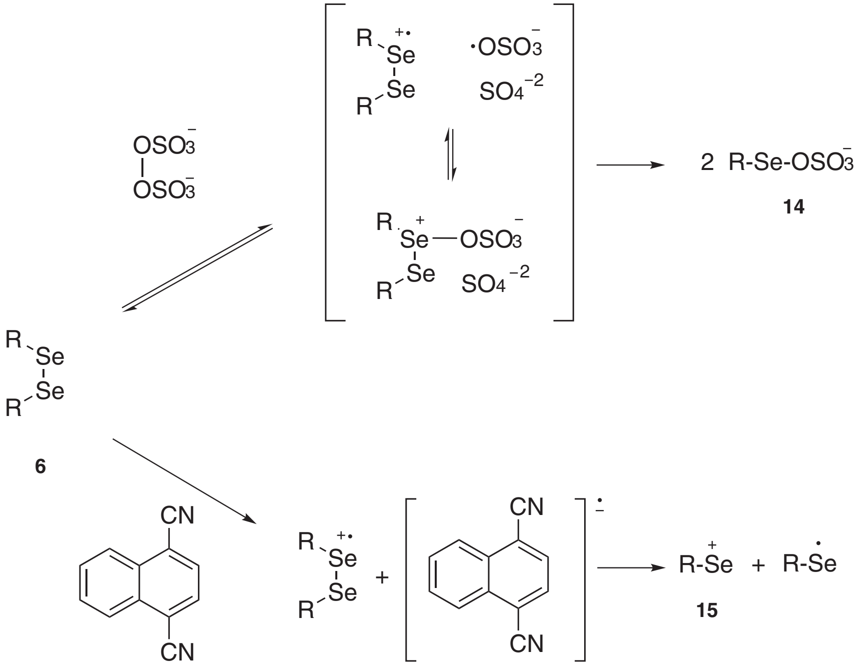
Scheme 1.4 Electrophilic selenium reagents.

The use of halides in synthesis often gives rise to side processes due to the nucleophilicity of the halide anions. For this reason, a series of new selenenylating agents with nonhalide counterions have been reported.

Some of them were directly prepared starting from the appropriate selenenyl halide with silver salts such as hexafluorophosphate **9** [9], hexafluoroantimoniate **10** [10], tolylsulfonate **11** [11], and triflate **12** [12].

This latter is probably the most commonly used electrophilic selenium reagent even if, in many cases, the stoichiometric amount of trifluoromethanesulfonic acid formed is not compatible with the stability of the substrates and/or of the products. More recently, Tingoli reported a similar procedure to prepare the *N*-saccharin derivatives **13** containing a sulfonamide anion that is scarcely nucleophilic and generating saccharin that is a very weak acidic species [13].

In other cases, the electrophilic reagent can be more conveniently produced by the *in situ* oxidation of **6** with several inorganic reagents: KNO_3 [14], $CuSO_4$ [15], $Ce(NH_4)_2(NO_2)_6$ [16], Mn(OAc) [17], or nitrogen dioxide [18]. Among these, starting from diphenyl diselenide, $(NH_4)_2S_2O_8$ [19] produces the strongly electrophilic phenylselenenyl sulfate (PSS) **14** through a mechanism that reasonably involves an electron transfer or an S_N2 reaction. A product derived from a single electron transfer has been proposed also as an intermediate in the reaction of diphenyl diselenide with 1,2-dicyanonaphthalene [20] that leads to the formation of the phenylselenenyl cation **15** as depicted in Scheme 1.5.



Scheme 1.5 Electrophilic selenium reagents through a single electron transfer mechanism.

Some other organic oxidizing agents such as *m*-nitrobenzenesulfonyl peroxide [21], (bis[trifluoroacetoxy] iodo)benzene [22], (diacethoxy iodo)benzene [23], and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [24] have been also used in some cases. The choice of the best reagent strongly depends on the chemical susceptibility of the substrate and its functional groups and is mainly dictated by the requirements of the addition reaction to be carried out.

In recent years, polymer-supported reagents have also attracted interest because they can provide attractive and practical methods for combinatorial chemistry and solid-phase synthesis.

Polymer-supported selenium reagents represent an interesting improvement for synthetic organic chemists because of their facile handling without the formation of toxic and odorous by-products. Some electrophilic selenium-based approaches for solid-phase chemistry have been reported by different groups and the use of these reagents allows easy purification and recycling of the reagent for a next reaction. In addition, it represents useful strategies especially for constructing libraries of heterocyclic derivatives [25]. Wirth and coworkers compared the efficiency of polystyrene, TentaGel, and mesopouros silica as a solid support for enantioselective electrophilic addition reactions [26].

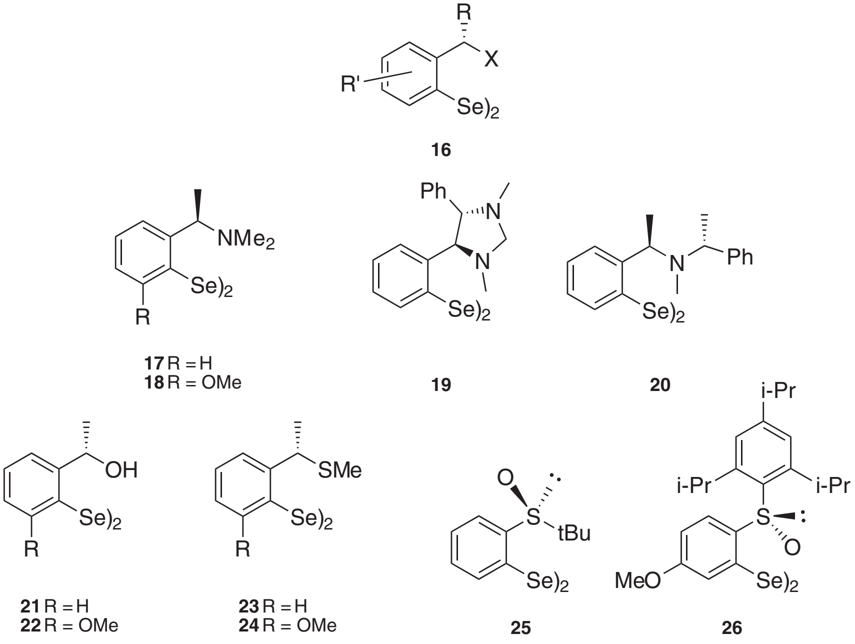
In a recent application, polystyrene-supported selenenylbromide was reacted with methyl acrylate and a primary amine to afford in a *one-pot* procedure a resin that has been used to prepare libraries of 2-pyridones, 1,4-diazepines, 1,4 oxazepines [27], and other nitrogen heterocycles [28].

Even if the mild reaction conditions usually required for the selenenylation of unsatured substrates represent an attractive aspect for this chemistry, some of these conversions suffer the drawback that the selenium reagent must be used in stoichiometric amounts. However, addition–elimination sequences using catalytic amount of diselenides in the presence of an excess of oxidizing reagent have been reported using peroxydisulfates [29] as well as hypervalent iodine compounds [30].

An electrochemical procedure to generate a selenium electrophile starting from diphenyl diselenide involves the use of tetraethylammonium bromide as redox catalyst and as electrolyte. The anodic oxidation of bromide to bromine initiates the reaction producing the electrophilic phenylselenenyl bromide from the diselenide [31].

During the last 10 years, several research groups devoted their efforts to the preparation of different optically active diselenides that have been used as electrophilic selenenylating agents precursors [32].

Since the first binaphthyl-based diselenides developed by Tomoda and Iwaoka [33], a series of interesting chiral scaffolds have been proposed and evaluated as chiral sources in asymmetric electrophilic addition and cyclofunctionalization reactions. Selected examples are collected in Scheme 1.6.



Scheme 1.6 Aromatic chiral diselenides.

Wirth and coworkers reported that easily accessible diselenides having the general structure **10** can be conveniently used to prepare electrophilic selenium reagents and promote asymmetric electrophilic addition reactions [34].

Starting from readily available chiral precursors, diselenides **17–24** can be prepared in one-step syntheses consisting of *ortho*-lithiation, reaction with elemental selenium and air oxidation in generally good overall yields. All these compounds have as common characteristic the presence of heteroatom able to interact with the nearby electrophilic selenium forcing the chiral moiety to come close to the reaction center and leading, at the same time, to a more rigid transition state. Both these conditions have been proposed to play an important role in the enantioselective addition to double bonds and we demonstrated that the substitution of the heteroatom with a methylene group determines a complete lost of diastereoselectivity [35].

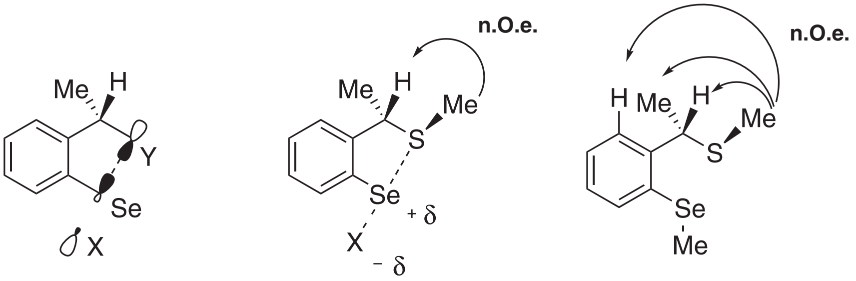
The existence of nonbonding interaction like that depicted in structure **27** has been demonstrated by several authors for a large number of organochalcogen systems using a combination of techniques such as X-ray crystallography, NMR, DFT calculations, and has been object of a recent review [36].

The major factor contributing toward nonbonding interactions in these compounds is identified as arising from the orbital interaction.

We first described a Se···S interaction in the selenenyl halides **28** [37] and **29** [38] prepared starting from diselenide **23**. For these reagents, we reported spectroscopic and chemical evidences for the existence of this interaction. X-ray analysis evidenced a T-shaped coordination geometry around the selenium atom with a distance between Se and S (2.497[7] Å for **29** and 2.344[2] Å for **28**) that is significantly shorter than the sum of the van der Waals radii (3.7 Å) [35].

The shorter distance observed in **28** compared to **29** seems to indicate a stronger interaction when the counterion is a chloride.

Comparison of nuclear Overhauser effect (n.O.e.) of arylselenyl halides **28** and **29** to the corresponding aryl methylselenide **30** proves a greater conformational rigidity reasonably deriving from the Se···S interaction atom, which is not only present in the crystal form but also in CDCl$_3$ solution (Scheme 1.7).



27

28 X = Cl
29 X = Br

30

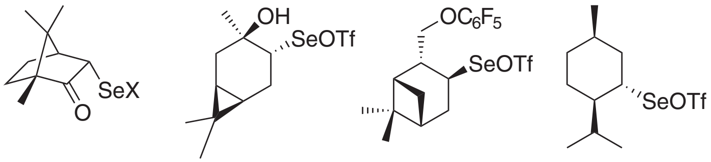
Scheme 1.7 Selenium–heteroatom nonbonding interaction.

Organoselenium compounds exhibiting intramolecular Se···N and Se···O interactions are particularly interesting since these interactions are expected to modulate the biological activity of the selenium compounds. Selenocyanates are commonly used as intermediates in the synthesis of diorganoselenates and are investigated as antitumor drugs. Jones, Mugesh, and du-Mont determined the X-ray structure of methyl-2-selenocyanatobenzoate in which the Se···O contact is sensibly shorter in comparison with the Se···N one [39].

More recently starting from (*S*)-ethyllactate and (–)-(1*R*)-*para*-toluensulfinate, Wirth and coworkers reported the syntheses of two new optically active sulfoxide containing diselenides **25** and **26** [40]. These were used to prepare new selenium electrophiles that have been successfully used for stereoselective functionalization of alkenes.

X-ray comparison between diselenides **25** and **22** evidences that the oxygen attached to the chiral center in compound **25** has no interaction with the selenium atom in the solid state.

Convenient methods for the synthesis of optically active nonfunctionalized or functionalized selenium reagents from mono- and bicyclic terpenes have also been developed in the recent period; Scheme 1.8 summarizes some of the most representative structures (**31–37**) [41].



31 X = Cl
32 X = Br
33 X = OTf
34 X = OSO_3H

35

36

37

Scheme 1.8 Terpene-based electrophilc selenium reagents.

In some of these cases, X-ray analysis and DFT calculations showed the existence of an intramolecular heteroatom-selenium interaction, which seems to be an important factor for the chirality transfer in the transition state of the addition reactions.

Concerning this class of diselenides, it is possible to generalize that the facial selectivity produced by the aliphatic electrophilic selenium reagent is usually lower in respect to those obtained using an aromatic core.

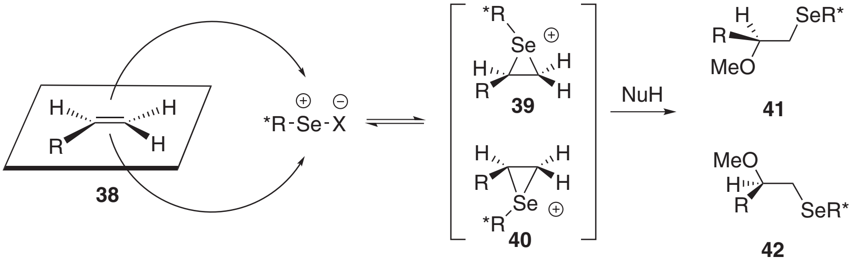
1.1.2
Reactivity and Properties

In many aspects, the properties of organoselenium compounds are similar to those of the better-known sulfur analogues. However, the introduction of the heteroatom, the manipulation of the resulting molecules, and, in particular, the removal of the selenium-containing functions occurs under much simpler and milder conditions than those required for the corresponding sulfur compounds.

The reaction of selenium electrophiles with alkenes consists in a stereospecific *anti*-addition that involves the initial formation of a seleniranium ion intermediate. This is rapidly opened in the presence of a nucleophile that can be external, leading to the addition products, or internal, giving the corresponding cyclized derivative.

The intermediate seleniranium ion can be ring-opened to afford two different regioisomers. The regiochemistry usually follows the thermodynamically favored Markovnikov orientation even if examples of *anti*-Markovnikov addition were reported, as a consequence of the coordinating effect of a hydroxyl group in the allylic position.

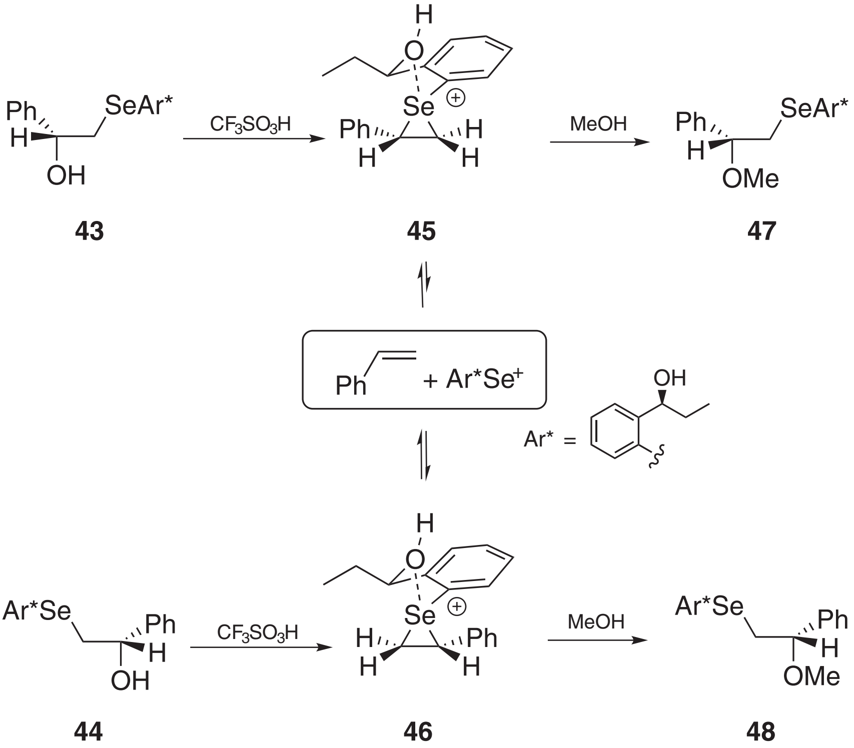
When the reagent is chiral, a differentiation between the two faces of unsymmetrically substituted alkenes can be observed (Scheme 1.9). Depending on the reaction conditions, the formation of the seleniranium ion can be reversible and at low temperatures the reaction is under kinetic control.



Scheme 1.9 Stereoselective addition.

Steric and electronic effects control the formation of the diastereoisomeric intermediates **39** and **40** and the ratio reflects the different stability between them. Subsequent reaction with a nucleophile affords the diastereoisomers **41** and **42** derived from the stereospecific ring opening of **39** and **40**, respectively.

The presence of an equilibrium between the starting materials and the seleniranium intermediates has been chemically demonstrated starting from the hydroxyselenides **43** and **44,** easily obtained by the nucleophilic ring opening of the corresponding optically pure (*R*)- and (*S*)-styrene epoxide (Scheme 1.10) [42].



Scheme 1.10 Mechanism of the enantioselective addition reactions.

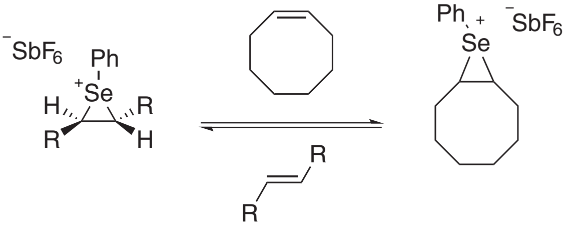
Treatment of **43** and **44** with trifluoromethane sulfonic acid generates selectively the corresponding seleniranium ions **45** and **46** according to an intramolecular S_N2 displacement of a molecule of water. In the case of **43**, only the seleniranium ion **45** is formed and the subsequent treatment with methanol affords the adduct **47** corresponding to the Re-attack of the selenium electrophile to the styrene double bond. *Ab initio* calculations on the stability of the intermediates indicated that **45** is more stable than **46**.

Under the same experimental conditions, the hydroxyselenide **44** produces the less-stable seleniranium ion **46**. After reaction with methanol, the formation of both isomers **47** and **48** in a 3 : 1 ratio clearly indicates a decomplexation–complexation mechanism that is involved in the above-mentioned equilibrium [43].

Even if the central tenet of this class of reaction is the formation of the high reactive seleniranium ions, only few examples were reported in which they have been independently synthesized and analyzed. Many studies have been performed with the assumption that the putative intermediate seleniranium ions are responsible for the observed products.

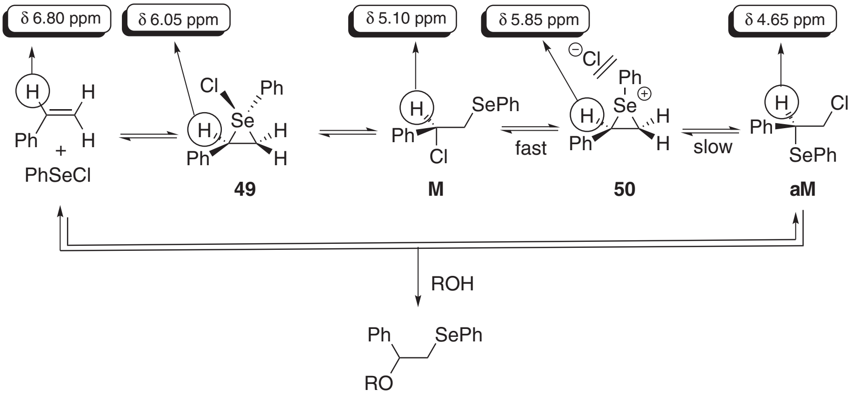
After seminal computational studies in which the enthalpic activation barrier for direct, intramolecular thiiranium–olefin and seleniranium–olefin transfer were compared for alkylthiiranium, arylthiiranium, and arylseleniranium ions [44] Denmark *et al.* reported a crossover experiment as the first direct observation of the transfer of a selenonium cation from one olefin to another [45].

On the basis of these observations, the authors suggest that the rapid olefin-to-olefin transfer represents one of the most likely pathways for racemization of the enantiomerically enriched seleniranium ions (Scheme 1.11).



Scheme 1.11 Crossover experiment.

Our recent NMR investigations on the haloselenenylation of styrene derivatives [46], according to other evidence previously reported by Garrat [47], demonstrate the presence of a more complicated equilibrium when the nucleophile is chlorine or a bromine. The initial formation of the Markovnicov's adduct is very fast and rapidly reaches the equilibrium with the anti-Markovnicov regioisomer. NMR analysis of the equilibrium mixture, combined with kinetic investigation, evidenced the presence of two different intermediates in the formation of the Markovnicov and anti-Markovnicov product that were assigned to the episelenurane **49** and seleniranium ion **50**, respectively (Scheme 1.12).



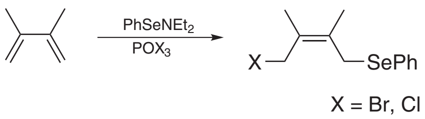
Scheme 1.12 Mechanism of the chloroselenenylation reaction.

When the anion is chloride, the treatment of the above-described equilibrium mixture with an oxygen-containing nucleophile such as methanol affords quantitatively the Markovnikov alkoxyselenide.

After 60 years since the first stereospecific selenoaddition reaction, some mechanistic aspects are still under investigation and a clear explanation of the species involved in these reactions should represent an important aspect in the development of more efficient and selective reactions.

Electrophilic selenenylation of dienes has not been extensively used and investigated. The first example of conjugated diene selenenylation reported that the reaction with PhSeCl gives either an allylic alcohol or an enone depending on the experimental procedure [48].

More recently, treatment of dienes with aryl selenenamides in the presence of phosphorus(V)oxyhalides has been proposed as a useful method to effect the 1,4-haloselenenylation of conjugated dienes. Similar experimental conditions applied to nonconjugated dienes afforded only mono-haloselenides (Scheme 1.13) [49].



Scheme 1.13 Conjugated electrophilic addition to dienes.

Furthermore, the reaction of divinylsulfide with selenium dibromide prepared from selenium and bromine in carbon tetrachloride gives, in near quantitative yield, the six-membered heterocyclic compound 2,6-dibromo-1,4-thiaselano that underwent spontaneous rearrangement to a five-membered thioselenolan-derivative [50].

1.2
Addition Reactions to Double Bonds

1.2.1
Addition Reaction Involving Oxygen-Centered Nucleophiles

Addition reactions to double bonds promoted by electrophilic selenium reagents are usually carried out in the presence of a solvent that acts as external nucleophile. Simple and efficient procedures to introduce oxygen and nitrogen nucleophiles have been reported and are currently employed in the functionalization of olefins. In the first case, the process is named oxyselenenylation and leads to the introduction of hydroxy-, alkoxy-, or acetoxy groups.

PhSeBr and acetic acid in the presence of acetic anhydride and KNO_3 promote the acetoxyselenenylation of alkenes, but this methodology suffers of considerably low regioselectivity in the case of terminal olefins [51]. An alternative and more efficient procedure involves the oxidation of diphenyl diselenide with (diacetoxy iodo) benzene in acetonitrile [23].

Currently the most relevant developments in this field of research concern the use of optically pure electrophilic reagents in the asymmetric synthesis of alkoxy- and hydroxy derivatives. Methoxyselenenylation of styrene has been used by several groups as a test reaction to compare the diastereoselectivity induced by different chiral selenenylating reagents and to compare the effect of the different experimental conditions as well as the structural features of the reagents.

Selected examples are collected in Table 1.1 and, even if in all the cases the diastereoselectivity is usually good, some general considerations on the ability of various electrophilic reagents to transfer the chirality to the newly generated center can be attempted.

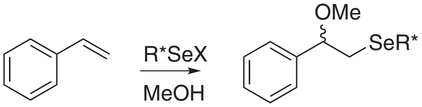
Considering the above-mentioned role of the heteroatom on coordinating to the electrophilic selenium atom, from the data reported in Table 1.1, sulfur atom (entries 10–11), in respect to oxygen and nitrogen atom (entries 1,2,8,9), seems to be more effective, leading to higher diasteromeric excesses at higher reaction temperatures. The results reported in entries 3–7 also suggest that the presence of a second chiral center could produce a positive effect in terms of diastereoselectivity. Using the electrophilic reagent derived from the oxidation of diselenide **20**, a match/mismatch effect related to the relative configuration of the two chiral centers has been described [52].

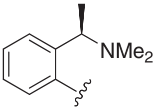
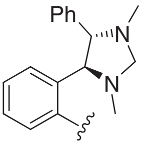
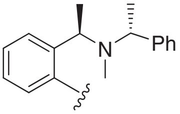
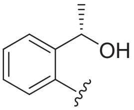
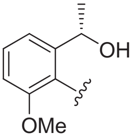
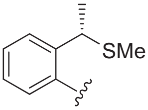
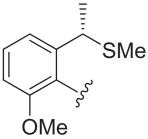
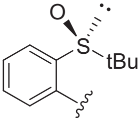
As shown in entries 8–9 and 10–11 reagents, with a methoxy group in the *ortho*-position to the selenium electrophile shows higher selectivities than unsubstituted one. Probably this arises from a different coordination of the side chain, even if detailed calculations [53] showed that the strength of coordination does not correlate with the trend of the experimentally observed selectivities. Probably the situation is different when the chiral moiety is a sulfoxide. In this case in fact, as already reported, no selenium heteroatom interaction was observed and the methoxy selenenylation of styrene proceeds with moderate diasteroselectivity (d.r. 6 : 1). For this reagent, the introduction of a substituent (MeO-) in the *ortho*-position to the electrophilic selenium atom dramatically reduces the yield (24%) as well as the diasteromeric excess (2 : 1).

The information gained from these experiments can be used as preliminary indications even if a strong dependence on the alkene structure as well as on the nucleophile and the solvent must be taken in consideration.

As an illustrative example when the conditions reported on entry 12 were applied to effect the methoxyselenenylation of 2-chlorostyrene or β-methyl styrene, the selectivity increases affording a diasteromeric ratios of 11 : 1 in dichloromethane. Other solvents such as THF, diethyl ether, and chloroform give considerably lower selectivity. Concerning the nucleophile, slight differences in selectivity have been observed using different alcohols, and this suggests that probably different nucleophiles coordinate in different ways to the selenium electrophile. Using the selenenyl triflates generated from oxygen-containing diselenides (**21**,

Table 1.1 Asymmetric methoxyselenenylation of styrene.



Entry	R*	X	T (°C)	de (%)	Yield (%)	Reference
1		TfO^-	0	35	64	[34c]
2		HSO_4^-	25	65	80	[34c]
3		TfO^-	−100	86	98	[34f]
4		HSO_4^-	−15	86	74	[34f]
5		HSO_4^-	25	76	95	[34f]
6		TfO^-	−78	90	40	[51]
7		HSO_4^-	25	94	70	[51]
8		TfO^-	−100	83	67	[34e]
9		TfO^-	−100	96	55	[34e]
10		TfO^-	−78	92	80	[36]
11		HSO_4^-	−30	96	72	[37]
12		TfO^-	−78	70	52	[38]

22), the selenenylation of styrene with methanol is more selective than with acetic acid.

Scianowsky *et al.* reported several examples of methoxyselenenylation mediated by terpene-based electrophilic selenium reagents [41f–n]. A large screening of *p*-menthane derivatives indicates that the diastereoselectivity is strongly correlated to the stability of the chair conformers of the terpeneselenenyl bromide as calculated using density functional theory [41h].

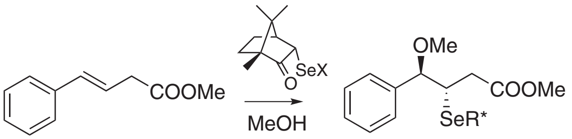
The electrophilic reagent **32** proceeds with the methoxyselenenylation of styrene at −78 °C in 86% yield with only 40% de [41a–e]. The results obtained with **35** and **36** indicate that a more rigid bicyclic structure and the presence of a coordinating heteroatom increase the diastereomeric excess at the price of a reduced reactivity (using **35**: 54% yield, 80% de; using **36**: 53% yield, 72% de) [41m].

An important role, even if not yet completely understood, is played in the selenenylation reaction by the counterion. On the basis of some results reported by Tomoda [32p], it can be suggested that a decrease in the nucleophilicity of the counterion reasonably correspond to an increase in the electrophilicity of the selenium reagent, and hence to an increased selectivity which is reflected in higher diastereomeric excesses.

The reaction of methyl cinnamate with different camphor-derived selenenyl reagents (**31–34**) at room temperature in methanol follows a similar trend (see Table 1.2). It is interesting to note that in the case of the sulfate **34**, the addition occurs with the opposite facial selectivity in respect to that observed with other anions [54].

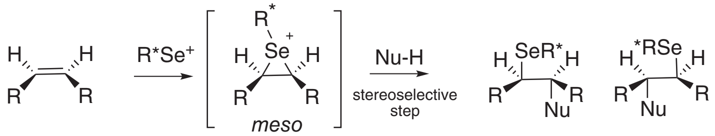
Similarly, the selectivity changes passing from the bromide **32** to the sulfate **34** for some linear olefins like (*E*)-β-methylstyrene, (*E*)-4-octene, and methyl-(*E*)-3-hexenoate, while for *Z*-symmetric alkenes, such as cyclohexene and cycloctene, the facial selectivity resulted to be unchanged. In this latter case, a different mechanism for the stereoselection can be envisioned: the electrophile attacks the (*Z*)-olefins leading to the formation of a *meso*-seleniranium ion. Consequently the

Table 1.2 Effect of the counterion on the facial selectivity [54].



X	*T* (°C)	Time (h)	Yield (%)	d.r.
Cl (31)	0	4	49	40 : 60
Br (32)	0	2	56	35 : 65
OTf (33)	0	5	77	42 : 58
OSO_3H (34)	25	24	94	85 : 15

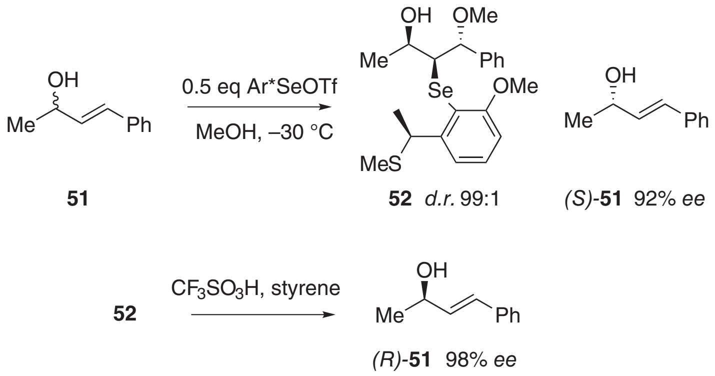
ring-opening reaction mediated by the nucleophile becomes the stereoselective reaction step. Since this occurs far from the chiral environment of the electrophilic reagent, this can explain the generally lower facial selectivity observed for these substrates (Scheme 1.14).



Scheme 1.14 Mechanism for asymmetric addition on *Z*-olefins.

Enantiomerically pure electrophilic selenium reagents prepared from diselenide **24** can be used to perform the kinetic resolution of allylic alcohols. The methoxyselenenylation of **51** effect using 0.5 equivalents of selenenylating reagent affords the formation of the corresponding addition products (e.g., **52**) with a facial selectivity ranging from 95 : 5 to 98 : 2. The reaction is regiospecific and the resolution resulted to be more efficient when aryl-substituted olefins were employed as substrates. From the crude, the unreacted alcohol can be recovered in optically enriched form with 90–94% *ee*.

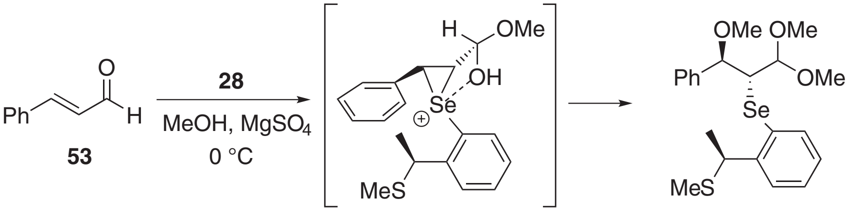
In order to complete the resolution, the arylseleno and the methoxy groups were eliminated from **52** by treatment with a catalytic amount of CF_3SO_3H in the presence of styrene. The regio- and stereoselectivity observed on different substrates have been correlated to a stabilizing interaction between the allylic oxygen and the selenium atom (Scheme 1.15) [55].



Scheme 1.15 Kinetic resolution of allylic alcohols.

Methoxyselenenylations of α,β-unsaturated aldehydes were first reported by Paulmier in 1991 using PhSeCl in MeOH at –30 °C [56]. The reaction proceeds with poor regio- and stereoselectivity through the formation of a dimethylacetal intermediate in which the double bond is a better nucleophile because it is no longer stabilized by conjugation and undergoes electrophilic addition via the seleniranium ion intermediate.

Very recently, the asymmetric version has been proposed using the chiral reagent **28** in the presence of $MgSO_4$–methanol at 0 °C. The reaction in this case resulted in the stereoselective formation of mainly one of the four possible isomers (Scheme 1.16) [57].



53 **54** **55** (81%) 72% *de*

Scheme 1.16 Methoxyselenenylation of α,β-unsaturated aldehydes.

A series of evidences demonstrated that probably in this case, the formation of the dimethylacetal is not the first reaction step and the methoxyselenenylation occurs on the corresponding hemiacetals **54**, in which a nonbonding interaction between seleniranium ion and the hydroxyl group in the allylic position controls the regiochemistry as well as the stereochemistry of the process.

When the electrophilic selenium addition is effected using water instead of methanol as external nucleophile, the introduction of a hydroxyl group and the synthesis of alcohols can be easily achieved.

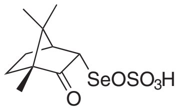
Chiral selenenyl sulfates prepared by oxidation of the corresponding diselenides with ammonium persulfate react with alkenes in acetonitrile in the presence of traces of water affording the hydroxyselenenylation products, generally in good yields and with a diastereoselectivity that mainly depends on the combination of reagents and substrates.

In order to effect hydroxyselenenylations reactions, the sulfate counteranion presents two important advantages: (1) it can be conveniently prepared in aqueous media, and (2) the reaction promoted by selenenyl sulfate derivatives can be performed at higher temperatures with respect to those required by other counteranions (e.g., from −30°/+40° against −100°/−78° for triflate analogues).

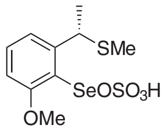
Selected results are summarized in Table 1.3 in order to compare the reactivity and the selectivity of three different chiral scaffolds. The hydroxyselenenylation of mono- and disubstituted olefins affords regiospecifically a couple of hydroxyselenides deriving from an *anti*-stereospecific addition, with good yields and moderate to excellent facial selectivity.

Camphor selenenyl sulfate (**34**) showed better selectivity for the alkyl-substituted substrates in contrast to sulfur-containing aryl selenenyl sulfate (**56**) that resulted

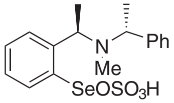
Table 1.3 Asymmetric hydroxyselenenylation.



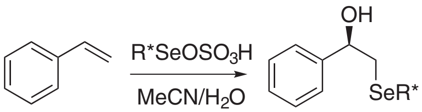
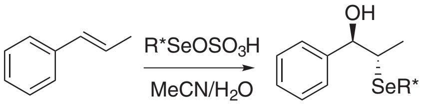
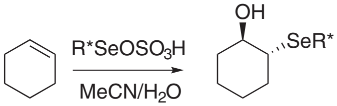
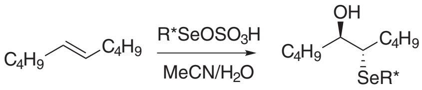
34



56



57

		34 [58]	**56 [36, 37]**	**57 [53]**
		d.e. (%) (yield (%))	**d.e. (%) (yield (%))**	**d.e. (%) (yield (%))**
a)		30 (68)	96 (65)	90 (40)
b)		30 (62)	96 (70)	62 (82)
c)		56 (68)	44 (60)	–
d)		88 (89)	76 (79)	–

in higher selectivities when the carbon–carbon double bond is substituted with a phenyl group. Concerning the sulfur-containing reagent, it was demonstrated that the presence of the methoxy group in the *ortho*-position in respect to the electrophilic selenium, as well as for the methoxyselenenylation reaction, effects a positive influence on the selectivity giving higher diastereomeric ratios.

Starting from cyclohexene is not surprising to observe that a low selectivity is produced by both reagents. In this case, as previously outlined, the first step leads to a *meso*-seleniranium ion and the stereoselection arises from the subsequent attack of a molecule of water, responsible for the seleniranium ring-opening reaction. This latter event occurs far from the chiral environment of the intermediate and it is reasonably less sterically and electronically controlled.

The reaction temperature is usually chosen based on the reactivity of the reagent, looking for the best compromise between reaction time and selectivity. Comparing sulfate derivatives, the sulfur-containing electrophilic selenium reagent showed the best reactivity: the reactions are fast even at −30 °C affording the best diastereomeric ratio. On the contrary, when the coordinating heteroatom is a nitrogen atom (**57**), the reactivity is strongly reduced and the reaction occurs only at 25 °C. These experimental conditions are enough to affect the hydroxyselenenylation of styrene derivatives but not of aliphatic olefins and the higher temperature is probably responsible for the reduced selectivity.

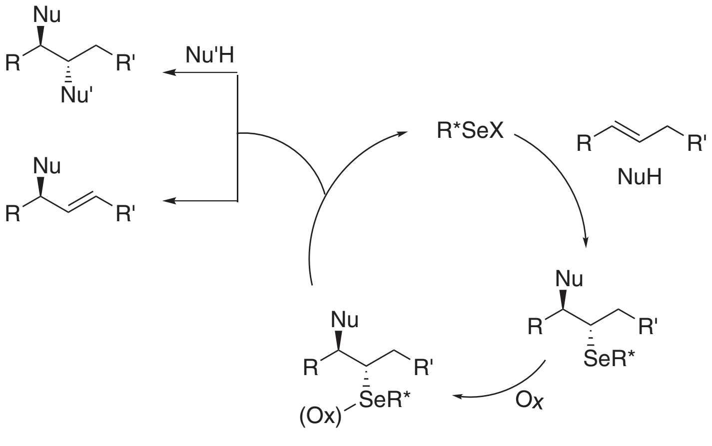
A promising development of these methodologies is certainly represented by the possibility to affect selenenylation and deselenenylation in *one-pot* using an excess of a suitable oxidant. This approach has received high attention during the last years from several research groups.

The first example was reported by Torii who effected the catalytic conversion of alkenes into allylic ethers or esters using catalytic amounts of diphenyl diselenide [59].

The strategy is to introduce a new functionality in a substrate after electrophilic activation of a carbon–carbon double bond and subsequently remove the organoselenium function accordingly with a two-step *one-pot* procedure.

The first step, depending on the experimental conditions, consists of α-methoxyselenenylation or hydroxyselenenylation and leads to an α-alkoxy or hydroxy selenide. In the second step, the selenium moiety is transformed into a good leaving group which in turn is removed through α,β-elimination or, less frequently, through direct nucleophilic substitution.

During the second step, the electrophilic selenenylating reagent is regenerated, allowing the use of a catalytic amount of the selenium-containing reagent (Scheme 1.17).



Scheme 1.17 *One-pot* selenenylation–deselenenylation sequence.

Several research groups have recently investigated the asymmetric version of the catalytic *one-pot* selenenylation–deselenenylation sequence. The asymmetric version of this experiment can be simply effected by replacing diphenyl diselenide with an optically pure selenenylating reagent. All these aspects will be fully treated in Chapter 9 and have been very recently object of some reviews [7h, i]. Here just some general concepts will be shortly introduced as an example of electrophilic selenium reagents.

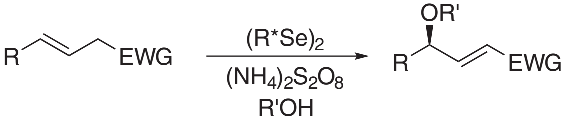
Tiecco and coworkers reported that ammonium persulfate was the best oxidant for the *one-pot* selenenylation–deselenenylation reaction and applied this strategy to effect the conversion of β,γ-unsaturated esters, amides, and nitriles into γ-alkoxy or γ-hydroxy α,β-unsaturated derivates, also using a catalytic amount of diphenyl diselenide [60].

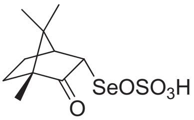
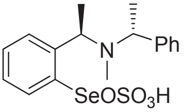
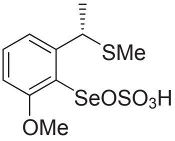
The selenenyl sulfate is produced *in situ* from the reaction of the corresponding diselenide with ammonium persulfate. It reacts with the alkenes to give alkoxy- or hydroxyselenenylation products. The reaction of these addition products with ammonium persulfate in excess is suggested to generate a selenonium ion which affords, by elimination, the observed reaction products and regenerates the electrophilic reagent.

An electron-withdrawing group in the allylic position is essential for the success of the reaction since simple unsubstituted alkenes gave rise to product mixtures. It was supposed that the driving force of the process is the stabilization by conjugation of the double bond formed during the deselenenylation.

With chiral diselenides, asymmetric catalytic reactions can be performed. Table 1.4 reports some results that put in evidence that passing from camphor selenenyl

Table 1.4 Asymmetric *one-pot* methoxyselenenylation deselenenylation sequence.



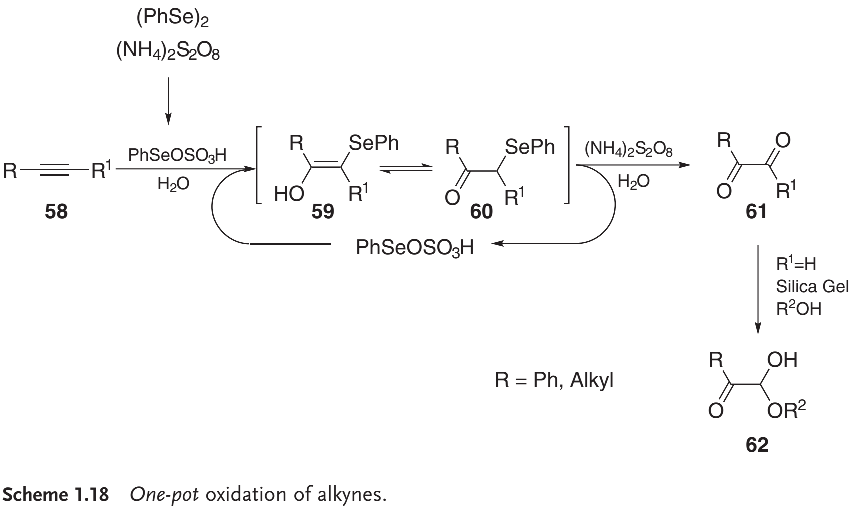
	% cat	R	EWG	R′	Yield (%)	*ee* (%)	Ref.
 **34**	100	Ph	COOMe	Me	72	65	[61]
	100	Et	COOMe	Me	71	86	[61]
	100	Me	COOMe	Me	60	70	[61]
	100	Me	CN	Me	60	70	[61]
 **56**	10	Ph	COOMe	Me	12	94	[53]
	100	Ph	COOMe	Me	50	94	[53]
 **57**	5	Ph	COOMe	Me	98	78	[37]
	5	Et	COOMe	Me	98	68	[37]
	5	Ph	COOMe	H	98	55	[37]

sulfate **34** [61] to aromatic selenenyl analogues **56** [36, 37] and **57** [53], probably the mechanism for the catalytic stereoselection is different. In the first case, in fact, to obtain a good facial selectivity a stoichiometric amount of selenenylating reagent is necessary even if, at the end of the reaction, camphoryl diselenide can be recovered quantitatively.

Regarding the aromatic reagents **57** and **56**, as already observed for the addition reactions, the nitrogen-containing derivative **57** is less reactive than those in which the electrophilic selenium is coordinated by a sulfur (**56**). In the first case, a stoichimetric amount of reagent is required in order to accelerate a very slow reaction but the amount of selenenylating agent did not affect the diasteroselectivity. In the latter one, using as electrophilic reagent **56**, moderate to good enantiomeric excesses were obtained with only 5% of the catalyst even at 20 °C.

A second possibility than a β-elimination of the oxidized selenium moiety from the selenenylation intermediate is the direct nucleophilic substitution resulting in a double functionalization of the double bond. In a very recent example, the first direct selenium-mediated dihydroxylation of olefins has been achieved with this approach [62]. The oxidant employed is a persulfate and in the proposed mechanism, the oxidized selenium moiety is substituted by a molecule of water. The diastereoselectivity (*syn* vs *anti)* is strongly dependent on the nature of the substrate and the method proved to be efficient even when a sulfur-containing chiral diselenide was used instead of diphenyl diselenide, affording the corresponding diols with an enantiomeric excess that strongly depends on the amount of catalyst. A more efficient and eco-friendly procedure has been also reported using hydrogen peroxide as oxidant but a completely different reaction mechanism is involved in this case [63].

Similarly diphenyl diselenide and ammonium persulfate have been also successfully used to oxidize carbon–carbon triple bonds (**58**) [64]. The reactions (see Scheme 1.18), performed in aqueous media, lead to 1,2-unprotected dicarbonyl



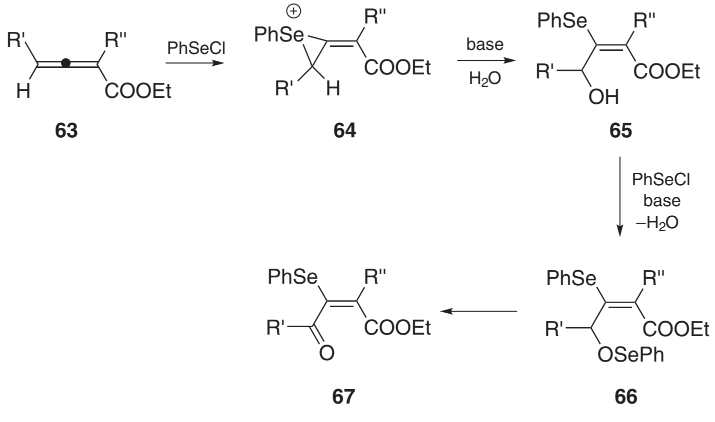
Scheme 1.18 *One-pot* oxidation of alkynes.

derivatives **61** starting from internal triple bonds and to α-keto hemiacetals **62** when the substrate contained a terminal alkyne. The reaction proceeds in *one-pot* starting with the hydroxyselenenylation of the triple bond and the formation of enol **59** that exists in equilibrium with the corresponding α-phenylseleno ketone **60**. The latter, in the presence of an excess ammonium persulfate and water, undergoes the nucleophilic substitution of the phenylseleno group with an hydroxyl group that is subsequently oxidized to a ketone or aldehyde, depending on the alkyne **58** (Scheme 1.18).

During the second step, the PhSe–sulfate is regenerated and the reaction can be performed using a catalytic amount of diselenide in the presence of an excess ammonium persulfate.

Electrophilic selenium reagents can also be used to functionalize allenic systems and usually the reaction is highly regio- and stereoselective.

The 2,3-allenoates **63** treated with PhSeCl in MeCN gave the corresponding 3-phenylseleno-4-oxo-2(*E*)-alkenoates. The addition of Li_2CO_3 as base improved the yield and the selectivity of the reaction. A possible mechanism involves a decomposition of selenate esters, as shown in Scheme 1.19. The electrophile PhSeCl reacted with the relatively electronrich C=C bond in 2,3-allenoates **63** forming the seleniranium ion intermediates **64**, which may be attacked by a molecule of water in a process facilitated by the presence of Li_2CO_3. The hydroxyselenenylation intermediate **65** subsequently reacts with another molecule of PhSeCl in the presence of Li_2CO_3 to produce H_2O and the selenate esters **66**, which may decompose to form the ketone functionality in 3-phenylseleno-4-oxo-2(*E*)-alkenoates **67**.



Scheme 1.19 Hydroxyselenenylation of allenes.

By increasing the amount of water, a competitive cyclization to the corresponding butenolides has been observed and represents an important criticism for this procedure.

The observed stereoselectivity may be explained by the favorable *trans*-arrangement of the phenylseleno and the ester group [65].

More recently, Ma and coworkers deeply investigated halo- and selenohydroxylations of allenyl phosphane oxides [66].

Their results confirmed that the electrophilic moiety adds to the central carbon atom of the allene and the hydroxyl group always attacks in the 3-position respect to the phosphorus atom.

All these reactions are characterized by an excellent regio- and (*E*)-stereoselectivity that should be correlated to the neighboring-group participation ability of the phosphane oxide [67].

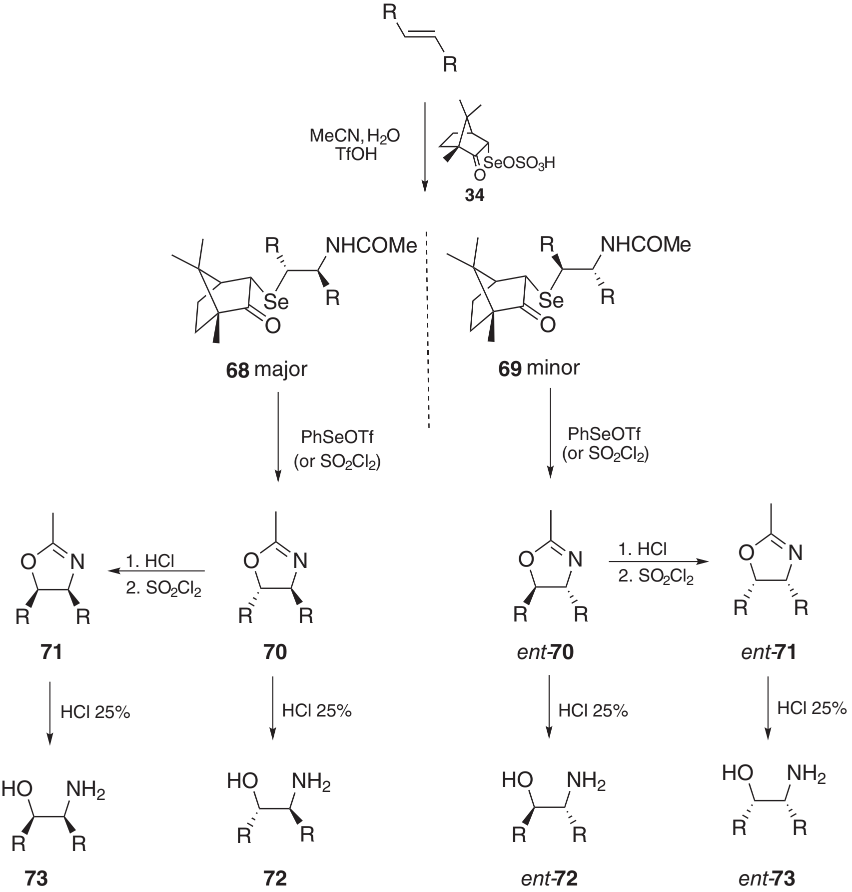
High regio- and (*Z*)-stereoselectivity was obtained by the same authors in the chloro selenenylation of (1- and 3- monosubstituted 1,2-allenyl) phosphonates when the reaction is carried out using PhSeCl as selenenylating reagent.

1.2.2
Addition Reaction Involving Nitrogen-Centered Nucleophiles

In consideration of the biological and pharmaceutical relevance of nitrogen-containing compounds, the addition reactions of an electrophilic selenium reagent and a nitrogen nucleophile to unsaturated substrates represent synthetically important processes with potential practical applications.

Toshimitsu and Uemura first reported a Ritter-type amide synthesis [68]. Treatment of an olefin with PhSeCl in acetonitrile and water in the presence of trifluoromethane sulfonic acid affords the simultaneous insertion of a phenylselenenyl and of an acylamino group to a carbon–carbon double bond. The reaction proceeds in poor yield on styrene and electron-rich olefins. In these cases, better yields were achieved starting from the corresponding hydroxy- or methoxyselenenylated products by treatment with water, trifluoromethansulfonic acid, a stoichiometric amount of nitriles, and using 2-pyridylselenyl chloride as selenenylating agent [69]. Similar reactions can be effected using different nitriles, like propionitrile, butyronitrile, benzonitrile, and ethyl cyanoacetate affording the corresponding selenoamides.

An asymmetric variant of this procedure has been proposed using camphorselenenyl sulfate as selenenylating agent. Even if the amidoselenenylation reaction occurs with moderate facial selectivity, the two diastereomeric addition products **68** and **69** can be completely separated by chromatography and obtained in optically pure form (Scheme 1.20) [70].



Scheme 1.20 Asymmetric amidoselenenylation and further stereospecific manipulations.

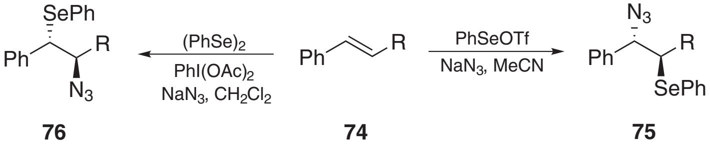
These compounds, subjected to deselenenylation, afforded enantiomerically pure derivatives.

The deselenenylation consists of the activation of the selenium moiety as a leaving group by transforming the selenide into selenonium ions by treatment with electrophilic selenenylating reagents or with SO_2Cl_2.

In these activated substrates, the presence of a suitably positioned nucleophilic substituent allows an intramolecular nucleophilic displacement that affords the corresponding heterocyclic derivatives. This intramolecular substitution occurs with inversion of configuration at the carbon atom bearing the selenium atom leading to the formation of the 4,5-*trans* oxazolines (**70**, *ent*-**70**); the hydrolysis and further treatment with thionyl chloride gave the corresponding *cis*-isomers (**71**, *ent*-**71**). Further manipulation consisted in the acidic hydrolysis of the four optically pure oxazolines in order to prepare the corresponding enantiomerically pure β-amino-alcohols. (**72**, *ent*-**72**, **73**, *ent*-**73**).

Enantiomerically pure thiazolines were prepared using a similar procedure. The mixture of diastereoisomeric amido selenides, treated with Lawesson's reagent, afforded the corresponding thioamido derivatives that were subjected to deselenenylation with the formation of a thiazoline structure [71].

Among the addition reactions which involve nitrogen nucleophiles, the azidoselenenylation of alkenes is one of the most important because both azido and phenylseleno group can give rise to several useful transformations. In addition to the already described manipulations of the selenenyl derivatives, the azido group can react with both nucleophilic and electrophilic reagents and can be used in 1,3-dipolar cycloaddition reactions. Krief first reported the azidoselenenylation of alkenes using a two-step *one-pot* procedure: a reaction with PhSeBr followed by the addition of sodium azide in DMF [72]. A similar reaction can be effected using PhSeCl, NaN_3 in DMSO or PhSe-pthalimide, azidotrimethylsilane in dichloromethane, even if the reactions carried out under these conditions suffer from very low regioselectivity [73]. Some years ago, Tiecco and coworkers demonstrated that the use of PhSeOTf and sodium azide in acetonitrile allows the synthesis of β-phenylselenoazides. The reaction is a stereospecific *anti*-addition in every case and the regiochemistry is determined by the structure of the starting alkenes. Complete regio- and stereoselectivity was observed in the azidoselenenylation of phenyl-substituted alkenes **74** when the reaction was carried out at 0 °C, obtaining the formation of the Markovnikov isomer **75** (Scheme 1.21) [74].



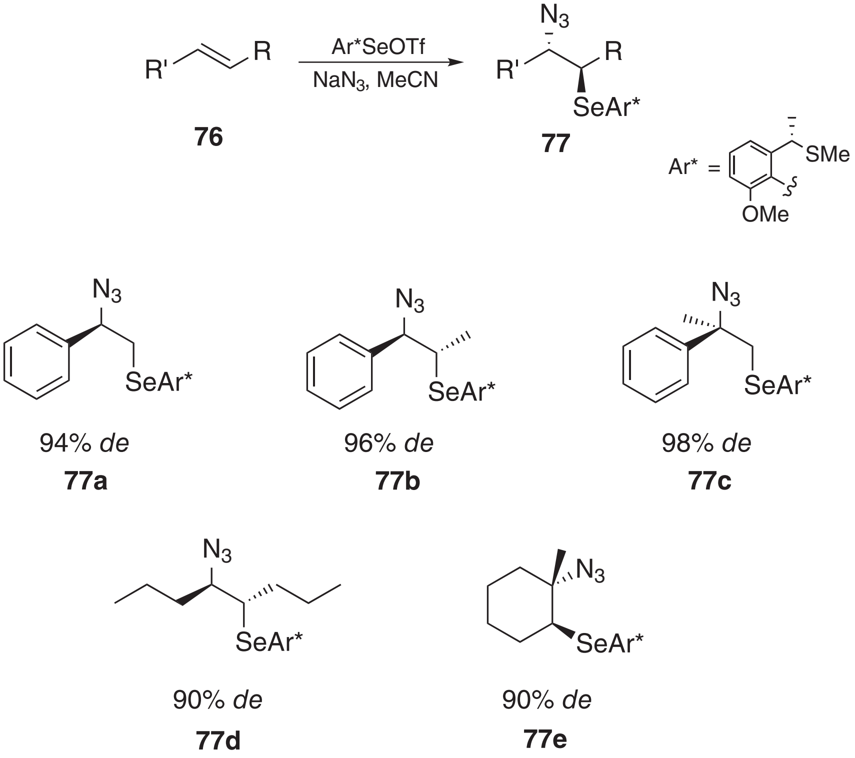
Scheme 1.21 Regiospecific azidoselenenylation reactions.

The *anti*-Markovnikov regioisomer **76** can be obtained by reacting the alkenes with PhSeSePh, NaN_3, and $PhI(OAc)_2$. In this case, the formation of the β-phenylseleno azides is the result of a radical addition initiated by the azido radical which is not stereospecific [75].

The electrophilic azidoselenenylation of *tert*-butyl cinnamyl ether has been used to prepare an intermediate that could be employed in the synthesis of the taxol side chain.

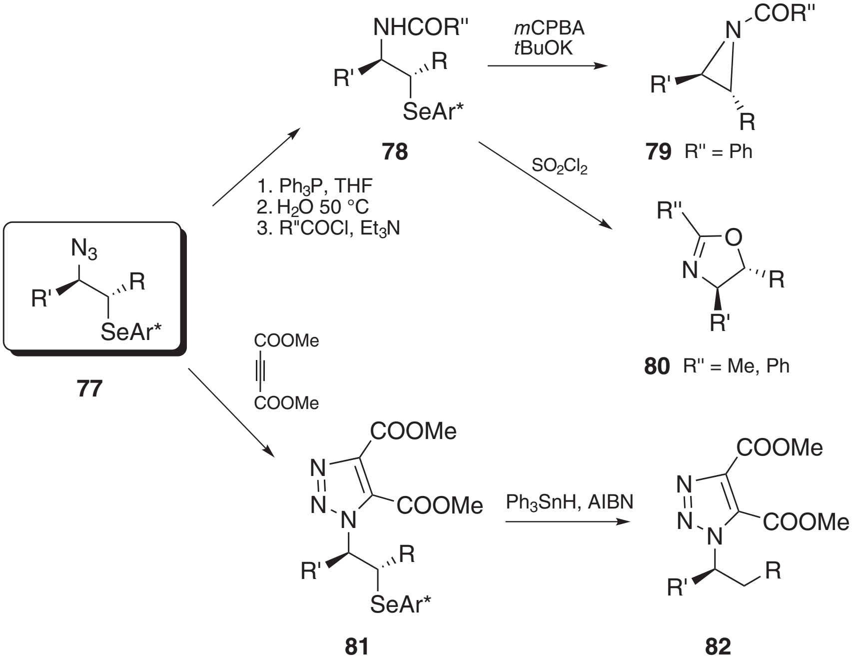
Asymmetric azidoselenenylation reactions were proposed using the selenenyl triflate prepared from the optically pure di-2-methoxy-6-([1*S*]-1-[methylthio]ethyl) phenyl diselenide (**24**) [76].

This reaction is stereo- and regiospecific and it is remarkable that it occurs with a high level of facial selectivity affording compounds **77a–e** in diasteromeric excess of up to 90% (Scheme 1.22).



Scheme 1.22 Asymmetric electrophilic azidoselenenylations.

The synthetic relevance of the enantiomerically enriched β-arylselenoazides has been shown using these compounds as substrates for a subsequent synthesis of a series of optically active nitrogen-containing compounds such as amides **78**, aziridines **79**, oxazolines **80**, and triazoles **81–82** (Scheme 1.23).



Scheme 1.23 Stereospecific manipulation of optically pure azides.

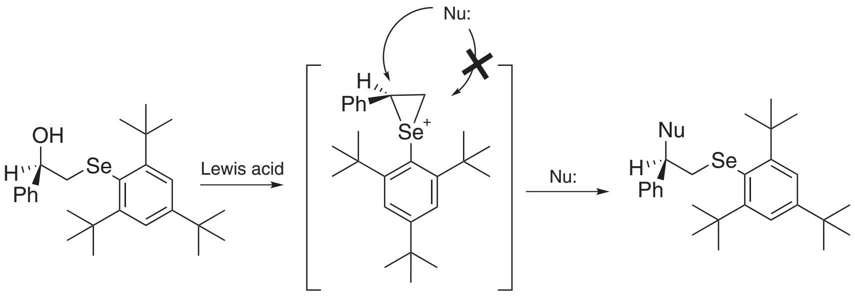
The azido group can be reduced to the corresponding amines by treatment with Ph_3P and H_2O at 50 °C and subsequently by treatment *in situ* with a suitable acid chloride into the corresponding amido selenides **78**. Subsequent oxidation with *m*CPBA afforded the corresponding selenoxide that underwent spontaneous deselenenylation with the formation of the optically active aziridine **79**.

In a different way, acetamido and benzamido selenides can be deselenenylated by treatment with SO_2Cl_2; in this case the reaction leads to the formation of oxazolines **80**.

Enantiomerically enriched azides can also be employed in 1,3-dipolar cycloadditions to allow the synthesis of triazol **81**. After the cycloaddition reaction, the deselenenylation can be effected with triphenyltinhydride and AIBN affording **82**.

1.2.3
Addition Reactions Involving Carbon-Centered Nucleophiles

Toshimitsu and coworkers reported in 1996 the first stereospecific carbon–carbon bond formation by the reaction of a chiral seleniranium ion **84** with carbon-centered nucleophiles such as alkenyl silyl ethers, trimethylsilyl cyanide, allyltrimethylsilane by the use of a 2,4,6-tri-*tert*-butylphenyl (TTBPSe) group bound to the selenium atom (Scheme 1.24) [77].

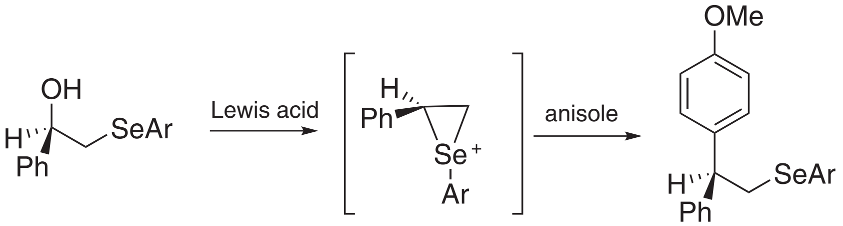


83c **84c** **85**

Scheme 1.24 Stereospecific carbon–carbon bond formation.

The steric protection of the selenium atom, deriving from the presence of the *tert*-butyl groups, has been proposed as necessary to prevent both the racemization of the stereogenic carbon atom and the attack of carbon-centered nucleophiles on the selenium atom.

Later, also aromatic compounds were used as nucleophiles and it was discovered that in this case the carbon–carbon bond forming reaction proceeds even without the steric protection of the selenium atom, and when a 2-pyridyl group is employed as the substituent, the stereospecificity of the reaction depends greatly on the reactivity of the aromatic compounds (Scheme 1.25) [78].



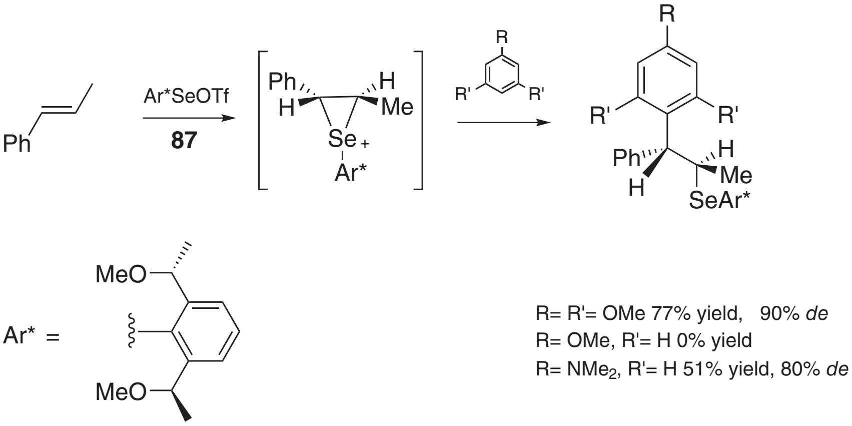
83a–c **84a–c** **86a–c**

a Ar = Ph 85% yield, 2% *ee*
b Ar = 2-pyridyl 89% yield, 95% *ee*
c Ar = 2,4,6-t-$Bu_3C_6H_2$ 85% yield, 98% *ee*

Scheme 1.25 Aromatic carbon-centered nucleophile.

For example, starting from optically active hydroxyselenide **83**, prepared by the nucleophilic ring-opening reaction of the corresponding enantiomerically pure epoxide, the seleniranium ion **84** can be selectively generated by treatment with $BF_3 \cdot OEt_2$. When the nucleophile is anisole, selenophilic attack is rarely observed and the attack of **84** produces the addition product **86**. The selectivity in the addition reaction increases when a bulky substituent is introduced in the *ortho*-position of the aryl group attached to the selenium atom **86c** or when an electron-deficient aryl group is directly bound to the selenium atom **86b**.

Asymmetric carboselenenylation reactions of olefins can be formed in good yields and high diastereoselectivity using the electrophilic selenenyl triflate **87** characterized by a C2-symmetric structure (Scheme 1.26) [79].



R= R'= OMe 77% yield, 90% *de*
R= OMe, R'= H 0% yield
R= NMe_2, R'= H 51% yield, 80% *de*

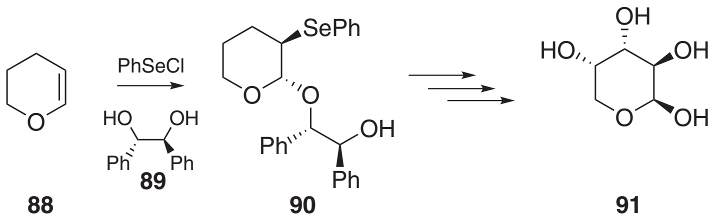
Scheme 1.26 Asymmetric carboselenenylation.

Not only heteroaromatic compounds but also electron-rich benzene derivatives such as *N,N*-dimethylaniline can be used as nucleophiles with selectivities ranging from 78% to 90% diasteromeric excess.

1.2.4
Addition Reaction Involving Chiral Nucleophiles or Chiral Substrates

In the previous section, we described several examples regarding the use of chiral organoselenium reagents to affect asymmetric synthesis. Here we are going to take in consideration that other strategies could be used to control the absolute configuration of the stereocenters generated by the addition process.

The selenenylation reaction of alkenes in the presence of enantiomerically pure nucleophiles has been employed in the preparation of cyclitols [80] as well as in the synthesis of carbohydrate derivatives (Scheme 1.27) [81].

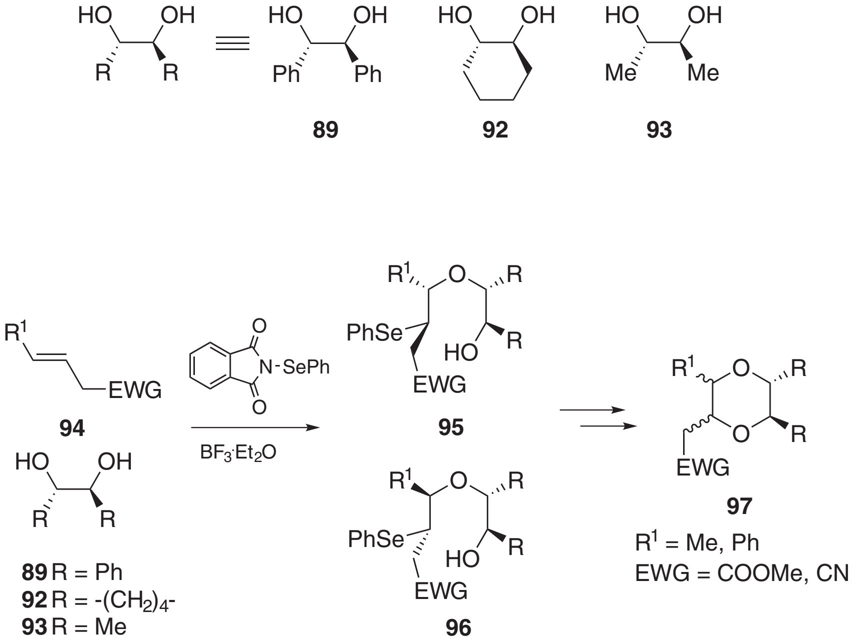


Scheme 1.27 Synthesis of L-Arabinose.

Oxyselenenylation reaction of 3,4-dihydro-2*H*-pyrane **88** with (*S*,*S*)-hydrobenzoin **89** affords a 1.2 : 1 mixture of (1*S*,2*R*)-oxyselenide **90** and its (1*R*,2*S*) diastereomer. After chromatographic separation, **90** was subjected to a series of stereoselective transformations affording enantiopure L-Arabinose **91**. In the same manner, D-Arabinose can be synthesized starting with the (1*R*,2*S*)-oxyselenide.

In another example, the regio- and stereospecific *anti*-addition of the enantiomerically pure diols **89**, **92**, **93** to a substituted alkene **94** promoted by *N*-(phenylseleno)phthalimide afforded enantiomerically pure diasteromeric selenoethers **95** and **96**.

These were separately transformed into the corresponding allylic ethers and finally into the four possible optically pure 1,4-dioxanes **97** by an intramolecular conjugated addition promoted by NaH (Scheme 1.28) [82].

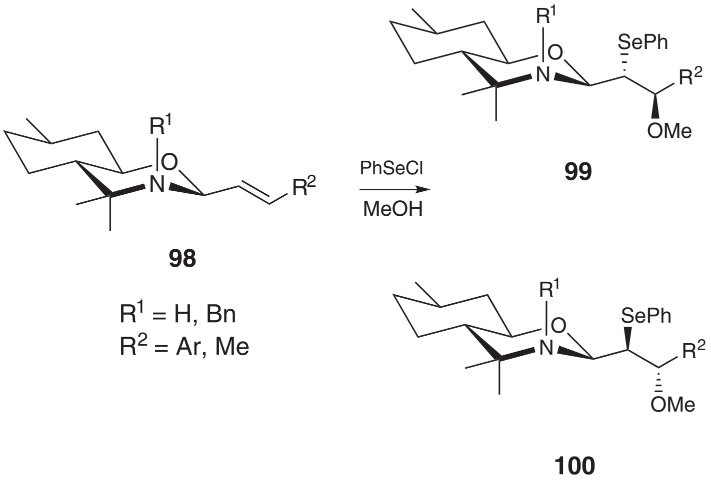


Scheme 1.28 Synthesis of the enantiomerically pure 1,4 dioxanes.

With *N*-Boc protected (*R*)-phenyl glycinol as nucleophile, enantiomerically pure 2,3,4-trisubstituted morpholines were prepared [83]. In this case, it is noteworthy that the addition reaction promoted by the electrophilic selenium reagent is completely chemiospecific and no traces of amidoselenenylation products were detected.

More recently, according to the "chiral pool approach" in asymmetric synthesis, mono- and bicyclic terpenes have been used as chiral substrates for azido- and hydroxyselenenylation reactions affording enantiomerically pure derivatives that represent interesting chiral-chelating auxiliaries for metal catalyzed conversions [61, 84].

The use of chiral auxiliaries covalently attached to the alkene has been also reported in the methoxyselenenylation of 2-vinylperhydro-1,3-benzoxazines **98**. The reaction afforded the α-methoxy selenides **99** and **100** with complete regio- and stereoselectivity and with a facial discrimination that, as well as the yields, are strongly dependent on the reaction conditions (Scheme 1.29) [85]. The stereoselection is strongly influenced by an intramolecular selenium–heteroatom coordination during the formation of the seleniranium intermediate.



Scheme 1.29 Methoxyselenenylation of 2-vinylperhydro-1,3-benzoxazines **98**.

A preferential chelation with oxygen rather than with nitrogen atom has been proven and it should be a consequence of the axial position of the substituent at the nitrogen atom, assuming that the selenium atom is coordinated by the axial rather than the equatorial lone pair of the oxygen.

1.3
Selenocyclizations

As already mentioned in Section 1.1 of this chapter, when an internal nucleophile is present in a suitable position of the alkene, the reaction with the electrophilic selenium species results in a selenocyclization. This class of transformations is particularly interesting due to the high importance of heterocyclic compounds both as final products and intermediates in synthetic strategies. Part of the success of these conversions resides in the ease of manipulation of the introduced selenium moiety which, as discussed earlier in this chapter, can be removed or substituted in different ways. Among others, the most useful approaches are radical deselenenylation or oxidation followed by β-elimination. As the other mechanisms involved in the addition of an electrophilic selenium reagent to a carbon–carbon double bond, selenocyclizations are also stereospecific *anti*-processes, since in this case also the reaction occurs through the initial formation of a seleniranium intermediate.

The course of the cyclization depends on many factors, that is, the structure of the selenium electrophile, its counterion, solvent, and the nature of external additives which can coordinate to the selenium atom [86]. Detailed mechanistic studies have been reported very recently. Denmark *et al.* [87] studied the selenocyclization of β,γ-unsaturated acids and derivatives promoted by PhSeCl or PhSeBr, showing that the process is actually more complex that usually believed, involving a kinetic formation of haloselenenylation intermediates which afterward convert into the thermodynamically favored cyclization products.

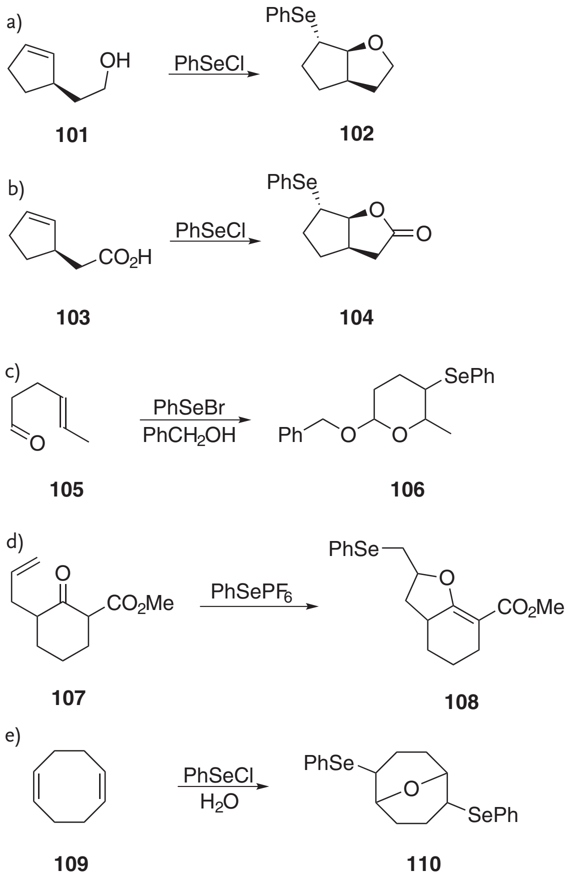
In most of the examples reported in the literature, selenocyclizations afford five- or six-membered ring products by means of *5-endo-trig*, *5-exo-trig*, or *6-endo-trig* cyclizations. However, the synthesis of larger membered heterocyclic compounds is also possible.

In most cases, the internal nucleophile attacking the seleniranium intermediate is an oxygen or a nitrogen nucleophile. Very important, even if less represented in the literature, are selenocyclizations with an internal carbon nucleophile. In these cases, the final product is a carbocycle.

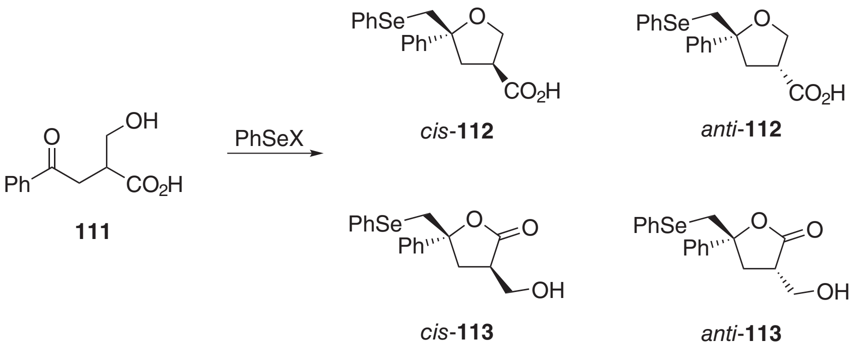
An overview of all these kinds of selenocyclizations will be reported in the following sections, focusing on the most recent examples.

1.3.1
Oxygen Nucleophiles

Selenocyclizations of alkenes bearing an internal oxygen nucleophile are the most thoroughly studied selenium-promoted cyclizations, due to the importance of oxygen-containing heterocycles. The most important oxygen nucleophiles involved in these processes are carboxylic acids and alcohols. The reactions originate lactones or cyclic ethers and can be named selenolactonizations and selenoetherifications, respectively. General examples are reported in Scheme 1.30a [88] and b [89]. The factors governing the outcome of these reactions have been recently investigated by synthesizing compound **111**, bearing both an hydroxy-group and a carboxylic acid in suitable positions to undergo these processes, and subjecting it to selenocyclization conditions, with different reactants and in the presence of different additives (Scheme 1.31) [90].



Scheme 1.30 Selenolactonizations and selenoetherifications.

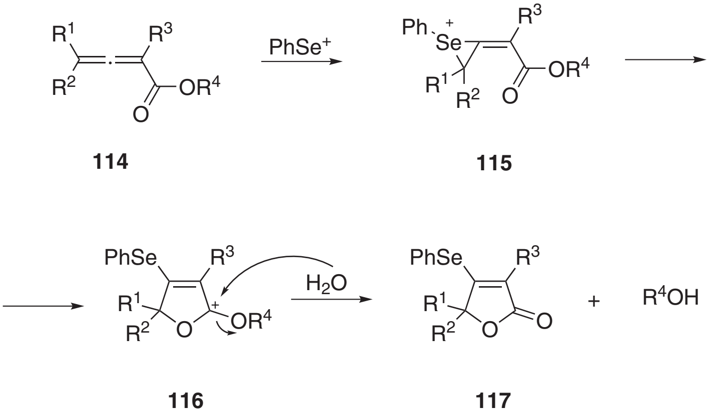


Scheme 1.31 Selenolactonizations versus selenoetherifications.

In situ generated hydroxyl groups can also participate in selenocyclizations. This strategy has been successfully applied in the synthesis of polycyclic compounds. An example in which the addition of an alcohol to an aldehyde generates *in situ* the hydroxyl group undergoing a *6-endo-trig* cyclization is shown in Scheme 1.30c [91]. Another possibility for the *in situ* generation of the nucleophile comes from the tautomerization of β-dicarbonyl systems. The resulting vinylic oxygen can participate in selenocyclization processes, thus offering a valid strategy for the syntesis of cyclic vinyl ethers (see Scheme 1.30d for an example) [92]. Dienes can undergo sequential hydroxyselenenylation–selenoetherifications if the hydroxyl group generated from the addition oh PhSeOH to one of the olefins can attack the seleniranium formed on the other double bond. In Scheme 1.30e, the conversion of 1,5-cyclooctadiene **109** into a functionalized cyclic ether (**110**) is shown as an example [93].

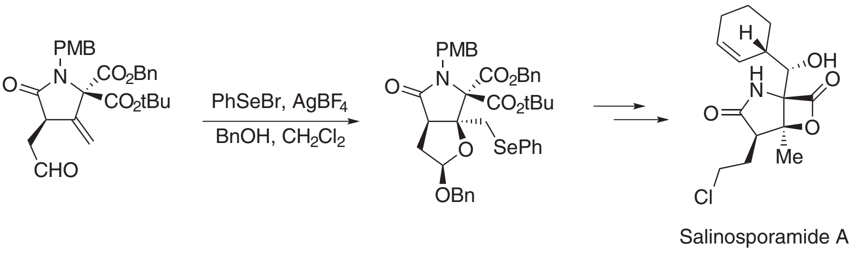
Alkenyl nitrones can also undergo selenocyclizations. These processes generate reactive cyclic iminium salts which, depending on the substitution pattern, can undergo reduction by $NaBH_4$ and/or methanolysis. In both the cases, the product is a 1,2-oxazine [94].

2,3-Allenoates have been reported to undergo selenocyclizations in the presence of PhSeCl and water (Scheme 1.32) [95]. The reaction is proposed to occur through the formation of a seleniranium ion on the more electrophilic double bond (**115**) and the subsequent attack of the carbonylic oxygen. The formed carbocation (**116**) reacts then with a water molecule to afford the final product **117**, after an intramolecular proton transfer and the elimination of a molecule of alcohol.



Scheme 1.32 Seleocyclizations of allenes.

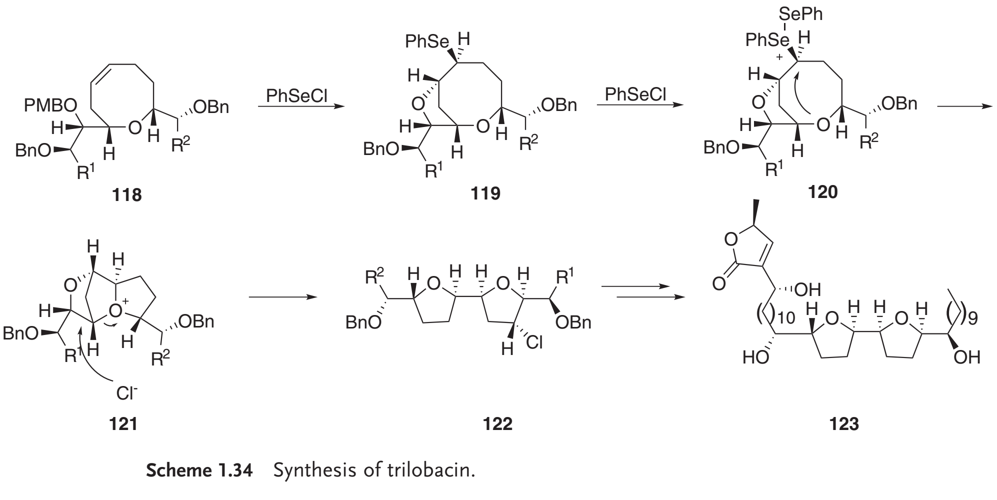
Selenocyclizations have also been widely used in total syntheses. In a recent report by Danishefsky and coworkers, a selenocyclization with an *in situ* formed nucleophilic hydroxyl group (cf. Scheme 1.30c) is used in a key step of the synthesis of salinosporamide A (Scheme 1.33) [96].



Scheme 1.33 Synthesis of salinosporamide A.

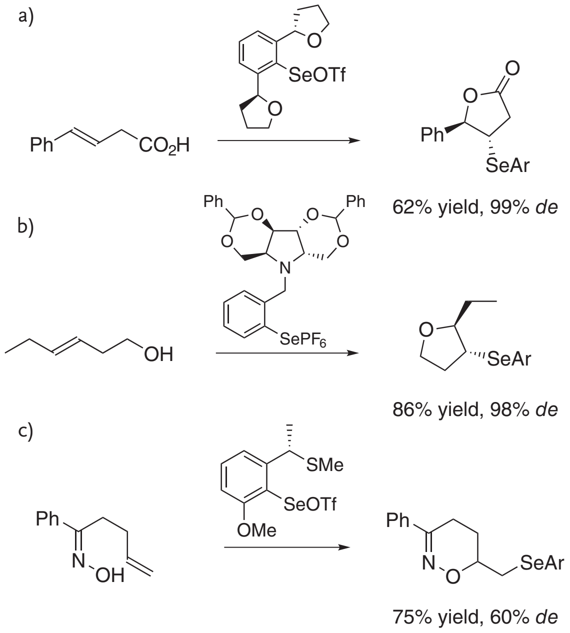
A selenocyclization is also used to synthesize the *erythro*-bis(2,2′)-tetrahydrofuran core of trilobacin [97]. In the key step of this total synthesis, PhSeCl promotes a nucleophilic transannular attack by an etheric oxygen to form the oxonium intermediate **121**. A subsequent nucleophilic attack of Cl^- on C22 originates intermediate **122**, which in a few steps is converted to target product trilobacin (**123**) (Scheme 1.34).

Asymmetric selenocyclization of unsaturated alcohols and carboxylic acids has also been widely explored. Since selenocyclizations are stereospecific processes and they usually occur with a good regioselectivity and facial selectivity (when a chiral nonracemic electrophilic selenium reagent is employed), they represent an interesting way to access enantioenriched heterocycles.



Scheme 1.34 Synthesis of trilobacin.

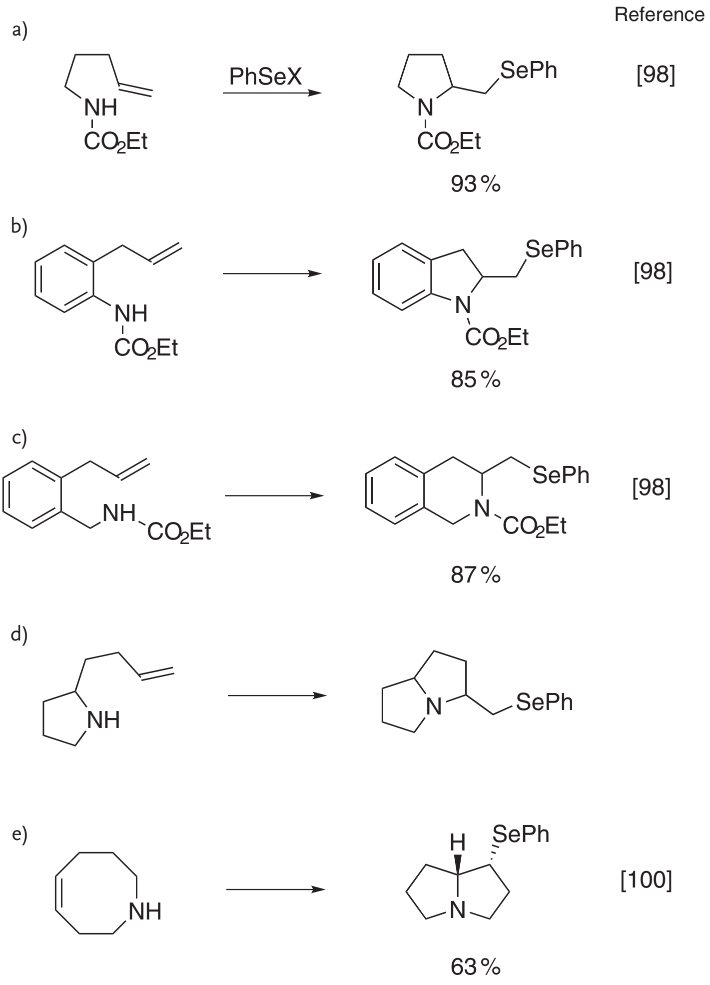
Almost all chiral selenium reagents synthetized have been tested in selenocyclization, together with selenofunctionalizations. Selected examples are reported in Scheme 1.35 [98]. The reaction is of general applicability and usually proceeds with good stereosectivities. The stereochemical outcome of the reaction is similar to that described for intermolecular oxyselenenylation processes.



Scheme 1.35 Asymmetric selenocyclofunctionalizations [99].

1.3.2
Nitrogen Nucleophiles

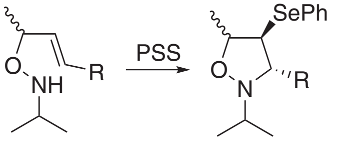
Selenocyclization with nitrogen nucleophiles have received great attention due to their high potential in the synthesis of nitrogen-containing heterocycles and thus in the total synthesis of alkaloids. The first examples in this area were reported by Clive and coworkers [100], who showed that primary amines are poorly reactive in selenocyclization conditions, while amines functionalized with an electron withdrawing group smoothly cyclize to afford the desired nitrogen-containing heterocycle [101]. Most of the early literature reports use unsaturated carbamates as substrates for selenocyclizations. Some selected examples are shown in Scheme 1.36.



Scheme 1.36 Cyclofunctionalization by nitrogen nucleophilic attack.

Secondary substituted amines are more reactive than primary amines and afford the expected products, as shown in Scheme 1.36d and e [102]. In both examples, substituted pyrrolizidines are obtained, but the method is general in scope.

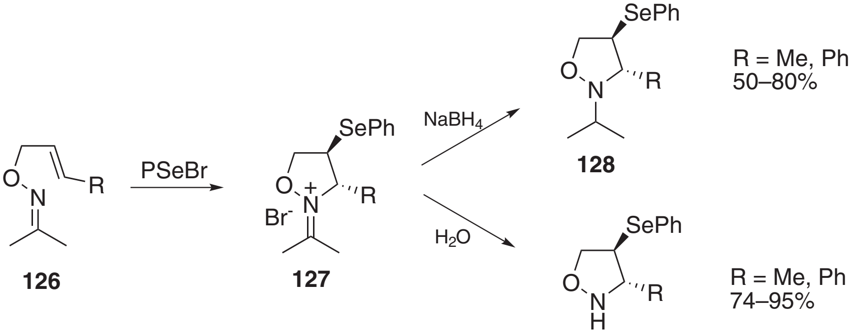
O-allyl hydroxylamines **124** have also been shown to react in the presence of PSS to give substituted isoxazolines **125** (Scheme 1.37). Two diasteroisomers of **125** were obtained [103].



124 **125** 67–79%

Scheme 1.37 Selenocyclization of *O*-allyl hydroxylamines.

Similarly to the previous example, *O*-allyl oximes **126** smoothly react in generating an intermediate iminium salt **127**, which can be easily converted into the final products either by reduction with $NaBH_4$ or by hydrolysis (Scheme 1.38) [104]. In the first case, *N*-alkyl oxazolines **128** are accessed, as in the example reported in Scheme 1.37; in the second one the hydrolysis afforded oxazolines **129** in very good yields.

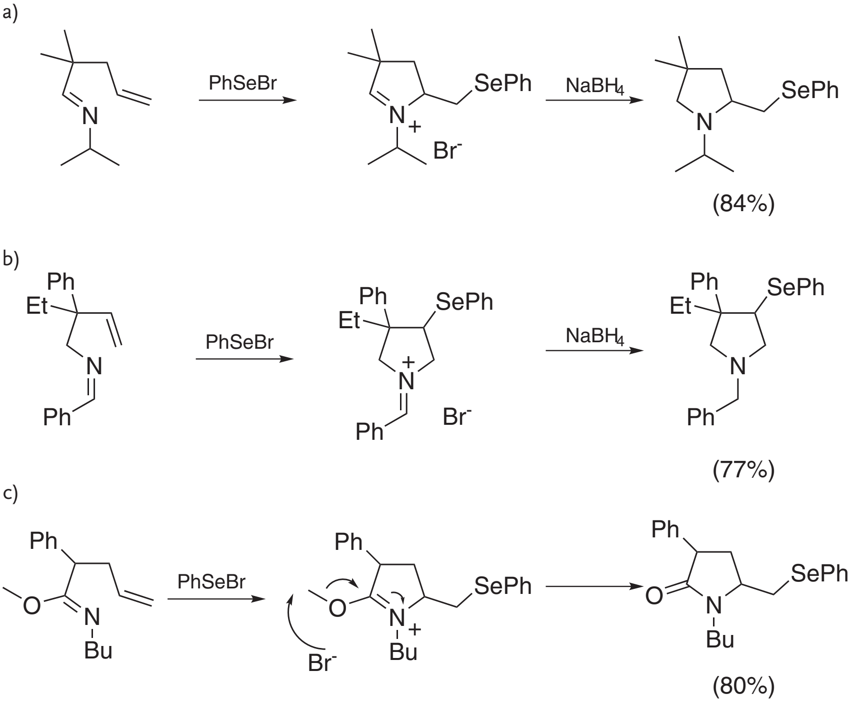


126 **127** **128** **129**

Scheme 1.38 Selenocyclization of *O*-allyl oximes via iminium salts.

The selenenyl triflate generated from the reaction of di-2-([1*S*]-1-[methylthio]-ethyl) phenyl diselenide (**23**) with silver triflate with various substituted *O*-allyl oximes afforded optically active isoxazolidines in high yields and with good diasteroselectivities up to 93 : 7. These heterocyclic compounds can be easily converted into the corresponding optically enriched 1,3-amino alcohols by N–O bond cleavage effected by treatment with zinc in aqueous acetic acid [105].

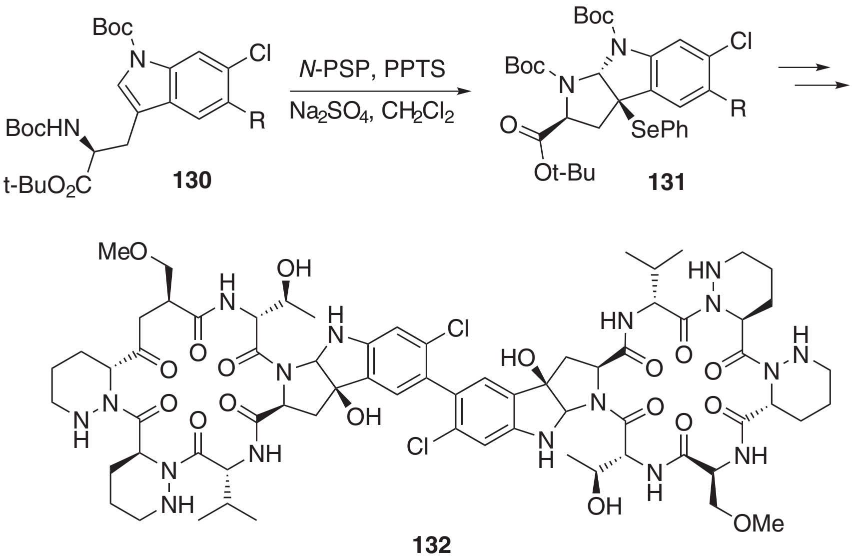
The imino nitrogen can also react with seleniranium intermediates to afford nitrogen-containing heterocycles. Some interesting examples are shown in Scheme 1.39.



Scheme 1.39 Selenocyclization of imines.

The imine can be either internal (Scheme 1.39a) or external (Scheme 1.39b) to the formed heterocycle [106]. In all the cases, an iminium intermediate is formed, which can be reduced to an amine (a pyrrolidine in the presented examples) by treatment with $NaBH_4$. In Scheme 1.39c, the conversion of an imidate into a γ-lactam is shown. In this case, the PhSeBr cannot be substituted by other electrophilic selenium reagents since the bromide anion is necessary for the conversion of the iminium salt intermediate to the final product, through a substitution occurring on the methyl group and having the product as the leaving group [107].

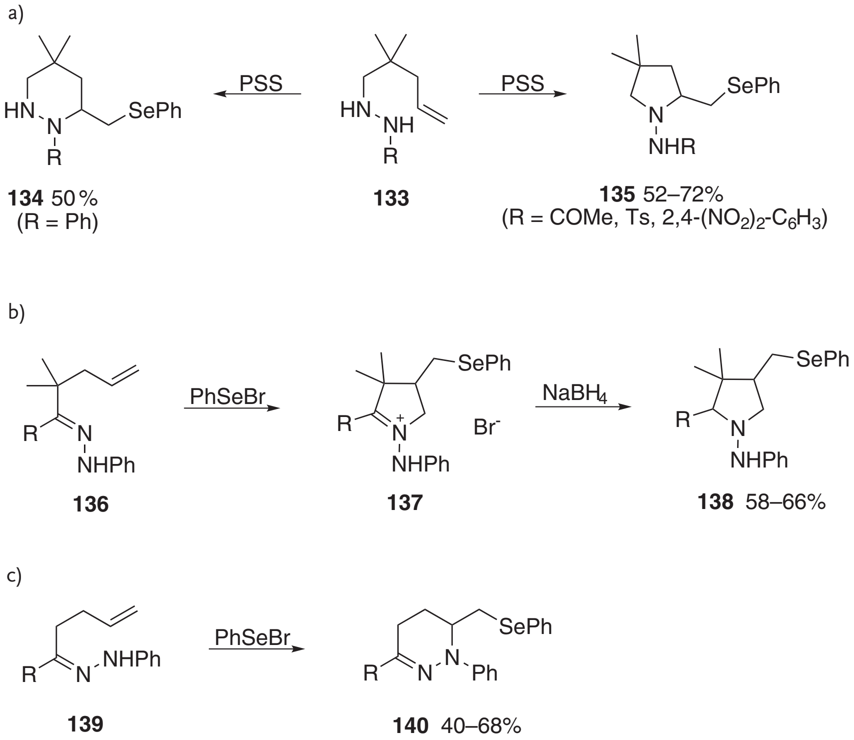
An interesting recent application of electrophilic selenium to promote a cyclization with an internal nitrogen nucleophile (**130**→**131**) has been reported by Yao and coworkers in the total synthesis of chloptosin **132**, a dimeric cyclopeptide which showed potent apoptosis-inducing properties (Scheme 1.40) [108].



Scheme 1.40 Synthesis of chloptosin **132**.

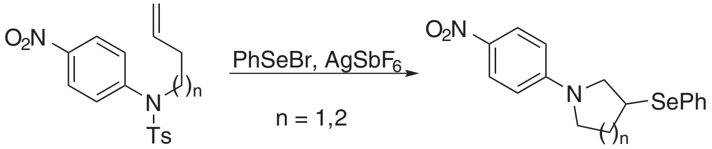
In some cases, more than a nucleophilic nitrogen is present in the substrate and a chemoselectivity issue arises. When the alkenyl hydrazine **133** (Scheme 1.41a) is reacted with PSS, in principle both the nitrogen atoms can act as nucleophiles. Tiecco and coworkers demonstrated that the reaction outcome depends on the substituent R on the nitrogen. When R = Ph, a *6-exo-trig* cyclization occurs affording pyridazine **134**. On the contrary, when an electron-withdrawing group is bound to the nitrogen, this is no more nucleophilic enough to react with the seleniranium intermediate, and the reaction occurs with the other nitrogen affording the pyrrolidineamine **135** as the product [109].

Some other interesting examples are reported in Scheme 1.41b and c. In this case, both an imino and amine nitrogen are present in the substrate, an alkenyl phenylhydrazone. Under the reaction conditions, no isomerization of the hydrazone is observed and the reaction outcome only depends on the geometry of the hydrazone in the starting material. Thus substrate **136** reacts with the imino nitrogen affording the intermediate **137** which can be reduced to pyrrolidineamine **138** (Scheme 1.41b). The other geometric isomer (**139**) reacts with the amino nitrogen to give tetrahydropyridazine **140** (Scheme 1.41c) [110].



Scheme 1.41 Chemoselectivity in the cyclofunctionalization of hydrazine derivatives.

Recently RajanBabu and coworkers reported that *N*-aryl-*N*-tosylamides undergo a detosylative cyclization promoted by electrophilic selenium reagent such as phenylselenenyl bromide to afford 5- or 6-membered nitrogen-containing heterocycles (Scheme 1.42) [111].



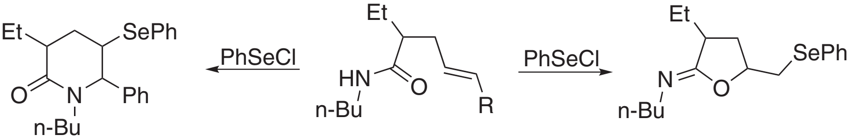
Scheme 1.42 Detosylative cyclization.

1.3.3
Competition between Oxygen and Nitrogen Nucleophiles

A more general issue about chemoselectivity arises when different nucleophiles, generally nitrogen and oxygen, are present in the same substrate and in principle both can react with the seleniranium intermediate to give different cyclization products. This problem has been extensively studied by different research groups.

Generally the observed outcome of the reaction only depends on the structure of the substrate, but a few cases have been reported in which a change in the experimental conditions is reflected in chemoselectivity of the process.

The first example of a competition between nitrogen and oxygen nucleophiles in selenocyclization was reported by Toshimitsu, who investigated this process in unsaturated amides (Scheme 1.43) [112]. When compound **141** (R = H) is allowed to react with an electrophilic selenium reagent, only the formation of product **142**, deriving from an oxygen attack on the seleniranium intermediate, was observed. The product is converted into a lactone during the work-up. On the other hand, compound **143** (R = Ph) affords the product of a *6-endo-trig* cyclization **144**, with the nitrogen acting as a nucleophile. The reason for this switching both in the regiochemistry and in the nucleophile is not clear. It should be considered, however, that amides react more often with oxygen in selenocyclizations. The reaction with nitrogen as a nucleophile can be promoted by the introduction of electron-withdrawing groups on the nitrogen and by the use of a base.



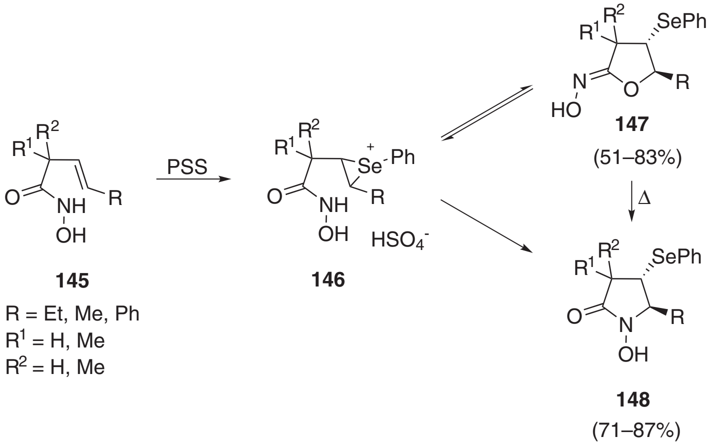
144 (73%)

141 R = H
143 R = Ph

142 (87%)

Scheme 1.43 Competition between nitrogen and oxygen nucleophiles in selenocyclization.

An illustrative example in which a change in reaction conditions reflects in the formation of different products is shown in Scheme 1.44. From the hydroxy carbamate **145** at low temperatures, the formation of product **146**, deriving from an oxygen attack on seleniranium **146**, is observed. At higher temperatures, the exclusive formation of the product derived from a nitrogen attack (**148**) is observed. The isolated product **147** can be completely converted to product **148** upon heating. This clearly shows that in these cyclizations different products can be originated by kinetic or thermodynamic control of the reaction [113].

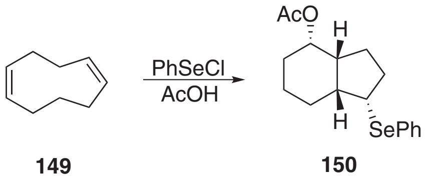


Scheme 1.44 Selenocyclization of hydroxy carbamic acids.

1.3.4
Carbon Nucleophiles

Carbocyclization occurs when a nucleophilic carbon, usually an olefin, a carbon in the α-position to a carbonyl group or an aromatic group attacks the seleniranium intermediate.

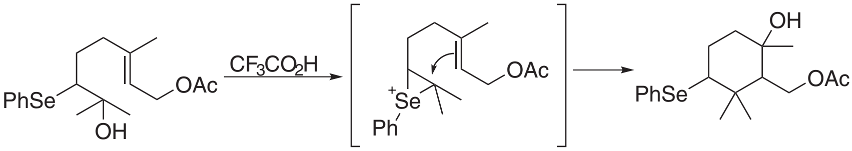
The first example has been reported by Clive and coworkers (Scheme 1.45) [114]. Diene **149** reacts in the presence of PhSeCl and acetic acid to afford bicyclic compound **150**. The initial attack of the olefin on the seleniranium intermediate leads to the formation of the carbocycle and a carbocation which can then be captured by a molecule of acetic acid.



Scheme 1.45 Carbocyclization of diene **149**.

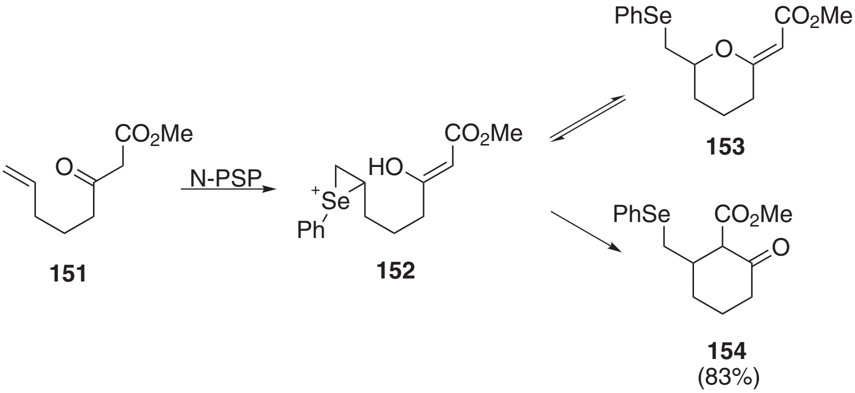
Toshimitsu and coworkers showed that diphenyl diselenide in the presence of molecular iodine in acetonitrile is effective for the carbocyclization of dienes. In this case, an acetamido group is attached to the product due to the solvolysis of the carbocationic intermediate [115].

The seleniranium intermediate can also be generated by reacting a β-hydroxyselenide with a strong acid (usually trifluoroacetic acid). This strategy is exemplified by the reaction reported in Scheme 1.46 [116].



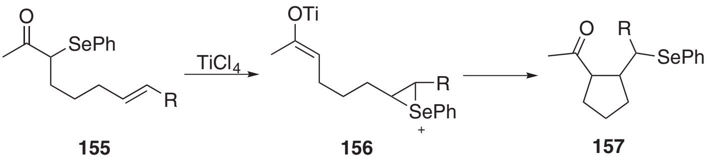
Scheme 1.46 Carbocyclization of hydroxyselenide.

Olefinic enolic bonds can also act as nucleophiles in selenium-promoted carbocyclizations. Ley and coworkers reported that β-dicarbonyl compound **151** reacts with *N*-PSP in the presence of a Lewis acid (ZnI_2, $AlCl_3$, or $SnCl_4$) to afford intermediate **152** (Scheme 1.47). Enolic oxygen is a better nucleophile and the initial formation of the selenoetherification product **153** is observed. Longer reaction times and the presence of strong acids lead to the formation of the thermodynamic carbocyclization product **154** [117].



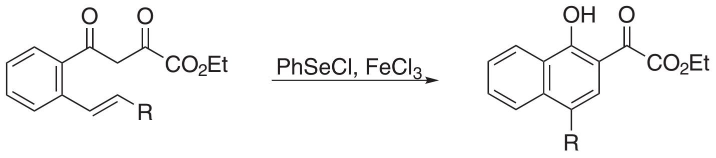
Scheme 1.47 Carbocyclization of β-dicarbonyl compound **151**.

α-Phenylseleno alkenyl ketones **155** can react with $TiCl_4$ in a carbocyclization process (Scheme 1.48). The reaction occurs through the formation of a titanium enolate **156**, while the phenylseleno group attacks the olefin [118].



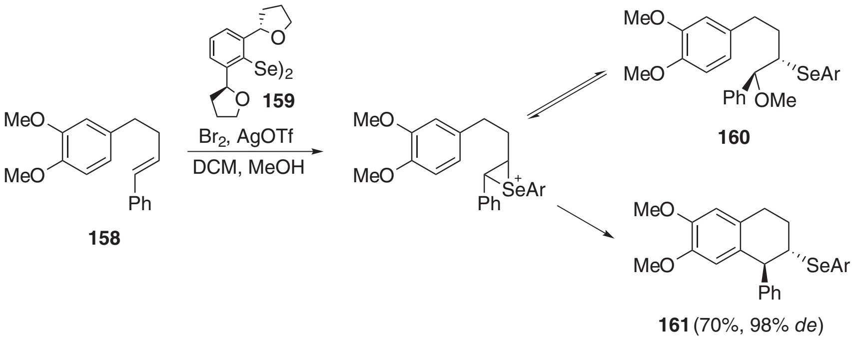
Scheme 1.48 Carbocyclization of enolates.

Wirth and coworkers reported that β-keto ester substituted stilbene derivatives undergo a cyclization and a subsequent 1,2-rearrangement of an aryl group when reacted with PhSeCl in the presence of Lewis acid (Scheme 1.49) [119].



Scheme 1.49 Carbocyclization of a β-keto ester.

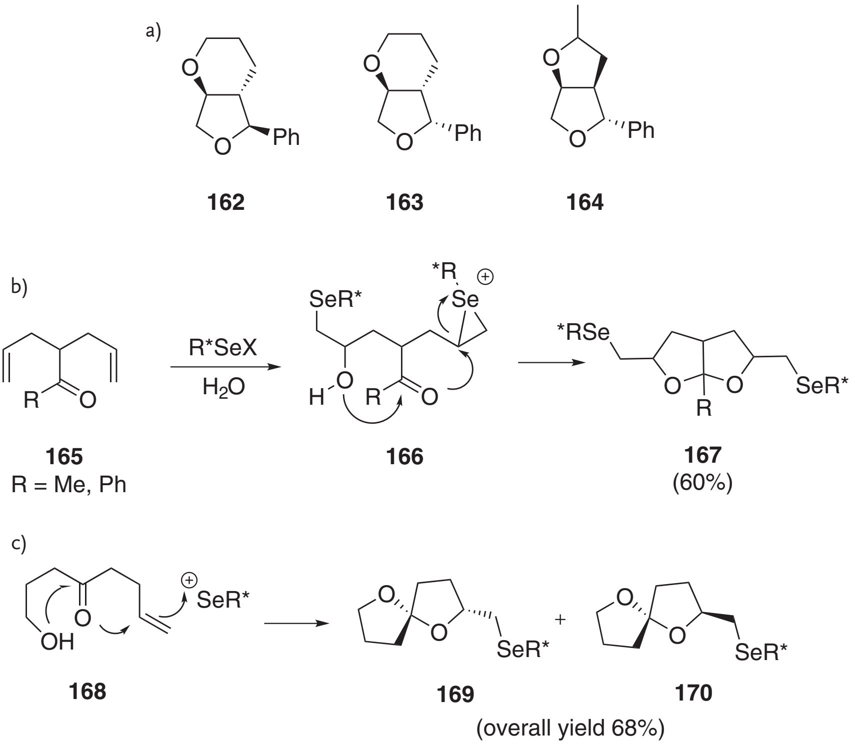
Aromatic carbons can also act as nucleophiles in electrophilic selenium promoted carbocyclizations. Deziel and coworkers reported that compound **158** reacts with a chiral arylselenenyl triflate derived from diselenide **159** in dichloromethane and methanol to afford an equimolar mixture of the methoxyselenenylation product **160** and carbocyclization product **161**. The former can be converted to the latter by treatment with trifluoroacetic acid. The carbocyclization product has been obtained in 70% yield and with 98% diastereoisomeric excess (Scheme 1.50) [120].



Scheme 1.50 Asymmetric carbocyclization.

1.3.5
Double Cyclization Reactions

More complex heterocyclic compounds can be prepared using multistep sequences as well as a direct double cyclization reaction. In the first example starting from the commercially available (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde, by means of two consecutive selenium-promoted cyclizations, the enantiomerically pure compounds **162**, **163**, and **164** can be obtained (Scheme 1.51a) [121].



Scheme 1.51 Synthesis of bicyclic compounds.

More interestingly, the synthesis of related perhydrofuro[2,3-*b*]furans **167** has been achieved by the double cyclization of bisalkenylketones **165** promoted by camphoryl selenenyl sulfate in the presence of water. The mechanism consists of a selenohydroxylation leading to the intermediate **166** that subsequently underwent a double cyclization affording the final bicyclic compound **167** (Scheme 1.51b) [122].

Using a similar procedure and starting from 1-hydroxyoct-7-en-4-one **168**, enantiomerically pure 1,6-dioxaspiro[4,4]nonanes **169** and **170** can be rapidly prepared (Scheme 1.51c) [123].

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