SYNTHESIS OF BIOLOGICALLY RELEVANT HETEROCYCLIC COMPOUNDS THROUGH THE CHEMISTRY OF SELENIUM

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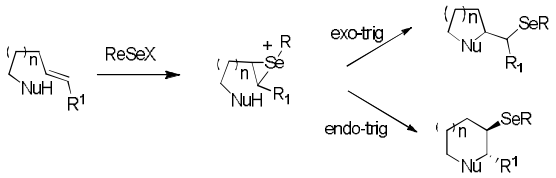
Abstract. *The rich and versatile chemistry of organoselenium compounds is particularly suitable for the synthesis of heterocycles. Asymmetric cyclization reactions promoted by selenium reagents as well as the use of vinyl selenones in domino processes allow the formation of a wide variety of interesting and biologically relevant heterocyclic compounds.*

Contents

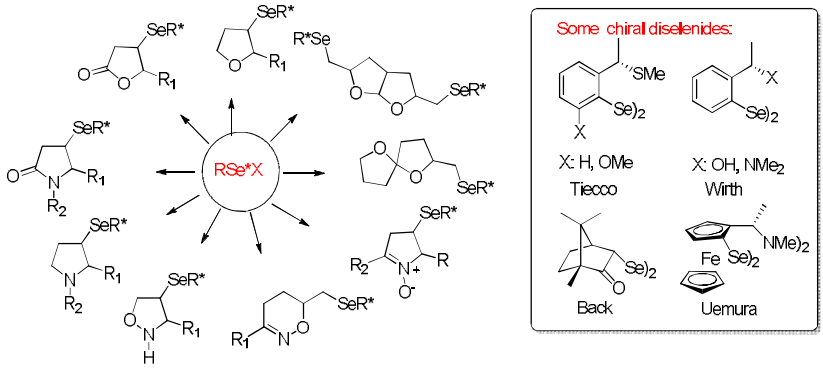
1.General considerations of selenium chemistry applied to the synthesis of heterocycles

The chemistry of organoselenium compounds is considered an important tool for the discovery of novel synthetic methodologies in the field of modern organic synthesis,[1-5] applied also with success in the synthesis of heterocycles compounds such as natural products or drug-like molecules. Selenium can be introduced as an electrophile, as a nucleophile, or as a radical and generally, it combines chemo, regio- and stereoselectivity with mild experimental conditions. One of the most interesting features of selenium chemistry for the construction of heterocyclic compounds is the cyclofunctionalization reaction (Scheme 1). When a nucleophilic functional group such as OH, COOH, NHR is present in a suitable position of the unsaturated hydrocarbon molecule, the reaction with the electrophilic selenium species makes possible the intramolecular reaction.[6] The electrophilic addition of selenonium groups to the carbon-carbon double bond provides the seleniranium intermediate, which then undergoes an *anti*-stereospecific attack by an internal nucleophile. Depending on the substitution of the double bond and the size of the ring that is formed, *exo* or *endo* cyclization can take place. Some selenium electrophilic reagents such as chloride, bromide and *N*-phenylselenophthalimide are commercially available, otherwise RSeX can be easily produced *in situ* by oxidation of diselenide with several inorganic reagents.



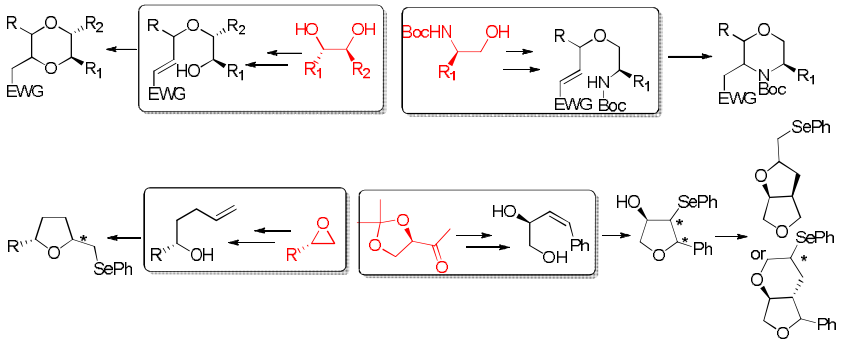
Scheme 1. Cyclofunctionalization reactions promoted by selenium electrophiles.

One of the most interesting aspects of the cyclofunctionalization reactions promoted by the selenium electrophilic reagents, is the possibility of performing either reagent-controlled or substrate-controlled asymmetric cyclization reactions. In the reagent-controlled approach, the capacity to synthesize optically pure electrophilic selenium reagents is a peculiar and unique property of organoselenium compounds. As showed in Scheme 2, the variety of heterocycles synthesized using optically active diselenides indicates the power and the robustness of the procedure in the construction of natural products and molecules of pharmaceutical interest.[7-18]



Scheme 2. Asymmetric synthesis promoted by chiral organoselenium reagents.

Substrate-controlled asymmetric cyclization reactions were also performed upon to synthesize enantiopure heterocycles using chiral phenylselenium reagents and enantiomerically pure substrates. As highlighted in Scheme 3, different mono and bicyclic heterocycles can be synthesized through simple conversions promoted by the versatility of selenium chemistry.[19-22]

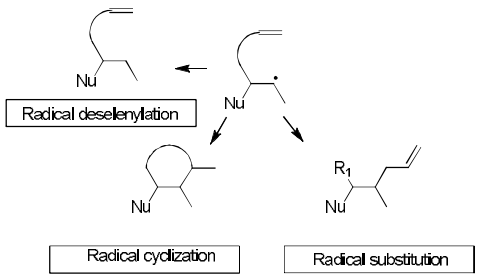


Scheme 3. Asymmetric synthesis promoted by chiral substrates.

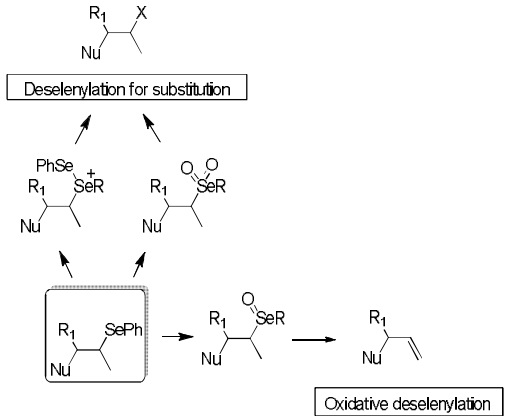
Despite for many aspects the properties of organoselenium compounds are similar to those of better-known sulphur derivatives, the manipulation of the resulting molecules occurs under mild reaction conditions and are greatly facilitated compared with reactions involving sulfur anologues.[23] As indicated in Scheme 4, the reaction with tin hydride leads to the homolityc cleavage of carbon-selenium bond and affords a carbon radical, which can directly abstract a hydrogen atom (radicalic deselenation) or it can add to a multiple bond present in the molecule, thus allowing the formation of a ring (radicalic cyclization). If the tri-*n*-butyl allyl tin is employed, there is the simultaneous deselenation and functionalization of the molecule and the allyl derivate is obtained (radical substitution).

Probably the more studied deselenenylation is the oxidation of aryl selenyl group to selenoxide with hydrogen peroxide or *m*-chloroperbenzoic acid (*m*-CPBA), followed by spontaneous *syn* elimination and

formation of alkene (Scheme 5). Another methodology involves the conversion of the RSe group into a good leaving group, such as the selenonium ion or the selenone, followed by a nucleophilic substitution reaction of S_N2 type. In fact, alkylselenide can be treated with PhSeX to form the selenonium ion, in which the outgoing group is diselenide, or converted to selenone, in the presence of an excess of oxidizing agent, in which the outgoing group is selenonile, the best known so far (Scheme 5).

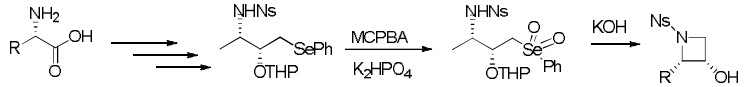


Scheme 4. Radical deselenylation.



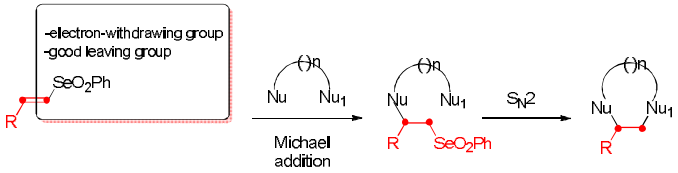
Scheme 5. Deselenylation processes.

The good leaving ability of the selenonyl group can be employed with success in the construction of heterocycles.[24-25] As reported in Scheme 6, enantiomerically pure substituited azetidines were synthesized through a ring closure reaction, which occurs by a stereospecific intramolecular nucleophilic substitution of the selenonyl group by the nitrogen atom.[24]



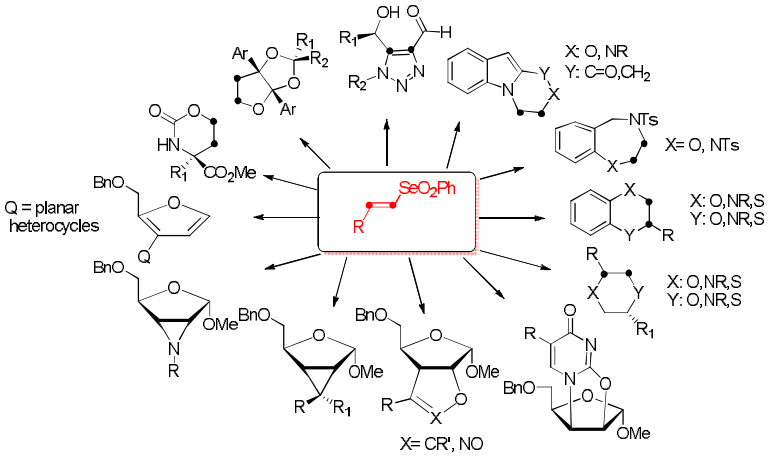
Scheme 6. Intramolecular nucleophilic substitution of the selenone.

When the selenone group is linked to double bond novel organic transformations can be realized. The vinyl selenones are under-investigated organoselenium compounds that have been recently rediscovered. Although their chemical structure is closely related to that of the homologous sulfur analogous, their reactivity presents marked differences. Vinyl selenones easily participate in 1,4-addition reactions and they are particularly suited for multiple bond forming reactions such as domino processes. In fact, the phenylselenonyl moiety is a strong electron-withdrawing group which activates the C-C double bond to nucleophilic additions and a good leaving group for intramolecular nucleophilic substitutions (Scheme 7).



Scheme 7. Michael Initiated Ring Closure Reactions (MIRC).

Recently, various research groups have focused their attention on the chemistry of vinyl selenones as 1,2-*bis* electrophiles for the assembly of complex heterocycles,[26-34] for the manipulation of nucleosides and sugar analogous,[35-37] for the asymmetric synthesis[38] also promoted by chiral auxiliary[39] and for the organocatalysis.[40-48] It should be emphasized that the molecules obtainable through the chemistry of vinyl selenones are cores of pharmaceutical interest or molecules suitable for the preparation of natural products (Scheme 8).



Scheme 8. Examples of chemical transformations using vinyl selenones.

In this personal account, our endeavours in the synthesis of biologically relevant heterocycles are summarized employing substrate inducted asymmetric cyclizations promoted by selenium chemistry and domino processes that using vinyl selenones as *bis* electrophiles.

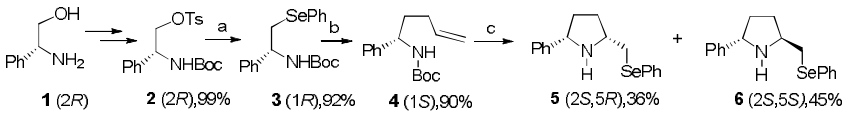
2. Synthesis of heterocyclic compounds through asymmetric cyclization inducted by chiral substrates

In the late 1980s, Evans first proposed the concept of privileged structures and in the original paper referred to the benzodiazepine nucleus. Later this concept has been extended to molecular scaffolds that are capable to provide useful ligands for a variety of receptors or enzymes through few structural modifications. Heterocyclic cores are ideal candidates for interactions with enzymes or receptors. [49-52] In fact, because of their rigidly and spatially organized non-planar structures, these compounds have affinity for three-dimensional binding sites of proteins acting as bio-targets. Organic chemistry has been making efforts to produce novel heterocycles by utilizing wide ranges of new reactants and developing efficient and widely applicable synthetic transformations. Of the methods available for preparing chiral heterocyclic compounds, the asymmetric synthesis inducted by chiral substrates still attracts a lot of attention and many structurally and functionally different heterocycles were synthesized in order to extend the existing chemical space. Indeed, this approach remains the preferred method in the total synthesis of optically active heterocycles, playing a significant role in medicine and materials as well as in natural products.

2.1. Asymmetric synthesis of nitrogen heterocyclic compounds

A simple glance at the Food and Drug Administration (FDA) databases reveals the structural significance of nitrogen-based heterocycles in the drug design and engineering of pharmaceuticals, with 59% of unique small-molecule drugs containing a nitrogen heterocycle.[53-54] Pyrrolidine ring system is one of the more representative nitrogen heterocyclic nucleus. It is present in a large number of natural products as well as in numerous therapeutic agents.[55] It was also employed as pivotal key intermediate in the synthesis of pyrrolizine and indolizidine alkaloids, that possess interesting biological properties. Hexahydro-1*H*-pyrrolizines have demonstrated an activity as glucosidase and glycosidase inhibitors and also possess properties as histaminic H1 and H3 antagonists.[56]

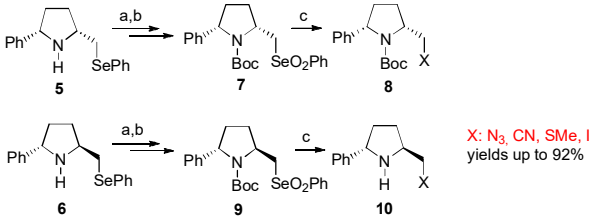
Several enantiomerically pure *cis*- and *trans*-2,5-disubstituited pyrrolidines **5** and **6**, were synthesized through an asymmetric cyclization using as chiral pool commercially available enantiopure aminoalcohols, **1** (Scheme 9).[57] These compounds after double protections can be easily transformed in δ-alkenyl amines **4** using the versatility of selenium chemistry by substitution of the tosyl group in the compound **2** with phenylselenolate anion and subsequently replacement of selenium moiety in the compound **3** with an allyl group. The final key step of the process is the substrate-controlled asymmetric 5-*exo*-*trig* selenocyclization of the *N*-Boc protected δ-alkenyl amines **4** promoted by *N*-(phenylseleno)phthalimide. When the starting products were completely consumed, an excess of $BF_3{\cdot}Et_2O$ was added to effect the N-Boc bond cleavage.



a) $(PhSe)_2$, $NaBH_4$, DMF, 40°C, b) CH_2=$CHCH_2SnBu_3$, AIBN, C_6H_6, 80°C; c) N-PSP, $BF_3.Et_2O$, CH_2Cl_2, r.t.

Scheme 9. Synthesis of enantiopure pyrrolidines.

Once incorporated, the selenium moiety can be converted into the selenones **7** and **9**, which can undergo substitution reactions with different nucleophiles giving pyrrolidines **8** and **10** containing azido, cyano, methylthio and iodo group without loss of enantiomeric purity (Scheme 10).[57]

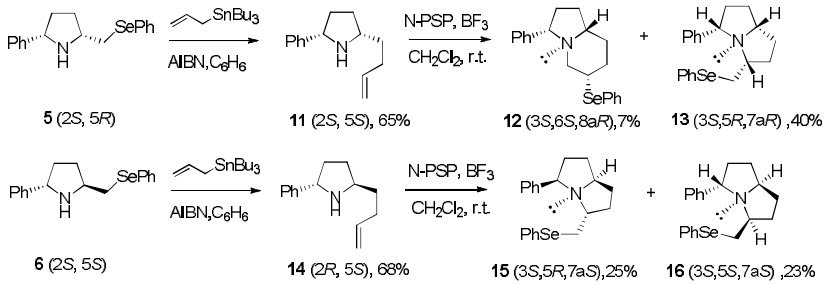


(a) (t-BuOCO)$_2$O, EtN$_3$, THF; (b) Oxone, MeOH, buffer solution, 80°C,
(c) NaN_3 or KCN or $NaSCH_3$ DMF, 160°C,18- crown-6

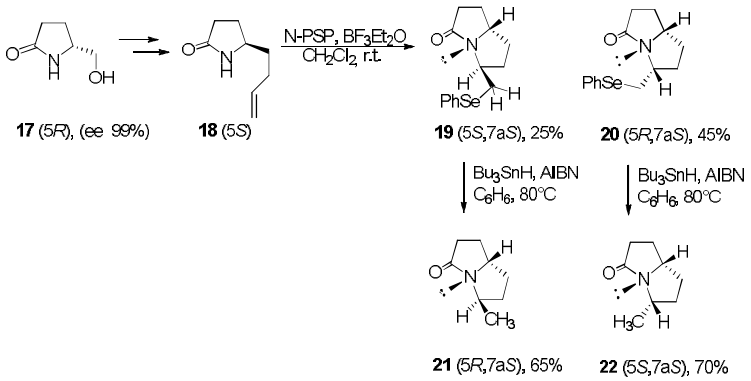
Scheme 10. Synthesis of variously substituted pyrrolidines

The radical replacement of the phenylselenyl moiety with an allyl group enables the obtainment of allylated pyrrolidines **11** and **14**, which can be used as starting materials to synthesize enantiomerically pure hexahydro pyrrolizines **13**, **15-16** and octahydroindolizine **12** through a second asymmetric cyclization reaction (Scheme 11).[58]

Similarly, starting from enantiopure (*R*) o (*S*) 5-(hydroxymethyl)pyrrolidin-2-ones **17**, enantiopure hexahydro-3*H*-pyrrolizin-3-ones **19** and **20** were obtained (Scheme 12).[59] The bicyclic compounds can be easily converted into the deselenated products **21** and **22**.



Scheme 11. Synthesis of enantiopure octahydroindolizine and hexahydro-1*H*-pyrrolizines.



Scheme 12. Synthesis of enantiopure hexahydro-3*H*-pyrrolizin-3-ones.

2.2. Asymmetric cyclization reactions for the synthesis of pseudo-oligosaccharides

Carbohydrates are important mediators in the interaction with hormones, enzymes, toxins, bacteria, viruses, thus offering therapeutic opportunities in biomedical field.[59-60] Despite the progresses made by modern carbohydrate chemistry, the development of saccharide-based drugs using classical carbohydrate synthesis can still be a difficult task. To this purpose pseudo-oligosaccharides endowed with similar biological properties, but structurally and synthetically simpler than their natural counterparts, have attracted interest as scaffolds for the synthesis of sugar mimics.

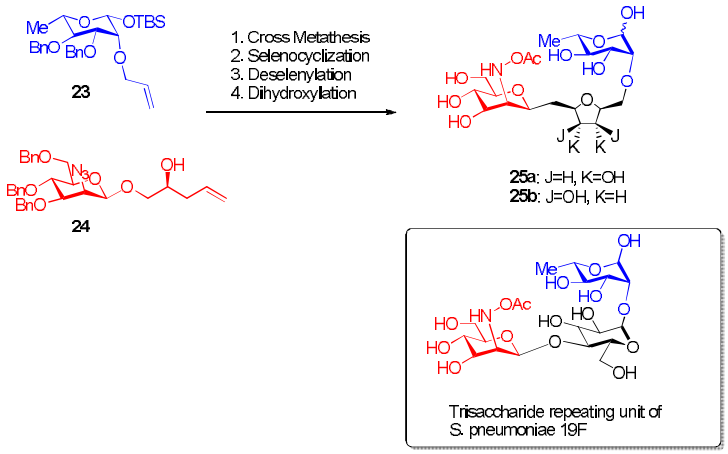
Different pseudo-oligosaccharides were synthesized employing a strategy that use the cross-metathesis reaction between two distinct sugar-olefins **23** and **24** followed by intramolecular selenocyclization of the obtained heterodimers as key step (Scheme 13).[61] In particular structural anologues **25a-b** of the trisaccharide repeating unit from Streptococcus pneumoniae 19F, that is responsible for respiratory tract infections and meningitis, were prepared. The inhibition ability of the pseudo-oligosaccharide **25a-b** were evaluated by a competitive ELISA assay using a rabbit polyclonal anti-19F serum.

The use of the selenium eletrophiles in the cyclization process provides various advantages in comparison with the iodocyclization reaction. The possibility to change the R group in the selenium electrophile (RSe^+) permits the separation of two diastereoisomers **27** and **28**, while using molecular iodine an inseparable mixture was obtained. Another advantage is the very mild conditions required for the elimination step, which allows the extension of the protocol to highly functionalized substrates. The selenocyclized products **27** and **28** were easily subjected to the elimination reactions by oxidation with hydrogen peroxide. The subsequent *syn* elimination of the selenoxides allowed the introduction of a new endocyclic carbon-carbon double bond suitable for further functionalizations (Scheme 14).

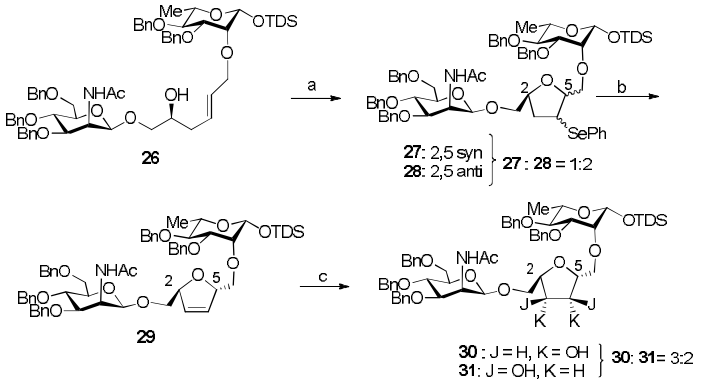
3. Domino processes for the synthesis of heterocycles using vinyl selenones

The development of efficient synthesis of privileged structures and bioactive compounds in an ecologically and economically favorable way is a great challenge in modern chemistry. To this end, the

research into new simple and direct strategies for the efficient creation of small molecules collections with rich functional and stereochemical diversity starting from simple building blocks is in constant growth. As witnessed by the number of reviews that have recently appeared, an intense research, focus on the development of multiple bond-forming transformations such as *one-pot* processes, domino and multicomponent reactions, has been reported.[62-70] According to Tietze,[71] domino or cascade reaction is a process in which two or more bond-forming events occur under the same reaction conditions without adding additional reagents or catalysts. Thus, subsequent reactions are based on the functional groups formed in the previous steps. These transformations, that avoid time-consuming protection/deprotection steps and isolation of intermediates, have several benefits that include atom economy, as well as economies of time, labor, resource management and waste generation. Considering their advantages, domino processes fall under the category of green chemical transformations.



Scheme 13. Synthesis of structural analogue of the trisaccharide repeating unit from the capsular polysaccharide of Streptococcus pneumoniae 19F.



a) $(PhSe)_2$, $(NH_4)_2S_2O_8$, CH_3CN, 80°C, 75%; b) H_2O_2, MeOH,rt, then $NaHCO_3$, C_6H_6, 80°C, 88%, c) OsO_4, NMO, H_2O: acetone 1:1, 62%

Scheme 14. Selenocyclization and *syn* elimination of selenoxide.

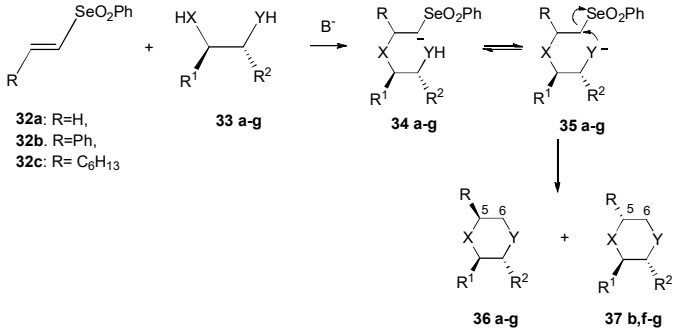
Vinyl selenones are a class of compounds that are particularly suited for such reactions. In fact, the phenylselenonyl moiety is either a strong electron-withdrawing group which activates the C-C double bond to nucleophilic additions, and a good leaving group in the subsequently nucleophilic substitutions. This

behaviour makes the vinyl selenones powerful *bis*-electrophiles with a great potential for domino reactions. My personal contribution in this field applied to the synthesis of the heterocyclic compounds is reported below.

3.1. Asymmetric domino processes for the synthesis of enantiopure 1,4-dioxanes, morpholines, thiomorpholine and piperazines

Domino processes involving vinyl selenones and commercially available enantiopure 1,2-diols, *N*-protected-1,2-amino alcohols, 1,2-thioalcohols and 1,2-diammines have been carried out to synthesize enantiopure 1,4-dioxanes, morpholines, thiomorpholines and piperazines.[38] Many important applications in medicinal chemistry of these heterocycles have been reported in the literature. Morpholine skeleton is a chiral core present in many therapeutical agents such as antitumor and anti-inflammatory.[72] The piperazine nucleus is present in a large number of compounds of pharmaceutical interest and some of these are in phase II clinical trials.[73]

On the basis of the accepted mechanism for the Michael inducted ring closure (MIRC) reaction in the presence of base the reaction of vinyl selenones **32a-c** with different enantiopure 1,2-*bis* nucleophiles **33a-g** gave the initial formation of the carbanions **34a-g**. The subsequent proton transfer produces the negative charge displacement on the other heteroatom **35a-g**, which operates intramolecular substitution of the $PhSeO_2$ group. The configurations of the carbon atoms with R^1 and R^2 were clearly unchanged in the final products with respect to those of the starting *bis* nucleophiles (Scheme 15). Assuming a chair conformation, the absolute configuration of the newly generated stereogenic center (carbon atom at C-5) is suggested on the basis of the values of the vicinal coupling constants between the proton H-5 and the two protons in position 6.



Scheme 15. Asymmetric Michael initiated ring closure (MIRC) reactions.

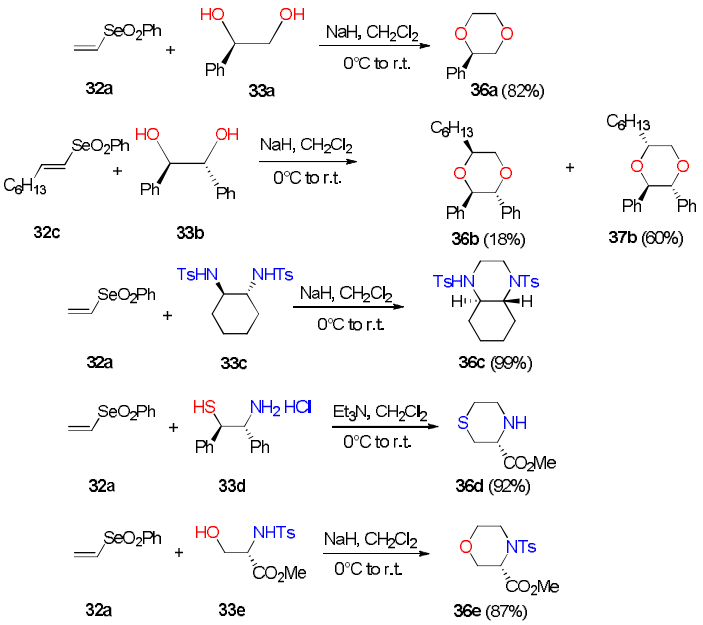
In Scheme 16, selected examples are reported of the enantiopure 1,4-dioxanes **36a-b, 37b**, piperazine **36c**, thiomorpholine **36d** and morpholine **36e** synthesized. In all cases sodium hydride was used as base except in the synthesis of thiomorpholine **36d** in which triethyl ammine was necessary to have an excellent yield.

As showed in Scheme 17, when the reaction was carried out using substituted selenones **32b-c** and bidentate nucleophiles, such as *N*-protected-1,2-amino-alcohols **33f-g**, the complexity of the NMR spectra of morpholines **36f-g** and **37f-g** obtained supports the reaction pathway that is associated with the initial formation of an oxygen anion. This effects the Michael addition at the β-position of the selenones, followed by the intramolecular displacement of the phenylselenonyl group by the nitrogen atom. A similar competition in the presence of a bidentate nucleophile has been observed by Aggarwal in the formation of morpholines *via* Michael initiated ring closure reactions of vinyl sulfonium salts.[74]

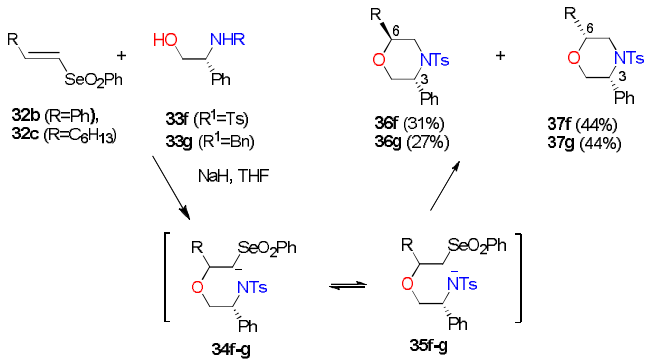
3.2. Domino processes for the synthesis of six and seven-membered benzo-1,4-heterocyclic compounds

A wide variety of six-membered bicyclic benzo fused 1,4-heterocycles was synthesized using various vinyl selenones, as *bis* electrophiles, and benzo 1,2-diols, 1,2-thiols and 2-(benzylamino)phenols and

N,N-1,2-phenylenebis(4-methybenzensulfonamide) as *bis* nucleophiles. Different biologically and pharmaceutically important nuclei such as 2,3-dihydro-1,4-benzodioxins **41a-c**, benzodithiines **41d-e** and 3,4-dihydro-2*H*-1,4-benzooxazines **41f-h** and 1,2,3,4-tetrahydroquinoxaline **41i** were obtained in *one-pot* and in good yields trough an addition-cyclization cascade (Scheme 18).[31]



Scheme 16. Synthesis of enantiopure 1,4-dioxanes, piperazines, thiomorpholine and morpholines.

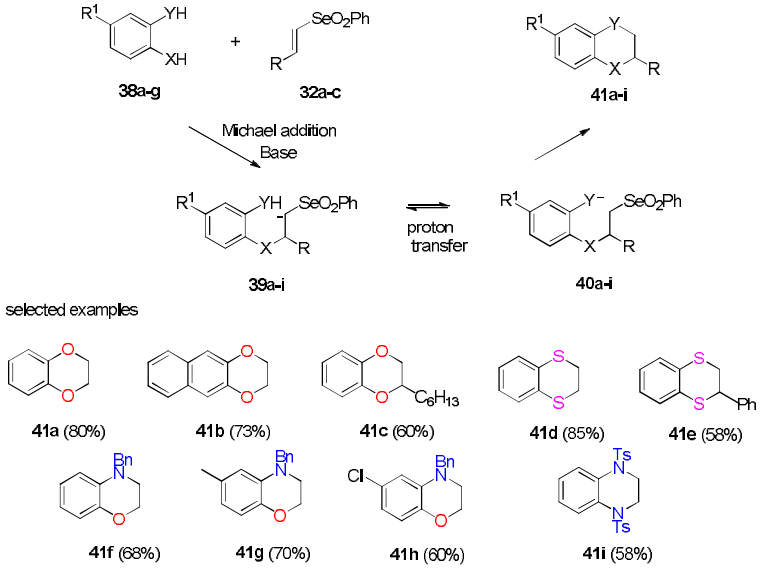


Scheme 17. Mechanism of domino process with substituted selenones and bidentate nucleophile.

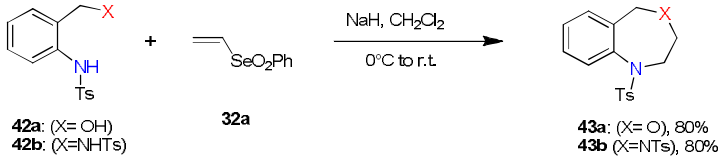
The 1,4-benzodioxine core is present in piperoxan, an α-adrenergic blocking agent, in fluparoxan, a potent antidepressant, in isovanillyl, a sweetening agent and in many natural products.[75] The 1,4-benzoxazine derivatives are potential drugs for treating infections, heart disease, diabetes, autoimmune and cardiovascular disorders[76] and several 1,2,3,4-tetrahydroquinolines have found applications as prostaglandin D2 and vasopressin V2 receptor antagonists.[77]

Using a similar domino process, also seven-membered benzo fused 1,4-heterocycles, such as 1,4-benzodiazepine **43a** or benzoxazepine **43b**, were synthesized in excellent yields starting from

N-tosyl-1,3-diamine **42a** and *N*-tosyl-1,3-amino alcohol **42b** (Scheme 19).[38] These benzo heterocyclic compounds have very important applications in medicinal chemistry, including dampening of the central nervous system and can act as a muscle relaxant.[78]



Scheme 18. Synthesis of 2,3-dihydro-1,4-benzodioxines, benzodithiines and 3,4-dihydro-2*H*-1,4-benzoxazines and 1,2,3,4-tetrahydroquinoxaline.



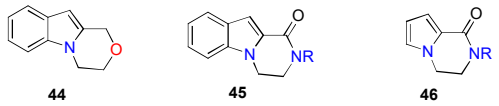
Scheme 19. Synthesis of 1,4-benzodiazepine or benzoxazepine.

3.3. Domino processes for the synthesis of heterocycle-fused indoles

Indole, more than a century after its first isolation from indigo dye, continues to inspire and influence developments in numerous areas like chemistry, biology, medicine and material science. Not surprisingly, the indole has been designed by Bandini as the "The Lord of the Ring " of the heterocyclic compounds.[79] Since its discovery, enormous efforts have been devoted to the development of ever more efficient synthetic protocols for the preparation and direct functionalization of this heteroaromatic compound and for the synthesis of its more complex derivatives.[80-81]

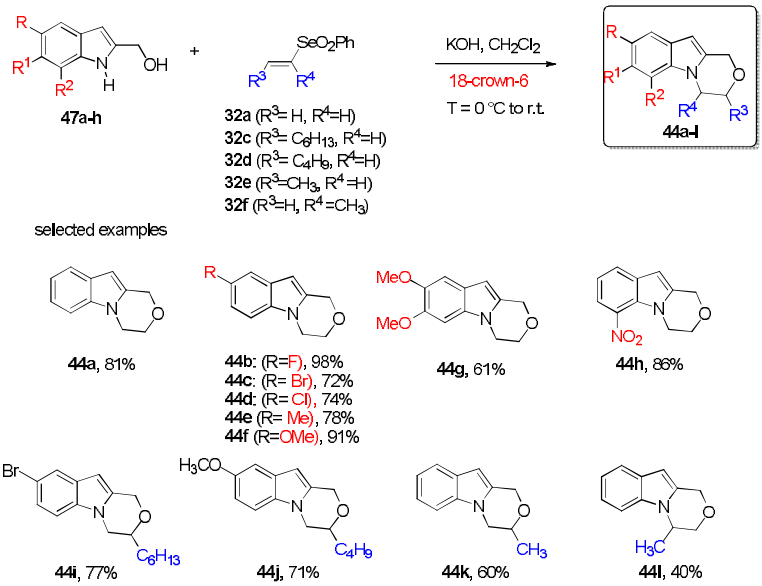
Structural diversity and complexity of pharmacologically active indole derivatives constitute a great synthetic challenge and in particular heterocyclicle-fused indoles play an important role as biologically active compounds and pharmaceuticals. For example oxazino[4,3-*a*]indoles **44** are investigated for their antidepressant and antitumoral properties[82] and a series of these chiral derivatives have been synthesized to evaluate the neuro-protective effects against $A\beta_{25\text{-}35}$-inducted neuronal damage.[83] Pyrazino [1,2-*a*]indoles derivatives **45** have received great attention due to their interesting antidepressant, anti-obesity and anti-inflammatory biological properties. Because of their ability to act as conformationally rigid peptidomimetics, some of these activities are correlated to the modulation as antagonist of histamine 3 receptor (H3). A wide number of patents and papers regarding the potential biological activity of pyrazino fused indoles have been developed.[84-86] Pyrazino fused pyrroles **46** are a structural motif of bromopyrrole

alkaloids including Longamide B and its derivatives. They are an important class of natural compounds with a broad range of biological activities (Scheme 20).[87-88]



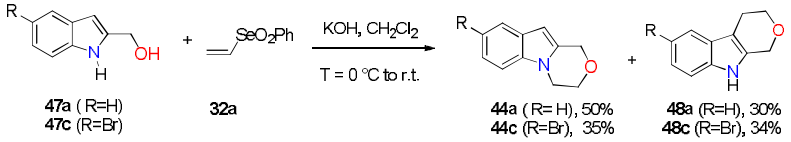
Scheme 20. Examples of polycyclic indolyl and pyrrolyl-based scaffolds.

A Michael addition/cyclization reaction cascade was carried out using (1*H*-indol-2yl) methanols **47a-h**, as Michael donors and different vinyl selenones **32a-f**, as Michael acceptors (Scheme 21).[33] After an extensive study for fine tuning of reaction conditions the crucial role of 18-crown-6 for achieving high selectivity was observed. As shown in Scheme 21, only the 3,4-dihydro-1*H*-oxazino[4,3-*a*]indoles **44a-l** were formed as single reaction products in good to excellent yields in the presence of 18-crown-6. Different electron-withdrawing or electron-donating groups and different substitution patterns on the indole ring together with different alkyl substitution on the vinyl selenones are well tolerated.



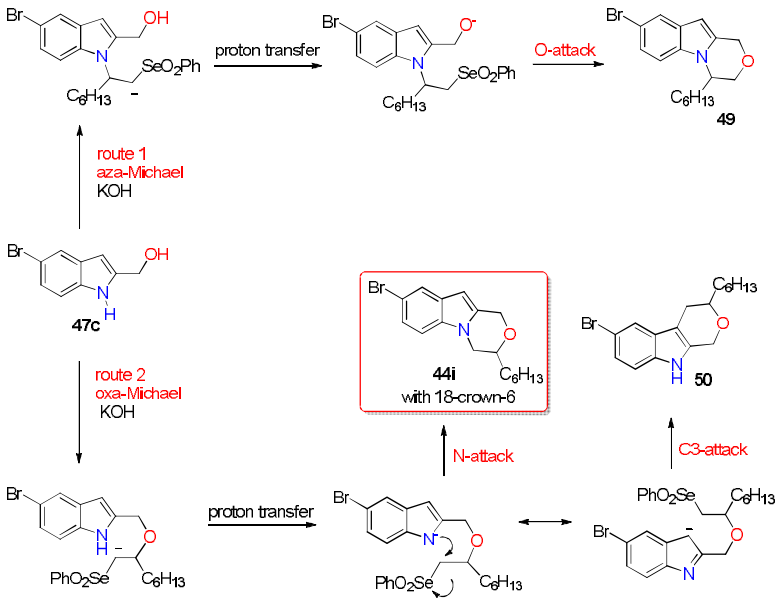
Scheme 21. High selectivity in domino processes using α and β substituted vinyl selenones in the presence of 18-crown-6.

On the contrary, poor selectivity in the MIRC reactions were observed in absence of 18-crown-6. Under these conditions, employing unsubstitued vinyl selenone **32a**, we have also the formation of the tetrahydropyrano[3,4-*b*]indoles **48a,c**, obtained through a C-3 alkylated process (Scheme 22).



Scheme 22. Poorly selectivity in absence of 18-crown-6.

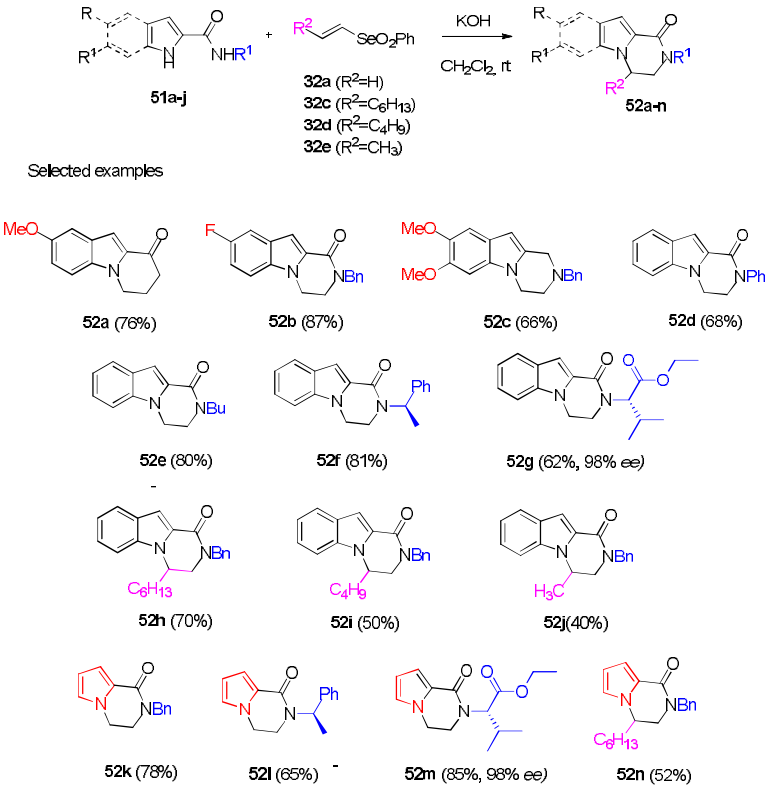
Using β-substituted selenone **32c,** two oxazino[4,3-*a*]indoles, **44i** and **49**, and pyrano[3,4-*b*]indole **50** were isolated in absence of 18-crown-6 (Scheme 23). The (1*H*-indol-2-yl)methanol **47c** has two nucleophilic sites for the initial Michael addition: the indolic N-H and the hydroxyl group. The formation of compounds **49,** with the alkyl chain in the α position of nitrogen atom, is initiated by an Aza-Michael addition. The subsequent proton transfer forms the oxygen anion that promotes the intramolecular displacement of the phenylselenonyl group (route 1, Scheme 23). On the contrary, compounds **44i** and **50**, with the alkyl chain in the α position of oxygen atom, can be generated when an initial oxa-Michael addition takes place (route 2, Scheme 23). In fact, in this case, the proton transfer generates a bidentate anion which can promote a N-cyclization affording **44i** or a C_3-cyclization affording **50**, respectively. The presence of crown ether is crucial for achieving the exclusive formation of the 3-substituted oxazine **44i**, derived from oxa-Michael attack followed by N-cyclization. The crown ether, by suppressing the tight ion pairing,[89] not only accelerates the reaction of the more nucleophilic "naked" oxygen during the formation of the Michael adduct, but also promotes the subsequent N-cyclization, preventing the C_3-attack. Crown ethers, in aprotic solvents and in presence of base, have already been employed in regioselective nucleophilic substitutions of indoles at the nitrogen atom.[90]



Scheme 23. Mechanism of MIRC reaction using (1*H*-indol-2-yl)methanol as *bis* nucleophile and β-alkyl substituted selenone.

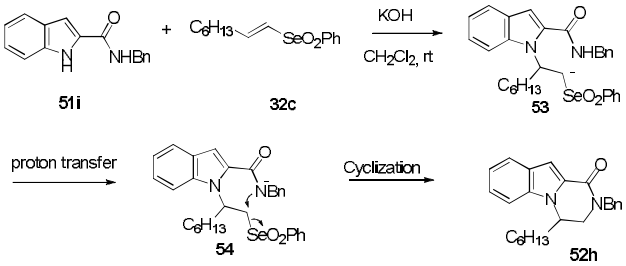
When the -CH_2OH group was replaced with amide at C-2 position, 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-ones **52a-j** and 3,4-dihydropyrazino[1,2-*a*]pyrrole-1(2*H*)-ones **52k-n** were obtained respectively using indole and pyrrole carboxamides as starting products (Scheme 24).[34] In these domino processes the presence of 18-crown-6 was not necessary to have selectivity. The presence of amide group at C-2 position increases the acidity of N1-H of heteroaromatic ring and makes the domino processes easier. The method showed a high substrate flexibility giving rise to products with three points of diversity. Different electron withdrawing or electron-donating groups on the aromatic ring as well as aryl and alkyl substituents at the amidic nitrogen are well tolerated. Moreover carboxamides derivated from amino esters gave enantiopure pyrazino-indoles **52g** and pyrrole **52m** in good yields. Such compounds are known to suffer racemization *via* 5(4*H*)-oxazolone intermediates depending on the nature of substituents and reaction conditions.[91] In our case no racemization was observed in the presence of cesium carbonate as base. Starting from *beta* alkyl substituted selenones, pyrazino-fused indoles **52h-j** and pyrrole

52n, bearing an alkyl chain in α-position of the nitrogen of the aromatic ring, were obtained in moderate-to-good yields. The structures of pyrazino indoles **52h-j** were assigned by analogy with those of known compounds.[92-94]



Scheme 24. Domino process by vinyl selenones and indole and pyrrole carboxamides. High substrates flexibility: three points of diversity.

The formation of compound, bearing an alkyl chain in alpha position of nitrogen atom of heteroaromatic ring, is consistent with an initial *aza*-Michael addition promoted by the nitrogen of the indole skeleton (Scheme 25).[93]

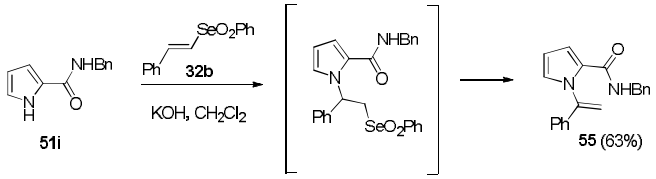


Scheme 25. Mechanism of MIRC reactions using 1*H*-indole 2-carboxamides.

A followed proton transfer generates the nitrogen anion on the amide functionality **54** that promotes, in turn, an intramolecular nucleophilic substitution of phenylselenonyl group to produce the pirazino fused

indole **52h**. The chemo selectivity of the attack is ascribable to the favorable acidity of the nitrogen: the p*Ka* value of the N-H of indole is 21, further increased by the presence of the electron-withdrawing group at the C2 position, whereas for the amide is 23-25 in DMSO. Moreover the presence of the amide at C2 position of the indole decreases the nucleophilicity of the C3 site granting a high region selectivity toward N1-alkylation, without the formation of products derived from the competitor C_3 site.[92]

Using vinyl selenone **32b**, bearing a phenyl group in the β position, and *N*-benzyl-1*H*-pyrrole-2-carboxamide **51i** the cyclized product was not isolated, while an *aza*-Michael addition-elimination product **55** was observed. Probably the formation of α phenyl-conjugated alkene is the driving force of the process and after the formation of Michael adduct, the elimination is favoured in respect to the cyclization (Scheme 26).



Scheme 26. Synthesis of *N*-benzyl-1-(1-phenylvinyl)-1*H*-pyrrole-2-carboxamide.

4. Conclusion

In conclusion the results described in this account demonstrate that organoselenium reagents can be successfully employed to effect the synthesis of different types of heterocyclic compounds. Privileged structures, observed in a large number of natural products and compounds of pharmaceutical interest were synthesized through asymmetric cyclization promoted by selenium electrophile reagents as well as through domino process using vinyl selenones. The hope is that the chemistry described in this personal account can find further developments and advances.

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