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Recent advances in selenocyclofunctionalization reactions

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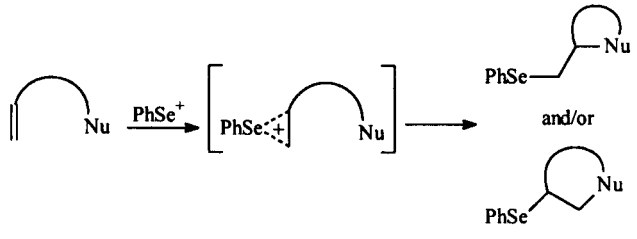
Contents

1. Introduction

Phenylselenofunctionalization reactions, i.e. the phenylselenium induced cyclization of alkenes bearing an internal nucleophile is a well known chemical procedure (Scheme 1).



Scheme 1.

Since the first example described, the selenolactonization of 4-pentenoic acids,[1] organo-selenium induced cyclization reactions have been widely explored in organic synthesis over the last decade as, depending on the nature of the internal nucleophile, a variety of five- and six-membered ring heterocycles can be prepared.

Cyclization of unsaturated alcohols and carboxylic acids leading to cyclic ethers and lactones, as well as several cyclization reactions leading to nitrogen heterocycles, are well documented in the literature as convenient pathways in the synthesis of natural products and related compounds.

It must be emphasized that different regioisomers can be produced in some cases by simply choosing conditions favorable to kinetic or thermodynamic control. In many respects, selenocyclofunctionalization can be comparable to the corresponding halo- or thiocyclization. However the selenium protocol has the advantage that the introduction of

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the heteroatom, the manipulation of the obtained product and the removal of the function are facilitated by simple and milder condition required, such as oxidation-*syn*-selenoxide elimination, hydrogenolytic removal, or nucleophilic substitution of the corresponding selenones.

The growing interest in selenocyclofunctionalization was demonstrated in some excellent reviews, focusing on this specific subject,[2] or outlining in a more general context of heterocyclofunctionalizations promoted by other electrophiles.[3]

This review intends to report recent progress in the area, specifically covering the literature from the 1986 to the present.

It must be remarked that most of the references cited are not restricted to the selenocyclization reaction, the scope of the present report, but are concerned also with the more general oxyselenenylation processes.

The authors apologize for the involuntary omission of any contributions.

2. New selenocyclofunctionalization reagents

The most common reagents employed to effect selenocyclofunctionalization reactions were for almost two decades the commercially available phenylselenenyl chloride and bromide. However these reagents have some drawbacks, since they are responsible for undesired reactions due to the presence of the halide counter-ions which, as strong nucleophiles, can compete with the internal nucleophile in the attack to the intermediate episelenonium ion.

Several phenylselenenylating agents free of the nucleophilic counter-ion, such as *N*-phenylselenophthalimide (NPSP),[2a,4] *N*-phenylselenosuccinimide (NPSS),[2a] phenylselenenyl hexafluoroantimoniate ($PhSeSbBF_6$),[5] phenylselenenyl hexafluorophosphate ($PhSePF_6$),[5] have been introduced later as useful substitutes to the phenylselenenyl halides.

Several other reagents have found wide use more recently: phenylselenenyl *p*-toluenesulfonate[6] and -triflate,[7] prepared by reacting PhSeCl with silver *p*-toluenesulfonate and -triflate, respectively, phenylselenenyl trifluoroacetate and triflate obtained by treatment of phenylseleneninic anhydride and diphenyl diselenide with trifluoroacetic or triflic anhydride[8] (Scheme 2).

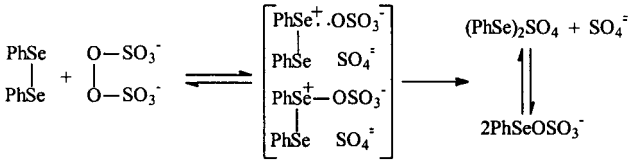
$$(PhSeO)_2O + 2PhSeSePh + 3Y_2O \longrightarrow 6PhSeOY$$
$$(Y = F_3CCO, F_3CSO_2)$$

Scheme 2.

(2,4,6-Triisopropylphenyl)selenenyl bromide (TIPPSeBr) is prepared in situ by brominolysis of the corresponding diselenide.[9]

A highly electrophilic selenium-copper complex, PhSeCN·$Cu(OTf)_2$, is generated reacting phenylselenenyl cyanide with copper (II) triflate in toluene or dichloromethane.[10]

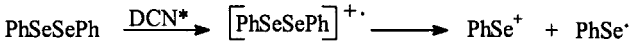
Several methods involve the oxidative cleavage of diphenyl diselenide with different oxidation reagents. A versatile and widely employed reagent is phenylselenenyl sulfate (PSS), easily produced through a single electron transfer (SET) process by oxidation of diphenyl diselenide with ammonium persulfate[11] (Scheme 3).



Scheme 3.

Different oxidating reagents, such as m-nitrobenzene sulfonyl peroxide,[12] ammonium nitrate (NH_4NO_3),[13] ammonium cerium (IV) nitrate $[(NH_4)_2Ce(NO_3)_6]$[14] and iodosobenzene diacetate $[PhI(OAc)_2]$[15] have been successfully employed, giving phenylselenenyl *m*-nitrobenzene sulfonate, -nitrate and -acetate, respectively.

The electrophilic $PhSe^+$ species has been produced by the photo-oxidative (SET) cleavage of diphenyl diselenide using DCN^* as electron acceptor[16] (Scheme 4).



Scheme 4.

3. Cyclofunctionalization of unsaturated alcohols

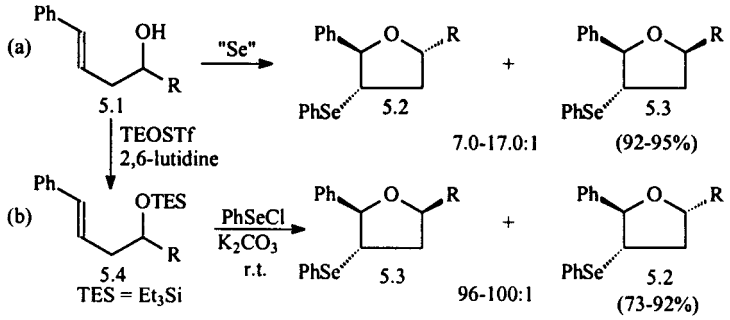
Cyclofunctionalization of unsaturated alcohols (phenylselenoetherification) is a very popular reaction providing easy acess to furans, tetrahydrofurans-, dihydrofurans and tetrahydropyrans.

It must be pointed out that although the electrophilic 5-*exo*-trig cyclization of substituted alkenols is one of the most versatile and succesful routes to substituted tetrahydrofurans[17,3a,b] and that the 5-*endo*-trig cyclization was traditionally reported as being unfavorable in accordance with the Baldwin rule,[18] this last process was later shown not to be an exception and is actually widely employed in selenoetherification reactions.

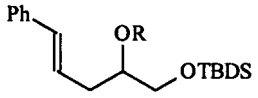
3.1. 5-*endo*-Trig

trans- and *cis*-2,5-Disubstituted tetrahydrofurans (**5.2**) and (**5.3**) are synthesized starting from *trans*-4-phenyl-3-buten-1-ol derivatives[19] (**5.1**) and from triethylsilylethers of the same substrates (**5.4**),[20] respectively, employing different selenenylating systems under different conditions. The phenylsubstituted substrates were chosen to facilitate the 5-*endo*-trig cyclization (Scheme 5).

By protocol (a), PhSeCl in DME in the presence of $ZnBr_2$ at $-55°C$ furnishes better *trans*-stereoselectivity (Rα:Rβ)



Scheme 5. R=$CH_2OTBDPS$, CH_2OCOBu-t, CH_2OCOPh_3, Me, Et, $CHME_2$.

and yields than other protocols: PhSeCl in DME in the presence of K_2CO_3 and PhSeOTf in DME at the same temperature. Less satisfactory results in the synthesis of the *cis*- stereoisomers were obtained by treatment of the substrate  (R=CH_2OMe, CHMeOEt, CMe_2COMe, TMS, TBS, Bn) with PhSeCl in CH_2Cl_2 or in different solvents in the presence of K_2CO_3 at rt.

The cyclization of the corresponding *trans*-4-furanyl-3-buten-1-ol derivatives occurs in good yields but with relatively poor stereoselectivity,[21] lower that the corresponding iodoetherifications procedures.

The phenylselenenyl sulfate promoted cyclization of α-vinyl β-dicarbonyl compounds (**6.1**), as well as the *trans*- stereospecific ring closure of 3-alkenols (**6.3**) and (**6.5**), with sequential oxidation- selenoxide elimination, give rise to furans (**6.2**) and 2,5-dihydrofurans (**6.4**) and (**6.6**), respectively[11b] (Scheme 6).

The in situ generated reagent (2,4,6-triisopropylphenyl)-selenenyl bromide provided a general solution to the stereoselectivity of the 5-*endo*-trig tetrahydrofuran forming process.[9] An enhanced diastereoselectivity was observed in many cases, in comparison with previously described results (Scheme 7).

The obtained selenides can be easily deselenenylated using *n*-Bu_3SnH (Scheme 8).

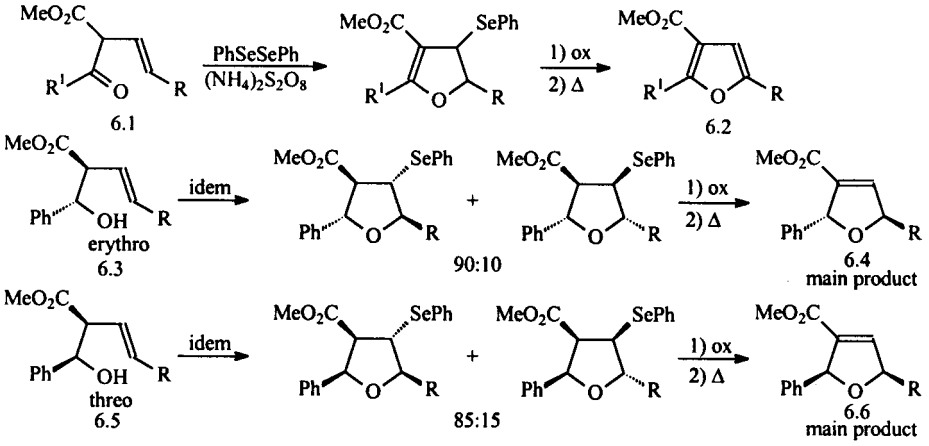
The enhanced stereo-selectivity achieved with the TIPP-SeBr reagent can be certainly attributable to the increased steric demands in the approach of the electrophile to the π-bond, preferentially occuring away from de allylic substituent.

Similar stereoselectivity outcome has been observed in the phenylselenenyl sulfate promoted cyclization of 2-carbomethoxy-3-alkenols (**9.1**) into tetrahydrofuran derivatives (**9.2**) and (**9.3**).[22] As shown in Scheme 9 compounds (**9.2**), in which the PhSe group is positioned in *anti* with respect to the allylic carbomethoxy group, are formed preferentially.

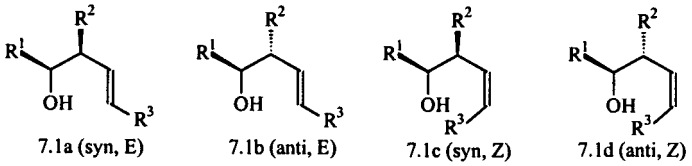
If the same reaction is performed using a catalytic amount of diphenyl diselenide and an excess of ammonium persulfate, the initially formed tetrahydrofurans undergo deselenenylation to give the 2,5-dihydrofurans (**10.1**)[22] (Scheme 10).

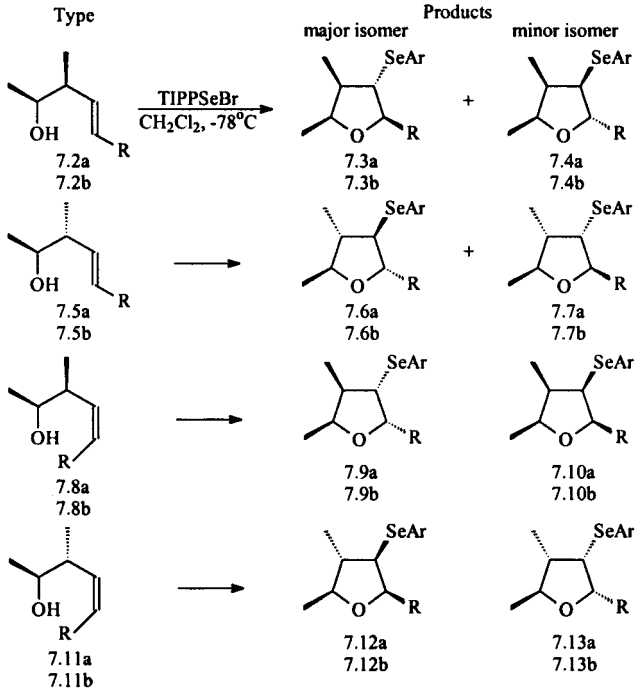
The entire process is highly stereoselective, the *erythro* alkenols (**9.1c**,**e**,**f**) giving the *trans*-2,5-dihydrofurans (**10.1c**,**e**,**f**) and the *threo* alkenols (**9.1g**,**i**,**j**) giving the *cis* derivatives (**10.1g**,**i**,**j**).

The 5-*endo*-trig selenoetherification of 2-silyl-3-alkenols



Scheme 6.

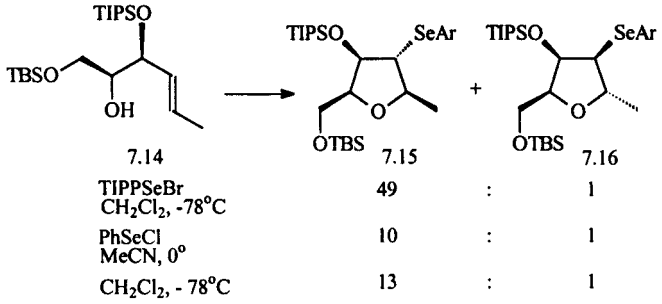




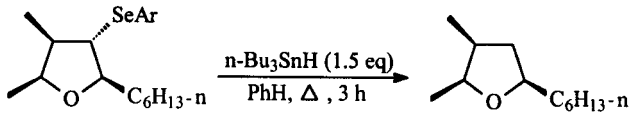
a) R = n-C_6H_{13} ; b) R = $(CH_2)_2CH(CH_3)_2$

Type	Alcohol	Isomeric products		Yield	Ratio (major:minor)	
		major	minor	%		ref. 27(a)
7.1[a]	7.2[a]	7.3a	7.4a	86	49:1	1.2:1
(*syn*, E)	7.2b	7.3b	7.4b	82	109:1	
7.1b	7.5[a]	7.6a	7.7a	85	>49:1	4:1
(*anti*, E)	7.5b	7.6b	7.7b	85	52:1	
7.1c	7.8[a]	7.9a	7.10a	82	24:1	32:1
(*syn*, Z)	7.8b	7.9b	7.10b	75	5:1	
7.1d	7.11[a]	7.12a	7.13a	86	19:1	1:0
(*anti*, Z)	7.11b	7.12b	7.13b	87	25:1	

(a) vide infra

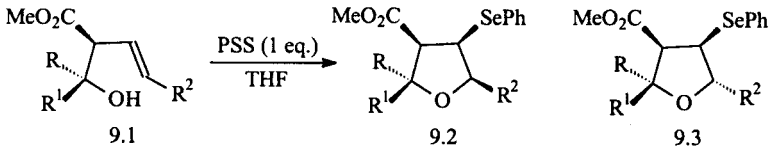


Scheme 7.



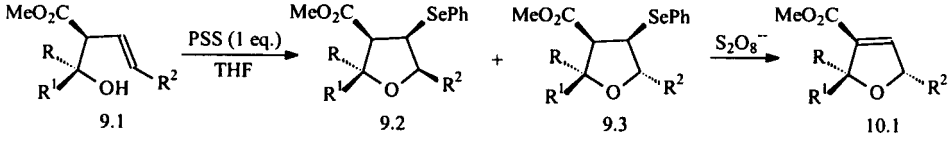
Scheme 8.

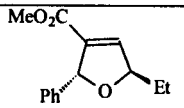
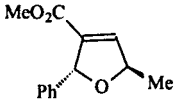
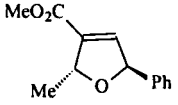
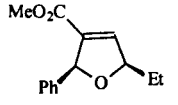
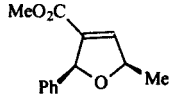
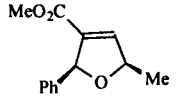
(**11.1**) gives tri- or tetra-substituted 2,4-*cis*-tetrahydrofurans (**11.2**) with excellent diastereoselectivity induced by 1,2-stereocontrol of the silicon group on the chiral allylic center[23,24] (Scheme 11).



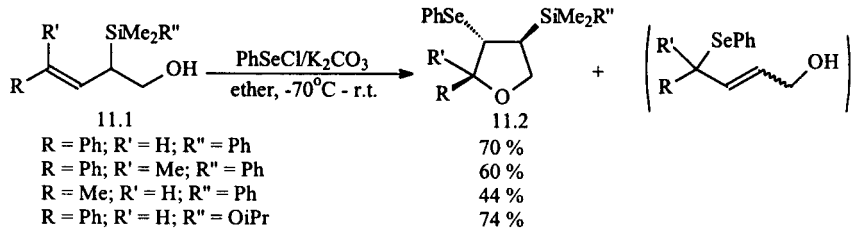
Comp.	R	R^1	R^2	9.2:9.3
A	Me	Me	Et	13:1
B	Ph	Ph	Et	10:1
C	Ph	H	Et	11.5:1
D	Ph	H	H	11.5:1
E	Ph	H	Me	13:1
F	Me	H	Ph	19:1
G	H	Ph	Et	19:1
H	H	Ph	H	11.5:1
I	H	Ph	Me	13:1
J	H	Me	Ph	19:1

Scheme 9.

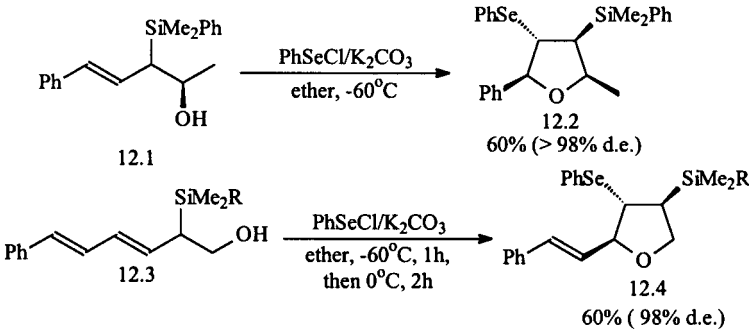


Alkenol 9.1	2,5-Dihydrofuran 10.1	Yield (%)
C		95
E		96
F		91
G		89
I		96
J		96

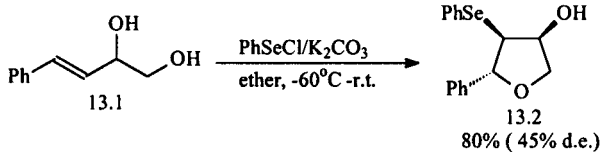
Scheme 10.



Scheme 11.



Scheme 12.

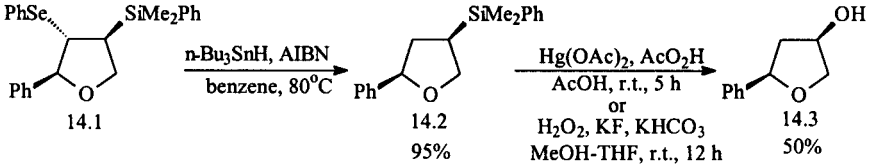


Scheme 13.

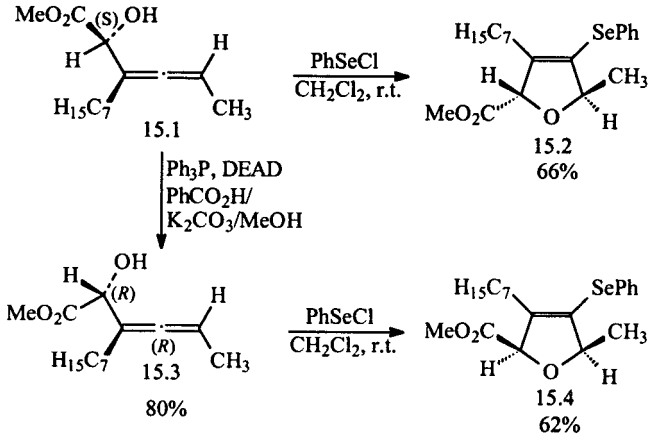
Analogous thiocycloetherification was performed employing PhSCl.

The reactions are performed under kinetic conditions giving only the 2,4-*cis* diastereoisomers, the 5-*endo*-trig process being favoured by the stabilization of the developing positive charge by the aromatic group. The absence of the aromatic group leads mainly to SE′ reactions, but the stabilizing effect of the Me group is still effective probably through C–H bond hyperconjugation.

This methodology has been extended to more complex systems having secondary alcohol functions (**12.1**) (double 1,2-stereocontrol giving a unique diastereoisomer with four chiral centers) or a dienyl system (**12.3**)[24] (Scheme 12).



Scheme 14.



Scheme 15.

A much lower stereoselectivity was observed with the silyl free allylic alcohol (**13.1**) and a reversal of the diastereoselectivity in favour of the *trans* isomer[23] (Scheme 13).

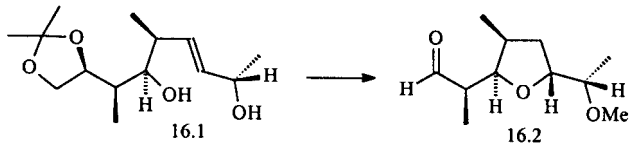
A rationale for the stereocontrol arising from the 5-*endo*-trig cyclization has been proposed on the basis of steric and electronic effects.

The PhSe group, as well as the silicon moiety, allow further functionalizations: the PhSe group can be removed through well known tin chemistry and the silyl group is a masked hydroxyl group. Therefore, the entire sequence offers an easy stereoselective access to the 3-hydroxy tetrahydrofuran skeleton (**14.3**)[24] (Scheme 14).

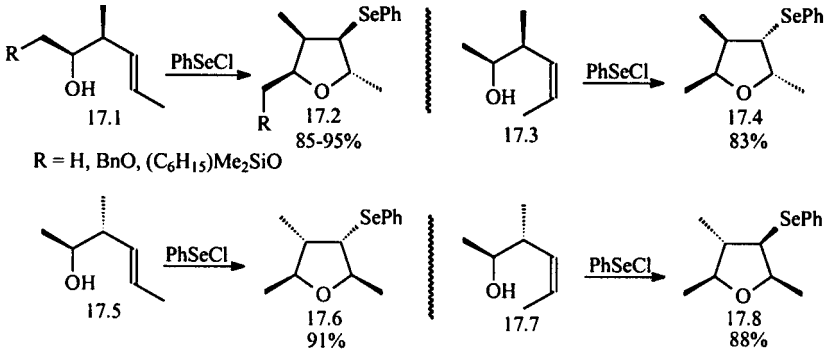
The diastereomeric allenyl carbinols (**15.1**) and (**15.3**) also react in a 5-*endo*-trig selenoetherification to give stereospecifically *trans*- and *cis*-2,5-dihydrofurans (**15.2**) and (**15.4**). Analogous bromocyclizations, performed by treatment with NBS, gave the corresponding bromoderivatives with comparable stereoselectivity[25] (Scheme 15).

The key transformation in the synthesis of tetranosin (Scheme 16) induced a study of homoallylic alcohol (**17.1**,**3**,**5**,**7**) selenoetherification to afford a stereocontrolled synthesis of substituted tetrahydrofurans exhibiting either 2,5-*cis* (**17.6**, **17.8**) or *trans* (**17.2**, **17.4**) relationship[26] (Scheme 17).

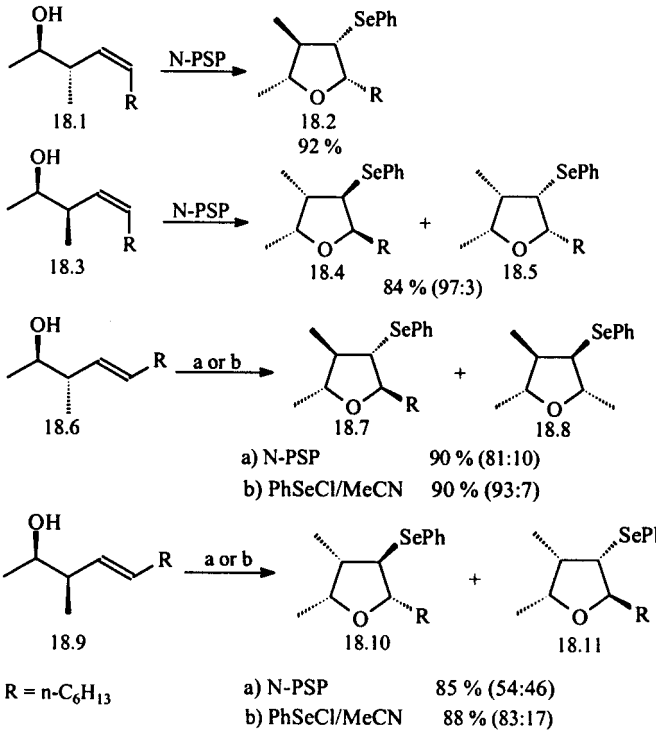
It is noteworthy that the iodoetherification of the same allylic alcohols affords the products exhibiting the opposite stereochemical relationship.[26]



Scheme 16.



Scheme 17.



Scheme 18.

However, ensuing investigations[27] furnished different stereochemical assignments for the selenoetherifications of related homoallylic alcohols (Scheme 18).

All the products were reduced with Ph_3SnH/AIBN, in benzene under reflux, to give the corresponding selenium-free trialkylated tetrahydrofurans.

3.2. 5-*exo*-Trig

This section summarizes mainly 5-*exo*-trig selenoetherification. Some examples of 6-*exo*- and 6-*endo*-trig process are also reported. A detailed investigation of the selenoetherification of γ-hydroxy alkenes (**19.1**–**6**), bearing an hydroxy, alkoxy or alkyl substituent on the allylic carbon has been reported and compared with the cyclization with other electrophiles.[28]

The results in Scheme 19 show that when an oxygenated substituent is present at the allylic carbon [compounds (**19.1**) and (**19.3**)] a *cis* stereoselectivity predominates in the selenocyclization.

The presence of a Z methyl group on the olefinic or in the allylic carbon (compounds **19.5**,**7**,**9**) induces *trans* product formation.

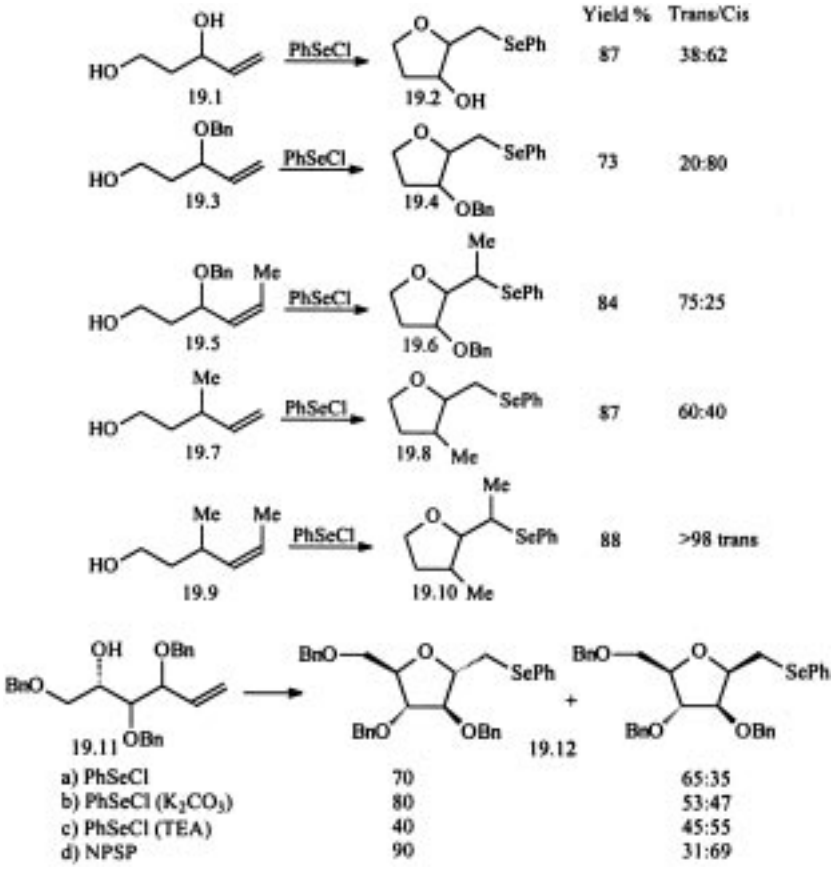
In some cases [compounds (**19.1**,**3**,**11**)] a decreased stereoselectivity was observed in comparison with the corresponding iodo-, bromo- and mercury cyclizations. Mechanistic analysis was given to rationalize the above results[28] (Scheme 19).

A systematic study regarding the regioselectivity in the selenoetherification of a large number of acyclic olefinic alcohols was performed with phenylselenenyl chloride and bromide at different temperatures and by an electrochemical process in which a mixture of diphenyl diselenide and alkenols are electrolyzed in organic solvents containing an halide ($Et_4N^+Br^-$ or $CaCl_2$) as mediator.[29]

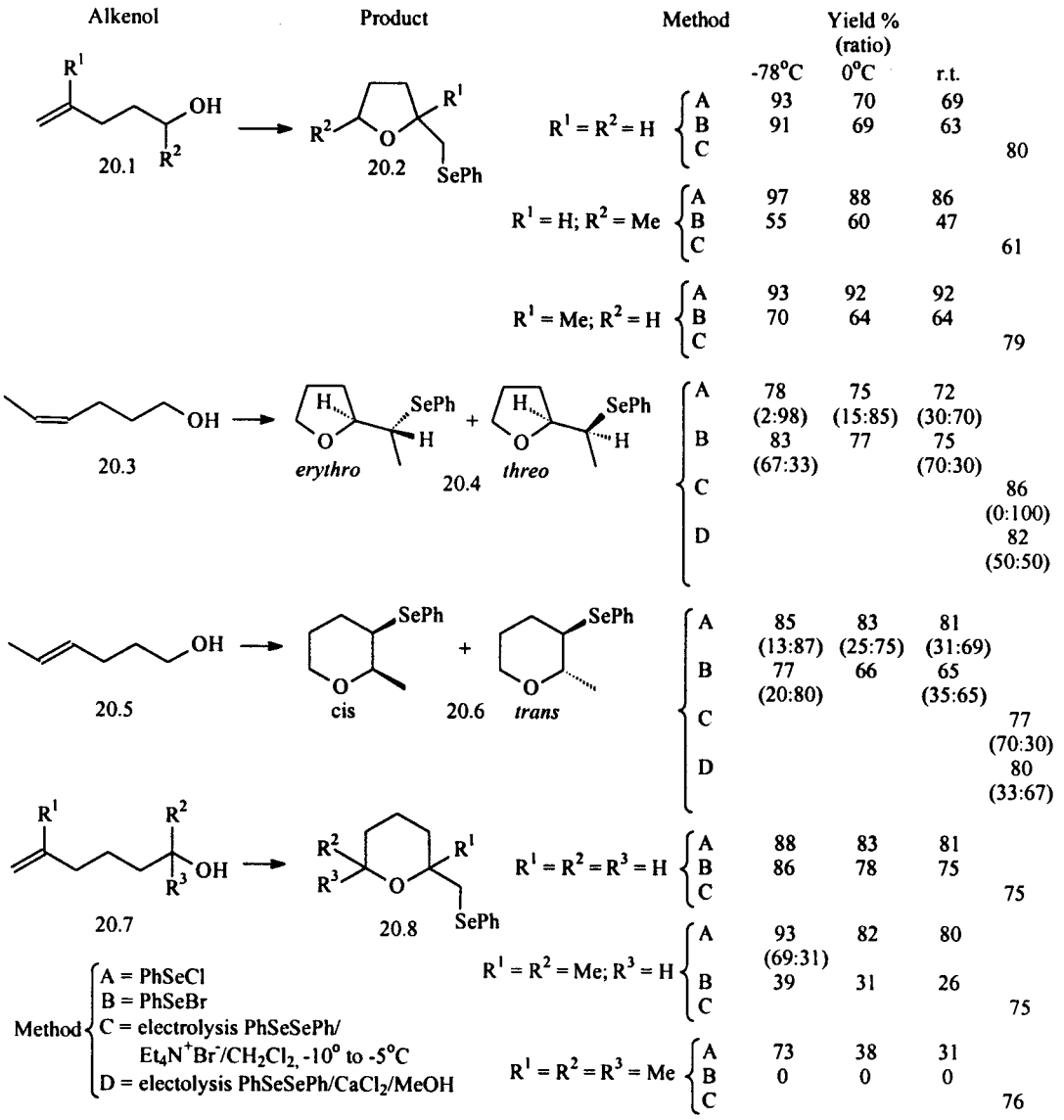
Δ^4 Alkenols (**20.1**,**3**,**5**) give cyclic five- (**20.2**, **20.4**) or six- (**20.6**) membered ethers (tetrahydrofurans and tetrahydropyrans) depending on substituents at the double bond and at the carbinol C-atom, whereas Δ^5 alkenols (**20.7**) are converted only into the six-membered ethers [tetrahydropyrans (**20.8**)]. It has been found that PhSeCl is more efficient than PhSeBr and that the yields decrease with the increasing reaction temperature (Scheme 20).

The easily accessible β-ketoester (**21.1**) undergoes selenocyclization via its enol form, giving a mixture of *cis*–*trans* products (**21.2** and **21.3**).[30] These can be easily converted into selenium-free hydroxy furans (**21.6**,**7**) (Scheme 21).

α,γ-Diallyl-β-ketoesters (**22.1**) react with PhSeBr to afford dihydrofuran derivatives (**22.2**), in moderate to good yields, together with minor amounts of the corresponding *exo*-isomers (**22.3**)[31] (Scheme 22).



Scheme 19.



Scheme 20.

Scheme 23 illustrates selenoetherifications performed using the phenylselenenyl cyanide-copper triflate complex.[10]

Phenylselenenyl triflate has been successfully employed in selenoetherification reactions. *cis*- and *trans*-allylcyclohexanol (**24.1**) and (**24.3**) react with PhSeOTf to give, respectively the fused *cis*-phenylselenomethyl tetrahydrofuran (**24.2**) and *trans* phenylseleno tetrahydropyran derivative (**24.4**) if the reaction is performed at 0°C in CH_2Cl_2. Otherwise, by carrying out the reaction at −78°C, the *trans* derivative (**24.5**) is formed from (**24.3**)[32] (Scheme 24).

Evidence was given supporting an equilibrium between the substrate and products (**24.4**) and (**24.5**), which are, respectively the thermodynamic and the kinetic products. The cyclohexenyl alcohols (**24.6**) give the tetrahydrofuran and tetrahydropyran derivatives (**24.7**).

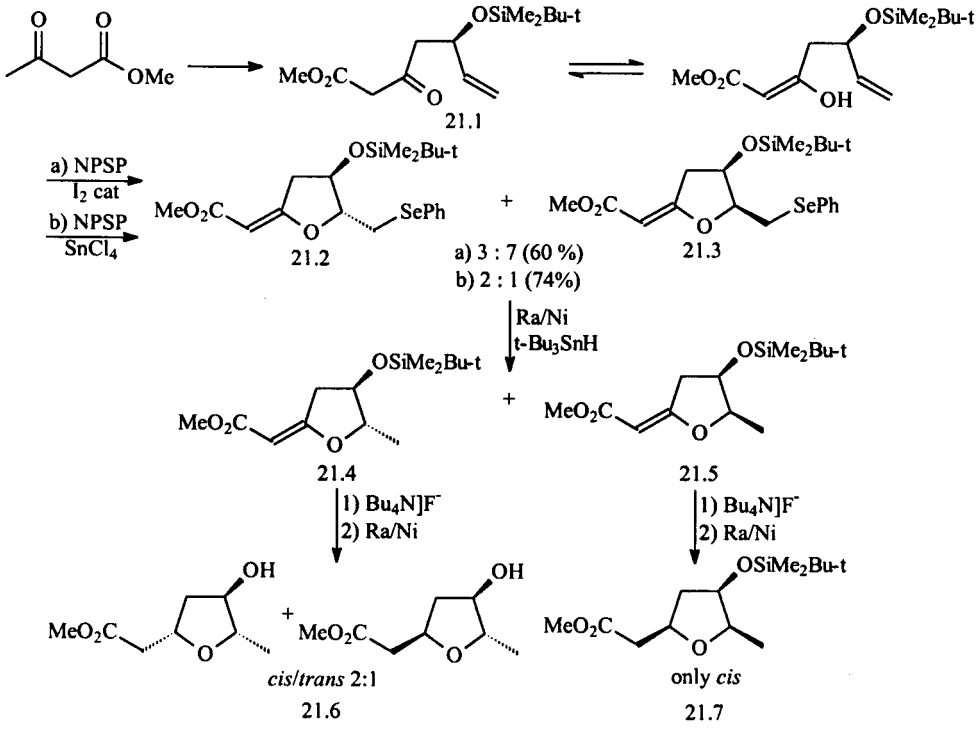
Dienols and trienols such as homogeraniol (**25.1**) homonerol (**25.3**) and farnesol (**25.6**) react with the same reagent to give polycyclic compounds (Scheme 25).[33]

Phenylselenenyl sulfate [PhSeSePh/$(NH_4)_2S_2O_8$] in MeOH or MeCN was widely employed for selenoetherification of alkenols (**26.1**) or allylphenols (**26.3**)[34,35] (Scheme 26).

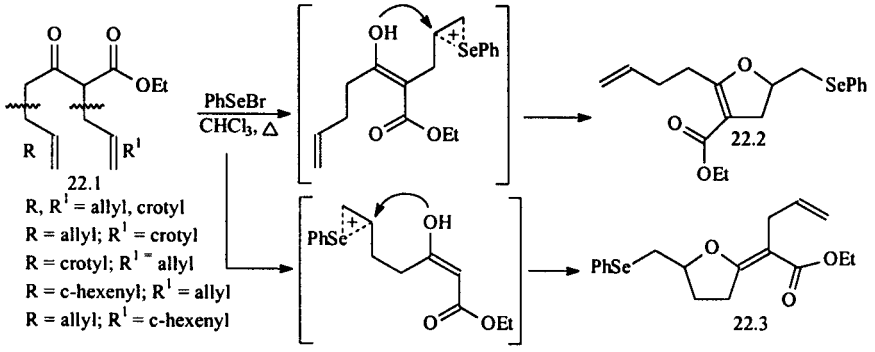
The easily enolizable allyl substituted β-diketones, β-ketoesters, β-ketonitriles and β-ketosulfones (**27.1,3**) react similarly[34] (Scheme 27).

Also the in situ generated hemiketals of alkenyl ketones and β-ketoesters (**28.1**) participate in similar cyclizations[34] (Scheme 28).

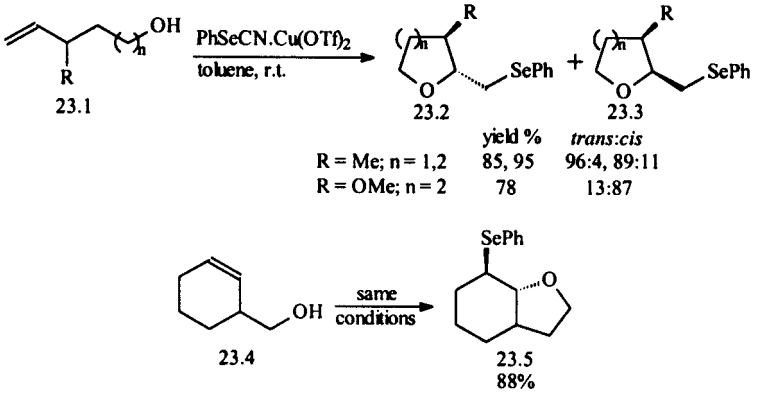
All the obtained selenides are easily submitted to oxidation (H_2O_2 in MeOH) and selenoxide elimination (reflux in benzene/10% $NaHCO_3$), to afford the corresponding enol ethers (**29.1–3**)[35] (Scheme 29).



Scheme 21.



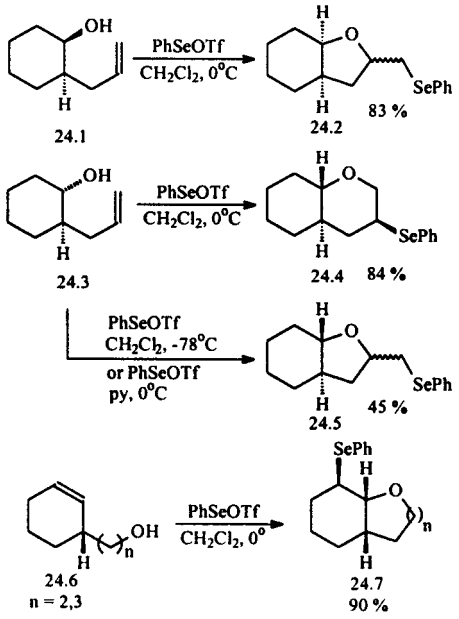
Scheme 22.



Scheme 23.

Similar selenoetherifications have been afforded by using the systems PhSeSePh/PhI(OAc)$_2$,[15] PhSeSePh/(NH$_4$)$_2$ Ce(NO$_3$)$_6$,[14] phenylselenenyl-*m*-nitrobenzene sulfate,[12] phenylselenenyl trifluoroacetate and triflate,[8] phenyl selenenyl-*p*-toluenesulfonate[6] and PhSe$^+$ species from the photooxidative cleavage of diphenyldiselenide.[16]

The 5-*exo*-trig cyclofunctionalization of 2-silyl-4-alkenols



Scheme 24.

(**30.1**) was exhaustively investigated by looking at the synthesis of tetrahydrofurans exhibiting three chiral centers (**30.2**) formed under kinetic control (E^+/base) with concomitant 1,3- and 1,4-stereoinduction.[36,37] The stereochemistry at the new chiral center would therefore be controlled by the silicon group at the homoallylic chiral center.

The first investigation performed with the simple silylalkenols (**30.1**; R^1, R^2=H) showed that the selenoetherification (E^+=PhSeCl) is less stereoselective than mercury-or iodocyclization (Scheme 30).

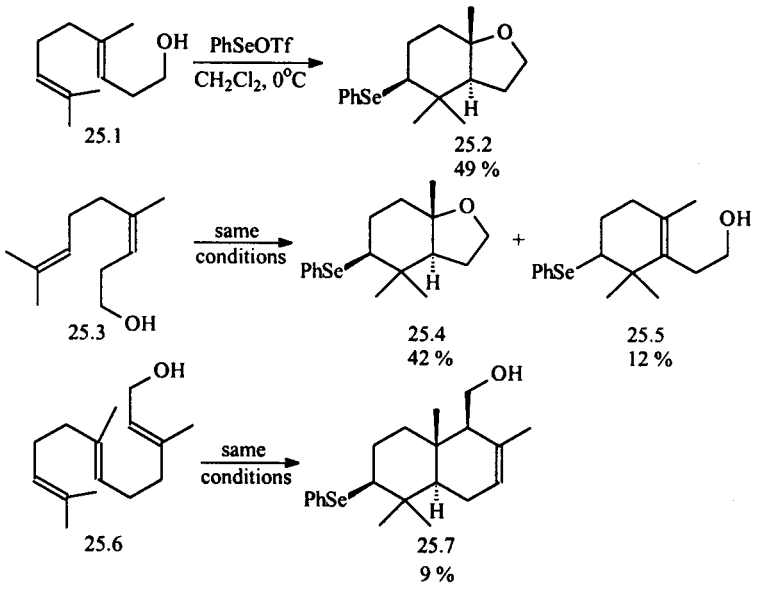
An additional interesting example of selenoetherifications is the single step conversion of dialkenyl ketones (**31.1**,**3**,**5**) into cyclic acetals (**31.2**,**4**,**6**) of practical importance employing phenylselenenyl chloride in aqueous acetonitrile.[38]

It has been proposed that the cyclization involves the formation of the hydroxyselenide (**31.8**) followed by intramolecular formation of hemiketal (**31.9**), whose hydroxy group traps the second episelenonium ion intermediate giving the spiroacetal (**31.10**) (as in the case of **31.1**) (Scheme 31).

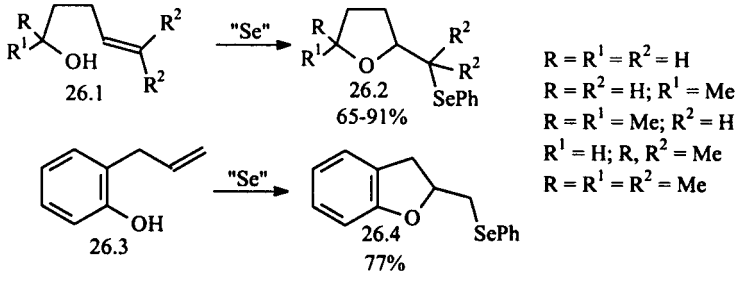
Selenoetherification reactions have been employed in multistep synthesis of several natural products or of related building blocks (see Refs. 39–50).

4. Phenylseleno mediated synthesis of *N*-heterocycles

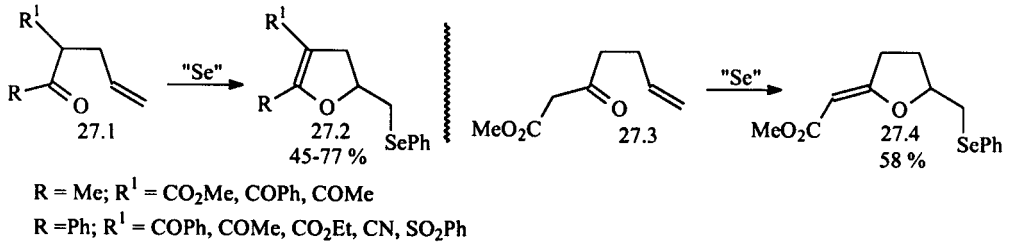
Nitrogen heterocyclic compounds can be obtained by the



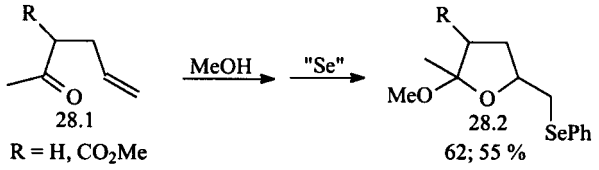
Scheme 25.



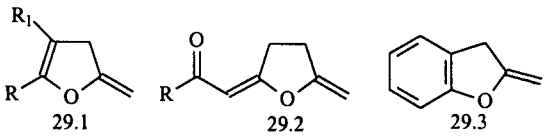
Scheme 26.



Scheme 27.



Scheme 28.



Scheme 29.

selenium promoted cyclization of alkenyl nitrogenated substrates. Different nitrogen heterocycles are afforded depending on factors such as the nature of the substituents at the alkenyl group, the nature of the 'gegenion', and the experimental conditions employed. Otherwise, in the case of nucleophilic group incorporation at the nitrogen functionality, competitive cyclization reactions can be observed. These can be governed by modification at the functional group or choosing conditions for kinetic or thermodynamic control.

4.1. Formation of C–N bond

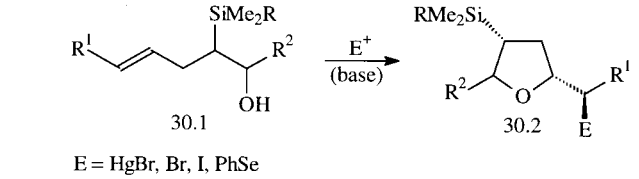
The cyclization of primary alkenylamines has been poorly explored due to the concurrence of undesired side reactions. However the cyclization of alkenylamines bearing electron withdrawing group at the nitrogen atom, is a process of general application.[51]

The reaction of phenylselenenyl halides with *N*-alkenylamides[52] produces pyrrolidine or piperidine derivatives, depending on the above mentioned factors. *N*-(4-pentenyl)-acetamide (**32.1**) gives pyrrolidine products (**32.2**), the yields being increased by the presence of substituents at C2 of the pentenyl group, and generally by the use of PhSeBr instead of PhSeCl. The addition of silica gel also facilitates the cyclization.[52] Otherwise, the introduction of a substituent at the terminal olefinic carbon atom (**32.3**) promotes the formation of piperidine derivatives (**32.4**). *N*-(2-ethylhex-5-enyl)acetamide (**32.5**) reacts only with phenylselenenyl iodide to give the corresponding piperidine (**32.6**) (Scheme 32).

Some synthetically useful conversions, such as oxidative or reductive deselenenylations, are depicted in Scheme 33.

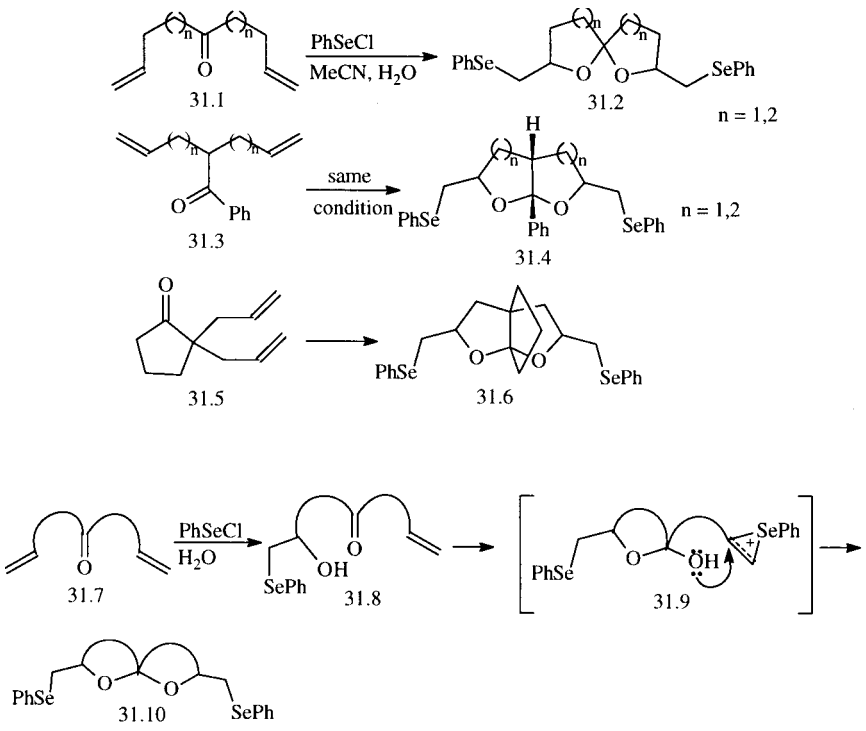
Similar *N*-alkenylamide cyclizations have been employed in the synthesis of bicyclic *N*-heterocycles, such as pyrrolizidine derivatives and Thienamycin skeleton.[52]

The above described cyclization of *N*-alkenylacetamides is carried out under acidic conditions, owing to the formation of hydrogen halides as side-product. Since these conditions lead to undesirable side-reactions in some cases, a modified



E^+ (conditions)	E	Yield %	*Cis/Trans* (30.3 : 30.4)
PhSeCl (K_2CO_3,ether, 70°C)	PhSe	70	69:31
NIS (CH_2Cl_2, -20°C)	I	89	86:14
$Hg(OAc)_2$ ($CaCO_3$, THF, -20°C, then KBr/H_2O)	HgBr	81	94:6

Scheme 30.



Scheme 31.

protocol was introduced that utilizes an imidate (**34.1**) as a masked amide group.[53] In this case the reaction is carried out under neutral conditions, since an alkyl halide is formed as the side-product (Scheme 34).

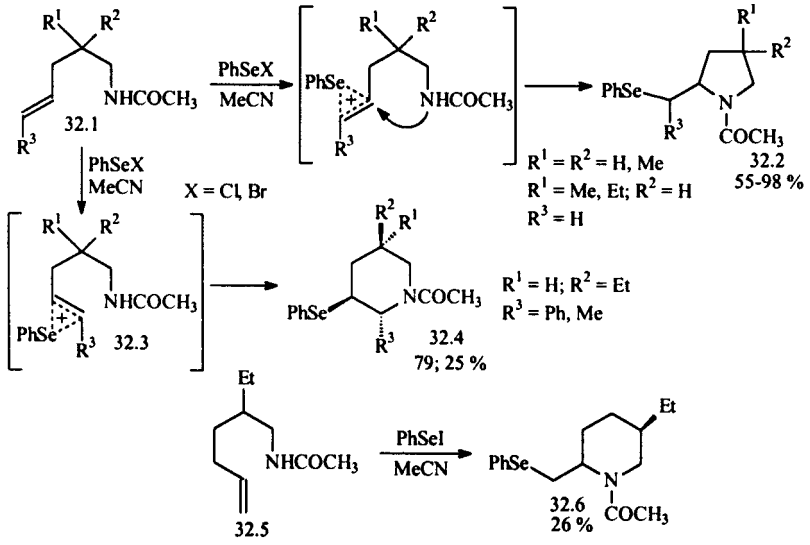
Phenylselenenyl sulfate was also successfully employed for the selenocyclization of alkenylamides[34] (Scheme 35).

3-Hydroxy-4-pentenyl- and 4-hydroxy-5-hexenyl carbamates, sulfonamides and amides (**36.1**), by treatment with phenylselenenyl halides in presence of silica gel, undergo regio- and stereoselective selenocyclization to afford, respectively the corresponding *N*-substituted *cis*-2(selenomethyl)-3-hydroxypirrolidine (**36.2**) in high yields and *trans*-2(selenomethyl)-3-hydroxypiperidine (**36.3**) in moderate yields[54] (Scheme 36).

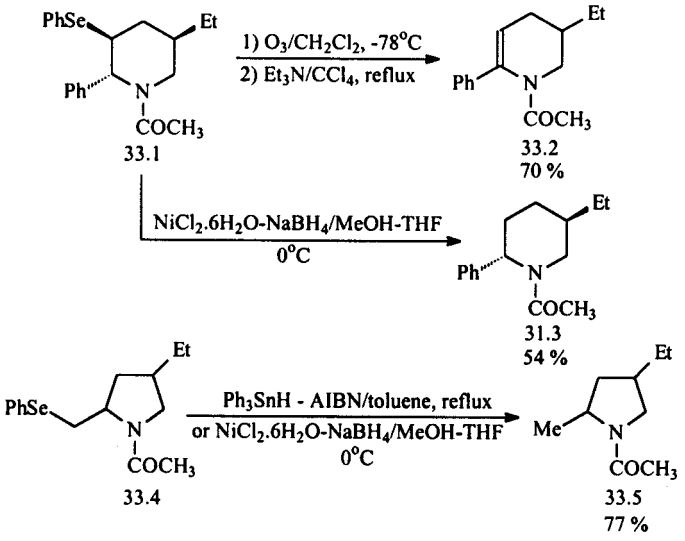
In the case of $n=1$ the reactions are fast and seems to be under kinetic control, whereas with $n=2$ the reactions are slow and presumably under thermodynamic control.

Synthesis of the biologically active diol (**37.2**) was achieved starting from the selenide (**37.1**)[54] (Scheme 37).

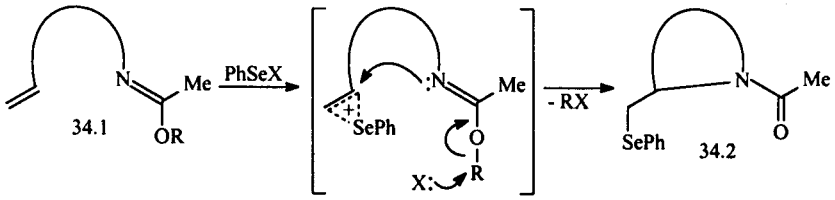
The reaction of 2-styrylacetanilides (**38.1**) with several electrophilic selenenylating reagents such as PhSeCl,



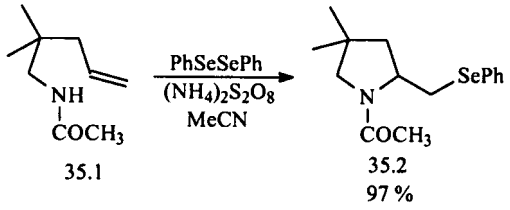
Scheme 32.



Scheme 33.



Scheme 34.



Scheme 35.

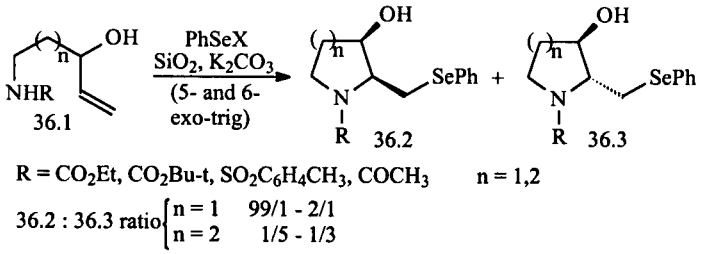
PhSeBr, PhSeSePh, NPSP, NPSS gives rise to variable mixtures of the corresponding 2-phenyl-3-phenylselenoindoles (**38.2**) and of the selenium-free 2-phenylindoles (**38.3**).[55] The best yield of (**38.2**) was obtained using 2.4 equiv. of N-PSS in CH_2Cl_2 in the presence of *p*-toluenesulfonic acid as catalyst (Scheme 38).

The reaction seems to occur via cycloamidoselenenylation with concomitant selenoelimination giving (**38.3**) followed by reaction with excess of NPSS to afford (**38.2**). The reductive deselenenylation of (**38.2**) is achieved by treatment with tri-*n*-butyltin hydride/AIBN or $NiCl_2/NaBH_4$.[55]

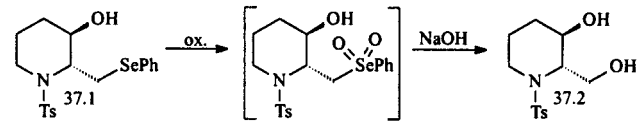
2-Vinylacetanilides (**39.1**) react with PhSeBr (2 equiv.) giving directly the corresponding indole (**39.2**), probably via cycloamidoselenenylation, spontaneous selenoelimination and hydrolysis of the amido group by the HBr generated in the reaction. The yields are poor and reached only 40% by changing the $COCH_3$ to a $COCF_3$ group[55] (Scheme 39).

Homoallylic tosylamides (**40.1**) underwent 5-endocyclization upon treatment with phenylselenenyl chloride giving *cis*- (**40.2**) or *trans*- (**40.3**) substituted selenopyrrolidines depending from the substituents and the conditions employed[56] (Scheme 40).

Secondary alkenyl amines undergo the expected cyclizations with eletrophilic selenium reagents. Alkenyl



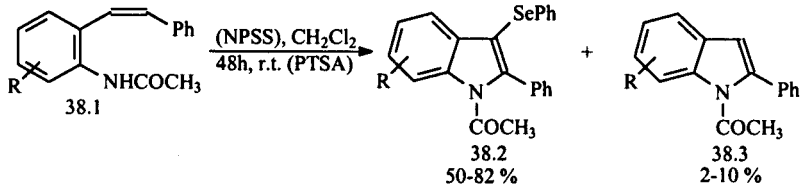
Scheme 36.



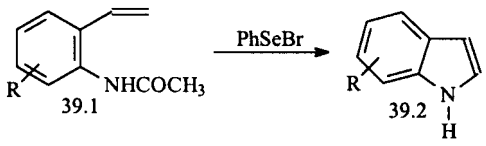
Scheme 37.

pirrolidines (**41.1**) are converted into pyrrolizidines (**41.2**) by treatment with phenylselenenyl sulfate[57] (Scheme 41).

Homoallylic benzylamines (**42.1**) react with phenyselenenyl bromide or chloride to give 4-*exo* or 5-*endo* cyclization products, respectively the azetidine (**42.2**) or the pyrrolidine



Scheme 38.

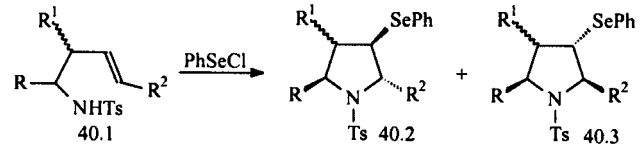


Scheme 39.

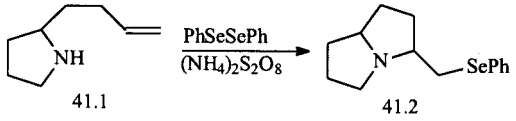
(**42.3**) products.[58] The process is sensitive to steric hindrance, the formation of (**42.2**) being favored by the presence of two substituents at the homoallylic carbon. With excess of the Se reagents 3-halopyrrolidines (**42.4**) are formed (Scheme 42).

4.2. Formation of C–O and C–S bond

In contrast to the previously described selenocyclization of *N*-(4-pentenyl)- and *N*-(5-hexenyl)acetamides, which occurs with a C–N bond formation, *N*-(3-butenyl)acetamide (**43.1**) cyclizes at the oxygen atom to give a cyclic imidate (**43.2**)[52] (Scheme 43).



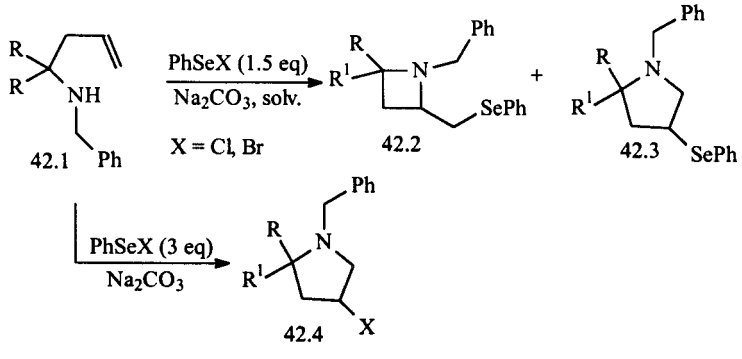
Scheme 40.



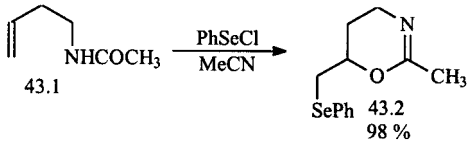
Scheme 41.

N-Allylic amides and thioamides (**44.1**,**4**) undergo selenocyclization to afford 2-oxazolines and 2-thiazolines (**44.2**,**5**) (5-*exo*-trig cyclization)[15,35,59] or dihydro-1,3-oxazines (**44.3**) (6-*endo*-trig cyclization)[59] in good yields (Scheme 44).

N-Allylic benzamides **44.6** are cyclized into the oxazolines **44.7**.[60]



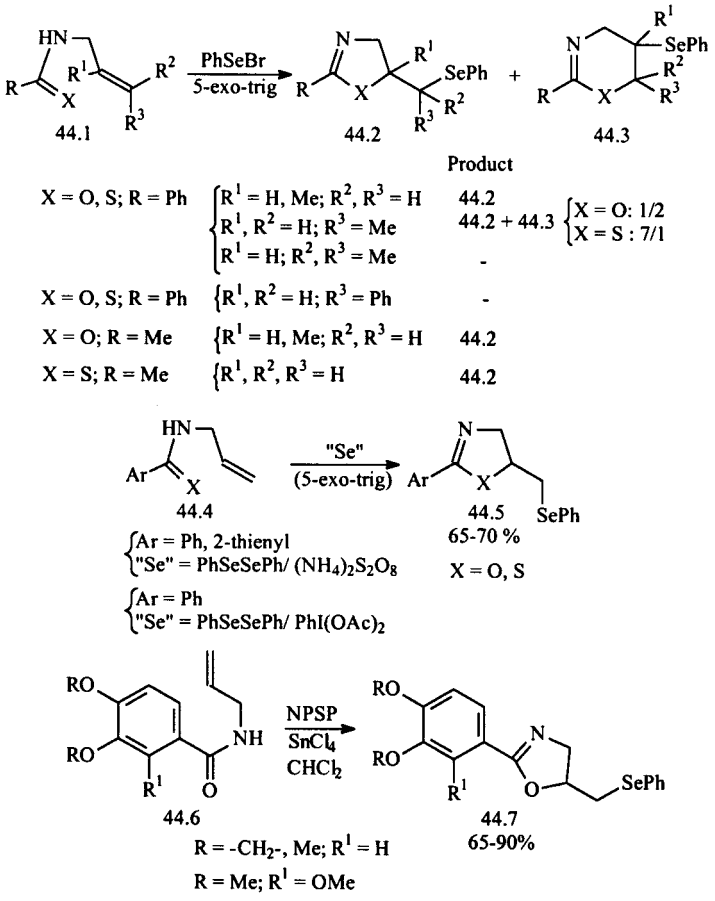
Scheme 42.



Scheme 43.

These results are consistent with the intermediacy of a episelenonium ion and attack by the O or S nucleophile on the opposite side of the carbon double bond.

Cyclofunctionalization products can be submitted to selenoxide elimination or to reductive deselenenylation[35,59] (Scheme 45).

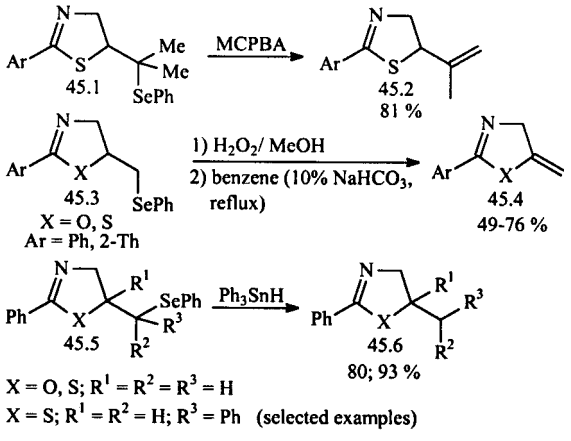


Scheme 44.

Additional efforts were directed toward the proton-induced cyclization of allylic thioamides giving thiazolines by treatment with *p*-toluenesulfonic acid in toluene at reflux.[59]

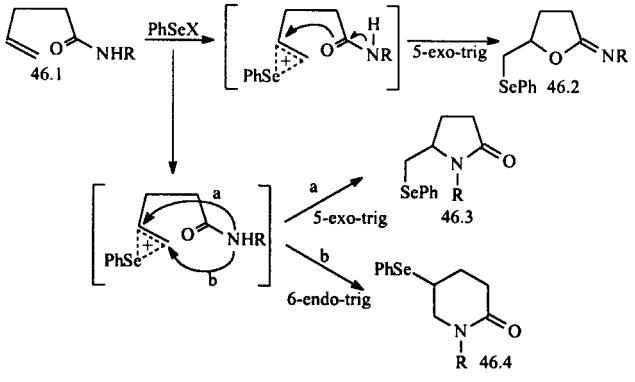
4.3. Competition in the formation of C–N or C–O bonds

When the nitrogen atom is incorporated in a functional group bearing an oxygen atom, the two nucleophilic atoms can compete in the attack on the episelenonium ion producing a C–N or C–O bond.



Scheme 45.

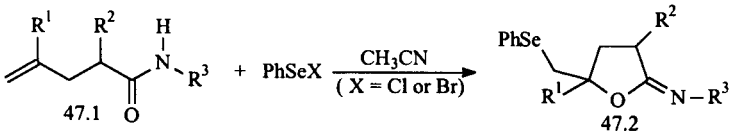
Alkenyl amides constitute the first example: phenylselenenyl halides react with 4-pentenamides (**46.1**) giving rise either to iminolactones (**46.2**) or to lactams (**46.3**,**4**) depending on the structure of the alkenyl moiety. The formation of iminolactones or lactams results, respectively from the oxygen or nitrogen attack on a transient episelenonium ion[59,61] (Scheme 46).



Scheme 46.

Scheme 47 summarizes the formation of iminolactones.[61]

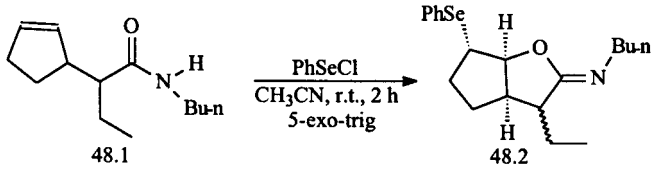
The reaction fails in same cases with X=Cl but is of general use for X=Br. The formation of bicyclic iminolactone (**48.2**), is depicted below[61] (Scheme 48).



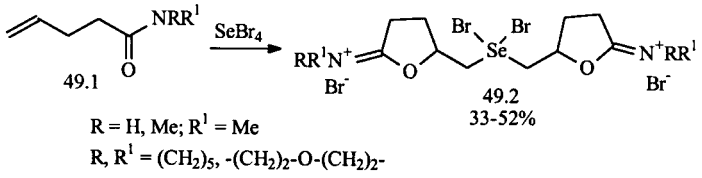
a : R^1 = H, R^2 = Et, R^3 = n-Bu
b : R^1 = Me, R^2 = Et, R^3 = n-Bu
c : R^1 = R^2 = H, R^3 = n-Bu
d : R^1 = H, R^2 = Ph, R^3 = n-Bu
e : R^1 = H, R^2 = Et, R^3 = Ph
f : R^1 = H, R^2 = i-Pr, R^3 = H

starting material	X in PhSeX	time h	product	yield %
47.1a	Cl	1	47.2a	87
47.1b	Cl	1	47.2b	94
47.1c	Br	2	47.2c	73
47.1d	Br	1	47.2d	67
47.1e	Br	12	47.2e	85
47.1f	Br	1	47.2f	80

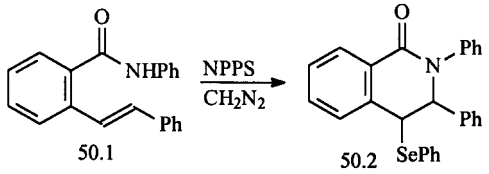
Scheme 47.



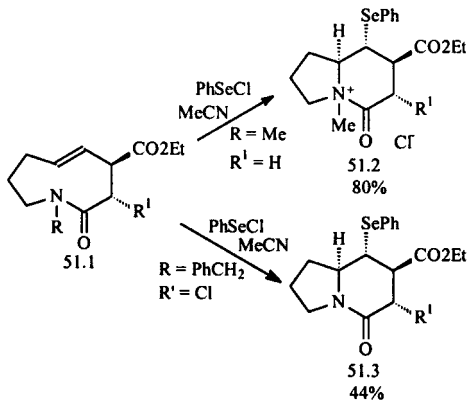
Scheme 48.



Scheme 49.



Scheme 50.



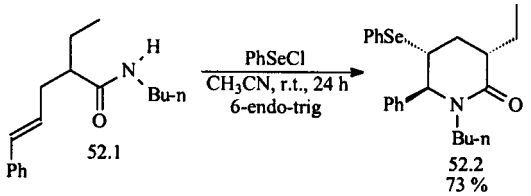
Scheme 51.

Dimeric derivatives (**49.2**) are obtained by reaction of *N*,*N*-dissubstituted alkenylamides (**49.1**) with selenium tetrabromide[62] (Scheme 49).

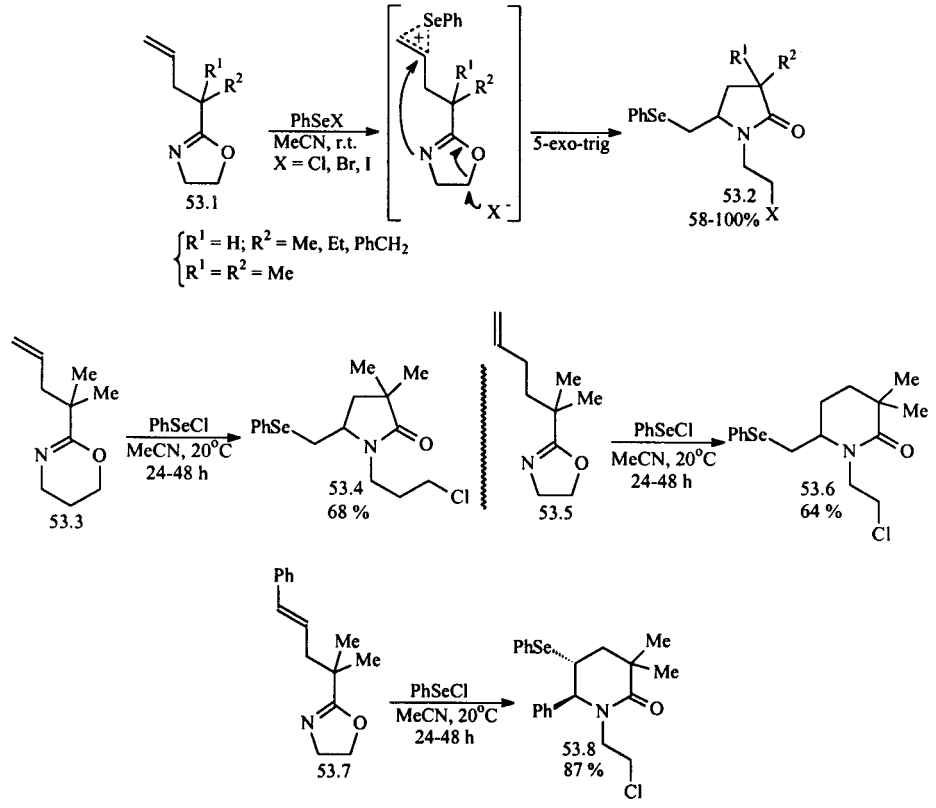
A 6-*endo*-trig selenocyclization giving the lactam (**50.2**) through C–N bond formation was observed by treatment of the *O*-alkenyl benzamide (**50.1**) with *n*-phenylsuccinimide[63] (Scheme 50).

A transanular 5-*exo*-trig cyclization giving bicyclic lactams (**51.2**,**3**) with complete regio- and stereoselectivity takes rise treating the 9-membered lactams (**51.1**) with phenylselenenyl chloride[64] (Scheme 51).

5-Phenylpent-4-ene (**52.1**) cyclizes to give the γ-lactam (**52.2**)[61] (Scheme 52).



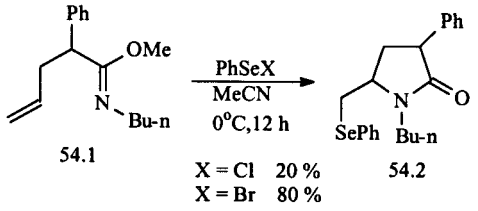
Scheme 52.



Scheme 53.

In contrast to olefinic amides, olefinic imidates (**53.1**,**3**,**5**,**7**) afford exclusively lactams (**53.2**,**4**,**6**,**8**) through the attack of a nitrogen atom and a halide ion, respectively on the episelenonium ion and on the carbon ring[61] (Scheme 53).

The acyclic imidate (**54.1**) also reacts with PhSeBr to give the γ-lactam (**54.2**) through the formation of a C–N bond[61] (Scheme 54).



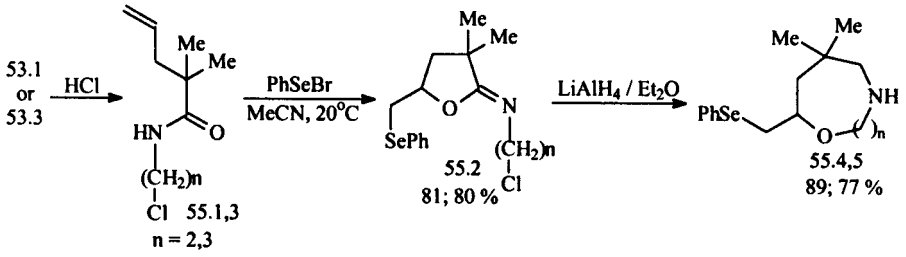
Scheme 54.

The imidates (**55.1**) and (**55.3**), by successive treatment with anhydrous HCl and PhSeBr/MeCN, produce the respective iminolactones (**55.2**) in excellent yields.[61,65] Submitting these compounds to $LiAlH_4$ reduction, a novel ring-enlargement reaction takes place leading to the eight and nine membered cyclic compounds (**55.4**,**5**), respectively (Scheme 55).

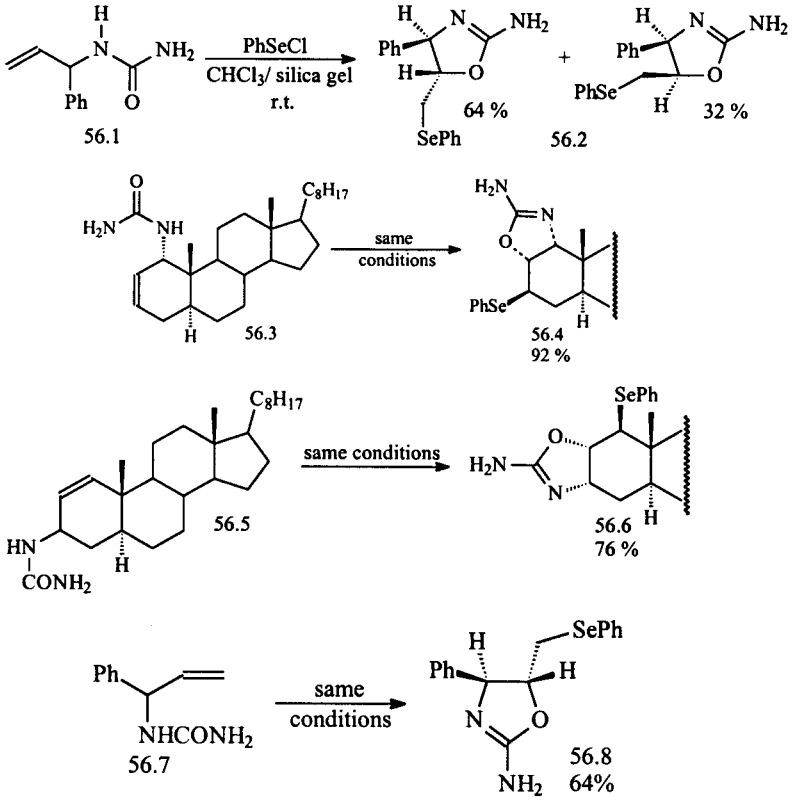
2-Oxazolines (**56.2**,**4**,**6**,**8**) are prepared starting from allylic ureas (**56.1**,**3**,**5**,**7**) through a 5-*exo* mode cyclization promoted by PhSeCl[66] (Scheme 56).

6-*endo* Cyclization are also observed[66] (Scheme 57).

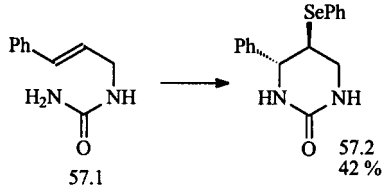
By employing *O*-methylisoureas (**58.1**,**4**,**6**) the regioselectivity can be modified, and depending on the experimental method used, 5-*exo*-*N*-cyclization or 6-*endo* *O*-cyclization can be promoted, giving imidazolines (**58.2**,**5**) or 5,6-dihydro-1,3-oxazines (**58.3**,**7**), respectively[67] (Scheme 58).



Scheme 55.



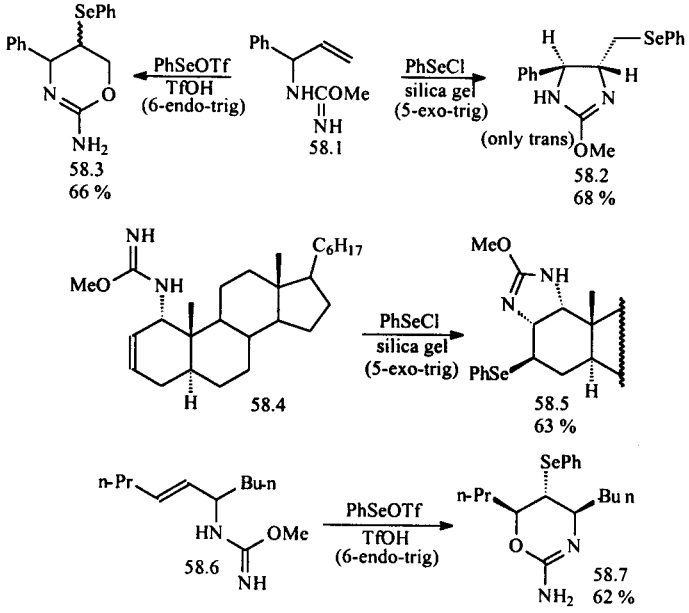
Scheme 56.



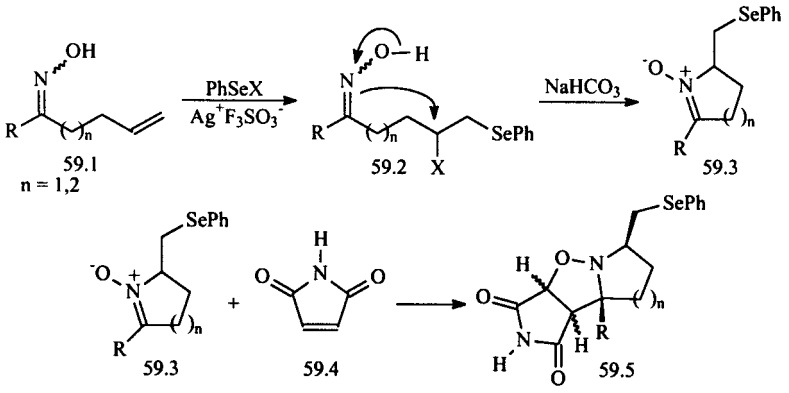
Scheme 57.

Alkenyl oximes (**59.1**) treated with PhSeCl or PhSeBr in the presence of an appropriate silver salt, give the adducts at the C–C double bond (**59.2**), which cyclize to methylselenonitrones (**59.3**) by treatment with anhydrous $NaHCO_3$.[68] The obtained selenonitrones undergo facial specific cycloaddition with *N*-methylmaleimide (**59.4**) (Scheme 59).

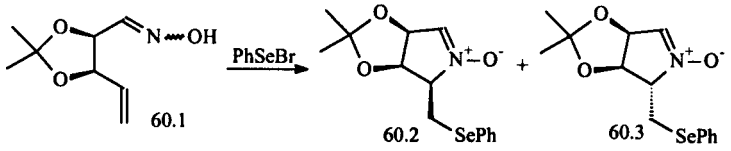
The oxime (**60.1**) by treatment with phenylselenenyl



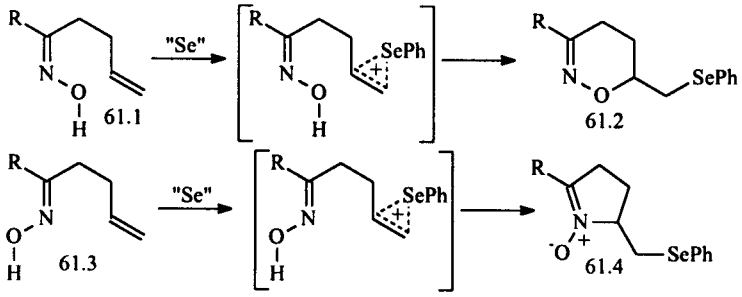
Scheme 58.



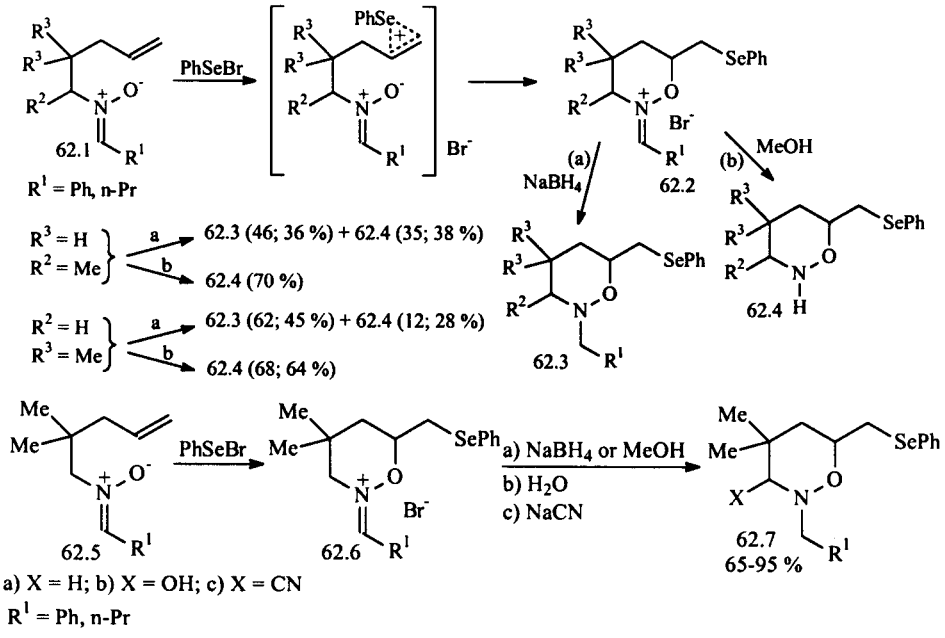
Scheme 59.



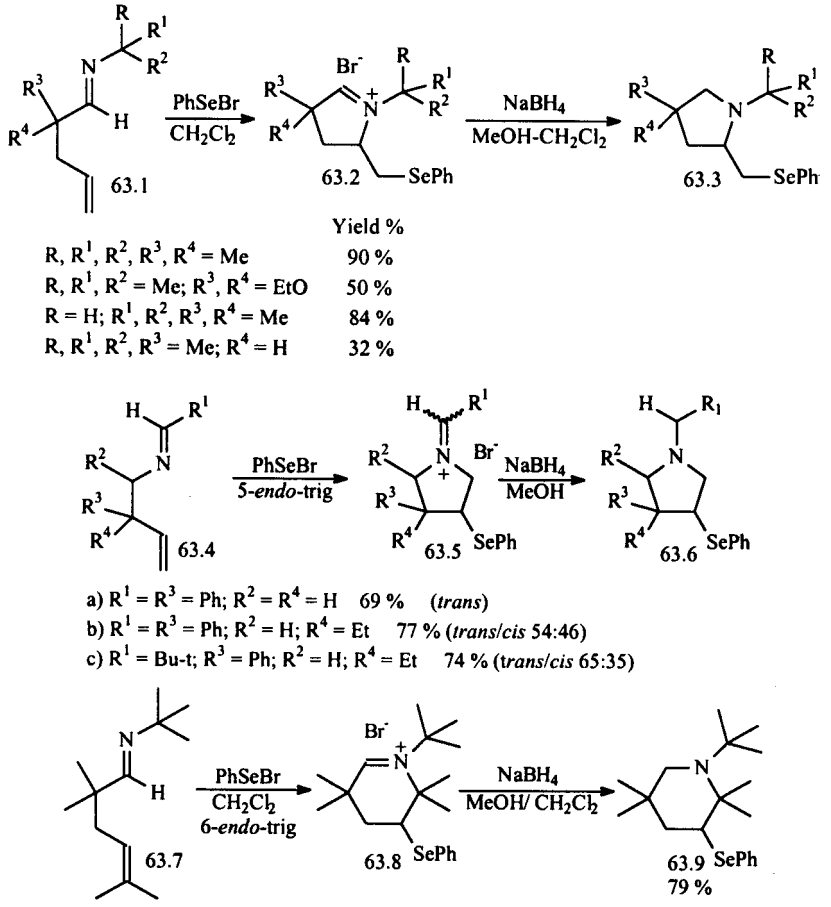
Scheme 60.



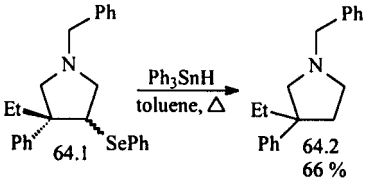
Scheme 61.



Scheme 62.



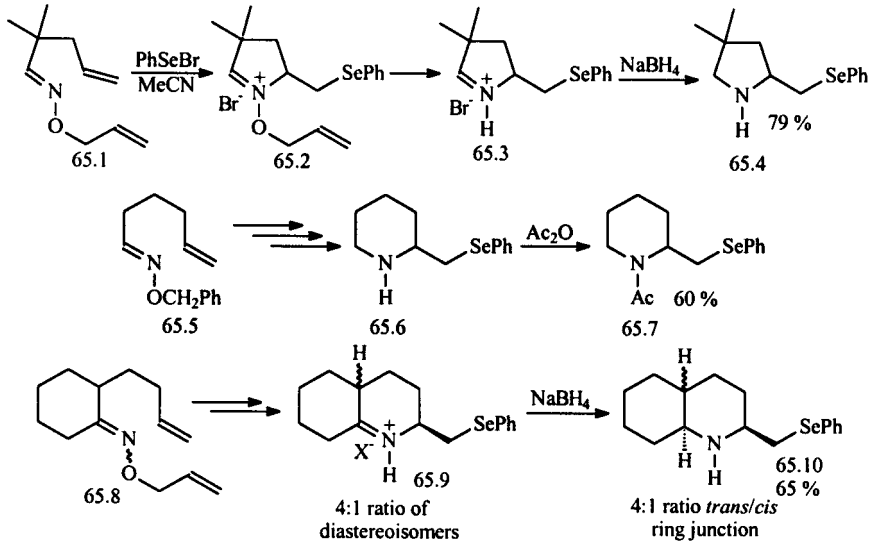
Scheme 63.



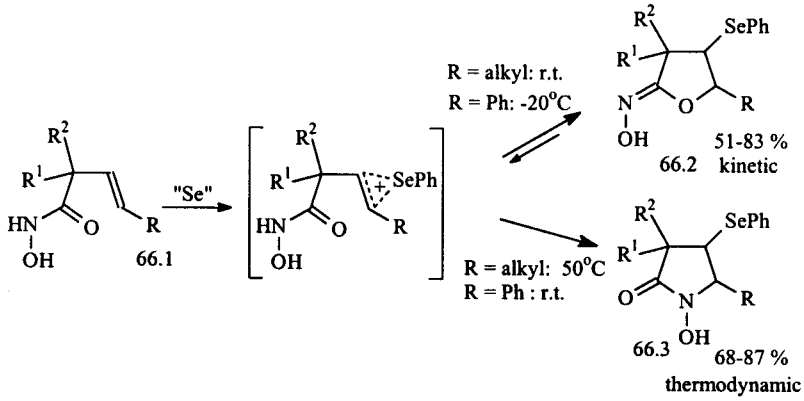
Scheme 64.

bromide gives a moderate yield of the two isomeric nitrones (**60.2**) and (**60.3**)[69] (Scheme 60). The structure of nitrone (**60.2**) is related to the natural product Australine that has been shown to exhibit antiviral activity.

Otherwise, by treatment of γ-alkenyl oximes (**61.1,3**) with the reagent produced from $(PhSe)_2$ and $(NH_4)_2S_2O_8$/



Scheme 65.

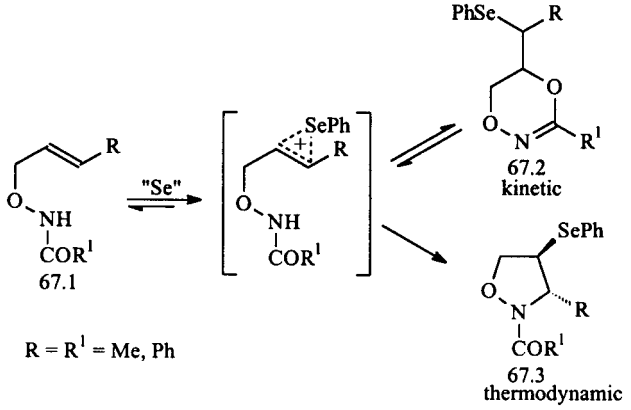


Scheme 66.

F_3CSO_3H, depending on the geometry of the oxime group, either the oxygen or the nitrogen atom can act as nucleophile to afford, respectively phenylselenomethyl substituted-1,2-oxazines (**61.2**) or cyclic nitrones (**61.4**)[70] (Scheme 61).

The nature of the R group influences the course of the reaction, but the ratios of the formed products do not reflect the Z/E ratios of the starting oximes, the formation of the five membered ring being largely preferred over the six-membered 1,2-oxazines.

1,2-Oxazines (**62.3**,**4**,**7**) are also accessible by the reaction of alkenyl nitrones (**62.1**,**5**) with PhSeBr to afford the capture of the intermediate episelenonium ion by the oxygen atom, followed by the treatment of the formed six-membered cyclic iminium salt (**62.2**,**6**) with nucleophilic reagents such as $NaBH_4$, MeOH, H_2O or NaCN[71] (Scheme 62).



Scheme 67.

The results formulated above demonstrate that the iminium salts with exocyclic C–N double bond give *N*-alkyl 1,2-ozaxines or *N*-unsubstituted 1,2-oxazine depending on the nucleophile employed, whereas iminium salts with endocyclic C–N double bonds led only to *N*-alkyl 1,2-oxazines. These results are in contrast with the reaction of five-membered cyclic iminium salts with $NaBH_4$/MeOH affording exclusively *N*-alkyl isoxazolidines (vide infra).[72]

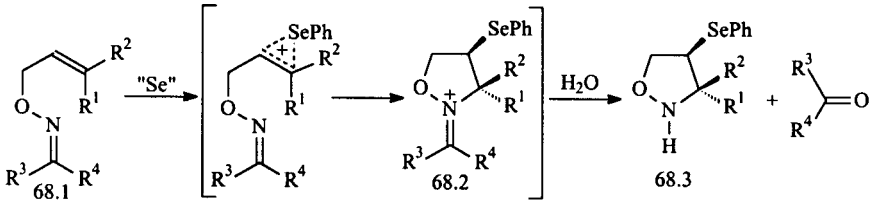
γ,δ-Alkenimines (**63.1**,**4**) react with PhSeBr in CH_2Cl_2 to produce cyclic pyrrolinium salts (**63.2**,**5**). When alkyl substituents are linked at the olefinic units (**63.7**), piperidinium salts (**63.8**) are formed. The yields are almost quantitative. Reduction of the crude iminium salts with $NaBH_4$ affords the corresponding pyrrolidines (**63.3**,**6**) and piperidines (**63.9**)[73,74] (Scheme 63). Comparable results were obtained by bromocyclizations.

The removal of the PhSe group is performed using triphenyltin hydride in toluene[74] (Scheme 64).

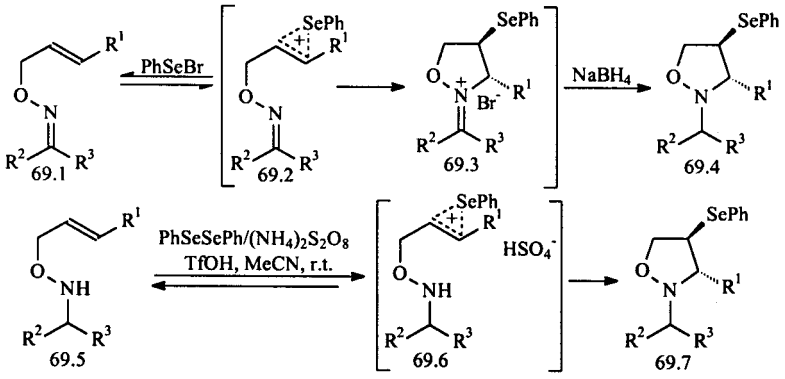
O-Allyl (**65.1**) and *O*-benzyl ethers (**65.5**) of alkenyl aldoximes and ketoximes (**65.9**) submitted to selenocyclization produce iminium salts such as (**65.2**), which undergo slow spontaneous fragmentation to give cyclic imines (**65.3**,**9**). These are easily reduced to pyrrolidines (**65.4**), piperidines (**65.6**) or tetrahydroisoquinolines (**65.10**) by treatment with $NaBH_4$[75] (Scheme 65).

Dialkenyl ketoximes ethers undergo analogous reaction sequence.[75]

Hydroxamic acid derivatives are ambident nucleophiles that undergo selenium induced ring closure reactions either through the oxygen or the nitrogen atom, depending on the experimental conditions.[76] Thus γ-substituted-β,



Scheme 68.



Scheme 69.

γ-unsaturated hydroxamic acids (**66.1**), by treatment with phenylselenenyl sulfate ($PhSeSePh/(NH_4)_2S_2O_8/F_3CSO_3H$/MeCN) afford cyclic phenylseleno *N*-hydroxy imidates (**66.2**) or phenylseleno *N*-hydroxy-γ-lactams (**66.3**), respectively under kinetic or thermodynamic control (Scheme 66).

O-Allyl hydroxamic acids (**67.1**) react with the same selenenylating reagent to give phenylseleno-1,2,4-dioxazines (**67.2**) or *N*-acyl isoxazolidines (**67.3**) as kinetically or thermodynamically controlled products, respectively depending on the structure of the substrate and/or the experimental conditions[77] (Scheme 67).

The same selenenylating reagent reacts with *O*-allyloximes (**68.1**) to give cyclic iminium salts (**68.2**) which are converted directly into isoxazolidine derivatives (**68.3**) by simple treatment with water. Identical results were obtained by using PhSeBr under little modified procedure [78] (Scheme 68).

N-Alkyl isoxazolidines (**69.4**,**7**) are produced in a modified sequence by reducing in situ the iminium salts (**69.3**) with $NaBH_4$[72] or by treatment of *O*-allyl hydroxylamines (**69.5**) with phenylselenenyl sulfate[79] (Scheme 69).

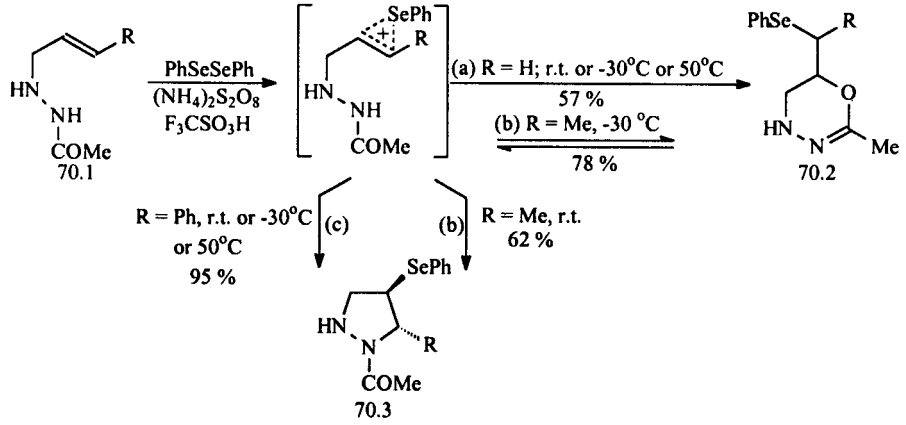
All of the last three methods[72,78,79] involve a *trans* stereospecific addition process as clearly demonstrated by the formation of a single isomer[78] (Scheme 68; R^1=H).

N-Allyl acetylhydrazide (**70.1**) treated with phenylselenenyl sulfate gives rise to six-membered 5,6-dihydro-4H-1,3,4-oxadiazines (**70.2**) or to five-membered *N*-acetyl pyrazolidines (**70.3**).[80] This is another example of a competitive process where the episelenonium ion intermediate can be trapped by the oxygen or nitrogen atom, depending on the substituent R and the experimental conditions employed (Scheme 70).

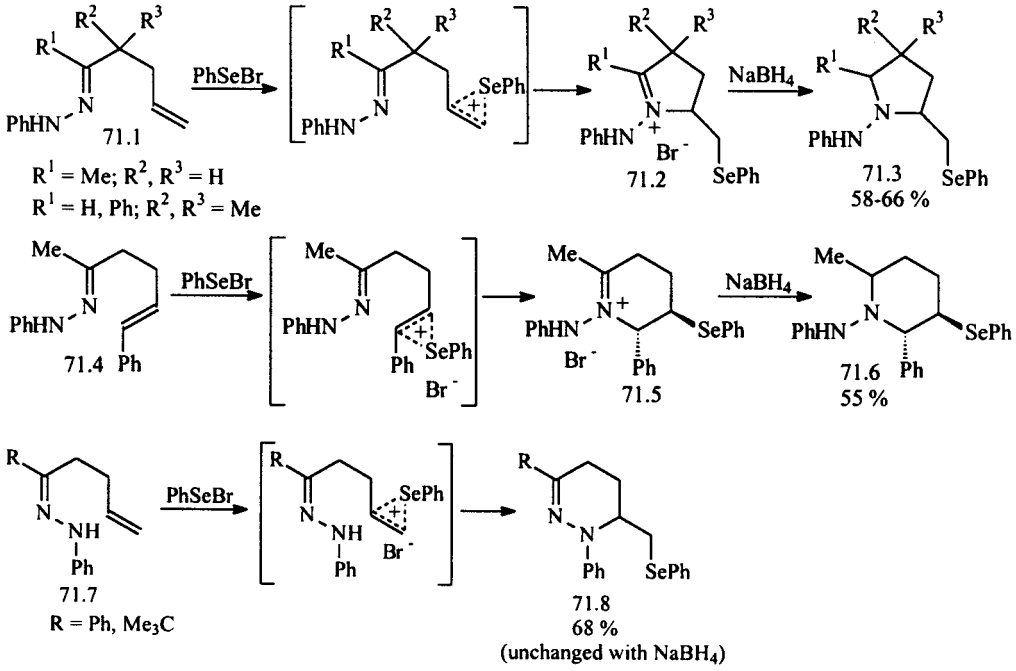
Scheme 70 shows that (**70.1a**) and (**70.1c**) give only one product, (**70.2a**) and (**70.3c**), respectively, independent of the temperature, while the product formation from (**70.1b**) can be controlled either kinetically or thermodynamically. The ring closure reaction is a *trans* stereospecific process in each case.

Alkenyl phenylhydrazones (**71.1**,**4**,**7**) react with PhSeBr to give intermediate episelenonium ions that are trapped stereoselectively by the imino or the amino nitrogen atom depending on the geometry of the starting material.[81] The cyclized products (**71.2**,**5**) are reduced by $NaBH_4$, giving pyrrolidinamine (**71.3**) and piperidinamine derivatives (**71.6**). The tetrahydropyridazine derivatives (**71.8**) remain unchanged with $NaBH_4$ (Scheme 71).

4-Pentenyl hydrazines (**72.1**) react with phenylselenenyl sulfate, and the episelenonium ion intermediate formed is trapped by the nitrogen atom bearing the phenyl group, giving the six-membered hexahydropyridazines (**72.2**).[82]

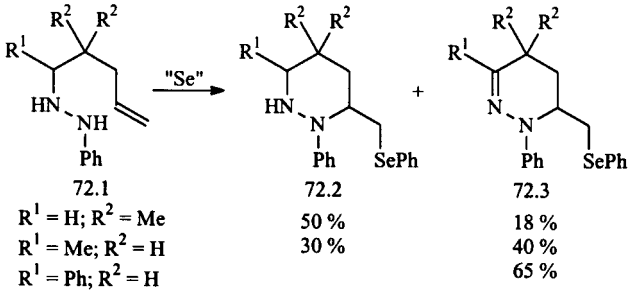


Scheme 70.

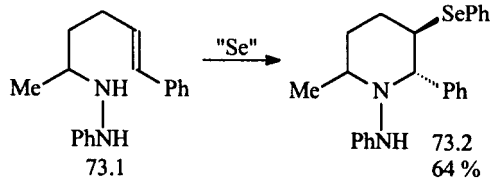


Scheme 71.

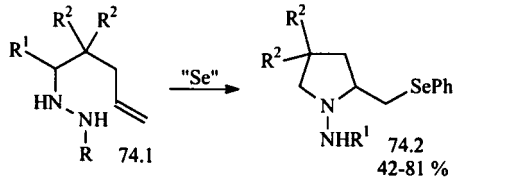
These are partially converted to the corresponding tetrahydropyridazines (**72.3**) during the column chromatography purification, the extension of this oxidation depending on the substituent R (Scheme 72).



Scheme 72.



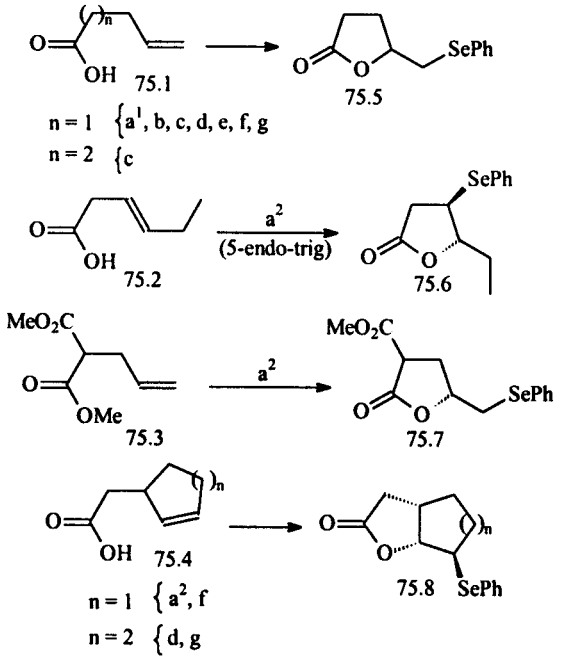
Scheme 73.



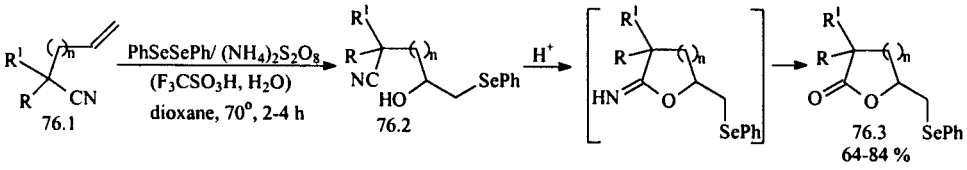
Scheme 74.

In the case of compound (**73.1**) the ring closure takes rise at the expense of the nitrogen atom linked to the alkenyl chain giving the piperidinamine (**73.2**) (Markovnikov adduct)[82] (Scheme 73).

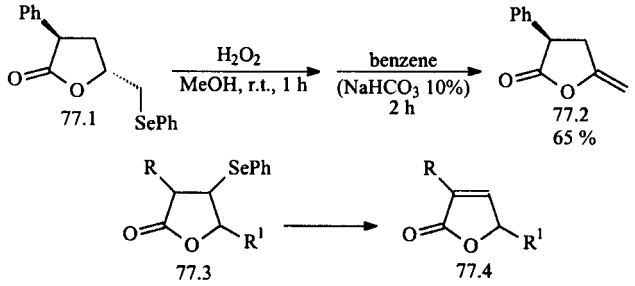
Alkenyl hydrazines with a terminal C–C double bond,



Scheme 75. (a^1) PhSeSePh/$(NH_4)_2S_2O_8$, MeOH, rt, 0.5 h, 86%.[34] (a^2) PhSeSePh/$(NH_4)_2S_2O_8$, MeCN, 70°C, 2–4 h, 70–98%.[34] (b) PhSeOSO$_2$ *p*-tolyl(PhSeCl+AgOSO$_2$ *p*-totyl), Et_3N, 3 h, 97%.[6] (c) PhSeOSO$_2$C$_6$H$_4$NO$_2$-m (PhSeSePh/*m*-$NO_2C_6H_4SO_3)_2$, MeCN, 0–40°C, 2–2.5 h, 93%.[12] (d) PhSeSePh/SET/DCN*, MeCN, 10–11 h, 70–74%.[16] (e) PhSeSePh/$Ce^{+4}NH_4$ nitrate, MeOH, 0.5 h, 72%.[14] (f) PhSeSePh/PHI(OAc)$_2$, MeCN, 40°C, 2–4 h, 94%.[15] (g) PhSeSePh/$Et_4N^+Br^-$ or $CaCl_2$/electrolysis.[37]



Scheme 76. n=1:(a) R=R[1]=H, Me; (b) R=H; R[1]=Me, Et, Ph, CN; n=2: R=R[1]=Me (20h) 67%.



Scheme 77.

bearing an electron withdrawing group at the terminal nitrogen atom (**74.1**), lead to pyrrolidinamine derivatives (**74.2**) as main products[82] (Scheme 74).

5. Selenolactonizations

The strongly electrophilic phenylselenenyl sulfate, phenylselenenyl *p*-toluenesulfonate, phenylselenenyl *m*-nitrobenzenesulfonate, the $PhSe^+$ cation generated from photosensitized cleavage of diphenyl diselenide, phenylselenenyl nitrate, phenylselenenyl acetate, as well as the electrochemical process (electrolysis of diphenyl diselenide/ unsaturated acids/ halide mediator) have been employed to afford the conversion of several types of unsaturated acids (**75.1**–**4**) into the corresponding seleno-lactones (**75.5**–**8**) (Scheme 75).

By treatment with phenylselenenyl sulfate, olefinic nitriles (**76.1**) afford phenylselenolactone (**76.3**) through the intermediate formation of the hydroxyselenenylation adducts (**76.2**)[83] (Scheme 76).

Oxidation and selenoxide elimination convert the selenolactones (**77.1**,**3**) into the corresponding olefinic compounds (**77.2**,**4**)[11b,35] (Scheme 77).

Butenolides (**78.3**) are formed by treatment of β,γ-unsaturated acids (**78.1**) with diphenyl diselenide and an excess of ammonium persulfate in acetonitrile.[84]

The conversion proceeds via a 5-*endo* cyclization promoted by phenylselenenyl sulfate, followed by the reaction of the formed lactone (**78.2**) with the persulfate anion affording the butenolide (Scheme 78).

The synthesis of several natural products included selenolactonization steps.[85–87]

6. Large rings

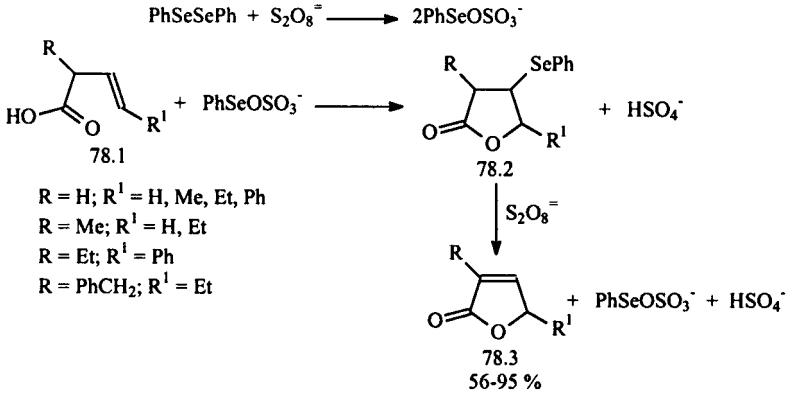
The constructions of seven membered and larger membered heterocycles by selenocyclization have been reported.[88] The following schemes depicting selenoetherifications to give seven and eight membered rings are self-explanatory (Schemes 79–81).[89,90,91]

The reaction of PhSeBr with (*S*)-*N*-(α,β-unsaturated acyl) prolinamides (**82.1**) produces seven- and six-membered bislactam derivatives (**82.2**,**3**) and (**82.4**), accompanied by the addition products (**82.5**,**6**), depending on the structure of the substrate[92] (Scheme 82).

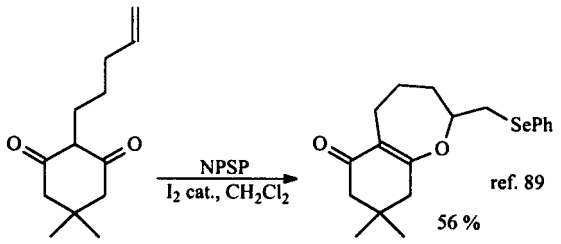
The electrophilic addition occurs in *anti*-fashion with a high degree of chirality transfer.

Compound (**82.2**) was submitted to appropriate manipulation to give the deselenenylated products[92] (**82.7**–**9**).

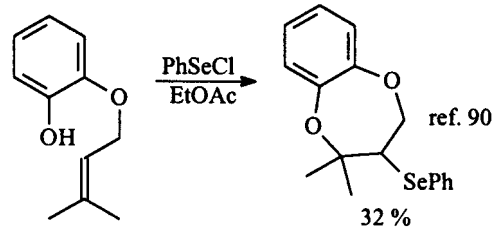
The selenocyclization of the olefinic urethanes (**83.1**) to give a seven membered ring (**83.2**) was part of the synthesis



Scheme 78.



Scheme 79.



Scheme 80.

of the Anatoxin-a (**83.3**), a nicotinic acetylcholine receptor agonist[93] (Scheme 83).

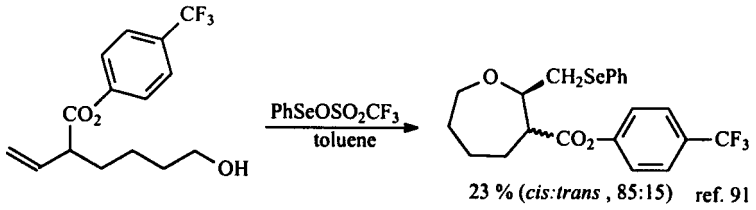
7. Asymmetric cycloselenofunctionalization reactions promoted by chiral selenium reagents

The application of organoselenium reagents to asymmetric synthesis has recently attracted the attention of several research groups.

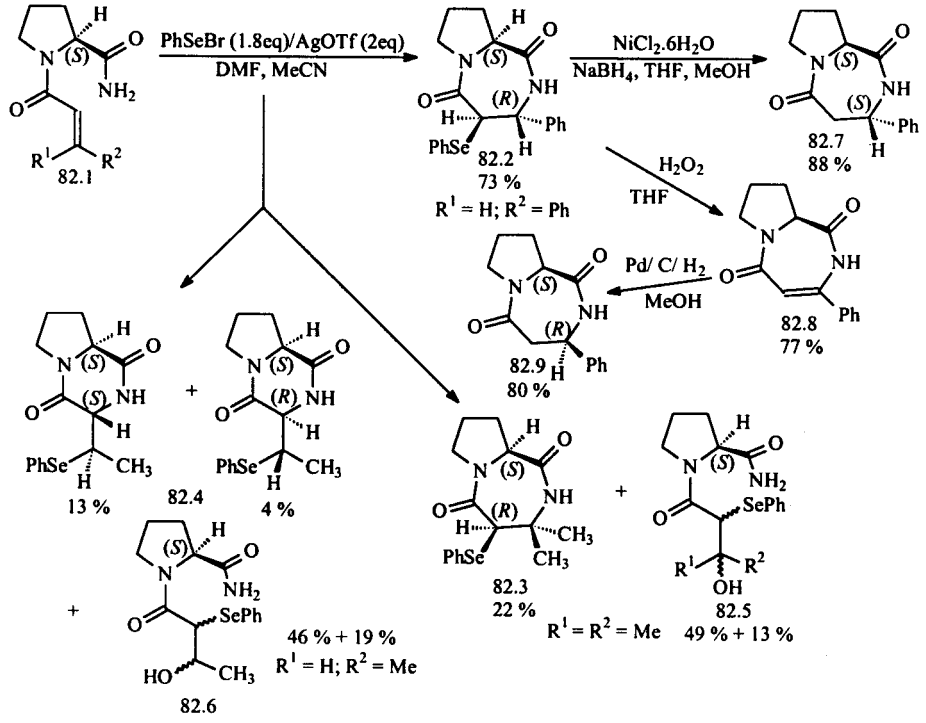
Efforts have been directed toward the preparation of different types of chiral diselenides which are converted 'in situ' into electrophilic chiral selenenylating agents employed to react with alkenes. In the presence of internal nucleophiles cyclization products are obtained with moderate to high asymmetric induction.[94]

Most of the various chiral diselenides described are characterized by structures where the Se atom is separated by four linkages from on oxygen, nitrogen or sulphur bond.

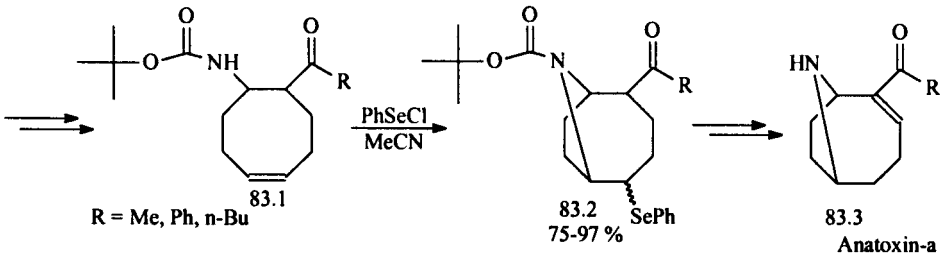
The resulting strong interaction between the Se atom and these heteroatoms (Scheme 84) increases the proximity



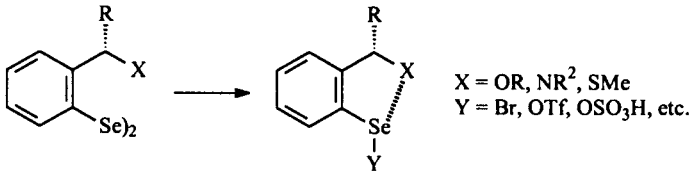
Scheme 81.



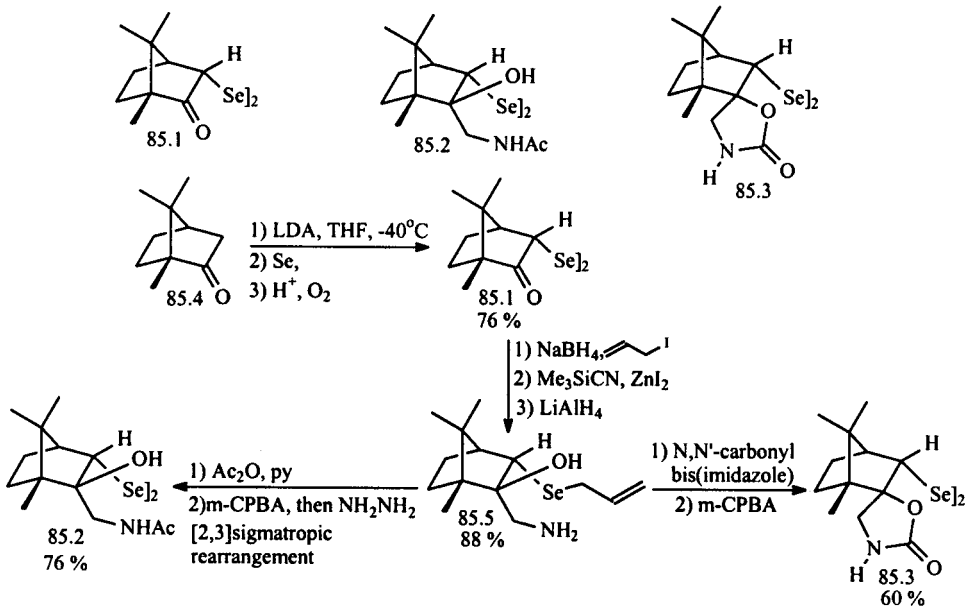
Scheme 82.



Scheme 83.



Scheme 84.



Scheme 85.

between the chiral source in the reagent and the reaction center in the transition state of the reaction, resulting in asymmetric induction. In some cases the existence of this interaction has been supported by theoretical calculations as well as by crystal structure determinations and NMR spectroscopy.[94]

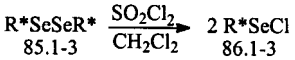
It is also known that the non-bonding Se-heteroatom interaction is predominantly an n–σ^* type orbital interaction[95–97] (Scheme 84).

7.1. Camphor based chiral diselenides

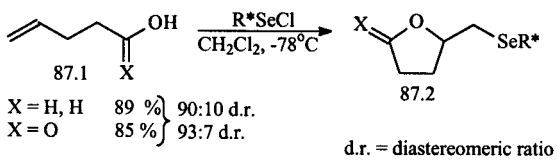
The three chiral diselenides (**85.1**–**3**) are prepared starting from (1*R*)-(+)-camphor (**85.4**)[98–100] following the sequence formulated in Scheme 85.

Diselenide (**85.1**) is prepared in 76% yield by simply treating (1*R*)-(+)-camphor (**85.4**) with LDA in THF followed by elemental Se at −40°C and air oxidation.

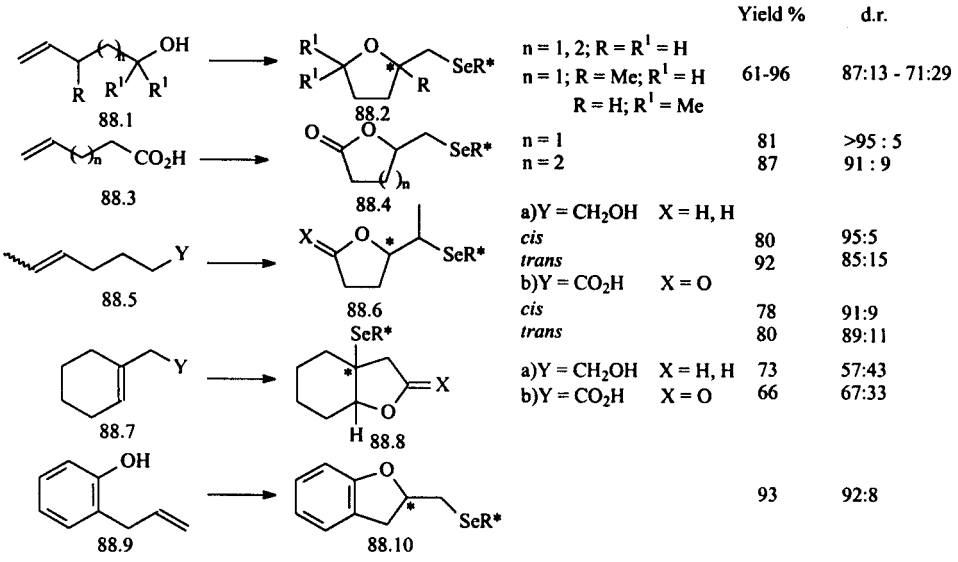
The preparation of (**85.2**) and (**85.3**) involves the $LiAlH_4$



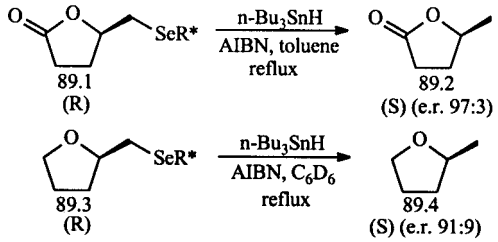
Scheme 86.



Scheme 87.

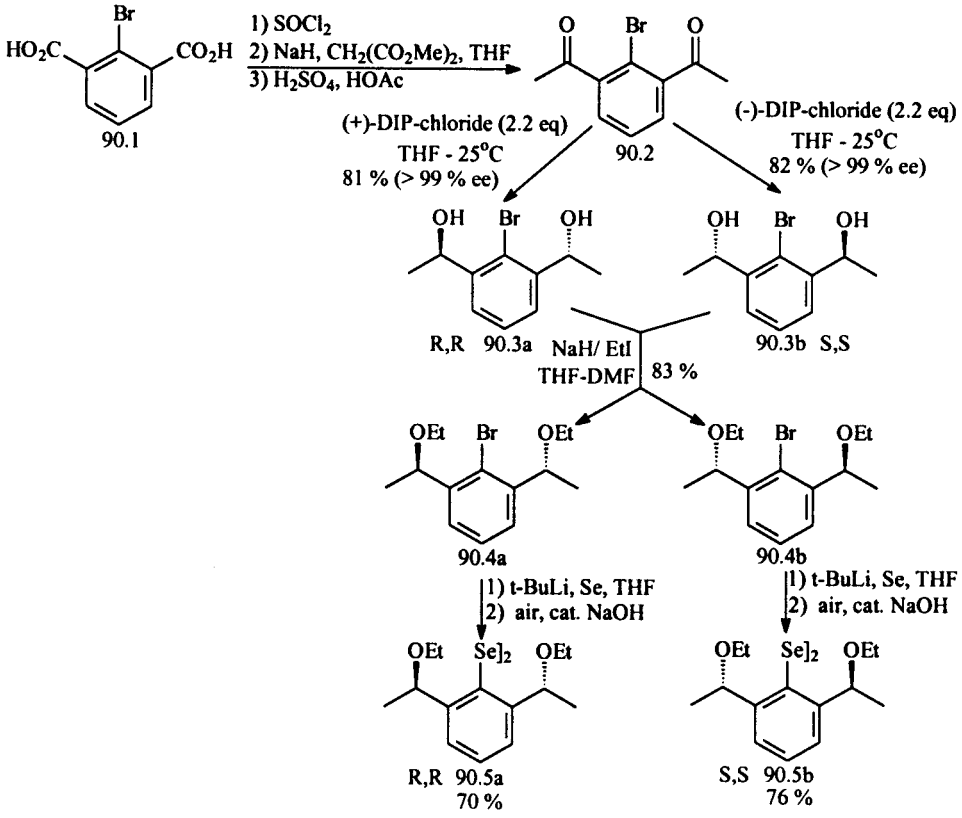


Scheme 88.



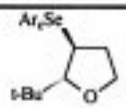
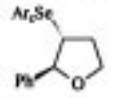
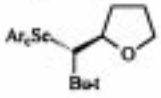
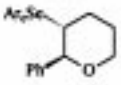
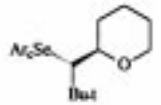
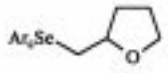
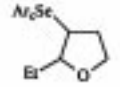
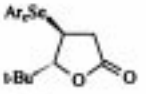
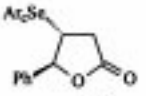
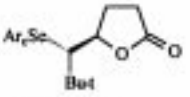
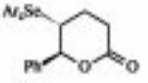
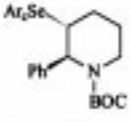
Scheme 89.

reduction of the cyanidrin derivative of (**85.1**), previously protected as allyl selenide to avoid the cleavage of the C–Se bond by direct reduction. The obtained amino alcohol (**85.5**) was converted into the *N*-acetylated derivative and, by sequencial oxidation with *m*-CPBA, into the corresponding selenoxide which suffers spontaneous [2,3]-sigmatropic rearrangement with removal of the protecting group. Reductive work-up with hydrazine regenerates the diselenide linkage giving (**85.2**).



Scheme 90.

Table 1. Asymmetric cyclization promoted by reagent **90.5a**

Entry	Olefin	Major Product	Diastereomeric Ratio	Yield (%)
1			12:1	77
2			12:1	92
3			9:1	89
4			29:1	95
5			8:1	77
6			2.3:1	96
7			2:1	73
8			20:1	72
9			13:1	72
10			10:1	84
11			40:1	65
12			25:1	89

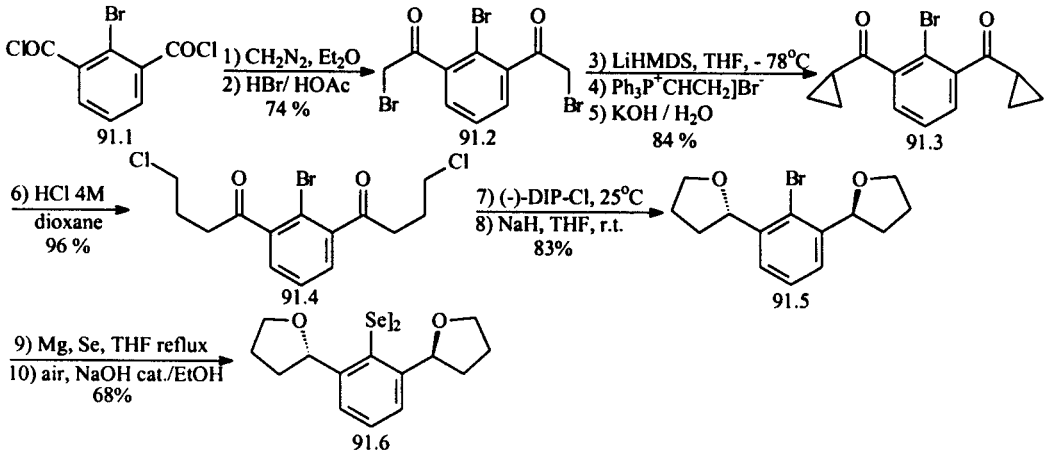
Alternatively, treatment of (**85.5**) with *N*,*N*-carbonyl bis(imidazole) followed by *m*-CPBA oxidation, leads to diselenide (**85.3**).

The treatment of each diselenide with SO_2Cl_2 in CH_2Cl_2 produces the corresponding selenenyl chlorides which are employed 'in situ' in the cyclization reactions (Scheme 86).

The cyclization of pent-4-en-1-ol and penten-4-oic acid (**87.1**) with the three chiral selenenyl chlorides showed that the higher diastereoselectivity was furnished by reagent (**86.3**)[99,100] (Scheme 87).

Scheme 88 summarizes the cyclization performed with several unsaturated alcohols and carboxylic acids[99,100] giving the corresponding furans (**88.2**, **6a**, **8a**, **10**) and lactones (**88.4**, **6b**, **8b**) (Scheme 88).

The deselenenylation of compound (**89.1**) and (**89.3**) giving the corresponding selenium free products (**89.2**) and (**89.4**) with optical rotation comparable with those of authentic



Scheme 91.

samples clearly confirms their optical purity and absolute stereochemistry (Scheme 89).[99,100]

7.2. (*R*,*R*) and (*S*,*S*)-bis[2,6-bis(1-ethoxyethyl) phenyl] diselenide

Following a previous multi-step synthesis of the title (*R*,*R*) chiral reagent,[101] a modified sequence[102] was established achieving a facile and economical access to both the title enantiomers, in accordance with Scheme 90.

The bromophthalic acid (**90.1**) is converted to the diketone (**90.2**) by conventional procedure. Treatment of (**90.2**) with commercially available (+) or (−)-β-chlorodiisopinocamphenylborane (DIP-chloride), affords the (*R*,*R*) and (*S*,*S*) diols (**90.3a**) and (**90.3b**), respectively.

The *R*,*R* corresponding ethyl ethers (**90.4a**) and (**90.4b**) are converted to the desired diselenides (**90.5a**) and (**90.5b**) by lithiation with *t*-BuLi followed by oxidative selenation.

The *R*,*R* diselenide (**90.5a**), by sequential treatment with Br_2 in CH_2Cl_2 at −78°C and AgOTf in MeOH, is converted into the corresponding electrophilic triflate. Table 1 summarizes the cyclization reactions of this reagent,[103] carried out in CH_2Cl_2 at −78°C in the presence of 2.5% of MeOH.

The results outlined in Table 1 indicate that in entry 1, 3 and 5 the 5-*endo*, 5-*exo* and 6-*exo* mode of cyclization takes rise with approximately the same degree of facial selectivity. A surprising reversal of facial selectivity occurs by substituting the *t*-butyl group for a phenyl group (entry 2). The entry 4 shows that the 6-*endo* cyclization furnishes the highest selectivity, whereas terminal olefins or olefins bearing a small alkyl substituent are cyclized with poor selectivity (entry 6 and 7).

Cyclization of unsaturated acids and carbamates occurs in good yield and with high facial selectivity, especially in the case of 6-*endo* mode (entry 11 and 12).

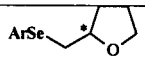
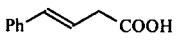
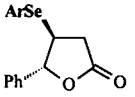
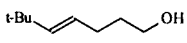
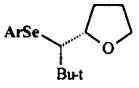
The absolute stereochemistry of some products was assessed by removal of the chiral organoselenium moiety by reaction with Ph_3SnH/AIBN and by comparing the optical rotation of the heterocycles with the values of authentic samples.

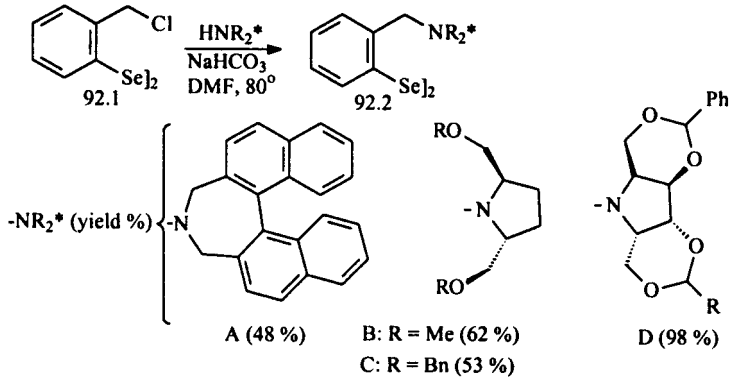
7.3. 2,6-Bis[(2*S*)-tetrahydrofuran-2-yl] phenyl diselenide

The title reagent, a rigidified analog of the preceeding one, was synthesized in accordance with scheme 91.[104]

The bis-bromoketone (**91.2**) is obtained from (**91.1**) via the intermediate diazoketone (step 1 and 2). (**91.2**) is converted to the cyclopropyl phosphonium salt (step 3 and 4) and successively to the bis-cyclopropenylketone (**91.3**) (step 5).

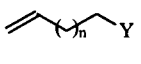
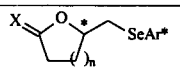
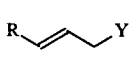
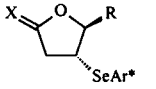
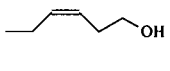
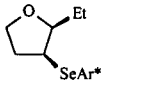
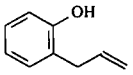
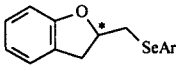
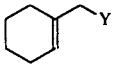
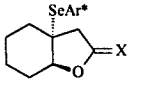
Table 2. Asymmetric cyclization promoted by reagents **90.5b** and **91.6**

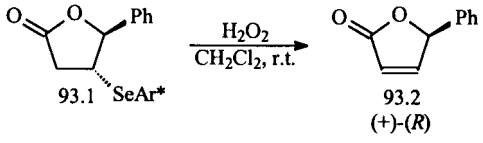
Entry	Olefin	Product	Ratio (yield) With **90.5b**	Ratio (yield) With **91.6**
1			2:1 (96)	10:1 (84)
2			13:1 (72)	>100:1 (62)
3			9:1 (89)	15:1 (61)



Scheme 92.

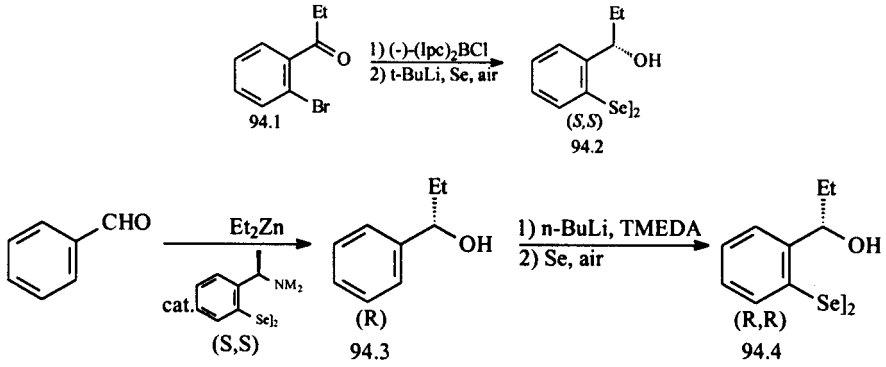
Table 3. Asymmetric cyclization promoted by reagent **92.2D**

Olefin	Product		Yield (%)	d.e. (%)
		n = 1,2 {Y = CH_2OH X = H, H; Y = CO_2H X = O}	100; 80 81; 90	22:59 57:39
		R = Et, Ph {Y = CH_2OH X = H, H; Y = CO_2H X = O}	86; 88 90; 87	>98:94 >98:92
			71	56
			83	13
		{Y = CH_2OH X = H, H; Y = CO_2H X = O}	62 77	13 93



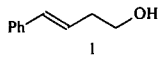
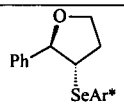
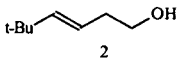
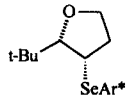
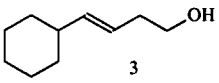
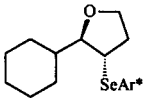
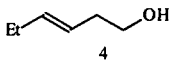
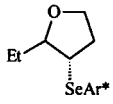
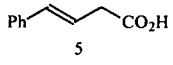
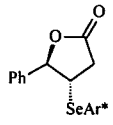
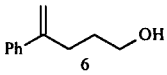
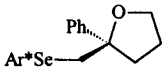
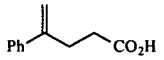
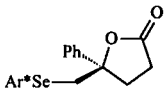
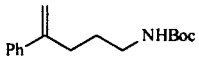
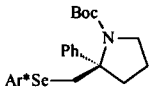
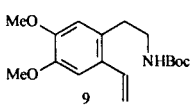
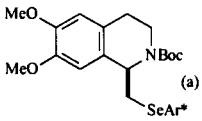
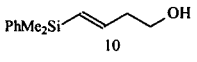
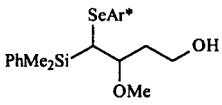
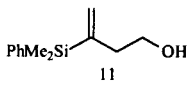
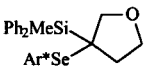
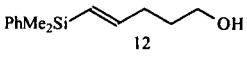
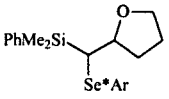
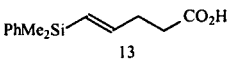
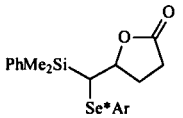
Scheme 93.

The bis-chloroketone (**91.4**) is obtained by treating (**91.3**) with HCl. The enantioselective reduction of (**91.4**) (step 7) gives the *S,S* diol, which, when treated with NaH, affords the desired bis(tetrahydrofuranyl) derivative (**91.5**) in 83% and 99% ee. The incorporation of selenium via the Grignard derivative of (**91.5**) (step 9) and air oxidation leads to the desired diselenide (**91.6**).



Scheme 94.

Table 4. Asymmetric cyclization reactions promoted by reagent **94.2**

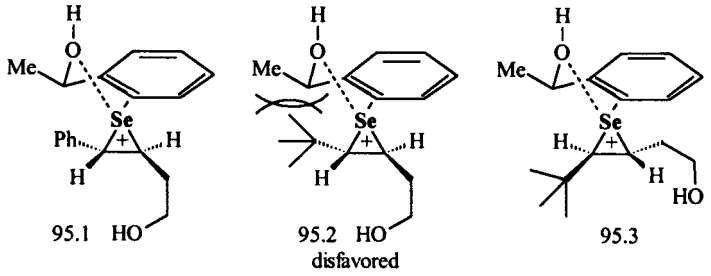
Alkene	Major Product	Yield (%)	de (%)
 1		87	84
 2		68	46
 3		64	49
 4		60	0
 5		41	72
 6		45	78
 7		58	85
 8		40	45
 9	 (a)	66	79
 10		20	78
 11		22	9
 12		34	82
 13		27	80

[a]See Refs. 111, 112.

The preparation of the electrophilic triflate derivative of (**91.6**) and the cyclization reactions, were carried out according to the previously described protocol.

Results from Table 2 clearly demonstrate that the rigidified reagent (**91.6**) exhibits an overall higher degree of asymmetric induction in comparison with the former diethoxylated reagent (**90.5b**). The *trans* phenylsubstituted olefin (entry 2) gives the highest selectivity with (**91.6**) and the unsubstituted olefin (entry 1) also exhibits good selectivity.

The *S* absolute stereochemistry of entry 2 product was



Scheme 95.

assessed by deselenenylation and comparison of the optical rotation of the obtained lactone with the value of an authentic sample.

7.4. Optically active diselenides bearing a tertiary amino group

Optical active diselenides (**92.2**) have been prepared from di-(2-chloromethylphenyl) diselenide (**92.1**) and appropriate chiral cyclic amines[105] (Scheme 92).

Among the above chiral diselenides, the last one (**92.2D**) exhibits synthetic advantage since the chiral amine is readily prepared from D-mannitol[106] and the coupling reaction with (**92.1**) takes rise in high yield.

Table 3 summarizes cyclization reactions of the corresponding hexafluorophosphate (prepared by sequential treatment with Br_2 in CCl_4 and $AgPF_6$/molecular sieves in CH_2Cl_2 at $-78°C$) with several unsaturated alcohols and carboxylic acids.

The absolute stereochemistry of the lactone (**93.1**) was determined by the optical rotation value of the corresponding butenolide (**93.2**) produced by oxidative deselenenylation (Scheme 93).

7.5. Di-[*o*-(1-hydroxypropyl)phenyl] diselenide and related reagents

The (*S*,*S*) enantiomer of the title reagent (**94.2**) was prepared from *o*-bromopropiophenone (**94.1**) by stereoselective reduction to corresponding (*S*)-alcohol employing (−)-β-chlorodiisopinocamphenylborane, followed by lithiation and oxidative selenation.[107] The (*R*,*R*) enanthiomer (**94.4**) was synthesized by the oxidative selenation of the lithiated (*R*)-1-phenylpropanol[108](**94.3**) obtained by the catalyzed enantioselective addition of diethylzinc to benzaldehyde[109] (Scheme 94).

To achieve good yields and efficient chiral transfer, the cyclization reactions, performed with the corresponding triflates prepared in situ, require the presence of methanol, which is assumed to stabilize the episelenonium ion. The results of the cyclization reactions promoted by reagent (**94.2**) are summarized in Table 4.[110]

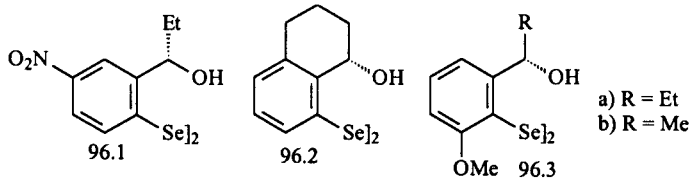
The cyclization of different substituted homoallylic alcohols (compounds 1–4) takes rise in a 5-*endo* mode. In the case of the phenyl derivative (compound 1), a *re*-attack of the selenium electrophile, followed by the anti-attack of the nucleophile to the formed episelenonium ion (**95.1**), gives the tetrahydrofuran with (*R*,*R*) stereochemistry at the newly formed chiral center. In the case of the t-butyl derivative (compound 2) a *si*-attack of the selenium is predominant to avoid a great steric interaction, and the attack of the nucleophile to the episelenonium ion (**95.3**) leads to the inverse configuration in the produced furan[110] (Scheme 95).

The *c*-hexyl derivatives (compound 3) give a 49% diastereoselectivity, whereas with the ethyl derivative (compound 4) no diastereoselectivity was observed. Compounds 6 and 7 lead to the formation of asymmetric tetrasubstituted carbon atoms, which are hardly accessible by other methods, with good diastereoselectivity. In the latter two cases the cyclization occurs in a 5-*exo* mode and involves a *si*-face attack of the selenium to the alkene leading to the more stable episelenonium ion. The subsequent *anti*-attack of the nucleophile gives the (*R*) configuration at the benzylic C atom.

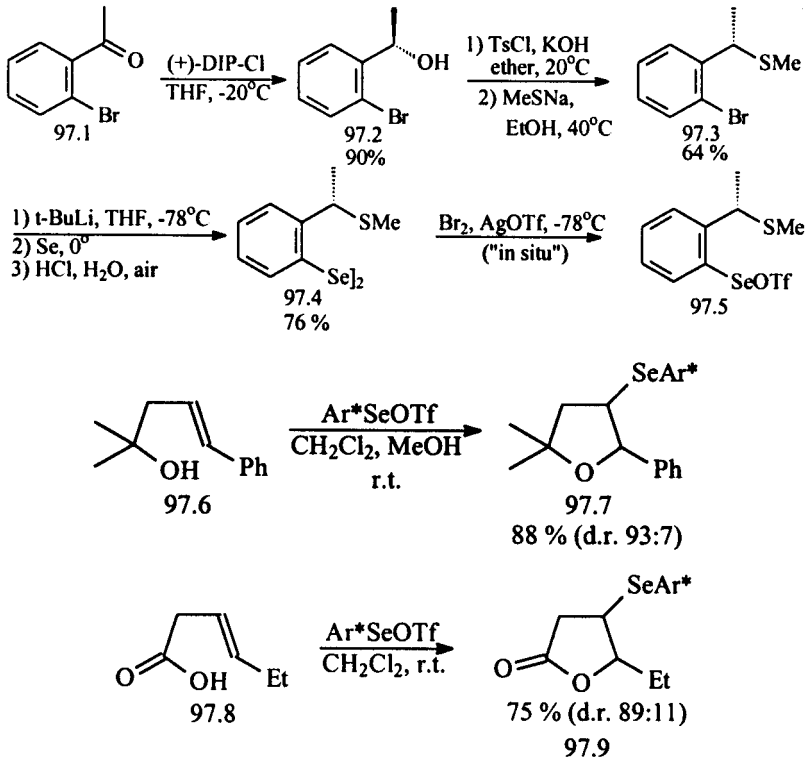
The cyclization with *N*-nucleophiles is also achieved as exemplified in the case of compounds 8 and 9 giving pyrrolidine and piperidine derivatives.

Different results were obtained with silyl substituted substrates: compound 10 furnishes only the addition product (by participation of MeOH), compound 11 shows poor diastereoselectivity, whereas in the case of compounds 12 and 13 cyclization in a 5-*exo* mode was observed with poor yields but high diastereoselectivity.

Some related chiral reagents (**96.1–3**) have been synthesized with the purpose of investigating the influence on



Scheme 96.

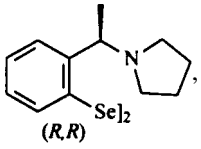


Scheme 97.

the diastereoselectivity by changing the electrophilicity of the Se cation through the attachment of an additional substituent at the aromatic ring, or by decreasing the conformational flexibility of the reagent in a more rigid structure (Scheme 96).

Compound (**96.1**) was prepared by treating with Na_2Se_2 the corresponding bromide[112] obtained by the already mentioned catalyzed enantioselective addition of diethylzinc to aldehydes.

Compound (**96.2**) was prepared via lithiation of tetralol.[112,113] Compounds (**96.3a,b**) were prepared, respectively by enantioselective addition of Et_2Zn to 3-methoxybenzaldehyde in the presence of the catalyst

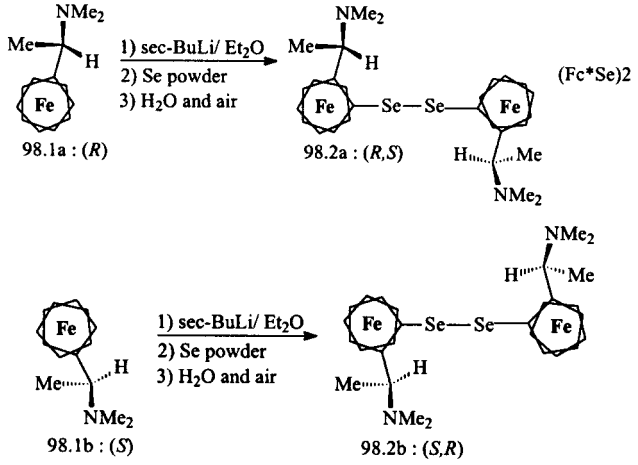


(*R*,*R*)

and by reduction of 3-methoxybenzaldehyde with (−)-$(Ipc)_2BCl$, followed by the sequential ortho-lithiation and oxidative selenation.[111]

X-ray analysis shows that the methoxylated reagent (**96.3b**) exhibits a strong interaction between the Se atom and the oxygen atom of the methoxy group. Increased stereoselectivity was observed in the cyclization reactions of this reagent with compounds 4, 5 and 9 of Table 4, in comparison with the non-methoxylated reagent.[111] An improvement in the selectivity was also achieved in the cyclization of compound 9 with the bicyclic reagent (**96.2**).[112] The cyclization product of reagent (**96.1**) with compound 9 was obtained in 64% yield, but it was not possible to determine the diastereomeric excess of the reaction.[112]

A new sulphur containing chiral diselenide (**97.4**) and the corresponding triflate (**97.5**) was recently synthesized in accordance with Scheme 97 and successfully submitted to selenocyclization reactions (**97.6**→**97.7**; **97.8**→**97.9**)[97] (Scheme 97).

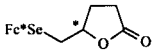
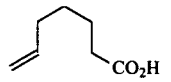
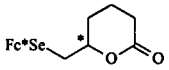
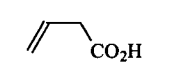
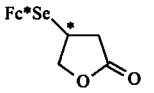
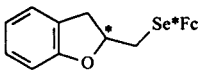
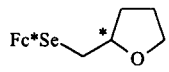
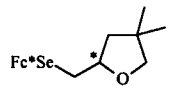


Scheme 98.

7.6. Chiral diferrocenyl diselenides

The (*R*,*S*)-diferrocenyl diselenide (**98.2a**) was synthesized in 77% yields by lithiation and oxidative selenation of (*R*)-[1-(dimethylamino)ethyl]ferrocene (**98.1a**). The (*S*,*R*) reagent (**98.2b**) was synthesized in 80% yield in a similar way, starting from the (*S*)-ferrocene (**98.1b**)[114,115] (Scheme 98).

Table 5. Asymmetric cyclization promoted by Se-ferrocenyl reagents

Substrate	Reagent and conditions	Product	Yield (%)	de (%)
	(R,S)Fc*SeBr (Et_3N), THF -78°C-r.t., 20h		70	>95
	(R,S)Fc*SeBr Same conditions		84	>95
	"		46	87
	"		56	34
	"		20	>95
	"		29	76
	"		55	75

No interaction between Se and N atoms was observed in (**98.2b**).

Asymmetric cyclization reactions, performed with the corresponding electrophilic bromides, are summarized in Table 5.[116]

The (*S,R*)Fc*SeBr reagent fails to react with the olefinic urethane, but the change of the counter-ion from Br^- to $BF4^-$, PF_6^- and OTf^- allows the cyclization reaction (Scheme 99).

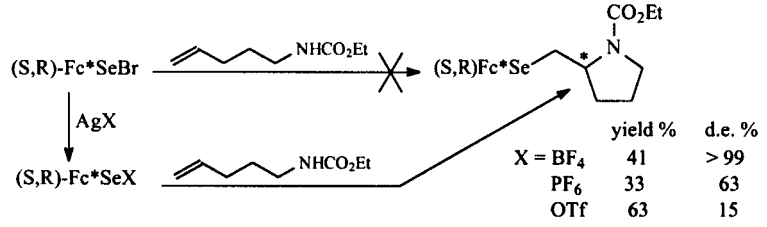
8. Conclusion

This review focuses on the growing importance achieved in the last decades by selenocyclofunctionalizations reactions as a precious tool for various selective organic manipulations.

New strongly eletrophilic selenium reagents have been employed in the well known selenoetherification and selenolactonization reactions, not only under the usual 5-*exo*-trig mode process but also under the traditionally disfavored 5-*endo*-trig mode. Several types of differently substituted seleno tetrahydrofurans, dihydrofurans and lactones with specific stereochemistry have been synthesized, that in some cases have been submitted to oxidative or reductive deselenenylation. Such selenocyclizations have also been employed in multistep synthesis of several natural products or of related building blocks.

The selenium promoted cyclizations of alkenyl nitrogenated substrates afford different nitrogen heterocycles depending on several factors, such as the alkenyl chain, the nature of the 'gegenion' and the experimental conditions employed. Otherwise, in the case of nitrogen nucleophile bearing an additional functionality, competitive reactions can take place leading to the formation of C–N or C–O bonds.

The asymmetric cyclofunctionalization reactions of a variety of unsaturated alcohols and carboxylic acids, and



Scheme 99.

some carbamates, promoted by different chiral selenium reagents have been summarized. The cyclic products are formed with medium to good diastereomeric excess.

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