Recent advances in selenium promoted or catalyzed electrophilic aminations of alkenes and alkynes

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Dedicated to Prof. Lorenzo Testaferri on the occasion of his 75th birthday

Abstract

In the last decades, synthetic methods for the construction of carbon-nitrogen bonds rapidly grew, due to the important applications of amino compounds in fine chemicals, biological and pharmaceutical sciences. The aminoselenylations of alkenes and alkynes are versatile reactions that usually occur with high regio- and stereo-control under mild reaction conditions. Linear and cyclic compounds can be prepared with wide functional and structural diversity using stoichiometric or catalytic amounts of electrophilic selenium reagents. This review collects recent advances in this attractive and fruitful research field.
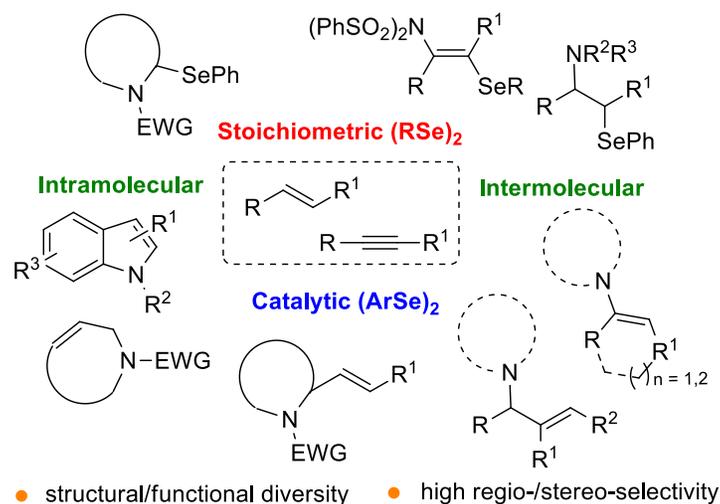
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1. Introduction

Nitrogen containing molecules are fundamental structural motifs in natural products and biologically active compounds. The access to a diverse array of functionalized compounds is critical in drug discovery projects and also for this reason in the past few decades, operationally simple new methodologies for C-N bond formation have been deeply investigated. In this field, the electrophilic seleno-functionalizations of carbon-carbon multiple bonds[1-8] offer interesting opportunities, also in consideration of the growing interest in the pharmacological and toxicological properties of selenium-containing compounds.[8-14] The reaction of alkenes with commercial selenium electrophiles, such as PhSeCl, PhSeBr or Phenylselenophthalimide (NPSP), has been deeply explored (Scheme 1). Other electrophilic reagents can be generated by oxidative cleavage of bench-stable diselenides using inorganic or organic oxidants, typically persulfates or hypervalent iodine species.
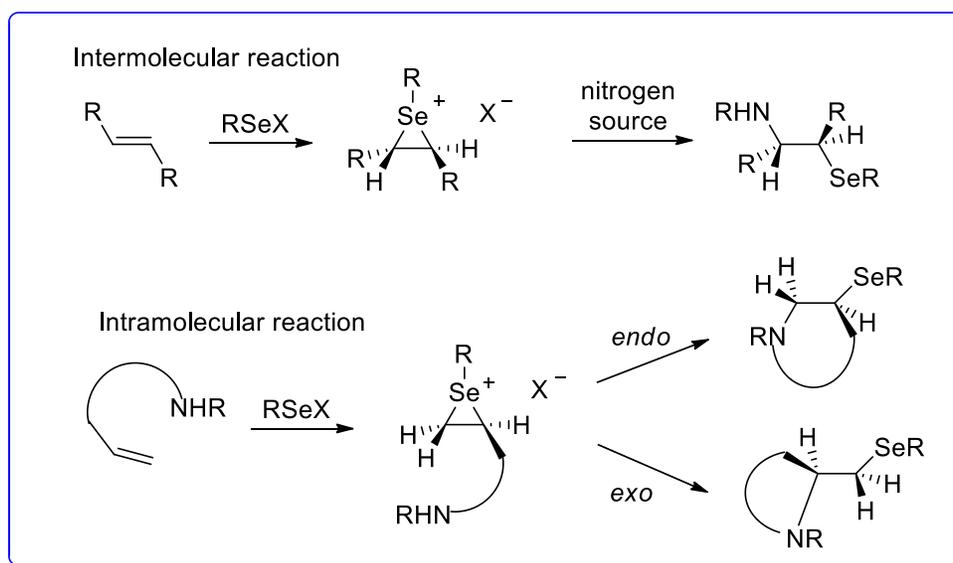
Scheme 1. Inter or intramolecular aminoselenylations of alkenes.

Mechanistically, the insertion of the selenium electrophile into the carbon-carbon unsaturated bond generates a cyclic seleniranium ion which is captured by the nucleophile with high regio- and stereo-control. The reaction can occur also intramolecularly, offering a powerful synthetic route to heterocycles. Since the selenium forms relatively weak σ-bonds, the incorporated selenium moiety can be used for further radical or ionic conversions leading to non selenium-containing substitution or elimination products. These reactions occur at a faster rate and under milder conditions than those of the corresponding sulfurated analogous. The

seleno-functionalizations have developed rapidly over the past 30 years and have become a useful tool for the chemo-, regio-, stereo- and also enantio-selective synthesis of organic molecules. However, if selenium-mediated C-O bond forming reactions have been extensively studied, the examples of C-N bond formation are relatively few. This survey will focus on recent advances in selenium-promoted or -catalyzed amino-functionalizations of double and triple bonds covering the literature of the last 15 years. Representative previous works will be also discussed in order to illustrate the synthetic potential of the method.

2. Intermolecular Aminoselenylations of C-C Double and Triple Bonds

The amidoselenylation and the azidoselenylation of alkenes are typical approaches for the introduction of nitrogen-centered nucleophiles. The amidoselenylation of alkenes by treatment with PhSeCl in acetonitrile and water in the presence of trifluoromethane sulfonic acid was pioneered by Toshimitsu and Uemura in the 80s (Scheme 2, method a).[15-16] These Ritter-type reactions proceed by the attack of the nitrogen atom of acetonitrile on the seleniranium ion to give an intermediate which undergoes hydrolysis. Similar reactions can be carried out with diverse nitriles, such as propionitrile, butyronitrile, and benzonitrile. NH_2CN (Scheme 2, method b) gave cyanamideselenylation products as the result of the nucleophilic attack on the seleniranium ion by the amino group, instead.[17] Enantiomerically pure amidoselenylation products have been isolated from reactions carried out with a camphor-derived diselenide as the chiral selenium source.[18]

a. PhSeCl, CF_3SO_3H, CH_3CN, H_2O, reflux
b. NPSP, *p*-TsOH, NH_2CN, CH_2Cl_2, rt
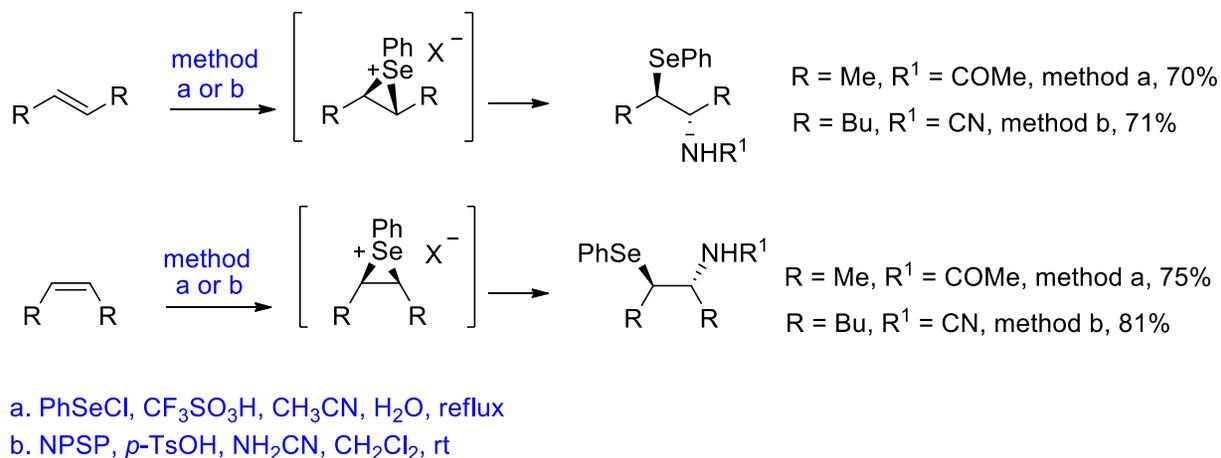
Scheme 2. First aminoselenylations of alkenes.

The amidoselenylation of alkenes is the key step of cascade processes useful for the synthesis of diversely functionalized 4,5-dihydro-1,3-oxazoles (Scheme 3).[19] In these protocols the electrophilic phenylselenyl sulfate, produced *in situ* by oxidation of the diphenyldiselenide with ammonium persulfate, reacts with an alkene in the presence of acetonitrile, H_2O and CF_3SO_3H (TfOH), and generates the amido selenylation products. In the further steps the selenoacetamides are converted into selenonium ions and finally into the 4,5-dihydro-1,3-oxazole as an effect of an intramolecular nucleophilic substitution by the amidic oxygen. 2-amino substituted-1,3-oxazoles were similarly formed from reactions with the cyanamide. The procedure was also adapted to the synthesis of the taxol side chain.[20]
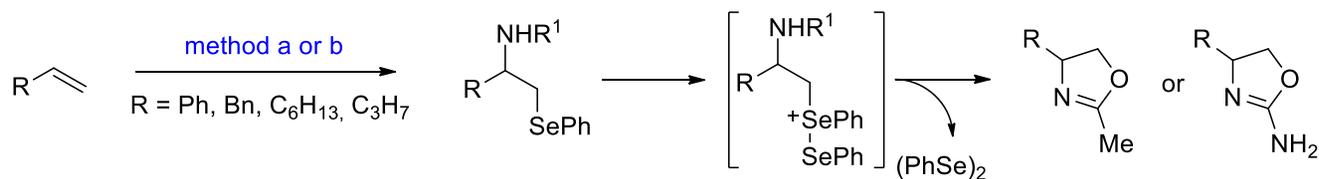
a. (PhSe)$_2$, (NH$_4$)$_2$S$_2$O$_8$, CH$_3$CN, TfOH, H$_2$O, 60°C, 60% yield for R^1 = COMe

b. (PhSe)$_2$, (NH$_4$)$_2$S$_2$O$_8$, NH$_2$CN, TfOH, 1,4-dioxane, H$_2$O, 80°C, 54% yield for R^1 = CN

Scheme 3. Cascade synthesis of oxazolines.

Hassner developed the first azidoselenylation of alkenes[21] by addition of PhSeCl and sodium azide to simple alkenes in DMSO at room temperature. The reactions proceed with good *anti* stereospecificity, but poor regioselectivity, favouring Markovnikov addition products, as reported in Scheme 4 (examples a-b).
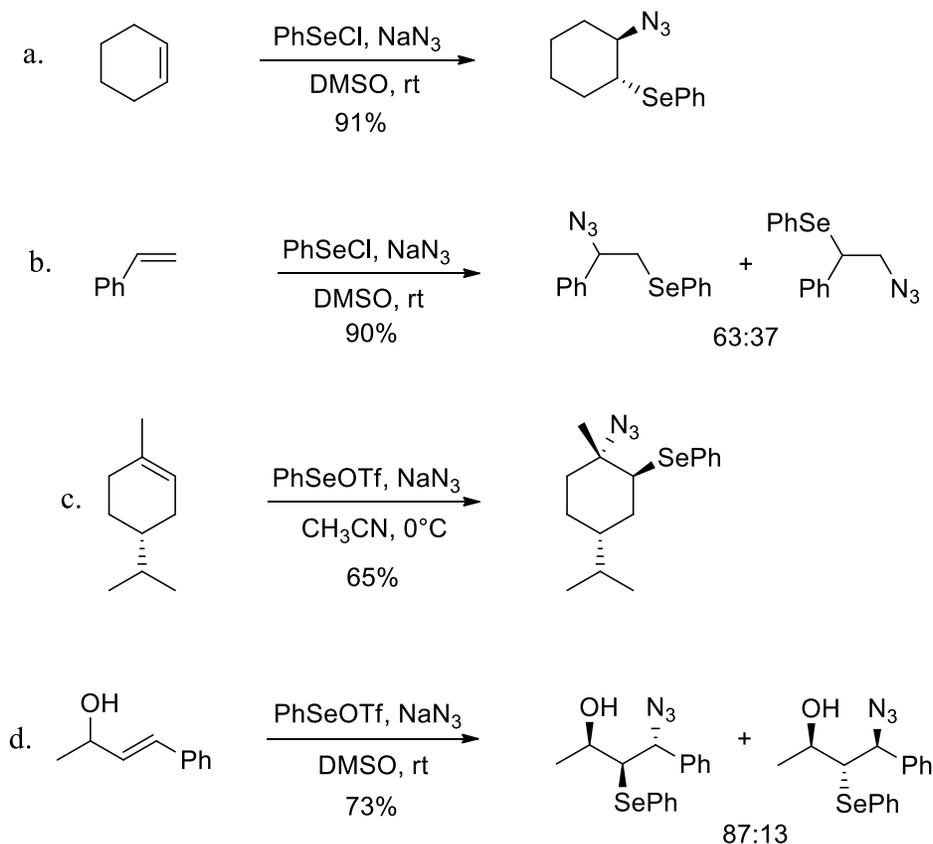
Scheme 4. Azidoselenylations of alkenes.

In the same scheme more recent examples of seleno-azidations of terpenes[22] and allylic alcohols[23] are also reported (Scheme 4, examples c-d). These reactions were performed with phenylselenyl triflate generated by anion exchange from the corresponding bromide in the presence of silver triflate (AgOTf). The chiral arylselenyl triflates reported in Scheme 5 have been successfully employed to control the facial selectivity of the azidoselenylation.[24-25] The intramolecular nonbonding interaction between the electrophilic selenium and the coordinating sulfur can force the chiral centre nearby the reactive centre and control the selectivity of the process with diastereoselectivity up to 97:3.[25]
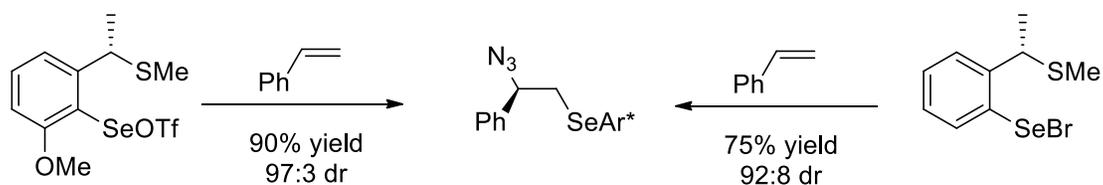
Scheme 5. Asymmetric azidoselenylations of alkenes.

Interestingly, anti-Markovnikov products were prepared with moderate diastereoselectivity through a radical-initiated azidation of alkenes with diphenyldiselenide, NaN_3 and (diacetoxyiodo)benzene (PIDA) in dichloromethane at room temperature (Scheme 6, method a).[26,27] Similar processes have been successfully applied to the functionalization of glycals (Scheme 6, method b).[28] In the reported examples, diversely protected D-galactal derivatives were transformed into the corresponding α-selenoglicosides with complete regio- and stereo-selectivity.

a. P = Ac, $(PhSe)_2$, PIDA, NaN_3, CH_2Cl_2, rt
b. P = Bn, NPSP, $TMSN_3$, TBAF, CH_2Cl_2, rt
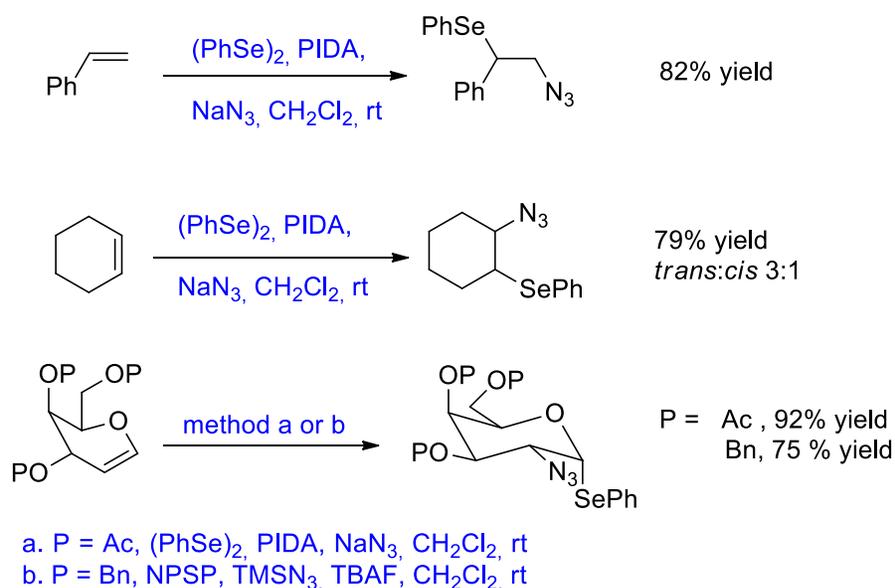
Scheme 6. Radical-initiated azidoselenylations of alkenes.

After the seminal works, new protocols have extended the scope of the selenoaminations to alternative nitrogen sources or optimized the generation of the electrophilic species according to the principles of sustainable chemistry. In 2015, Tang described a new amidoselenylation of styrene derivatives using NPSP as both the selenium and nitrogen source in the presence of $TiCl_4$ (Scheme 7).[29] In the proposed mechanism the reactions proceed through the formation of a seleniranium ion that can be trapped by the phthalimide nitrogen. Terminal and internal *E* or *Z* alkenes gave products in good yields, high Markovnikov-type regioselectivity and *anti*-stereospecificity. *N*-(phenylseleno)succinimide (NPSS) did not work in similar transformations.
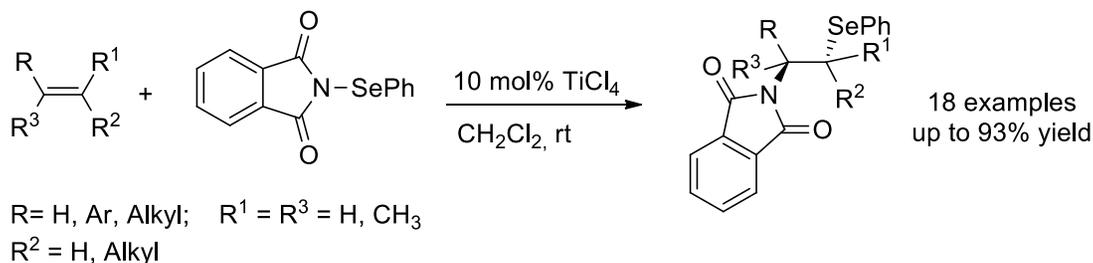
Scheme 7. TiCl$_4$–imidation of alkenes with *N*-phenylselenophthalimmide.

The production of electrophilic selenium species by oxidation of easy to handle and bench-stable diselenides under green conditions has been intensively investigated. Several protocols for the amido- or amino-selenylation of alkenes that avoid the use of strong acids or transition-metal salts have appeared in the recent literature. An example is the addition of saccharin to styrene or variously mono- or di-substituted alkenes successfully investigated in 2016 (Scheme 8).[30] The reaction was carried out with diphenyl diselenide and potassium persulfate as the oxidant to generate a selenylating agent with a non-nucleophilic counterion. The transition metal-free method was also applied to the addition of other pharmaceutically relevant amino sources such as sulfonimides, di-, tri- or tetra-azoles, and purines.
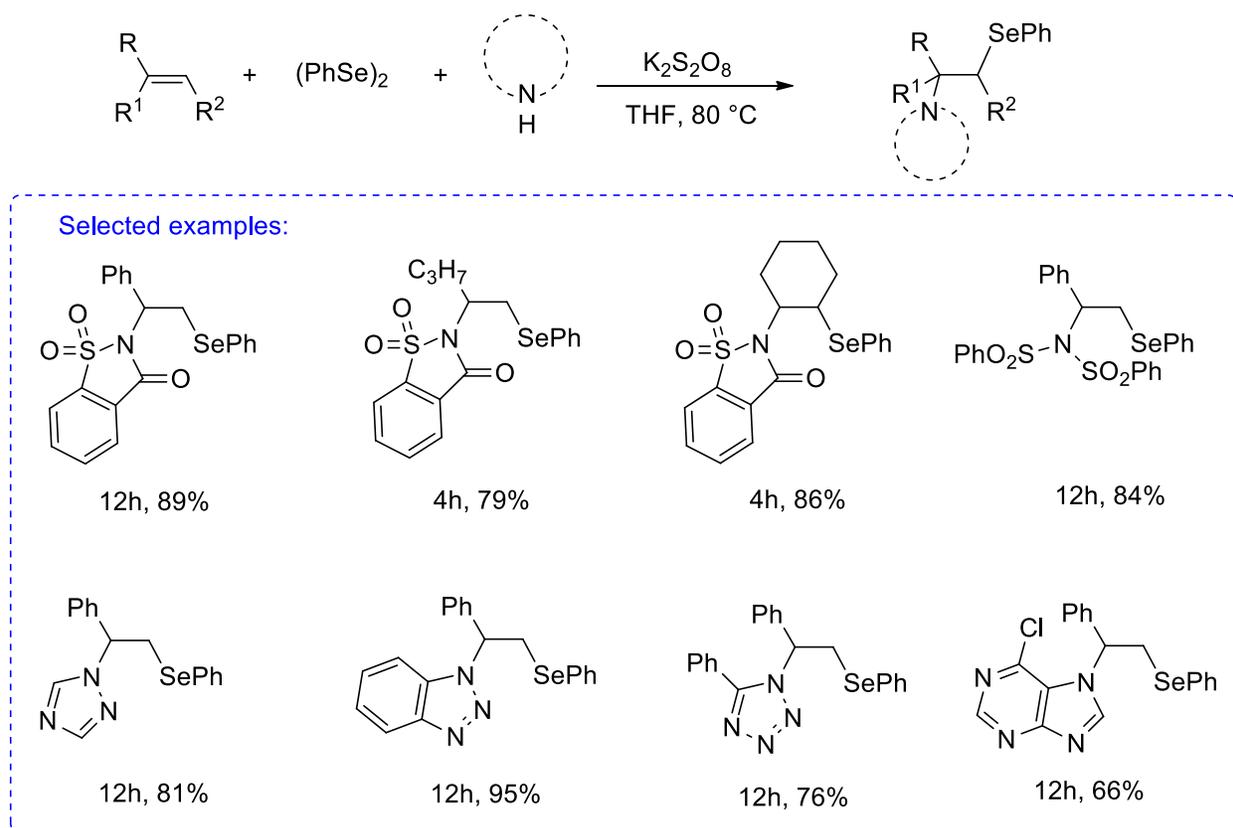
Scheme 8. Aminoselenylation reactions of alkenes with sulfonimides, azoles or purines.

The addition of benzotriazoles to alkenes was also promoted by molecular iodine (Scheme 9).[31] As reported in the scheme, the iodine reacts with equimolecular amounts of diselenide inducing a fast Se-Se bond cleavage and the *in situ* formation of the electrophilic species. Good yields were obtained with styrene

derivatives. Conversely, modest results were collected when reactions were performed with alkyl monosubstituted alkenes or cyclic alkenes.
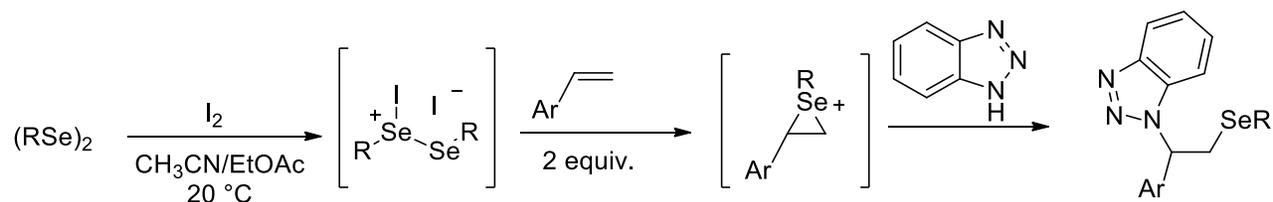
Scheme 9. Iodine-mediated aminoselenylation of alkenes with benzotriazoles.

A similar protocol involving a diselenide, molecular iodine and an alkene provided the access to 1,2-selenosulfonamides with high regioselectivity and broad structural and functional group tolerance (Scheme 10).[32] Contrary to what observed in the previous case, authors suggest the involvement of radical selenium species in the reaction mechanism.
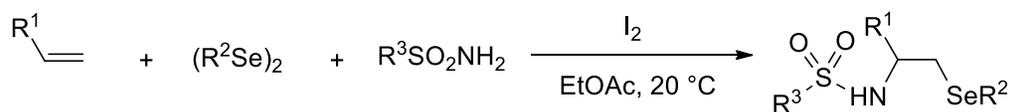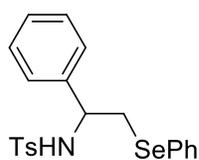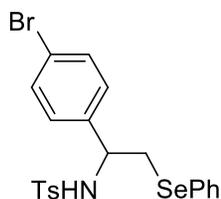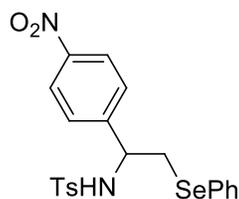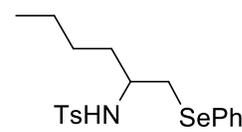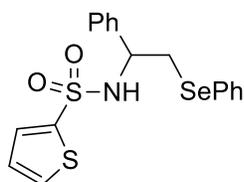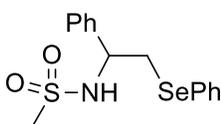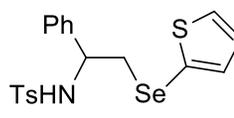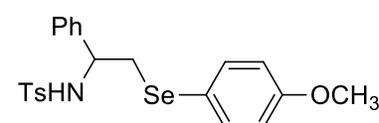
Scheme 10. Iodine-mediated sulfonamidoselenylation of alkenes.

The production of electrophilic selenium species from different diaryl diselenides by using oxygen as terminal oxidant has been also developed (Scheme 11).[33] Several examples are disposable with a broad nitrogen source scope including benzotriazoles, di- and triazoles, purines, and sulfonimides. Notably, the reaction gave good results also on a gram-scale. Mechanistic insights seem to confirm a ionic pathway with the formation of classical seleniranium intermediates.
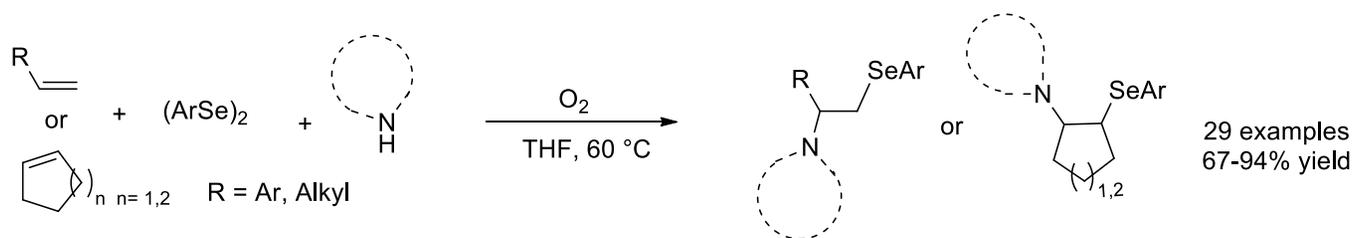
Scheme 11. O$_2$-mediated oxidation of diselenides for aminoselenylation reactions.

In Scheme 12, an electrochemical aminoselenylation of styrene derivatives is described. This method gave products with wide nitrogen scope, high regioselectivity and reasonable to good yields under additive-free conditions at room temperature.[34] It also extended the scope of the intermolecular aminoselenylation of alkenes to anilines, not employed before.

N source = benzotriazoles, pyrazoles, sulfonamides and anilines
HFPI = 1,1,1,3,3,3-hexafluoro-2-propanol
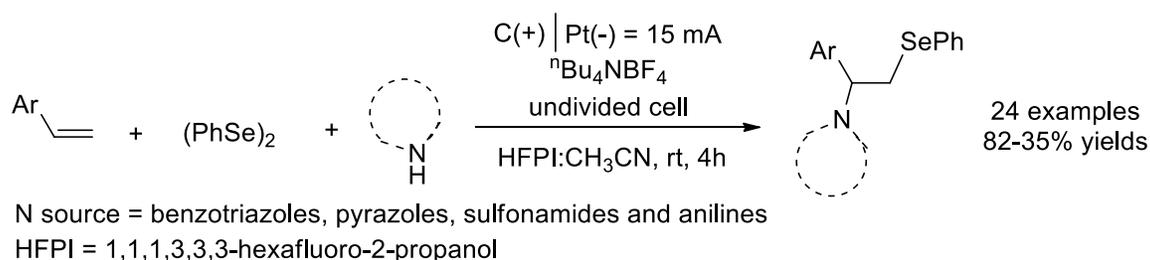
Scheme 12. Electrochemical aminoselenylations.

Very recently, nitrogen containing functional groups have been also incorporated onto C-C triple bonds for a convenient and stereo-controlled access to synthetically valuable vinyl selenides.[35-38] In 2016 the first highly regio- and stereo-selective functionalization of alkynes with diphenyldiselenide and N-fluorobenzenesulfonimide (NFSI) has appeared in the literature (Scheme 13).[39]
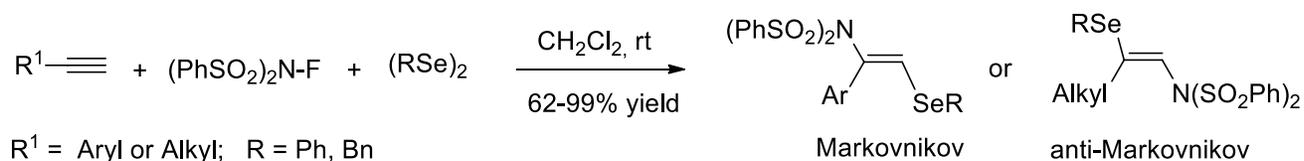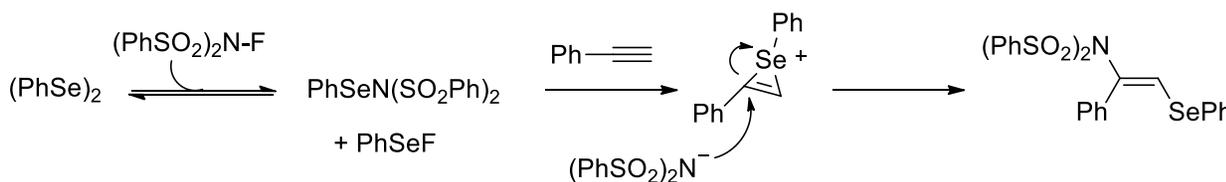
Scheme 13. Imidoselenylations of alkynes.

NFSI is a strong oxidant. It can generate the two electrophilic selenium species reported in Scheme 13, and also acts as nitrogen source. Reactions were carried out on both aryl and aliphatic terminal alkynes and gave

enamides with opposite regiochemistry and *anti* selectivity. Authors suggested that the formation of the products is electronically controlled with nucleophilic attack at the benzylic carbon (Markovnikov regioselectivity) in the case of aryl-substituted alkynes, or sterically controlled (*anti*-Markovnikov regioselectivity) in the case of alkyl-substituted alkynes. Also internal alkynes were successfully functionalized. Interestingly the related thiamination of alkynes occurred only under Lewis acid catalysis, probably as a consequence of the lower stability of the sulfur electrophilic species with respect to the selenylated one.

The same combination of NFSI and diselenides was used for the decarboxylative functionalization of alkynes (Scheme 14).[40] In these reactions polyseleno substituted enamides were formedin good to excellent yields by effect of sequential addition of the selenium electrophile to C-C unsaturated bond followed by elimination of CO_2. The reaction is general and both aryl propiolic acids and alkynyl carboxylic acids are competent substrates. The unsubstituted propiolic acid gave the triseleno derivatives in 81% yield. In the case of aryl-substituted propiolic acids better results were obtained in the presence of electron-donating groups on the aromatic ring. Unfortunately cinnamic acids were unreactive. The scope of the diselenides was also wide, including not only variously substituted aryl diselenides, but also diheteroaryl and dialkyl diselenides.
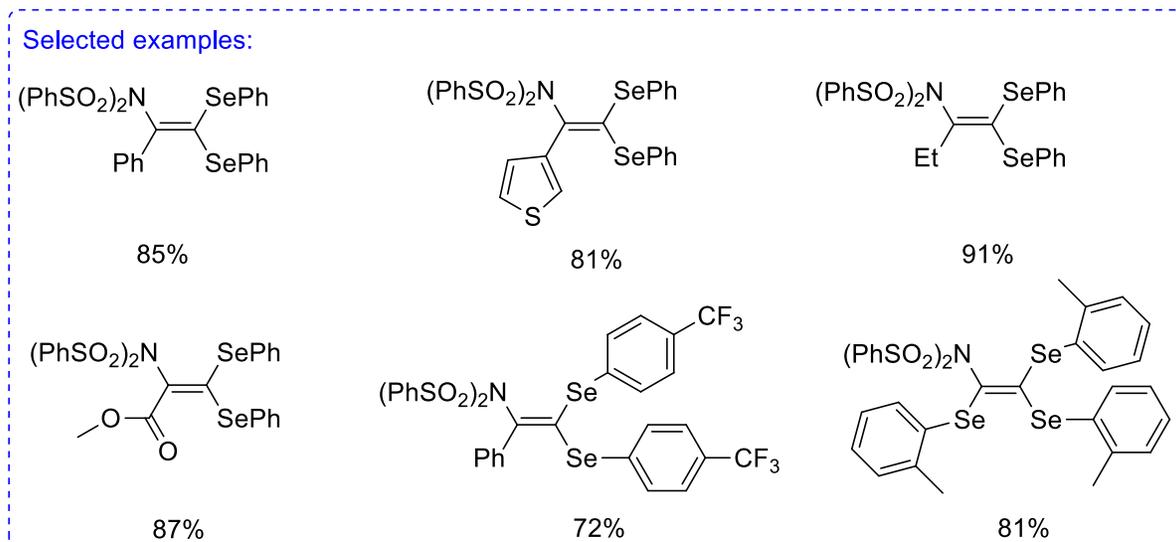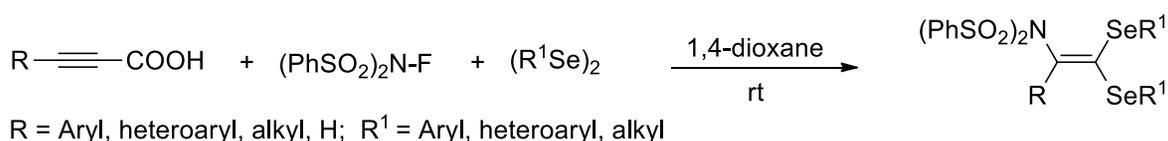
Scheme 14. Decarboxylative imidoselenylations of alkynes.

3. Intramolecular Aminoselenylations of C-C Double or Triple Bonds

Electrophilic selenocyclizations (cyclofunctionalizations) of alkenes containing internal nitrogen nucleophiles are very well documented[1-6] and some of these reactions have found interesting applications in the preparation of complex molecules and alkaloids. Representative examples are reported in Scheme 15.
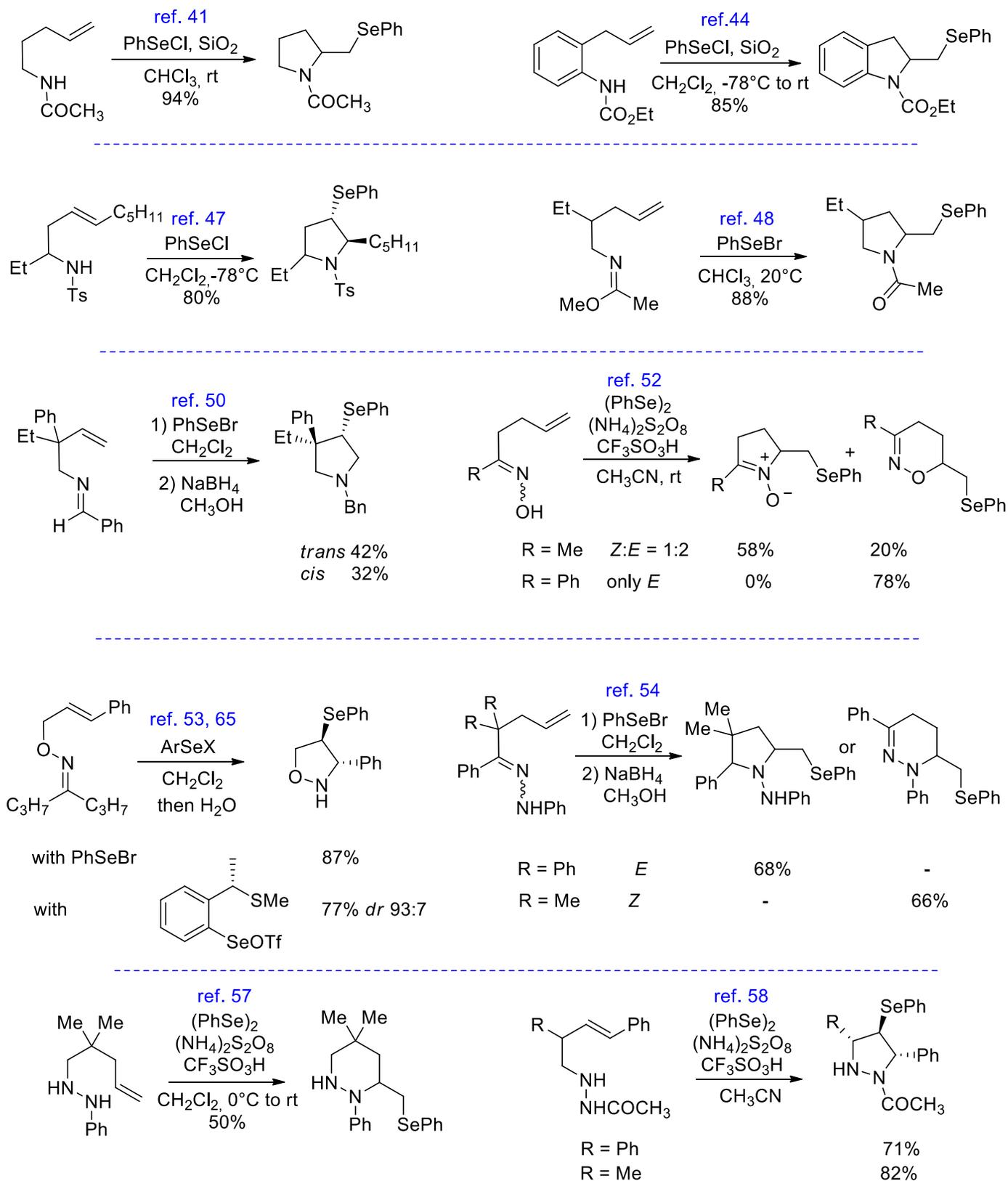
Scheme 15. Synthesis of nitrogen-containing heterocycles by intramolecular aminoselenylations of alkenes.

    Common substrates are alkenes bearing electron-deficient nitrogen containing functional groups such as amides, carbamates, and sulfonamides.[41-47] The nucleophilicity of sp^2 hybridized nitrogen atoms is sufficient to

intramolecularly trap the seleniranium intermediates. In fact, several ring forming reactions were performed with unsaturated imidates, imines and its derivatives such as oximes and hydrazones.[48-54] In these processes, the ring-closure reaction can be followed by fragmentation,[48] reduction with borohydrides or hydrolysis of the initially formed iminium compounds. Primary alkenamines seem not competent substrates for selenocyclizations,[45] however, successful reactions were performed with unsaturated hydroxylamines or hydrazines.[55-58] In general, *exo* or *endo* cyclization modes can occur, depending on the chain length, substitution pattern, nature of the nitrogen protecting group and geometrical alignment of the substrate as well as the ring size of the formed product. A number of 5- or 6-membered heterocycles have been formed, not only through 6-*exo-trig*, 6-*endo-trig*, or 5-*exo-trig* cyclizations, but also through less common 5-*endo-trig*[59] ring closures. Related asymmetric cyclizations have been developed starting from chiral diselenides.[60-65]

Interestingly, in the presence of bidentate nucleophilic groups, competitions in the ring closure by the different atoms can lead to different heterocycles. An example is the cyclization of alkenamides in which both the oxygen and the nitrogen atom could give rise to rings of the same size. In these cases the cyclization afforded cyclic imidates and not lactams as a consequence of the exclusive formation of the C-O bond. A recent example is reported in Scheme 16.[66] Isobenzofurans were obtained in acceptable to good yields, regardless of the nature of the substituent at the nitrogen atom. Remarkably, some selenium-promoted cyclizations with hydroxamic acids have been driven towards the exclusive formation of lactams as a function of the experimental conditions employed.[67-68]
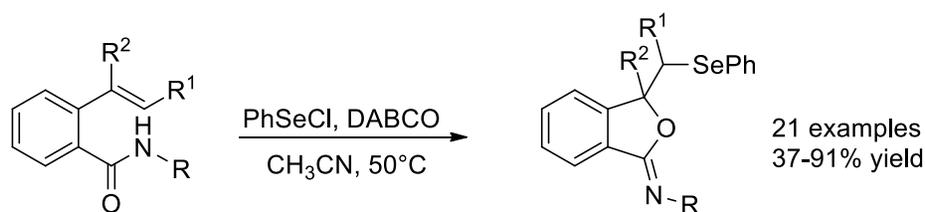
Scheme 16. Imidates from selenocyclizations of amides.

In the recent years new synthetic protocols have been studied for the assembly of challenging and/or pharmaceutically attractive heterocyclic scaffolds by intramolecular aminoselenylation. An example is the formation of the azetidines reported in Scheme 17.[69-70] Homo-allylic secondary amines, when treated with phenyselenyl halides, can generate azetidines or pyrrolidines as the result of an 4-*exo-trig* or 5-*endo-trig* cyclization, respectively. It was recently demonstrated that the regioselectivity of the process is strictly related to the substitution pattern. The introduction of one or more substituents (Thorpe-Ingold effect) in the open-chain reactant had beneficial effects on the yield of cyclization. Moreover the nature and the position of the substituents deeply affected the outcome of the reaction. In fact, γ-substituted homoallylic amines gave azetidines in reasonable to good yields, complete regioselectivity and good diastereoselectivity, favouring the 2,4-*cis* diastereoisomer. With a phenyl group located in the δ-position, the regioselectivity of the reaction was completely reversed furnishing mainly 2,5-*cis*-pyrrolidines. Similar reactions were used to generate halopyrrolidines.[71]

R= H or Me; R^1 = Me, Et, *i*Pr, *t*Bu, Ph   35-72% yield   for R = H *cis*:*trans* > 8:2

R= H or Me; R^1 = Me, Et, *i*Pr, Ph   55-88% yield   for R = H *cis*:*trans* > 8:2
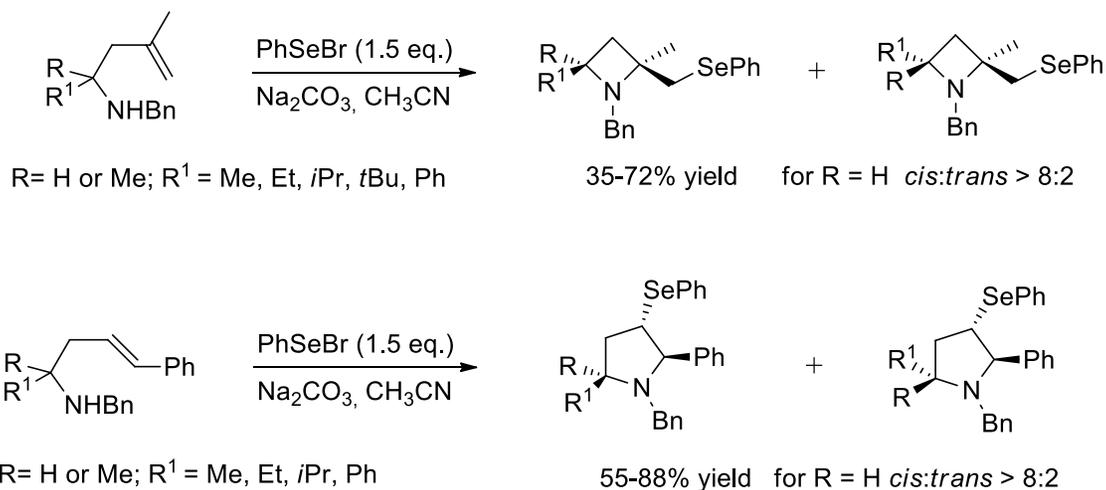
Scheme 17. Regioselective synthesis of azetidines and pyrrolidines.

Enantiopure pyrrolidines[72] and pyrrolizines[73] were synthesized from commercially available aminoalcohols usingthe 5-*exo-trig* ring closure reaction promoted by *N*-(phenylseleno) phthalimide in the presence of a catalytic amount of BF$_3$·Et$_2$O as the key step. Tin-mediated radical allylations of selenides were employed for the insertion of the allylic groups on the chiral source, taking advantage of the relatively easy homolytic cleavage of the SePh group. An example of the synthetic sequence is shown in Scheme 18.

a. ⌇⌇SnBu$_3$, AIBN, C$_6$H$_6$, 80 °C; b. NPSP, BF$_3$·Et$_3$O, CH$_2$Cl$_2$, rt
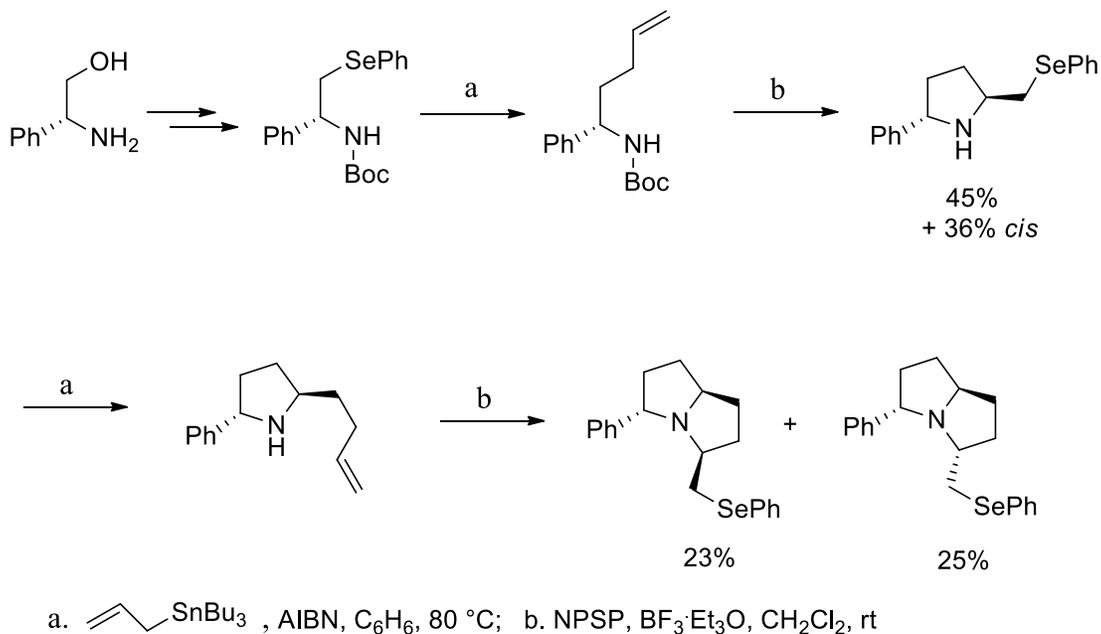
Scheme 18. Synthesis of enantiopure pyrrolidines and pyrrolizines.

Recently, selenocyclizations provided access to the bicyclic hydantoins reported in Scheme 19.[74] Hydantoins are useful intermediates in the synthesis of α-aminoacids and exhibit several biological activities. For these reasons these compounds are considered attractive targets in drug discovery programs. Reactions were regioselective and generated Markovnikov-type hydantoin derivatives in poor to good yields through a 5-*exo-trig* cyclization. The diastereoselectivity was moderate and compounds with bridgehead substituents

and phenylseleno groups in *cis* configuration were achieved, mainly. The method tolerated several substitutions at the double bond, and gave access to products with good structural diversity. The mechanism and selectivity of the reaction were investigated by density functional theory (DFT) methods.[75]

11 examples
25-96% global yield
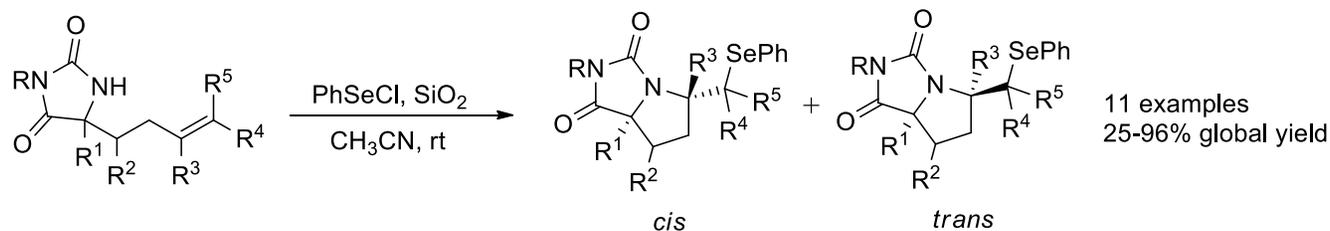
Scheme 19. Synthesis of bicyclic hydantoins.

As mentioned before, the selenium–mediated aminocyclization of C-C double bonds found useful application in the total synthesis of natural products (Scheme 20).

89%

(+) - Okaramine C

NW-G01

Chloptosin
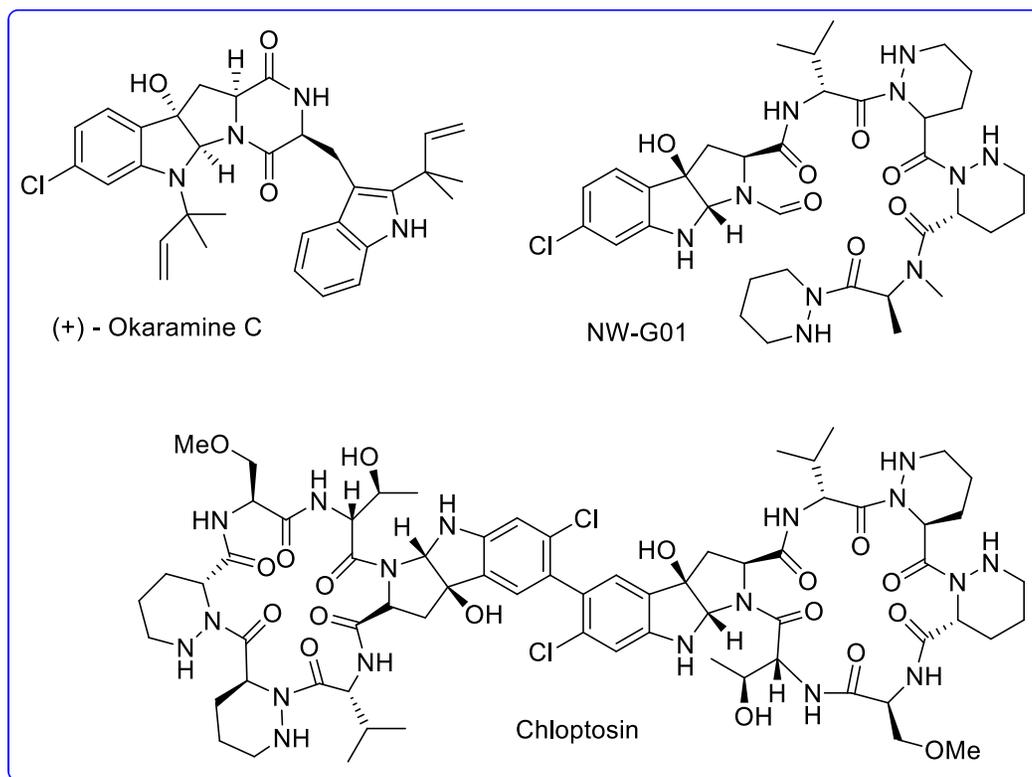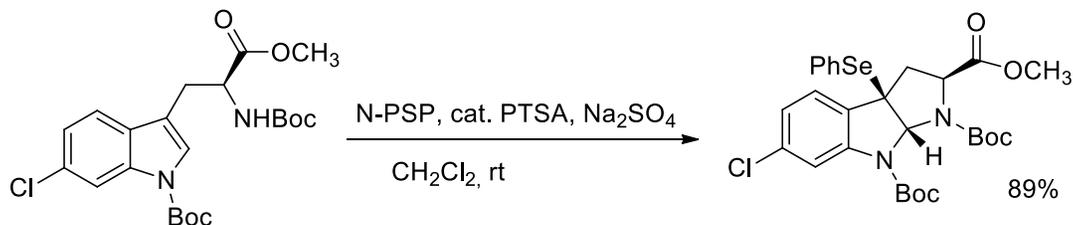
Scheme 20. Synthesis of the pyrroloindole fragment of some alkaloids.

Since the pioneering works by Danishefsky[76-77] and Crich[78] the NPSP-mediated cyclization of L-tryptophan derivatives has been mechanistically investigated and employed for the rapid and stereoselective assembly of the synthetically challenging hexahydropyrrolo[2,3-b]indole core of Okaramine C and other alkaloids.[79-81]

The selenocyclization reaction afforded the indicated kinetically favoured *exo* isomer with high diastereo control. Recently, Ley*et al.*[82] employed such reaction in the total synthesis of Chloptosin, a structurally challenging anticancer agent isolated from culture broth of *Streptomyces*, and Hatakeyama*et al.*[83] in the synthesis of the cyclic hexapeptide antibiotic NW-G01 from fermentation broth of *Streptomyces alboflavus*. In both cases, the hydroxylated heterocyclic core, typical of the aforementioned alkaloids, was obtained under mild conditions by oxidative deselenylation with wet *m*-CPBA in the presence of K_2CO_3.

In 2013 an organocatalyzed asymmetric variant of this cyclization has been developed. Tryptamine derivatives reacted with NPSP in the presence of a BINOL-based phosphoric acid affording pyrrolo[2,3-b]indoles with good yields and enantiomeric excess values in the range 71-89%.[84] Different substitution patterns were tolerated, regardless the electronic nature and the position of the substituent on the indoline ring. The protocol was applied to the synthesis of the key chiral precursor of the (+)-alline (Scheme 21).
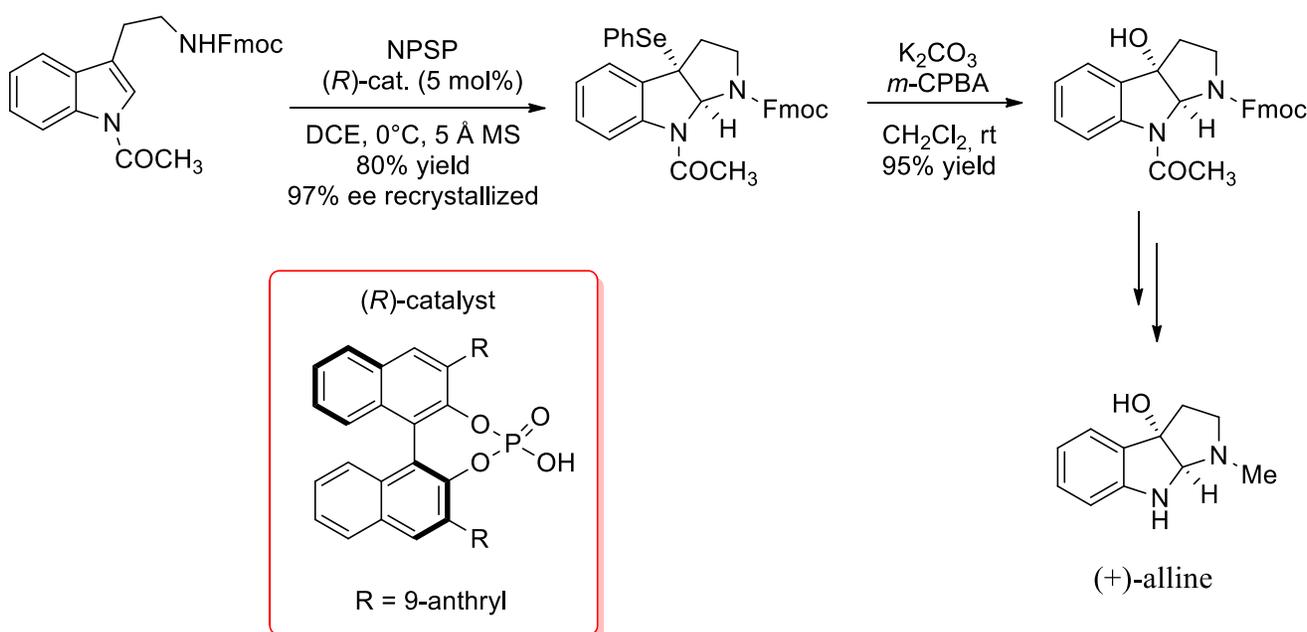
Scheme 21. Asymmetric organocatalyzed intramolecular aminoaselenylation.

Also in selenocyclizations novel methods for the generation of the electrophilic selenium species have been attempted. A visible-light promoted selenocyclization of alkenes has been recently developed (Scheme 22).[85] PhSeBr was generated *in situ* from equimolar amounts of diphenyldiselenide and tetrabromomethane with Blue LED irradiation without the need of inert atmosphere. The reaction occurred at room temperature, not only in dichloromethane, but also in nucleophilic solvents such as methanol, with excellent results in terms of yields and reaction times. The method gave an efficient access to pyrrolidines and piperidines and it was applied to the short synthesis of the racemic γ-lycorane, an alkaloid isolated from *Amaryllidaceae.* Interestingly, the selenocyclization is followed by a radical ring closure through homolytic cleavage of the selenium moiety with tris(trimethylsilyl)silane (TTMSS) and AIBN in benzene under reflux. The forth ring was obtained in an acceptable 44% yield, together with 41% yield of the by-product due to hydrogen abstraction.
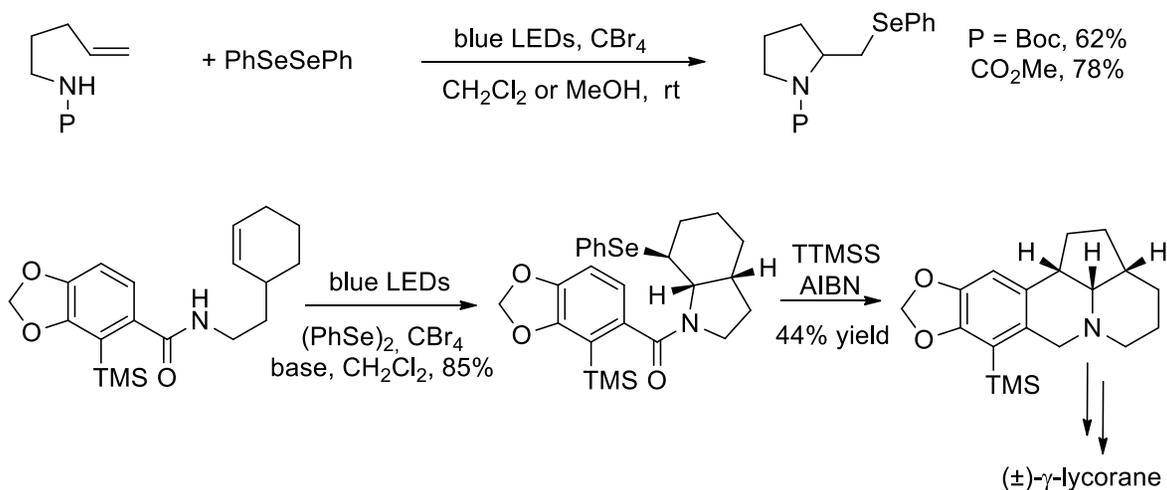
Scheme 22. Visible-light promoted intramolecular aminoselenylations and synthesis of γ-lycorane.

This year, the photocatalytic selenoaminocyclization of the *N*-tosyl-4-pentenamine in the presence of a catalytic amount of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) has been successfully investigated (Scheme 23).[86] This first sporadic example of photocatalytic aminocyclization is an interesting result towards the goal of sustainable intramolecular selenoaminations, since it uses ambient air for the generation of the electrophilic species and provides only water as the by-product.
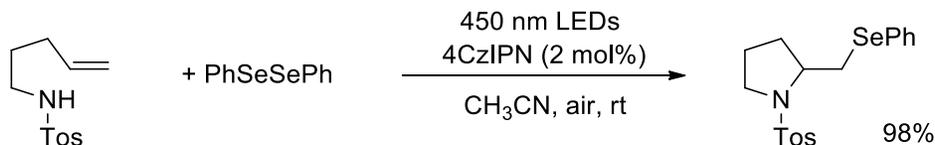
Scheme 23. Photocatalytic intramolecular aminoselenylation.

Selenocyclizations were not restricted to alkenes, since also alkynes proved to be competent substrates. These reactions have given access to pharmaceutically relevant seleno-substituted heteroaromatic compounds such as indoles and pyrazoles. Scheme 24 shows the Cs_2CO_3-assisted copper-catalyzed selenofunctionalization of 2-alkynylanilines for the formation of 3-fenylselenylindoles.[87] Mechanistic studies suggested the cooperation of the diselenide and copper salt in the generation of the electrophilic species.
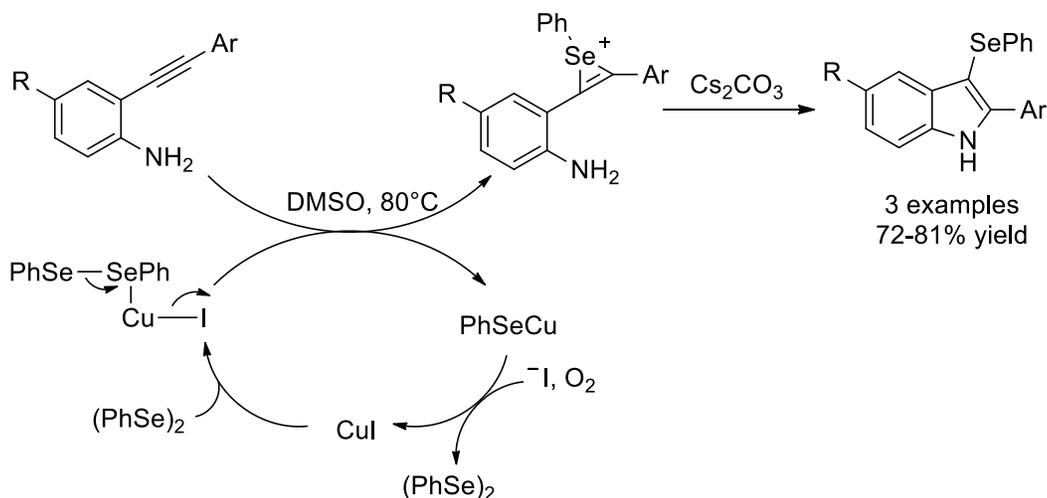
Scheme 24. Synthesis of 3-selenylindoles by intramolecular aminoselenylation of alkynes.

Similarly, the formation of 3-organoselenoquinolines have been observed upon treatment of (2-aminoaryl)-2-ynols with diaryl or dibutyl diselenides and an excess of $FeCl_3$ as the result of a regioselective 6-*endo-dig* cyclization (Scheme 25, route a).[88] Interestingly, *2*-alkynylbenzamides, failed to generate isoquinolin-1(2*H*)-ones.[89] As expected for amides, the oxygen/nitrogen competition favoured the C-O bond formation and the generation of 4-arylselenyl-1*H*-isochromen-1-imines (Scheme 25, route b).
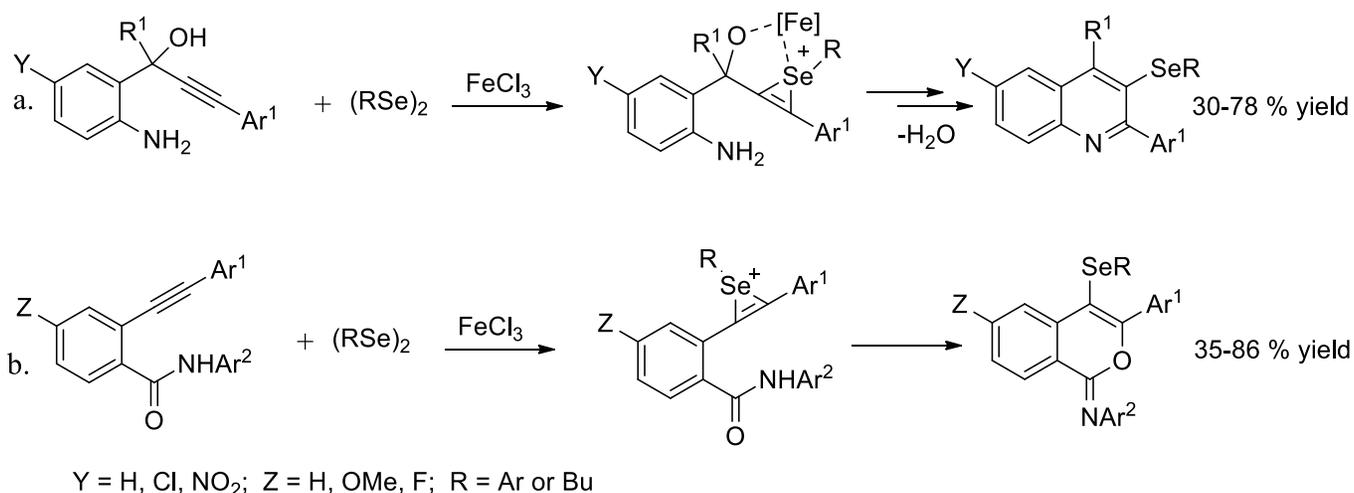
Scheme 25. Synthesis of 4-arylselenyl-1*H*-isochromen-1-imines .

Scheme 26 shows a new metal- and halogen-free route for the synthesis of 4-arylselenyl-1*H*-pyrazoles[90] employing alkynyl hydrazones, diorganyl diselenides and Oxone®. ^{77}Se NMR and High Resolution Mass studies suggested that the oxidation of the diselenides with Oxone® in EtOH at 70 °C produces several electrophilic selenium species such as $PhSeOSO_3^-$, benzeneseleninic acid ($PhSeO_2H$) and the corresponding ester ($PhSeO_2Et$). Selenylated pyrazoles were recovered in high yields with broad substrate scope.
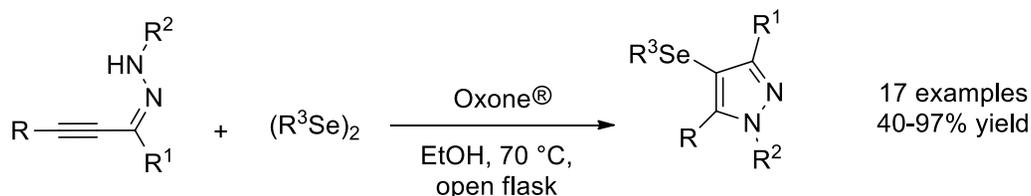
Scheme 26. Synthesis of 4-arylselenyl-1*H*-pyrazoles.

Finally, in 2012 Menichetti and co-workers disclosed the synthesis of benzo[b][1,4]selenazines by the reaction of *N*-sulfonylamino diselenides with electron-rich alkenes, a catalytic amount of a copper(II) Lewis acid and triethylamine.[91-92] *E* and *Z* disubstituted electron-rich alkenes gave products with retention of configuration. Authors suggested a mechanism involving a [4+2]-cycloaddition between the electron-rich alkene and the intermediate 2-iminoselone, rather than a classical electrophilic selenocyclization, as reported in Scheme 27. Similar compounds were synthesized and evaluated as carbonic anhydrase inhibitors.[93] These metallo-enzymes play an important role in the response to oxidative stress and some isoforms are drug targets in diseases such as cancer, epilepsy and arthritis.
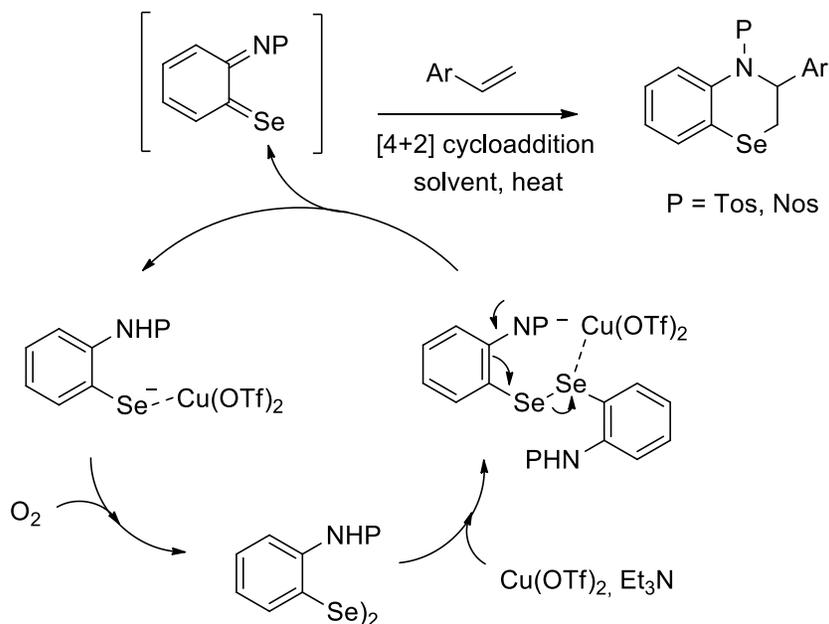
Scheme 27. Synthesis of benzo[b][1,4]selenazines.

4. Electrophilic Selenium-catalyzed Amination of Alkenes

Functionalizations of alkenes by domino selenylation/deselenylation sequences using catalytic amounts of diselenides have been the object of intense investigations.[4,94-96] The availability of organic or inorganic oxidants able to regenerate *in situ* the active electrophilic selenium species is crucial in these reactions. Recently, catalytic selenofunctionalizations of alkenes for the introduction of nitrogen functional groups have attracted great interest as atom-economic, cost-effective and environmentally friendly alternative to transition metal-catalyzed oxidative aminations of olefins. The poor stability of the nitrogen-containing

substrates and products under the oxidative conditions required makes this approach particularly challenging. Scheme 28 shows the selenium-catalyzed imidation of alkenes developed by Breder *et al.* in 2015.[97] Only 5 mol% of PhSeSePh and one equivalent of NFSI, as both the oxidant and the nitrogen source, were sufficient to generate allylic or vinylic imides in acceptable to high yields depending on the structure of the starting alkene.
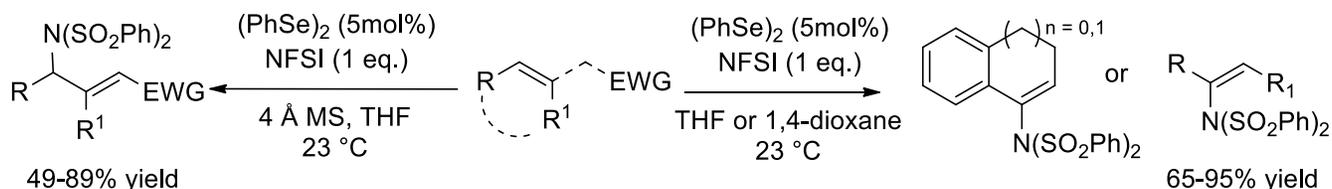
Scheme 28. Selenium-catalyzed allylic or vinylic imidation of alkenes.

The allylic amination was compatible with the presence of a variety of electron-withdrawing groups such as esters, amides, nitriles, ketones, phosphonates, and sulfones. The use of cyclic or linear alkenes gave vinylic imides in good to excellent yields. Such reactions can be reasonably explained by the catalytic cycle reported in Scheme 29. Firstly, the NFSI oxidizes the diphenyl diselenide to form the electrophilic selenium species. Next, the addition to the alkene generates the cationic adduct that undergoes the elimination. The elimination step occurs regioselectively, depending on the structure of the starting alkenes. The fluoride acts as a base and assists the elimination that regenerates the diselenide for the completion of the catalytic cycle.
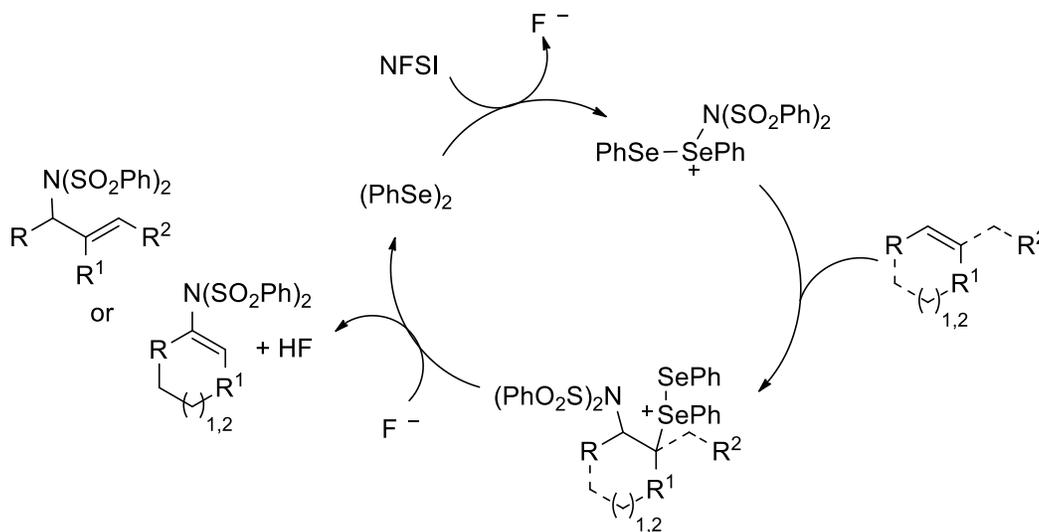
Scheme 29. Catalytic cycle for the allylic and vinylic amination of alkenes.

The first enantioselective variant of the catalytic allylic amination of alkenes recently appeared in the literature.[98] Four new chiral diselenides derived from an enantiopure diol were rationally designed and tested as catalysts, but in the best case, the product was obtained in 81% yield with a moderate 75:25 *er*.

Zhao *et al.* developed a method for the preparation of allylic 3-aminoalcohols from commercial or easily accessible allylic alcohols by treatment with 5 mol% of PhSeSePh and NFSI in the presence of bases (Scheme 30).[99] The hydroxylic oxygen completely controlled the regioselectivity of the process due to non covalent

interactions with the selenium cation. Interestingly, the formation of mixtures of amination products were observed when protected alcohols were employed under similar reaction conditions.

Control experiments revealed that the presence of the base is crucial for the success of the reaction, in fact in acidic conditions the initially formed 3-amino allylic alcohol decomposes to the corresponding unsaturated aldehyde. *Z* aminoalkenes were isolated in good yields and excellent regio- and stereo-selectivity from reactions carried out with 1,2-disubstituted alkenes without the need of any base, but with prolonged reaction times.
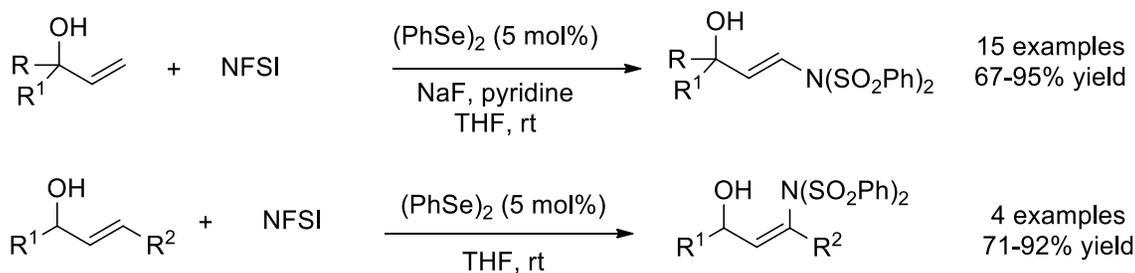
Scheme 30. Selenium-catalyzed amination of allylic alcohols.

Last year it was demonstrated that not only diselenides, but also phosphine selenides were able to catalyze vinylic aminations of terminal alkenes (Scheme 31).[100] After careful investigations for the best phosphine ligand, enamines were obtained in high yields and good to excellent *E/Z* ratio.
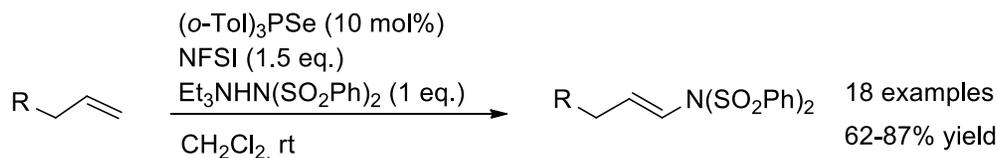
Scheme 31. Vinylic aminations catalyzed by a phosphine selenide.

Catalytic intramolecular vinylic aminations have been also developed using substrates with internal nitrogen nucleophiles for an efficient and practical access to heterocyclic compounds. Breder[101] and Zhao[102] groups independently, developed the synthesis of indoles starting from *ortho*-vinylanilines using catalytic PhSeSePh and stoichiometric NFSI. The nature of the protecting group plays a key role in this process, since this group modulates the acidity of the N-H with effects on the nucleophilicity. In fact, if reactions with substrates protected with tosyl, mesyl, and nosyl groups gave products in good yields, those with carboxamide protected substrates were unsuccessful. The method has a wide scope since different substitution patterns were tolerated on the alkene and aromatic ring. A broad range of functionalized indoles were synthesized and the protocol was also extended to the preparation of azaindoles (Scheme 32).
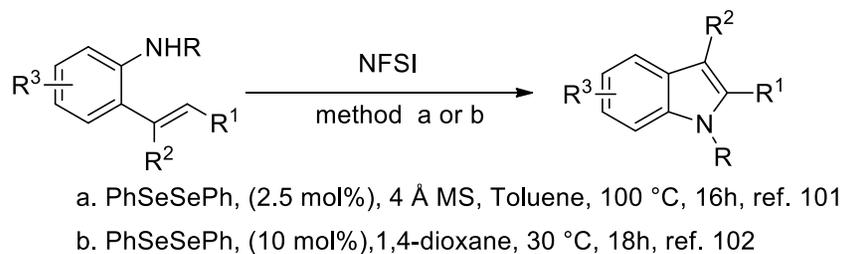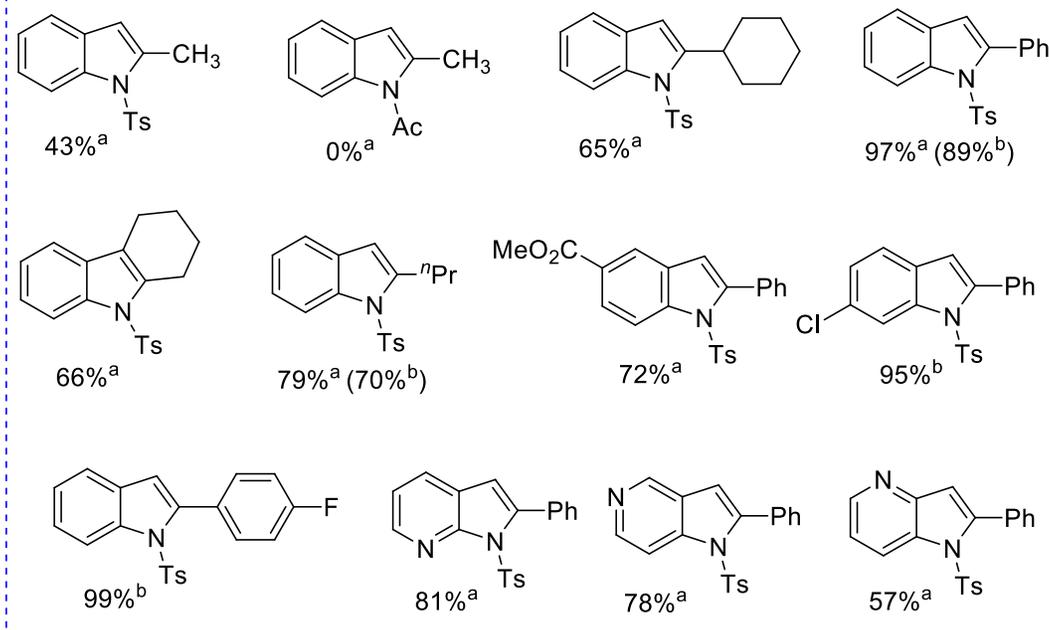
Scheme 32. Selenium-catalyzed synthesis of indoles and azaindoles.

The synthesis of pyrazolo[5,1-*b*]quinazolinones has been achieved starting from easily available (*E*)-3-styryl substituted quinazolin-4(3*H*)-ones and using the same catalytic system in acetonitrile under reflux in the presence of molecular sieves (Scheme 33).[103] The 2,3-heterocycle-fused quinazolinone core is frequently found in natural products and compounds with pharmacological properties such as antimicrobial and anticancer agents. Several products with broad structural diversity at the aromatic rings have been obtained in good yields. The protocol has been scaled up to gram scale.
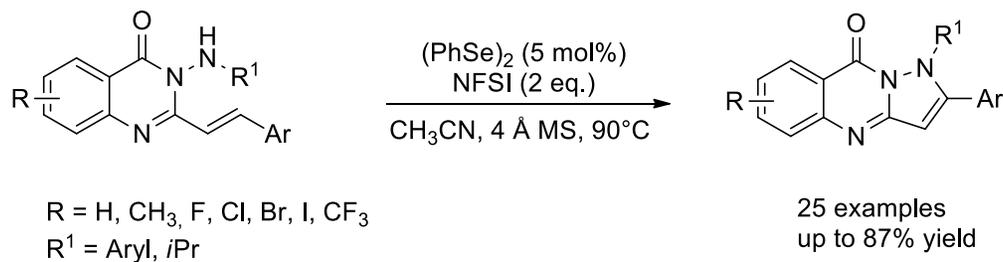
Scheme 33. Selenium-catalyzed synthesis of pyrazolo[5,1-*b*]quinazolinones.

Analogously, isoquinoline derivatives were accessible from *ortho*-styryl substituted benzaldehyde hydrazones or oximes.[104] Scheme 34 shows a representative example. The formed isoquinolinium imide has been reduced with NaBH4 or converted into a fused pyrazoloisoquinoline by a 1,3-dipolar cyclo addition reaction with 4-ethynylanisole.
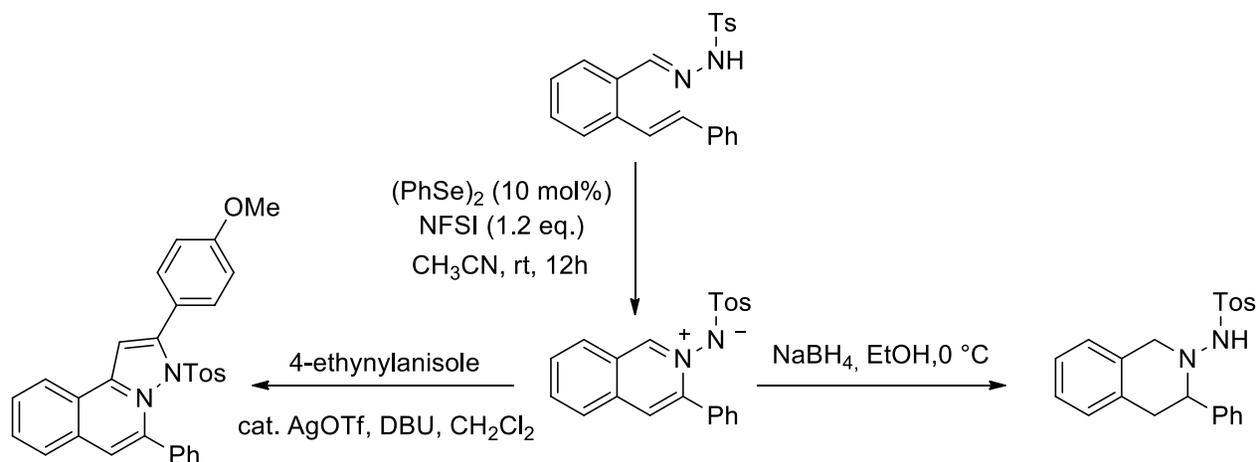
Scheme 34. Selenium-catalyzed synthesis of isoquinoline derivatives.

Catalytic PhSeSePh and fluoropyridinium triflate (FP-OTf) were used in the presence of NaF for the oxidative cyclization of unsaturated sulfonamides. Cyclizations in the *exo*-mode gave 2-alkenyl-substituted pyrrolidines or piperidines in reasonable to good yields (Scheme 35).[105] Azepines were obtained when reactions were performed with substoichiometric amounts of the base. An HF-assisted rearrangement of the initially formed pyrrolidines seems to be responsible of the ring expansion.
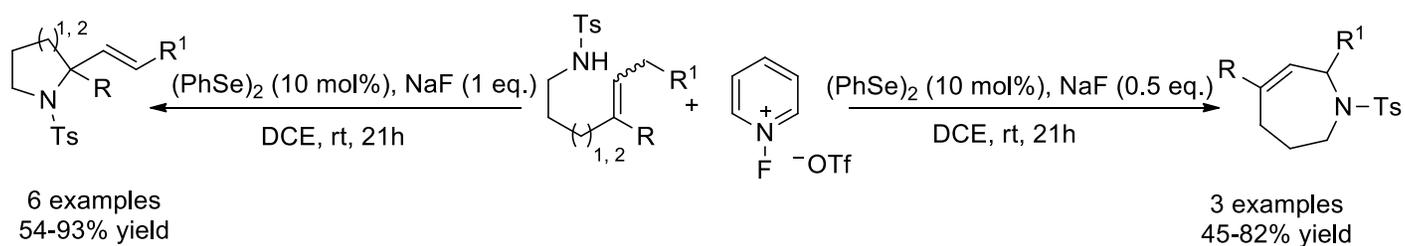
Scheme 35. Selenium-catalyzed synthesis of nitrogen 5-7 membered heterocycles.

Very recently, the catalytic system PhSeSePh and FP-OTf was also employed for the first selenium-catalyzed amination of dienes with pyridines (Scheme 36).[106] The reactions, carried out in acetonitrile and tetrahydrofuran with dibenzyl diselenide, gave a variety of pyridinium salts in moderate to good yields and complete C2-selectivity. The method nicely complements Heck-type reactions characterized by selectivity for the C1 position. The new protocol was employed regardless of the steric hindrance not only with aryl, alkyl, and cyclic 1,3-dienes, but also with terpene and styrene derivatives. In most experiments the fluoropyridinium reagent acts not only as the oxidant, but also as the pyridine source. However, the procedure has been adapted to the insertion of other pyridine derivatives suitably added to the reaction mixture. The intramolecular version of the reaction gave intermediates with potential applications in the synthesis of natural products.
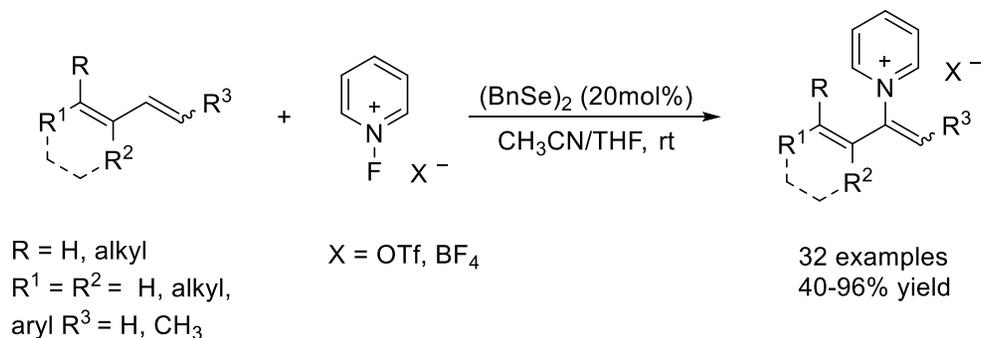
Scheme 36. Selenium-catalyzed pyridination of dienes and alkenes.

Finally a cooperative selenium-iodine catalyzed cyclization of tryptamine derivatives was reported by Ishihara *et al.* (Scheme 37).[107] Catalytic amounts of PhSeSePh and I_2 in the presence of *N*-chlorosuccinimide (NCS) gave C3a-chlorohexahydropyrrolo[2,3-*b*]indoles in good to excellent yields. Such chlorine-containing compounds are useful intermediates in the total synthesis of (-)-Psychotriasine and (-)-5-*N*-Acetylardeemin (Figure 1).
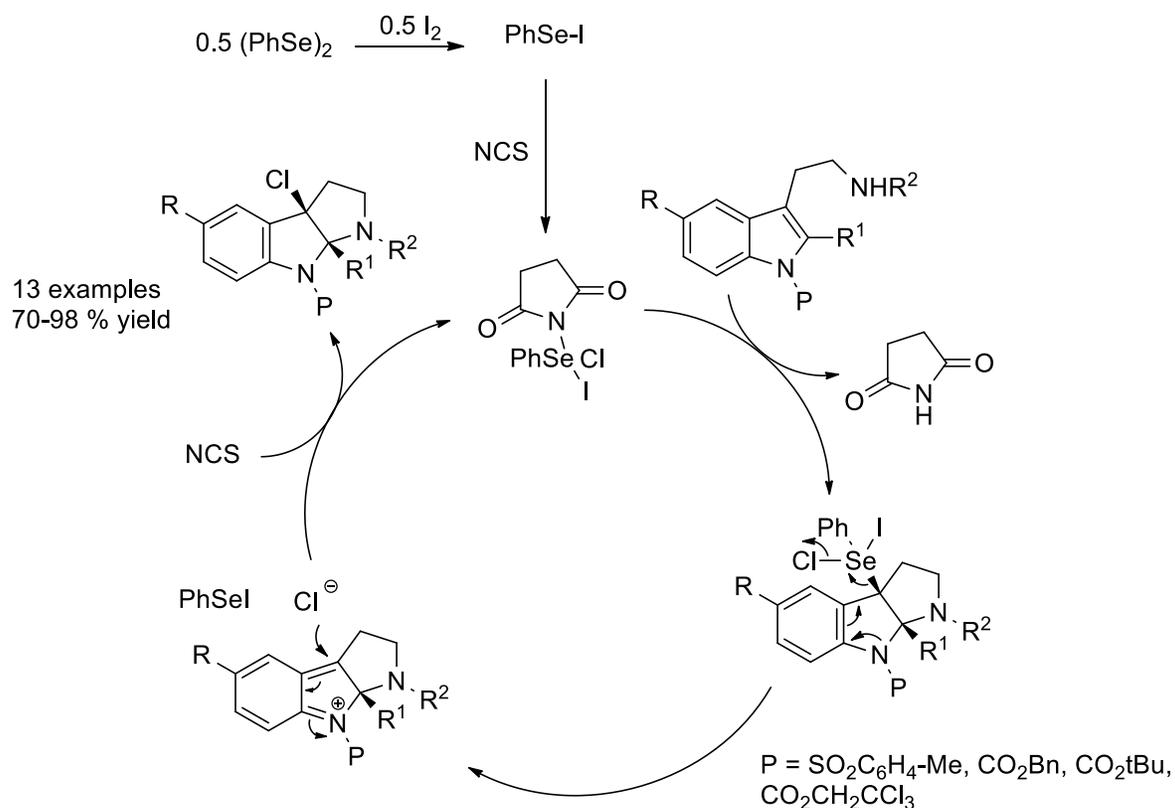
Scheme 37. Chlorocyclization of tryptamine derivatives by selenium-iodine cooperative catalysis.
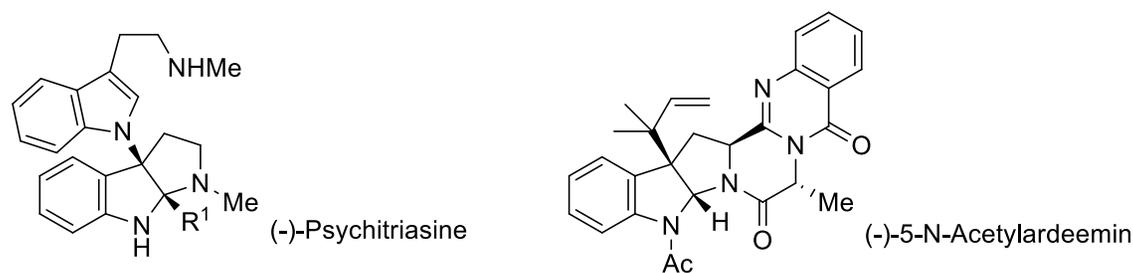
Figure 1. (-)-Psychotriasine and (-)-5-*N*-Acetylardeemin.

NMR studies provided evidence of the formation of the Se(IV) derivatives. Authors proposed that the PhSeI, initially generated by reaction of the iodine with the diselenide, was further oxidized by NCS to generate the effective selenium electrophile. After the ring closure an iminium ion was formed by deselenylation. The nucleophilic attack of the chloride onto the iminium ion generated the final product.

5. Conclusions

In conclusion, in the last years, new methods for the inter- and intramolecular, selenium promoted or catalyzed amination of alkenes or alkynes have been reported. Recent advances refer to the exploration of new nitrogen sources or oxidative systems for reactions featured by broad scope, wide functional group tolerance, high regio-and stereo-selectivity, and mild reaction conditions. A particular attention has been devoted to catalytic methods. However, despite the numerous advances, some challenges remain to be addressed particularly in the development of catalytic enantioselective methods.

Acknowledgements

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Francesca Mangiavacchi obtained her M.Sc. degree in Pharmaceutical Chemistry and Technology at the University of Perugia in 2016. She received a research fellowship by L'Oreal Paris on the "Synthesis of new redox catalyst and study of their interaction with biological structure" and a research fellowship by Consorzio Interuniversitario Nazionale Metodologie e ProcessiInnovativi di Sintesi (C.I.N.M.P.I.S.) on the "Synthesis of organoseleno compounds as potential agents in the inflammatory process and bacterial infection of cystic

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Francesca Marini obtained her M.Sc. degree with honors in Pharmaceutical Chemistry and Technology from the University of Perugia in 1990. After a research fellowship of Mediolanum Farmaceutici S.p.A. on the "Synthesis of Heterocyclic Derivatives of Biological Interest", she received in 1994 the PhD in Chemical Sciences under the Supervision of Prof. Marcello Tiecco with the doctoral thesis "Cyclization reactions promoted by organoselenium compounds. New syntheses of heterocyclic compounds." In the same year she became Assistant Professor at the University of Perugia and from 2006 she is Associate Professor at the same University. Her main scientific interests concern the use of organoselenium reagents in the development of new synthetic methodologies.