# RECENT ADVANCES IN THE SYNTHESIS OF FIVE- AND SIX-MEMBERED SELENA-HETEROCYCLES

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***Abstract.*** *Organoselenium compounds play an increasingly important role in chemistry and biochemistry. Amongst the wide variety of selenium-containing systems, selena-heterocycles are versatile derivatives with broad applications in organic synthesis, catalysis, medicinal chemistry, and biology. In this context, taking into account the poor stability of most selenylating reagents or intermediates, the development of simple, mild and versatile synthetic methodologies towards functionalised selena-heterocycles remains an attractive yet challenging topic. This chapter will be focusing on recent advances on the synthesis of different classes of selenium-containing five- and six-membered ring systems.*

**Contents**



## 1. Introduction

Selenium-containing small molecules occupy a central position in chemical science, with different applications in organic synthesis, material sciences and polymer chemistry.[1,2,3] Organoselenides are often employed as synthetic intermediates, ligands, and catalysts.[4,5,6,7] Furthermore, owing to their antioxidant, enzyme modulator, and anticancer properties, selenium-containing organic molecules play an increasingly important role in medicinal chemistry and biology.[8,9,10,11,12] In particular, due to their unique properties, five- and six-membered selena-heterocycles have attracted a great deal of interest.[13,14] A wide variety of differently substituted, functionalised, selenium-containing heterocycles have been used as versatile intermediates in organic synthesis and as catalysts in stereoselective transformations. In this regard, the presence of heavy chalcogen atoms such as selenium, offers the possibility to exploit intramolecular and intermolecular chalcogen bonding interactions in order to modulate the catalytic properties of selenated catalysts.[15,16] In addition, a number of selena-heterocycles have been reported to possess an array of biological activities, including antioxidant, antitumor, enzyme modulator, antimicrobial and anti-biofilm activities.[17,18,19] The antiviral properties of a number of selenium-containing heterocycles have also been described, thus the investigation of the protease activity of organoselenium systems is highly important, in order to propose novel potential drug candidates. For example, Ebselen, which arguably represents one of the most deeply investigated selenium-containing heterocycles, have been very recently found to exhibit a promising biological activitiy against the main protease $M^{pro}$ of SARS-CoV-2. Notably, the study reported that, among 10.000 evaluated molecules, Ebselen behaves as the best non-reversible inhibitor of the SARS-CoV-2 encoded protease.[20]

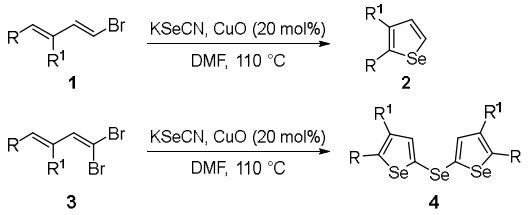
In this context, taking into account the paramount importance of selenium-containing heterocycles, the development of reliable procedures for their synthesis has attracted considerable interest and several methodologies have been reported over the past years. The mildness of the reaction conditions as well as the functional group tolerance represent crucial parameters that need to be considered in order to develop synthetically valuable approaches. Additionally, the possibility to access systems characterized by a high molecular complexity plays a key role in terms of successfully developing new catalysts and drug candidates.[21]

In this chapter, recent advances in the synthesis of selenium-containing five- and six-membered heterocycles reported in the last two decades are reviewed.

## 2. Synthesis of heterocyclic systems containing selenium

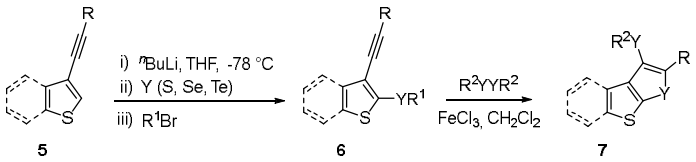
Five- and six-membered heterocyclic ring systems containing selenium atoms found applications in many areas of chemical sciences, including the development of materials, conductors, optoelectronic devices, and photosensitizers for photodynamic therapy (PDT).[22,23,24] In this scenario, the study of convenient and general methodologies for their synthesis represents an active area of organic chemistry and, therefore, several procedures have been developed over the past years. The present section of this chapter focuses on recent advances on the synthesis of five- and six-membered heterocyclic ring systems containing selenium atoms.

Potassium selenocyanate is a commonly employed reagent for the introduction of selenium atoms into organic structures. Ranu *et al*. reported a copper-catalysed procedure for the synthesis of selenophenes **2** from 1,3-dienyl bromides **1**. Furthermore, when 1,3-dienyl-*gem*-dibromides **3** were used as substrates, the corresponding selanyl selenophenes **4** were obtained (Scheme 1).[25]




**Scheme 1.** Synthesis of selenophenes and selanyl selenophenes from 1,3-dienyl bromides and 1,3-dienyl-*gem*-dibromides.

Acetylenes can be employed as precursors of chalcogenophene derivatives through electrophilic cyclization.[26,27,28] Zeni *et al*. described the synthesis of chalcogenophene[2,3-*d*]thiophenes **7** through the $FeCl_3$-promoted intramolecular cyclization of **6**, conveniently prepared from **5** by chalcogen insertion and alkylation sequence (Scheme 2). Notably, compounds **7** can be further functionalised with boronic acids or with aldehydes towards more complex systems.[27,28]



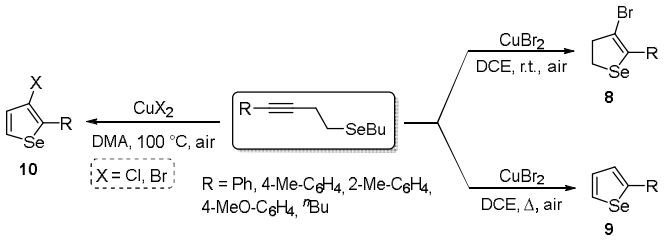

**Scheme 2.** Synthesis of further functionalizable chalcogenophene[2,3-*d*]thiophenes **7**.

Zeni *et al*. reported the Cu(II) halide-mediated cyclization of homopropargyl selenides into different selenophene derivatives. Indeed, substituted dihydroselenophenes **8** and selenophenes **9** could be obtained in 1,2-dichloroethane by varying the reaction temperature. On the other hand, synthetically useful and further functionalisable 3-haloselenophenes **10** were selectively achieved when 1,2-dichloroethane was replaced by dimethylacetamide (Scheme 3).[29]

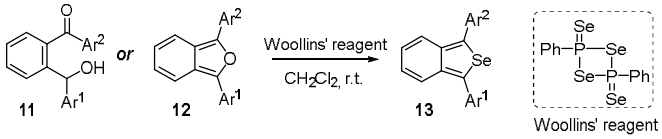
The Woollins' reagent, a selenophosphorous compound structurally related to the sulfur-containing Lawesson reagent, has been employed as an efficient selenium delivery system. Amaladass *et al*. reported that substituted ketoalcohols **11** or benzo[*c*]furanes **12** were easily converted into the corresponding diarylbenzo[*c*]selenophenes **13** upon treatment with Wollins reagent in dichloromethane at ambient temperature (Scheme 4).[30]

Sasaki *et al*. developed a simple procedure for the synthesis of selenophene **17**, bearing four phosphoryl moiety, from bis(diethoxyphosphoryl)acetylene and sodium hydroselenide. Addition of NaHSe

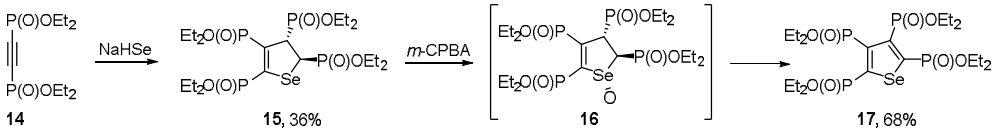
to **14**, followed by an intramolecular ring closure of the α,β-unsaturated selenide intermediate, leads to the formation of 2,3-dihydrotetraphosphorylselenophene **15**. Aromatization of **15** could be achieved under oxidative conditions through the selenoxide **16**, which easily undergoes dehydration providing the selenophene **17** (Scheme 5).[31]




**Scheme 3.** Zeni's Cu(II) halide mediated synthesis of substituted dihydroselenophene and selenophene derivatives.

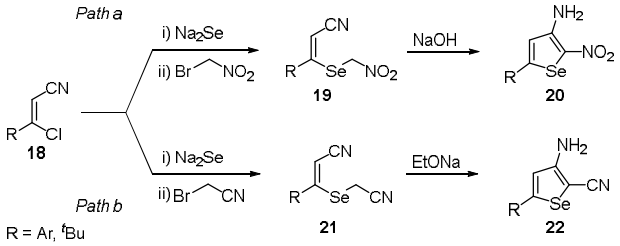



**Scheme 4.** Synthesis of diarylbenzo[*c*]selenophenes by using Woollins'reagent.




**Scheme 5.** Synthesis of selenophene **17** from bis(diethoxyphosphoryl)acetylene.

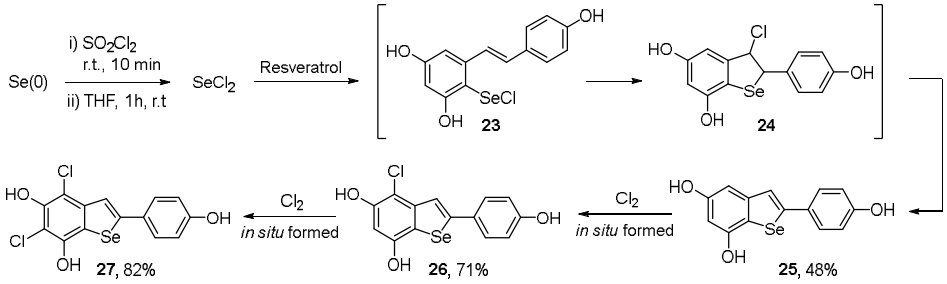
Sodium selenide ($Na_2Se$) was used as nucleophilic selenium species to prepare functionalised selenides **19** and **21**, which behaved as key intermediates for the synthesis of substituted 3-amino-2-nitroselenophenes **20** and 2-cyanoselenophenes **22** under mild conditions (Scheme 6).[32,33] Notably, the so obtained cyano-substituted selenophenes **22** were also further functionalised by using the Friedländer condensation to access selenium-containing analogues of Tacrine, a well-known acetylcholinesterase inhibitor.[33]




**Scheme 6.** Synthesis of nitro- and cyano-subtituted 3-amino- selenophenes.

During the course of our investigations in the study of chalcogen-containing natural-product-derived antioxidants,[11,34,35] we reported the synthesis of a novel class of resveratrol derivatives featuring a 2-phenylbenzoselenophene skeleton. Benzoselenophene **25** and its monochloro- and dichloro-substituted derivatives (**26** and **27**) were conveniently achieved upon treatment of resveratrol with elemental selenium and sulfuryl chloride. The reaction reasonably involves the electrophilic aromatic substitution of the resorcin

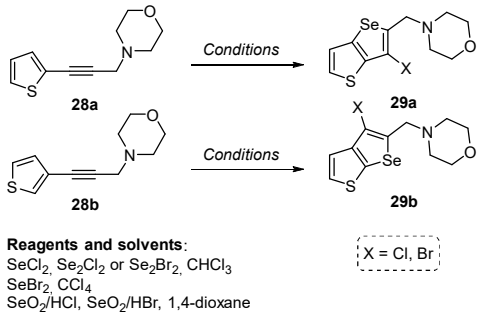
moiety of resveratrol with *in situ* generated $SeCl_2$ to yield **23**, which subsequently undergoes intramolecular addition to the double bond to give **24** and further HCl elimination to provide **25** (Scheme 7). Monochloro- and dichloro-substituted benzoselenophenes **26** and **27** are plausibly formed through chlorination reactions with $Cl_2$, generated from $SO_2Cl_2$ by dismutation. Notably, a fine tuning of the reaction stoichiometry enabled a selective entry to compounds **25**, **26**, **27**. All the novel resveratrol-derived benzoselenophenes proved to behave as effective antioxidants, being more efficient than resveratrol and exhibiting both GPx-like properties and chain-breaking antioxidant activity.[34,35]




**Scheme 7.** Synthesis of resveratrol-derived benzoselenophenes.

An interesting strategy for the synthesis of highly substituted dibenzoselenophenes through a one-pot domino hexadehydro-Diels-Alder reaction of triphenylphosphine selenide with tetraynes was also recently reported by Hu *et al.* [36]

Arsenyan developed a simple procedure for the conversion of ethynylthiophenes **28a,b** into selenopheno[2,3-*b*]thiophene derivatives **29a,b** by using selenium halides as selenium electrophilic species (Scheme 8). When $SeO_2$ was employed in this transformation in place of selenium dichloride/dibromide, lower yields of **29a** and **29b** were observed.[37]

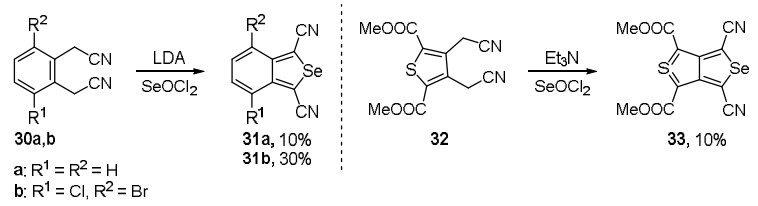



**Scheme 8.** Synthesis of selenopheno[2,3-*b*]thiophene derivatives from ethynylthiophenes and selenium halides.

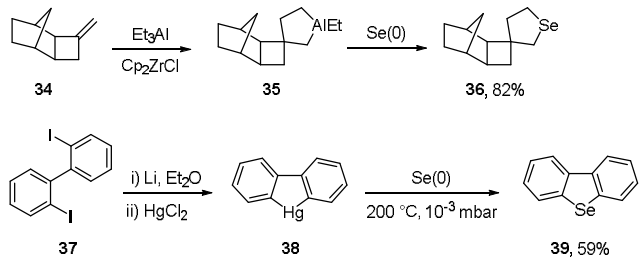
Selenium oxychloride ($SeOCl_2$) was also used as selenium transfer reagent for the synthesis of selenophene derivatives. In this context, the selenylation of dinitriles **30a,b** and **32** with $SeOCl_2$ in the presence of bases was exploited by Roger et al. to develop a synthetic route to access, albeit in moderate yields, polyfunctionalised systems **31a,b** and **33** (Scheme 9).[38]

The reaction of selenium with metallacycloalkanes, such as aluminacyclopentanes and magnesacyclopentanes commonly generated *in situ* through the Dzhemimilev catalytic cyclometallation of olefins, provides an interesting route towards five-membered selenium-containing heterocycles. D'yakonov *et al.* used this methodology for the conversion of **34** into the spiro dihydroselenophene derivative **36**, exploiting the reactivity of the corresponding aluminacarbocycle **35** (Scheme 10). A related procedure was applied to allenes and acetylenes enabling the synthesis of different selenophene derivatives.[39,40] The

selenium-metal exchange reaction was also used for the synthesis of the dibenzoselenophene **39**.[41] Lithiation of **37** with elemental lithium and subsequent treatment with $HgCl_2$ afforded **38** which can be easily converted into **39** upon Se-Hg exchange (Scheme 10). Notably, the use of elemental lithium instead of *n*-BuLi proved to be a more efficient strategy.

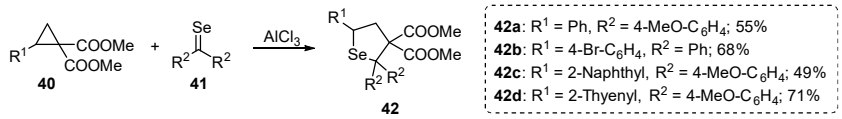



**Scheme 9.** Synthesis of selenophene derivatives **31** and **33** from dinitriles **30**,**32** and $SeOCl_2$.



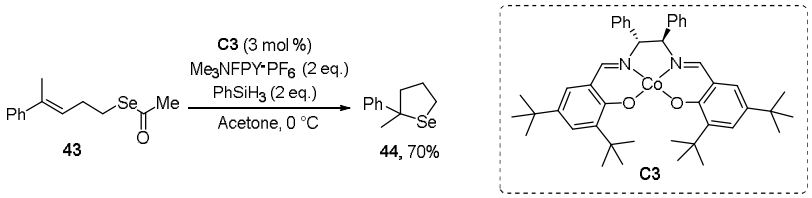

**Scheme 10.** Synthesis of selenium-containing heterocycles through selenium-metal exchange reactions.

Functionalised tetrahydroselenophene derivatives **42** are also obtained through the Lewis acid-catalysed [3+2] cycloaddition reaction of selenoketones **41** with donor-acceptor 2-substituted cyclopropane 1,1-dicarboxylates **40** (Scheme 11).[42]



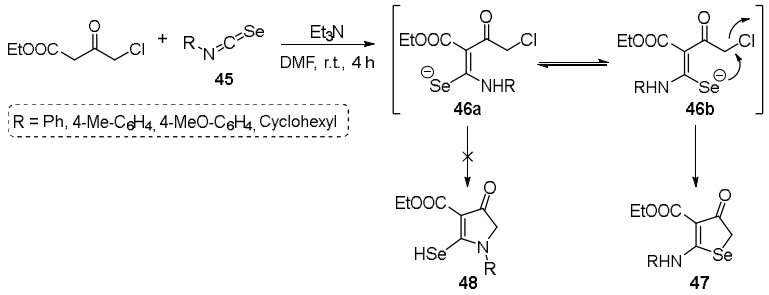

**Scheme 11.** Synthesis of tetrahydroselenophene derivatives from selenoketones and donor-acceptor cyclopropanes.

The tetrahydroselenophene **44** was obtained from the alkenyl selenolester **43** through a Markovnikov-selective cobalt-catalysed hydrogen atom transfer/radical-polar crossover (HAT/RPC) process. The reaction occurs in the presence of the cobalt catalyst **C3**, 4,6-trimethyl-*N*-fluoropyridinium hexafluorophosphate and phenylsilane (Scheme 12).[43]



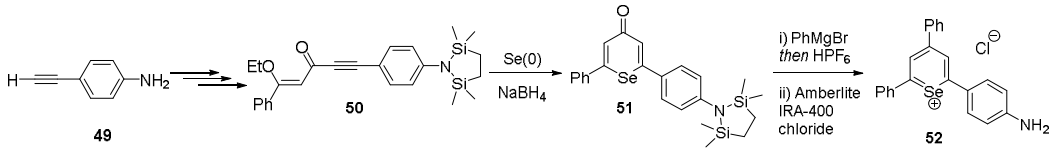

**Scheme 12.** Cobalt-catalysed synthesis of the tetrahydroselenophene **44** from the alkenyl selenolester **43**.

Isoselenocyanates **45** were also employed for the synthesis of functionalised amino-substituted 4,5-dihydro-4-oxo-selenophenes **47**. Intermediates **46a,b**, formed from isoselenocyanates and chloroacetoacetate in the presence of a base, undergo intramolecular cyclization to afford **47**. Notably, the ring-closure leads exclusively to **47**, formed through the nucleophilic attack of the selenolate **46b**; the pyrrole derivative **48**, arising from the nucleophilic attack of the nitrogen atom of **46a**, is not observed (Scheme 13).[44]



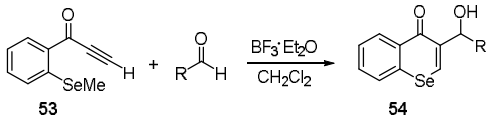

**Scheme 13.** Synthesis of functionalised dihydro-4-oxo-selenophene derivatives from isoselenocyanates and chloroacetoacetate.

Selenopyrylium derivative **52** was synthesized by Detty *et al*. from the α,β-unsaturated enol ether **50**, prepared from *p*-aminophenylacetylene **49** in four steps. The synthesis of the selenopyranone **51** was achieved upon treatment of **50** with disodium selenide, generated *in situ* from elemental selenium and sodium borohydride. The reaction proceeds through two conjugate additions of selenium-centered nucleophiles and represents the key step in the synthesis of **52**, which is easily obtained from **51** by the addition of phenylmagnesium bromide to the ketone, followed by dehydration with $HPF_6$ and ion-exchange on Amberlite (Scheme 14).[45]



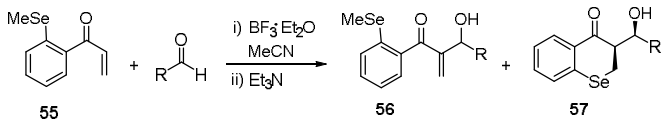

**Scheme 14.** Synthesis of selenopyrylium derivative **52**.

The synthetic versatility of methyl-aryl selenides is also demonstrated by their application in the synthesis of six-membered heterocycles. Selenochromene-4-one derivatives **54** were efficiently synthesized by Kataoka *et al*. from methyl-aryl selenide **53** through a 6-*endo-dig* cyclization, smoothly occurring in the presence of boron trifluoride diethyl etherate, and subsequent aldol reaction with aldehydes (Scheme 15).[46]




**Scheme 15.** Synthetic route towards selenochromene-4-ones **54** from methyl-aryl selenide **53**.

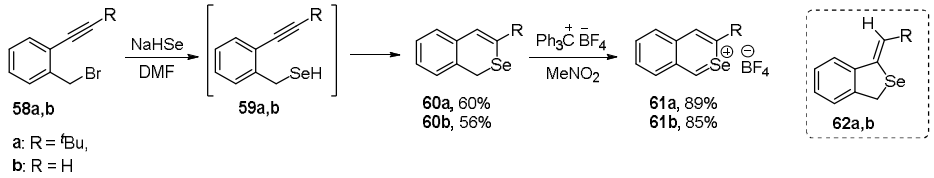
The same group also reported that the methylseleno-substituted α,β-unsaturated ketone **55** reacts with aldehydes, in the presence of boron trifluoride diethyl etherate and triethylamine, to afford Baylis-Hillman adducts **56** along with selenochromanones **57** (Scheme 16).[47,48]




**Scheme 16.** Synthetic route towards selenochromanones **57** from methyl-aryl selenide **55**.

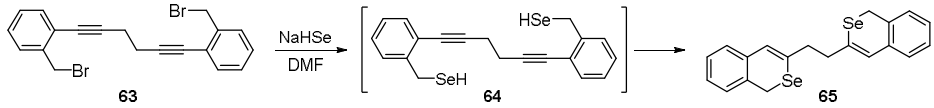
Notably, an alternative interesting route toward substituted selenochromanes is represented by the reaction of allyl alcohols with (phenylseleno)trimethylsilane and aluminium bromide. A sigmatropic rearrangement of the initially formed adduct leads, indeed, to 4-substituted selenochromanes in good yield.[49]

Functionalised selenols have often been used as reactive key intermediates for the synthesis of selenium-containing heterocycles. For example, *o*-ethynylbenzyl selenols **59a,b**, generated *in situ* from the corresponding bromides **58a,b** upon treatment with NaHSe, are not isolated and undergo intramolecular cyclization to yield isochromenes **60a,b**. Further reaction of **60a,b** with tritylium tetrafluoroborate enables the synthesis of 2-benzoselenopyrylium tetrafluoroborates **61a,b** (Scheme 17). The formation of (*Z*)-1-methylidene-2-selenaindans **62a,b** was also observed.[50]



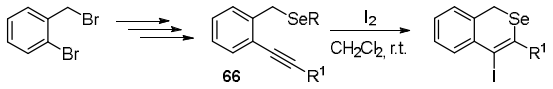

**Scheme 17.** Synthesis of isochromenes and benzoselenopyrylium derivatives through selenols **59**.

A similar approach was also employed for the synthesis of the bis-isoselenochromene **65** from the bis-acetylene derivative **63**. The key selenol intermediate **64** is generated by using NaHSe as the selenium nucleophile reagent. **64** is then *in situ* converted into **65** through a double *endo-dig* cyclization (Scheme 18).[51]



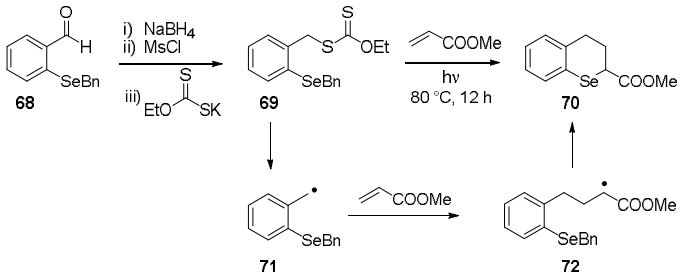

**Scheme 18.** Synthesis of the bis-isoselenochromene **65** through the selenol intermediate **64**.

The iodocyclization of suitable selenium-containing systems represents a versatile tool for the synthesis of heterocycles. For example, Zeni *et al*. reported that 2-alkynylbenzyl selenides **66**, prepared in two steps (selenylation and Sonogashira coupling) from 1-bromo-2(bromomethyl)benzene, could be converted into 3-substituted-4-iodo-1*H*-isoselenochromenes **67** through iodocyclization (Scheme 19).[52]



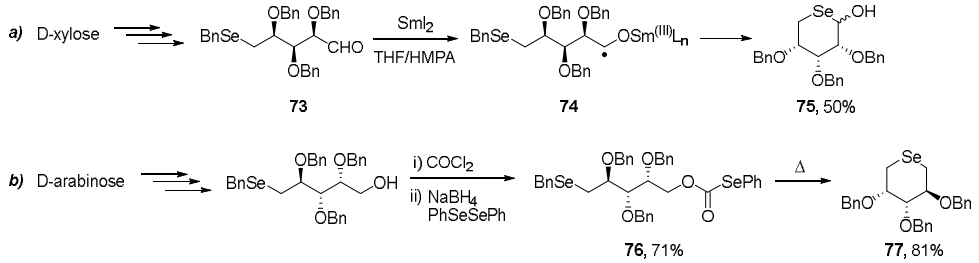

**Scheme 19.** Synthesis of 1*H*-isoselenochromenes **67** through iodocyclization of 2-alkynylbenzyl selenides **66**.

A number of radical cyclizations for the synthesis of selenium-containing heterocycles have also been developed. Schiesser *et al*. reported the synthesis of selenochromanes **70** from the radical precursor xanthate **69**, easily prepared from the aldehyde **68**. The selenium containing benzyl radical **71** is generated from **69** under photochemical conditions. Addition of **71** to electron-poor alkenes leads to the formation of radical **72**, which undergoes intramolecular homolytic substitution to yield the selenochromane **70** (Scheme 20).[53]




**Scheme 20.** Schiesser and co-workers' radical approach to selenochromanes.

A radical approach was also exploited by Schiesser *et al*. to access selenosugars in which the "anomeric" centre is oxygenated. The aldehyde **73**, easily prepared from the corresponding mesylate upon reaction with sodium benzylselenolate, was treated with samarium(II) iodide in THF/HMPA to generate the radical species **74**. Intramolecular homolytic substitution of the carbon-centered radical in **74** at the selenium atom affords **75** together with the expulsion of the benzyl group (see Scheme 21, *part a*). Notably, selenosugar **75** was obtained as a pair of enantiomers.[54] On the other hand, selenosugars of the type **77** can be obtained through thermolysis of benzylseleno-substituted selenoformate **76**, prepared in rather good yield from the corresponding sugar (see Scheme 21, *part b*). Interestingly, in the case of selenoformates, the mechanism of the intramolecular cyclization reasonably proceeds through the nucleophilic substitution of the benzylseleno moiety, instead of the above-mentioned homolytic path.[55]



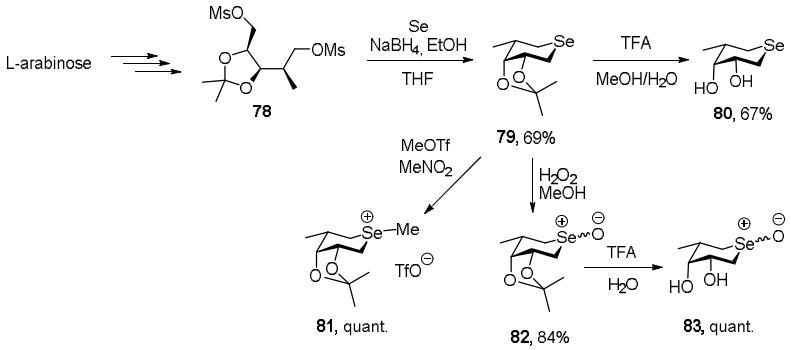

**Scheme 21.** Schiesser and co-workers' approaches to selenosugars.

Arabinose-derived selenosugars, isosteres of the glycosidase inhibitor isofucofagomine, could also be prepared upon reaction of *in situ* generated sodium selenide with the dimesylate **78**. The reaction affords the *O*-protected selenosugar **79** which can be easily deprotected under TFA conditions providing the diol **80**. On the other hand, **79** can be converted into the selenonium salt **81** by seleno-methylation or into the protected selenoxide **82**, upon reaction with hydrogen peroxide. The selenoxide **83**, bearing the free diol moiety, is achieved from **82** by cleaving the acetonide protecting group with TFA (Scheme 22).[56]

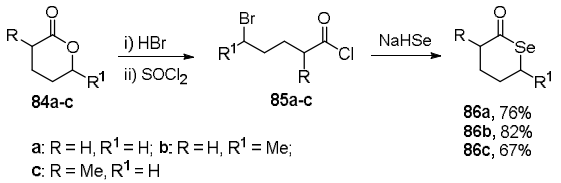
Sodium hydroselenide (NaHSe) was also employed as selenium nucleophilic reagent for the synthesis of selenolactones **86a-c**. Substituted δ-bromo acyl chlorides **85a-c**, prepared from δ-valerolactones **84a-c** by hydrolysis with hydrogen bromide and subsequent treatment with thionyl chloride, undergo nucleophilic ring-closure to yield tetrahydroselenopyran-2-ones **86a-c** (Scheme 23).[57]

Selenocarbonyl derivatives can be used as dienophiles and dipolarophiles enabling the construction of a variety of selenium-containing heterocycles. For example, selenoaldehydes **87**, generated *in situ* from the

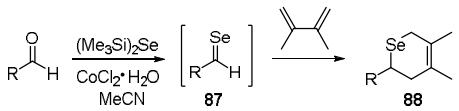
corresponding aldehydes by a selenosilane-mediated procedure, reacted with 2,3-dimethyl-1,3-butadiene to yield 3,6-dihydro-2*H*-selenopyrans **88** through hetero Diels-Alder cycloaddition reactions (Scheme 24).[58,59]




**Scheme 22.** Synthesis of arabinose-derived selenosugars.




**Scheme 23.** Synthesis of selenolactones **86** from δ-valerolactones **84**.



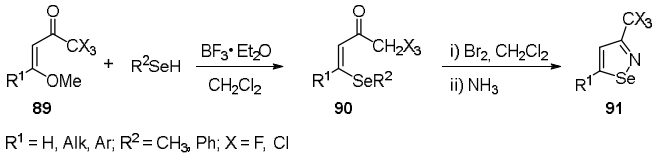

**Scheme 24.** Hetero Diels-Alder cycloaddition reactions of selenoaldehydes with 2,3-dimethyl-1,3-butadiene.

### 3. Synthesis of heterocyclic systems containing selenium and nitrogen

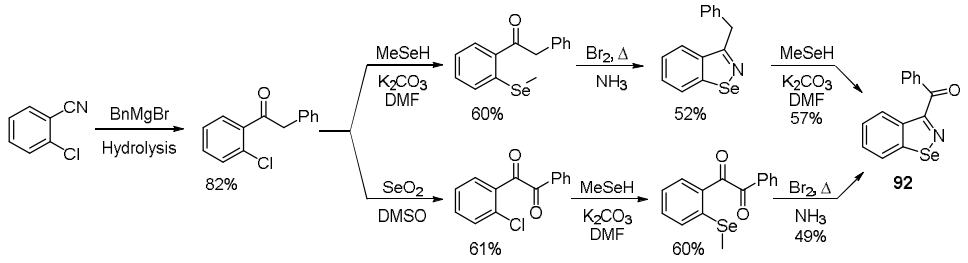
Selena-heterocycles containing nitrogen atoms include several classes of systems with broad application in organic synthesis and biology. The antioxidant, enzyme inhibitor, and antimicrobic properties of a number of selenium-nitrogen heterocycles, such as selenazoles, selenazolidines, and selenadiazoles have been indeed investigated. Ebselen (a benzoisoselenazol-3(2*H*)-one derivative) is arguably one of the most studied organoselenium compounds. On the other hand, the use of selena-heterocycles as ligands or catalysts is well documented and, for example, cyclic isoselenoureas, are employed in enantioselective catalysis. The present section focuses on recent developments on the synthesis of selenium-nitrogen heterocyclic ring systems.

Selenols can be used as effective selenium-centered nucleophiles and their reactivity can be exploited to access valuable intermediates for the synthesis of a wide variety of selenium-containing heterocycles. For example, *Z*-vinyl-selenides **90**, obtained from enol ethers **89** and selenols in the presence of boron trifluoride diethyl etherate, undergo cyclocondensation with bromine and ammonia to yield the corresponding 1,2-selenazoles **91** bearing the trifluoromethyl or the trichloromethyl moiety (Scheme 25).[60]

The synthesis of 3-benzoylbenzo[*b*][1,2]selenazol **92** was pursued by exploiting the reactivity of selenols. In both the strategies developed by Christiaens *et al*. (Scheme 26), the key steps for the synthesis of **92** are: *i*) the introduction of the selenated group through the reactivity of methyl selenol with suitable aryl chlorides, and *ii*) the intramolecular cyclization with bromine and ammonia leading to the formation of the selenazol core.[61]

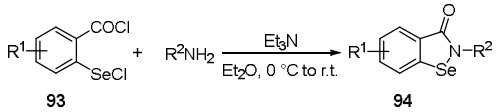



**Scheme 25.** Synthesis of trihalomethyl-substituted 1,2-selenazoles **91**.



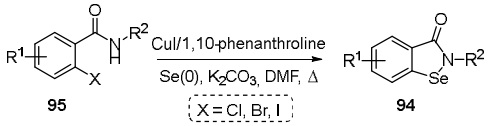

**Scheme 26.** Two approaches to 3-benzoylbenzo[*b*][1,2]selenazol **92** through selenide intermediates.

Since the discovery of the glutathione peroxidase-like properties of Ebselen and its analogues, a number of synthetic routes have been developed towards such selenazole derivatives. Very recently, the activity of Ebselen against the main protease $M^{pro}$ of SARS-CoV-2[20] shed new light on the importance to develop general procedures for the preparation of variously substituted Ebselen-like systems **94**. A common route towards this class of molecules is based on the reactivity of 2-(chloroseleno)benzoyl chlorides **93**, usually generated from the corresponding *o*-carboxy-substututed diaryl diselenides upon reaction with thionyl chloride, with amines (Scheme 27).[62] Notably, such a procedure has also been applied to the synthesis of chiral Ebselen-like derivatives by using enantioenriched amines[63] as well as to the preparation of peptide-containing Ebselen analogues.[64]




**Scheme 27.** Common route for the synthesis of Ebselen and Ebselen analogues.

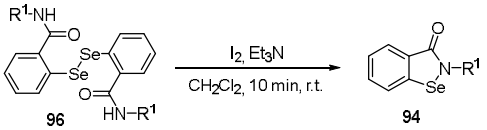
Kumar *et al*. also developed an alternative and efficient copper-catalysed procedure for the synthesis of Ebselen analogues **94** by using 2-halobenzamides **95** as starting material. The reaction smoothly occurred in DMF by using CuI, 1,10-phenanthroline and elemental selenium in the presence of potassium carbonate (Scheme 28).[65] A similar procedure was also applied to the synthesis of related aza-derivatives.[66]




**Scheme 28.** Copper-catalysed synthesis of Ebselen analogues from 2-halobenzamides.

Very recently, Nascimento, *et al*. reported a simple and efficient conversion of *o*-amidoaryldiselenides **96** into the corresponding Ebselen-like *N*-substituted benzoisoselenazol-3(2*H*)-ones **94** (Scheme 29). The reaction proceeds through the formation of a selenenyl iodide which undergoes intramolecular nucleophilic attack of the nitrogen atom onto the electrophilic selenium atom to afford **94** in good yield. Notably, compounds **94** were not isolated when $Br_2$ or $H_2O_2$ were used as the oxidant instead of $I_2$. These

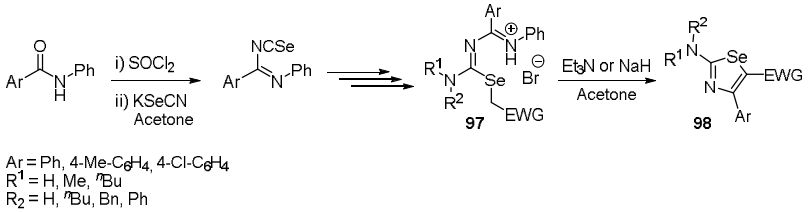
experimental data are in line with results of DFT calculations, which demonstrated that different weak interactions between the chalcogen and the neighbouring heteroatoms take place as a consequence of the modulation of the selenium electrophilicity. Indeed, whilst diselenides, selenenyl bromides and selenenic acids exhibit weak Se···O interactions, Se···N interactions are prevalent in selenenyl iodides which, therefore, can be exploited for the synthesis of Ebselen-like systems **94**.[67]




**Scheme 29.** Synthesis of Ebselen-like systems from *o*-amidoaryldiselenides.

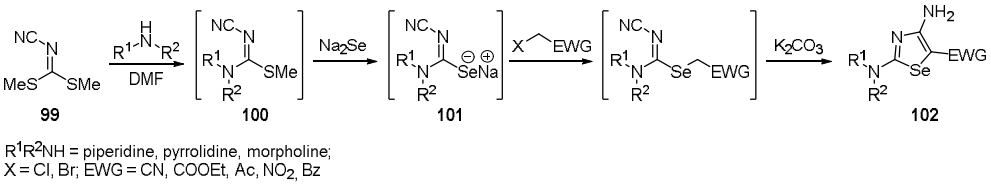
The synthesis of Ebselen-like benzoisoselenazolones through a 8-aminoquinoline-directed copper/manganese cocatalyzed C-H selenylation of benzamides was also recently reported by Singh *et al*.[68]

Heimgartner *et al*. also reported the use of isoselenocyanates (prepared from benzamides and KSeCN) in the synthesis of 1,3-selenazoles **98**. Derivatives **97** were first obtained from isoselenocyates through a three-step process; further treatment of **97** with $Et_3N$ or NaH in acetone provided substituted 1,3-selenazoles **98** (Scheme 30).[69]



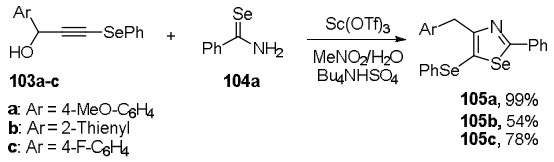

**Scheme 30.** Synthesis of functionalised 1,3-selenazoles from benzamides and KSeCN.

Disodium selenide was also used by Thomae *et al*. as the nucleophilic reagent for the synthesis of the key intermediate **101**, exploited for the synthesis of trisubstituted 1,3-selenazoles **102**. Indeed, sequential reaction of **99** with amines, $Na_2Se$, activated alkyl halides, and potassium carbonate enabled the one-pot formation of **102** in good yields (Scheme 31).[70]



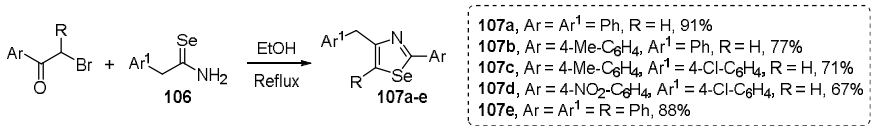

**Scheme 31.** One-pot synthesis of trisubstituted 1,3-selenazoles **102**.

Undergoing a variety of selective reactions, selenoamides are valuable precursors of *N*,*Se*-heterocycles and, therefore, have been widely employed for the construction of selenium-containing rings. Synthetically useful 1,3-selenazoles **105a-c** were regioselectively achieved from 3-selanylpropargyl alcohols **103a-c** and benzoselenoamide **104a** under phase-transfer conditions in the presence of $Bu_4NHSO_4$ (Scheme 32). The reaction proceeds through the scandium triflate-nitrometane-$H_2O$-mediated formation of an α-selanyl propadienyl cation which, upon reaction with the selenoamide, affords an allene intermediate finally converted into the corresponding 1,3-selenazole *via* intramolecular cyclization.[71]



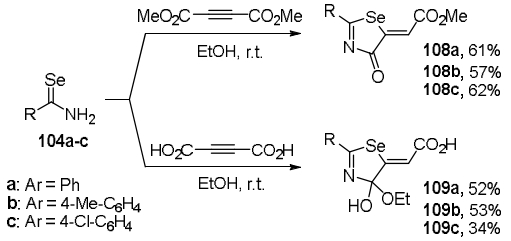

**Scheme 32.** Synthesis of 1,3-selenazoles **105** from selenoamides and 3-selanylpropargyl alcohols.

Geisler *et al*. reported a simple synthesis of substituted 1,3-selenazoles **107** from α-bromoketones and selenoamides **106**, smoothly occurring in refluxing ethanol (Scheme 33).[72]



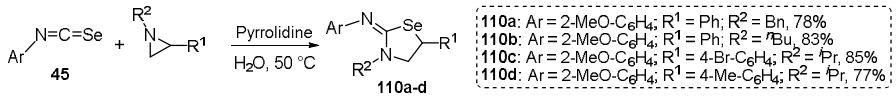

**Scheme 33.** Synthesis of 1,3-selenazoles **107** from selenoamides and α-bromoketones.

Selenoamides **104a-c** can also be employed for the synthesis of functionalised dihydro-1,3-selenazole derivatives upon reaction with acetylenedicarboxylates. Interestingly, while 4,5-dihydro-1,3-selenazol-4-ones **108a-c** where achieved from dimethyl acetylenedicarboxylate, the use of acetylenedicarboxylic acid provided 4,5-dihydro-1,3 selenazol-4-ols **109a-c** (Scheme 34).[73]



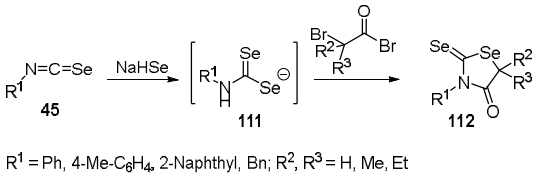

**Scheme 34.** Synthesis of dihydro-1,3-selenazole derivatives **108** and **109** from selenoamides.

Punniyamurthy *et al*. reported an efficient synthesis of selenazolidine derivatives **110** through the pyrrolidine-catalysed [3+2] cycloaddition of isoselenocyanates **45** with aziridines (Scheme 35). The proposed reaction mechanism involves the formation of selenourea-type reactive intermediates from pyrrolidine and isoselenocyanates. The intermediate reacts with aziridines to afford the corresponding nucleophilic ring-opening product which, finally, undergoes intramolecular cyclization yielding **110a-d** and releasing the catalyst.[74]




**Scheme 35.** Synthesis of selenazolidines **110** through [3+2] cycloaddition of isoselenocyanates with aziridines.

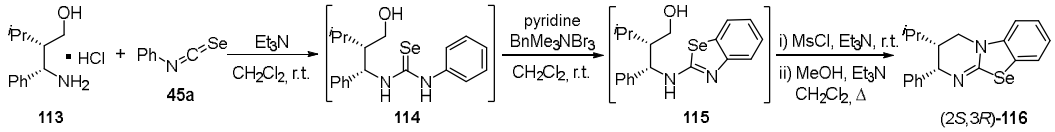
Isoselenocyanates **45** were also employed by Koketsu *et al*. as precursors of diselenocarbamates **111** upon treatment with sodium hydroselenide. The so generated diselenocarbamates are useful synthetic intermediates and can be *in situ* treated with suitable bromoacetyl bromides to afford 2-selenoxo-1,3-selenazolidin-4-ones **112** (Scheme 36).[75] Notably, acryloyl isoselenocyanates can also be used for the synthesis of selenazine derivatives.



$R^1$ = Ph, 4-Me-$C_6H_4$, 2-Naphthyl, Bn; $R^2$, $R^3$ = H, Me, Et

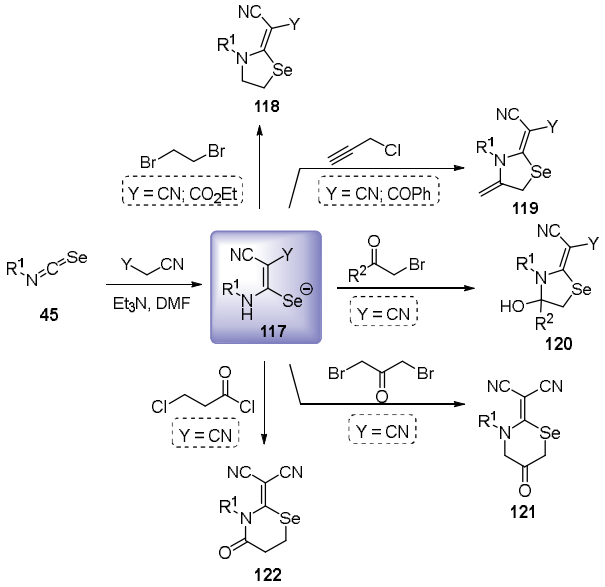
**Scheme 36.** Preparation of **112** from isoselenocyanates through diselenocarbamate intermediates.

Very recently, Smith *et al*. reported the one-pot synthesis of the chiral isoselenourea **116** from **113** and phenyl isoselenocyanate **45a**. The selenourea **114** is *in situ* cyclised to the derivative **115** through an unprecedented seleno-Hugerschoff reaction. Treatment of **115** with MsCl and triethylamine, followed by heating, enabled the formation of the isoselenourea **116** in 64% yield (Scheme 37). The catalytic activity of (*2S,3R*)-**116** in nitronate conjugate addition and formal [4+2] cycloadditions, as well as the importance of O···chalcogen interactions in enantioselective catalysis were also investigated.[15]



**Scheme 37.** One pot synthesis of chiral isoselenourea (*2S,3R*)-**116**.

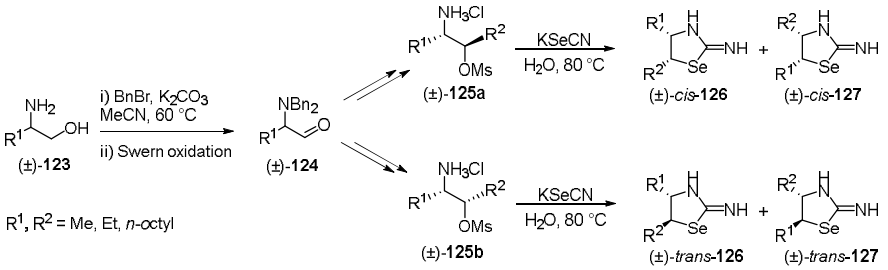
The versatility of isoselenocyanates as building blocks for the synthesis of selenium-containing five- and six-membered heterocycles is well demonstrated by the work of Heimgartner *et al*.[76,77,78] Keten-*N,Se*-acetal intermediates **117**, generated through the base-promoted reaction of malononitrile or ethyl cyanoacetate with isoselenocyanates, are indeed treated with different halogen-containing electrophiles providing access to a variety of substituted 1,3-selenazolidine derivatives **118**-**120** (Scheme 38).[76,77,78]



**Scheme 38.** Heimgartner and co-workers' approaches to functionalised selenium-containing heterocycles through the reactivity of isoselenocyanates.

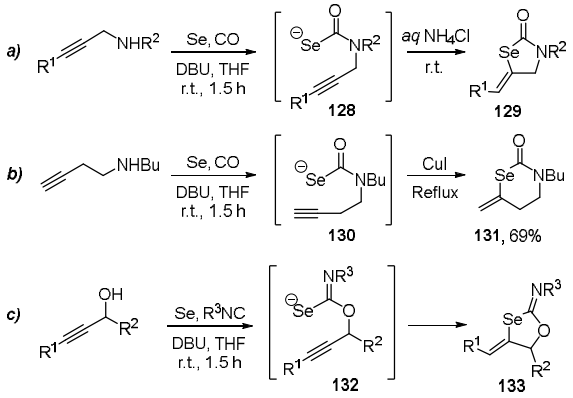
Furthermore, functionalised 1,3-selenazines **121** and **122** can be achieved upon reaction of keten-*N,Se*-acetal intermediates with 1,3-dibromoacetone or 3-chloropropanoyl chloride.[76]

Ueda *et al*. reported the synthesis of biologically active enantioenriched substituted 2-imino-selenazolidines from amino alcohols **123**. The key step of the process is the reaction of *O*-methanesulfonyl β-amino alcohol hydrochlorides **125**, synthesized from the *N*,*N*-dibenzyl aldehyde **124** in six steps, with potassium selenocyanate. (Scheme 39) The proposed mechanism, accounting for the stereochemical outcome of the reaction, foresees the conversion of (±)-**125a** and (±)-**125b** into the corresponding aziridines, which undergo ring opening reaction with KSeCN and subsequent intramolecular cyclization to afford (±)-**126** and (±)-**127**.[79] Remarkably, such substituted 2-imino-selenazolidines exhibited a strong inhibitory activity against inducible nitric oxide synthase (iNOS).[80]



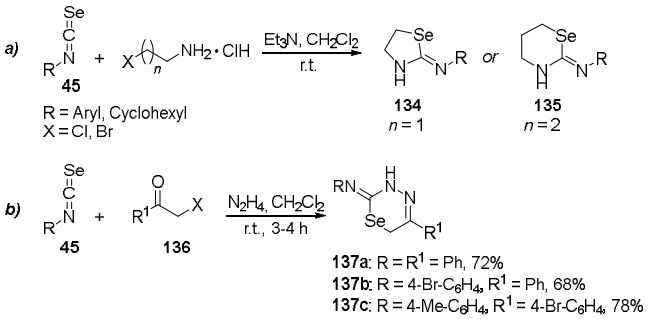

**Scheme 39.** Synthesis of 2-imino-selenazolidines **126** and **127** as inducible nitric oxide synthase inhibitors.

Kambe *et al*. reported the stereoselective synthesis of 5-alkylideneselenazolin-2-ones **129** from 3-aminoalkynes, selenium, and carbon monoxide (Scheme 40, *part a*).[81] The proposed reaction mechanism involves the formation of a carbamoselenoate intermediate **128** which undergoes intramolecular proton-assisted nucleophilic addition of selenium to the triple carbon-carbon bond to afford the corresponding five-membered heterocycle. This methodology could also be extended to the synthesis of the 1,3-selenazin-2-one **131** from the corresponding homopropargylamine (Scheme 40, *part b*).[81] In this case, the addition of CuI was required in order to promote the intramolecular reaction of the carbamoselenoate **130**. Notably, the same group developed a related procedure to access 2-imino-functionalised 1,3-oxaselenolanes **133** from propargylic alcohols, selenium, and isocyanides (Scheme 40, *part c*).[82] Oxyimidoylselenoates **132**, *in situ* generated through selenoimidoylation reaction of the parent propargylic alcohol with selenium and isocyanides, undergo intramolecular addition to the carbon-carbon triple bond to provide the corresponding 2-imino-4-alkylidene-1,3-oxaselenolanes **133**.



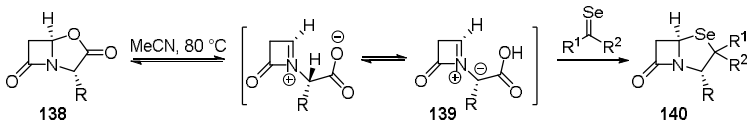

**Scheme 40.** Synthesis of selenium-containing heterocycles **129**, **131**, **133** through carbamoselenoate or oxyimidoylselenoate intermediates.

During their study of new methodologies for the synthesis of chalcogen-containing heterocycles, Heimgartner *et al*. reported that isoselenocyanates **45** smoothly react with halo-substituted amine hydrochlorides to afford the corresponding 1,3-selenazolidin-2-imines **134** or 1,3-selenazinan-2-imines **135** (Scheme 41, *part a*).[83] The same authors also reported an efficient synthesis of 2-imino-1,3,4-selenadiazines **137** by treating isoselenocyanates **45** with phenacyl halides **136** and hydrazine (Scheme 41, *part b*).[84]




**Scheme 41.** Synthesis of selenium-containing heterocycles **134**, **135**, **137** from isoselenocyanates.

A variety of sterically hindered selenocarbonyl compounds were also employed in 1,3-dipolar cycloadditions with ylides **139**, generated by thermolysis of oxazolidinones **138**, to prepare differently substituted selenapenames **140** (Scheme 42).[85]

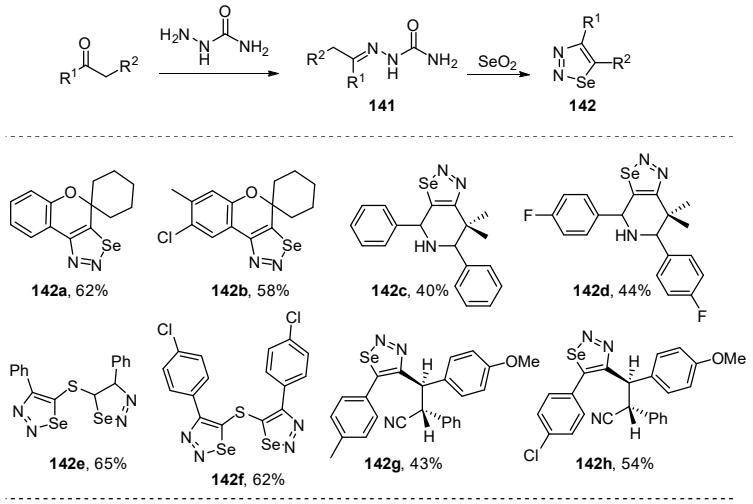



**Scheme 42.** Synthesis of selenapenames **140** from ylides **139** and sterically hindered selenocarbonyl compounds.

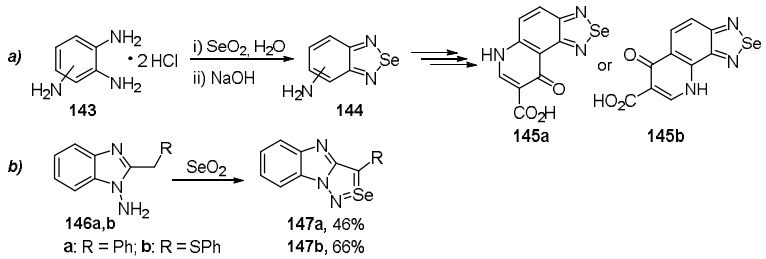
Selenium(IV) oxide was used by different authors as an efficient reagent for the synthesis of a series of mono and bis-1,2,3-selenadiazole derivatives **142** through the oxidative cyclization of mono- and bis-semicarbazones **141** (Scheme 43).[86,87,88,89,90] A number of modified procedures, including the use of silica supported sodium hydrogen sulfate ($NaHSO_4/SiO_2$) as heterogeneous catalyst under microwave irradiation, or the use of acid promoters, have been proposed in order to optimize the reaction. These methodologies have also been applied to the synthesis of carbocycle-fused systems **142a-d**. The *in vitro* antimicrobial activity of some 1,2,3-selenadiazole derivatives has also been studied.[86,87]

Aminobenzoselenadiazoles **144** were achieved from the corresponding triamine dihydrochlorides **143** upon cyclization with $SeO_2$ and alkalization of the reaction mixture (Scheme 44, *part a*). Aminobenzoselenadiazoles **144** could also be employed as valuable substrates for the synthesis of selenadiazoloquinolones **145** through the Goulde-Jacobs reaction.[91,92] A related cyclization reaction with $SeO_2$ was also applied to suitably substituted dioximes to afford a series of 3,4-diaryl-1,2,5-selenadiazol analogues of combretastatin A-4 which exhibited interesting *in vitro* anti-proliferative activity.[93] Labanauskas *et al*. reported the synthesis of benzimidazo[1,2-c][1,2,3]selenadiazoles **147** by the selenylation reaction of derivatives **146**, bearing an active methylene group, with $SeO_2$ (Scheme 44, *part b*).[94]

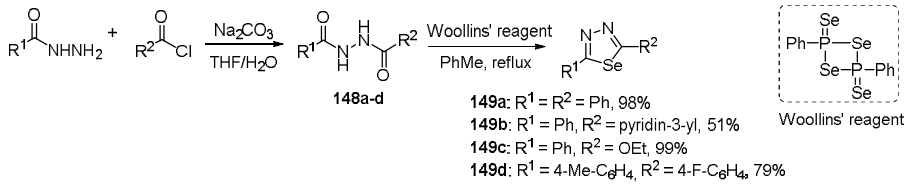
The chemistry of the Woollins' reagent has also been applied to the synthesis of selenium-containing heterocycles. For example, 2,5-disubstituted 1,3,4-selenadiazoles **149** were achieved upon selenylation and cyclization of 1,2-diacyl hydrazines **148**, smoothly occurring with Wollins reagent in refluxing toluene (Scheme 45).[95,96]




**Scheme 43.** Synthesis of 1,2,3-selenadiazole derivatives from $SeO_2$ and semicarbazones **141**.



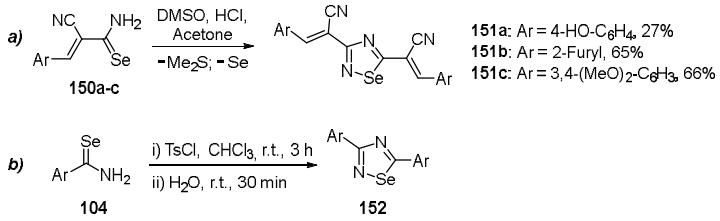

**Scheme 44.** Synthesis of selena-heterocycles **145** and **147** through $SeO_2$-based methodologies.




**Scheme 45.** Synthesis of 1,3,4-selenadiazoles through selenylation and cyclisation of 1,2-diacyl hydrazines with Woollins' reagent.

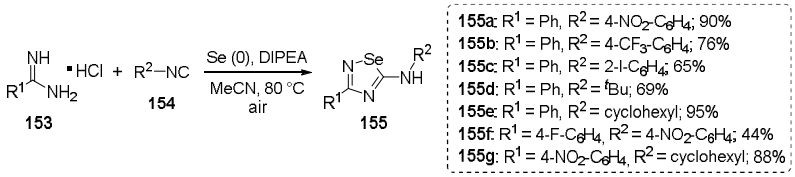
The reactivity of selenoamides has also been exploited for the preparation of selenadiazoles through oxidative dimerization reactions. 3,5-Disubstituted 1,2,4-selenadiazoles **151a-c** were smoothly achieved from cyanoselenoacetamides **150a-c** using a DMSO/HCl/acetone system (Scheme 46, *part a*).[97] Similarly, Zhao *et al*. reported the synthesis of 3,5-diaryl 1,2,4-selenadiazoles **152** by the reaction of aryl selenoamides **104** with tosyl chloride (Scheme 46, *part b*).[98]

Cyanoselenoamides have also been employed as valuable precursors of functionalised 1,3-selenazoles[99] and hexahydroselenazolo[3,2-*a*]pyridine derivatives.[100]



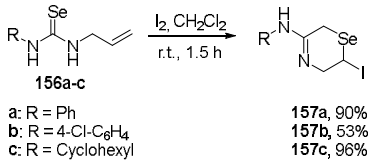

**Scheme 46.** Synthesis of 3,5-disubstituted 1,2,4-selenadiazoles **151** and **152** from selenoamides.

Fang *et al*. reported a facile metal-free approach for the synthesis of 1,2,4-selenadiazoles **155** from isocyanides **154**, elemental selenium and imidamides **153** (Scheme 47). Compounds **155** are formed through an aerobic radical-cascade and $O_2$ is used as the green oxidant to promote the cycloaddition reaction, which leads to the formation of $H_2O$ as the sole by-product. The reaction mechanism reasonably proceeds through a SET (single electron transfer) process and involves the formation of isoselenocyanates from isocyanides **154** and elemental selenium. Oxidation of isoselenocyanates affords key selenium radical intermediates which are converted into **155** according two different cyclization mechanisms.[101]



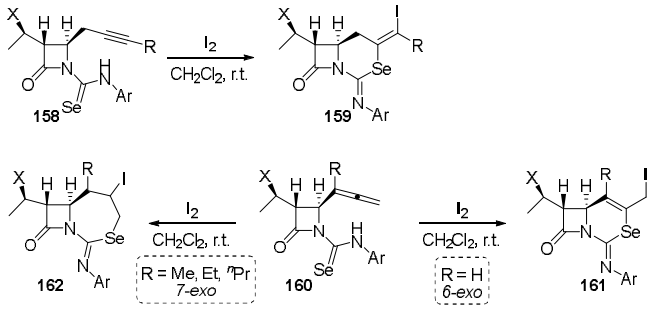

**Scheme 47.** Synthesis of 1,2,4-selenadiazoles **155** from imidamides, isocyanides, and elemental selenium.

Koketsu *et al*. reported the synthesis of substituted 1,3-selenazines by the iodocyclization of *N*-allylselenourea derivatives **156**. The reaction smoothly occurred in dichloromethane at room temperature through a 6-*endo* ring-closure to afford the corresponding 5-iodo-4*H*-5,6-dihydro-1,3-selenazines **157** in good yield (Scheme 48).[102]



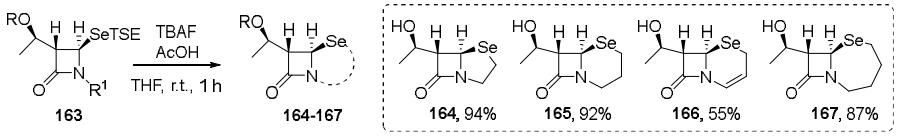

**Scheme 48.** Synthesis of 1,3-selenazine derivatives **157** through iodocyclization of *N*-allylselenoureas **156**.

The iodocyclization of selenourea derivatives was also applied to the synthesis of selenacephems. Key alkyne selenoureas **158**, prepared by *N*-alkylation of the corresponding propargyl-azetidinones with isoselenocyanates, were converted into the corresponding six-membered ring selenacephems **159** through a highly regioselective intramolecular cyclization (Scheme 49, upper reaction). Allene-selenoureas were also able to undergo electrophilic iodocyclization reactions. However, for these substrates the regiochemistry proved to be strongly influenced by the nature of the R group at the allenyl position. Indeed, while the reaction of unsubstituted allene-selenoureas **160** with iodine under standard conditions afforded 3-selena-1-dethiacephems **161**, selenazepines **162** were obtained when alleneselenoureas bearing alkyl or aryl groups at the allenyl position were employed in the iodocyclization reaction (Scheme 49, lower reactions). The regioselectivity of the iodine-assisted intramolecular nucleophilic attack of the selenium atom of the selenourea onto a iodonium intermediate, which proceeds through a 6-*exo* or 7-*exo* cyclization mode depending on the nature of the substituents on the allene moiety, accounts for the observed substrate effects.[103]



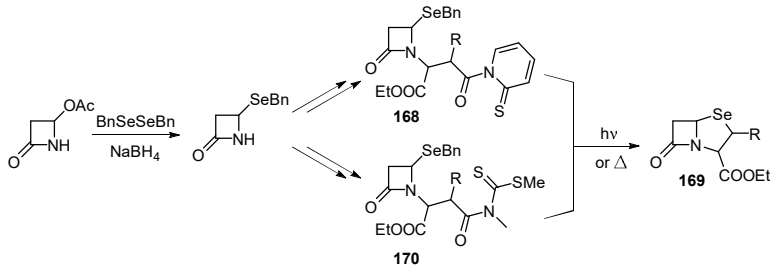
**Scheme 49.** Garud's methodology for the synthesis of selenacephems **159**, 3-selena-1-dethiacephems **161**, and selenazepines **162** through iodocyclization of alkyne- or allene-selenoureas.

Garud *et al*. developed a simple and efficient TBAF-mediated approach to a variety of differently substituted selenium-containing β-lactams. 2-(Trimethylsilyl)ethyl-selenides **163**, bearing a suitable electrophilic moiety onto the $R^1$ group of the nitrogen atom, were easily converted into the corresponding selenapenams (type **164**), selenacephems (type **165,166**), and selenazepines (type **167**) as reported in the Scheme 50. In the presence of fluoride anions, the 2-(trimethylsilyl)ethyl protecting group on the selenium atom of **163** is chemoselectively cleaved and the resulting selenolate anion undergoes annulation reaction with the electrophilic moiety.[104]



**Scheme 50.** TBAF-induced synthesis of selenapenams, selenacephems and selenazepines. Selected examples. TSE=$(CH_2)_2SiMe_3$.

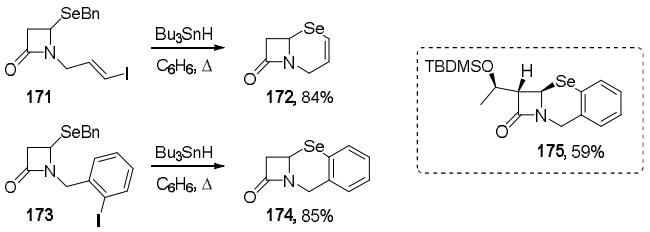
Radical reactions have also been applied to the synthesis of a variety of selenium-containing β-lactams. Schiesser *et al*. prepared pyridinethioneoxycarbonyl esters **168** (Barton ester) which behave as radical precursors and, upon irradiation, provide selenapenams **169** in moderate yield (Scheme 51). Notably, the same authors found significant yield improvements by using thiohydroximate ester derivatives **170** as radical precursors.[105]



**Scheme 51.** Schiesser and co-workers' radical approach to selenapenams **169**.

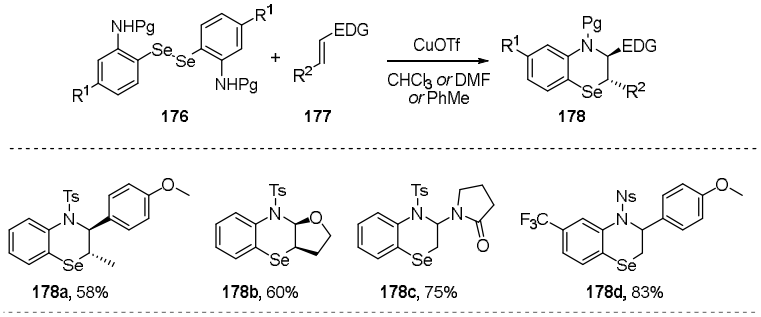
Schiesser *et al*. also reported the synthesis of selenacephems **172** and **174** in good yield through the tributyltin hydride-promoted intramolecular substitution occurring at the selenium atom of iodided **171** and **173**. Remarkably, a related procedure involving the use of triphenyltin hydride under standard radical

conditions (AIBN in refluxing benzene) was also efficiently applied to the synthesis of enantioenriched benzo-fused selenacephem **175** (Scheme 52).[106]




**Scheme 52.** Schiesser and co-workers' $Bu_3SnH$-induced synthesis of selenacephems.

Benzo[*b*][1,4]selenazines **178** were prepared from 2-*N*-tosyl- or 2-*N*-nosyl-amino diselenides **176** and electron-rich alkenes **177** (Scheme 53) by a copper(II)-mediated one-pot process.[107,108] The reaction involves the formation of transient electron-poor *o*-iminoselenoquinones, which behave as diene and efficiently react with electron-rich alkenes through an inverse electron demand hetero Diels-Alder reaction. The 1,4-elimination at the selenium atom of a selenolate ion, leading to the generation of the heterodiene, represents the key step of the mechanism; catalytic amounts of copper(II) trifluoromethanesulfonate are required for the activation of the selenium-selenium bond.



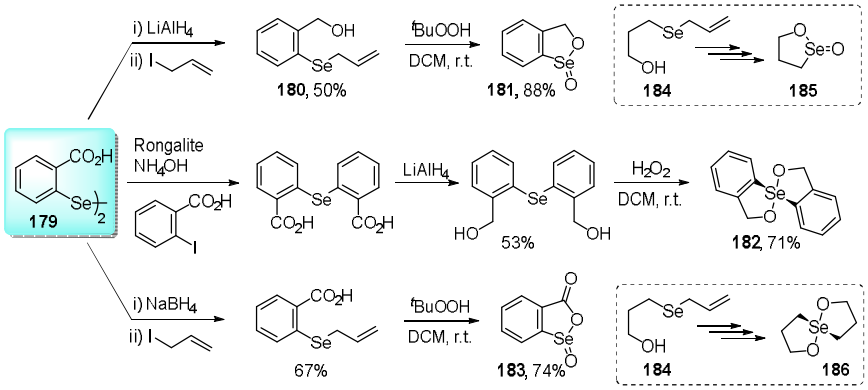

**Scheme 53.** Copper(II)-mediated one-pot synthesis of benzoselenazines **178** from amino diselenides **176** and electron-rich alkenes **177**.

**4. Synthesis of heterocyclic systems containing selenium and other heteroatoms (O, S, P)**

Selena-heterocycles containing oxygen, sulfur, and phosphorous atoms are versatile systems with applications in organic synthesis and in medicinal chemistry. For example, the anti-HIV and anti-HBVactivities of pyrimidine- and purine-derived oxaselenolanes have been described.[109] Additionally, the introduction of oxygen and/or sulfur heteroatoms in selenium-containing heterocycles offer the possibility to modulate the catalytic properties of these systems by exploiting the extent of intramolecular chalcogen bonding interactions (IChb).[110,111] However, the synthesis of O-, S-, and P-containing selena-heterocycles have been far less explored with respect to their nitrogen-containing related systems. This section focuses on recently developed synthetic approach towards heterocyclic systems containing selenium and oxygen, sulfur, and phosphorous atoms.

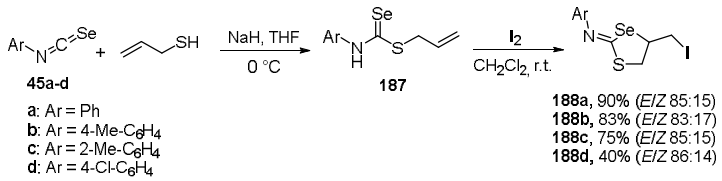
Back *et al*. employed the diselenide **179**, commonly prepared from anthranilic acid, as a versatile substrate for the synthesis of cyclic seleninates and spirodioxyselenuranes (Scheme 54). Se-allylation and reduction of **179** affords the allyl selenide **180** which can be converted into the cyclic seleninate ester **181** upon treatment with *tert*-butyl hydroperoxide. The $^t$BuOOH-induced oxidation proceeds through the formation of an allyl selenoxide intermediate which undergoes [2,3] sigmatropic rearrangement to provide a selenenate ester. Further oxidation to the corresponding allyl seleninate and a subsequent cyclization lead to

the formation of the cyclic seleninate **181** and allyl alcohol.[112] Related procedures, based on functionalization and oxidation sequences involving the selenium atom, were efficiently applied to the synthesis of the spirodioxyselenurane **182** and the seleninate **183**.[112] Similarly, aliphatic derivatives **185** and **186** could be achieved from the corresponding δ-hydroxy allyl selenide **184** (Scheme 54).[113,114] Notably, such selenium-containing heterocycles were demonstrated to possess remarkable thiol-peroxidase-like properties and, therefore, the above-mentioned methodologies have been widely exploited to access a number of differently substituted derivatives, whose antioxidant properties have been investigated.[112,113,114,115]




**Scheme 54.** Back and co-workers' synthesis of cyclic seleninates and spirodioxyselenuranes from diselenide **179**.

Isoselenocyanates have also been used as valuable precursors of 2-imino-1,3-thiaselenolanes (Scheme 55). Addition of allyl mercaptan to isoselenocyanates **45a-d** provides *S*-allyl-selenothiocarbamates **187** which are efficiently converted into the corresponding thiaselenolanes **188a-d** via iodocyclization.[116]

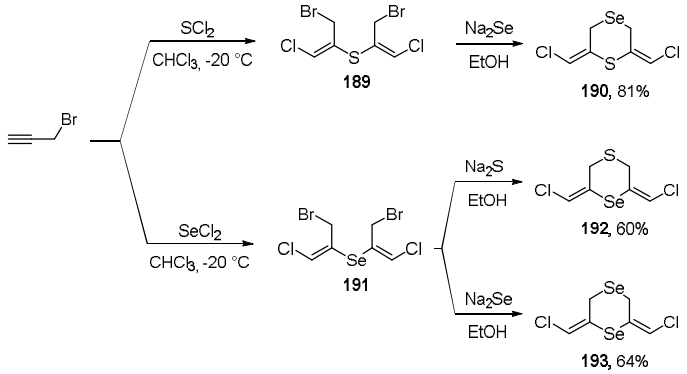



**Scheme 55.** Synthesis of 2-imino-1,3-thiaselenolanes **188** from isoselenocyanates **45**.

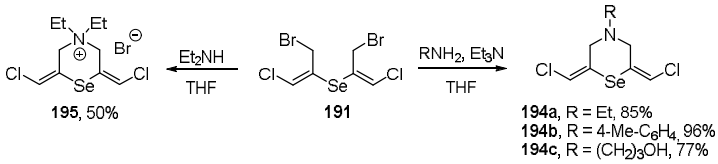
Amosova *et al*. reported the synthesis of a series of sulfur- and selenium-containing six-membered heterocycles by exploiting the reactivity of sulfur and selenium dichlorides with multiple bonds. The addition reaction of $SCl_2$ and $SeCl_2$ to propargyl bromide proceeds with anti-Markovnikov regioselectivity, providing the corresponding halo-substituted divinyl sulfide **189** and selenide **191**. Subsequent nucleophilic intramolecular ring-closure with sodium sulfide or sodium selenide, occurring by chemoselectively substitution of the bromine atom, leads to the formation of thiaselenanes **190**, **192** and diselenane **193** bearing the chlorinated chain (Scheme 56).[117] Divinyl selenide **191** also reacted with amines to give the corresponding *N*-substituted-selenomorpholines **194a-c** in good yield (Scheme 57). Furthermore, the quaternary selenium-containing ammonium salt **195** was achieved when diethylamine was used as the nucleophile (Scheme 57).[118]

The reactivity of selenium dichloride with multiple carbon-carbon bonds was also exploited for the synthesis of 1,4-benzoxaselenine **197** and **199** bearing chlorinated chains. Propargyl phenyl ether reacts with $SeCl_2$ in a chemo-, regio-, and stereo-selective manner to afford the heterocycle **197** in good yield. The reaction mechanism is thought to involve the formation of the selenirenium cation **196** which is converted

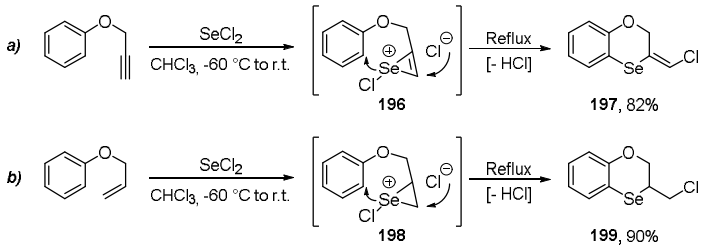
into **197** by electrophilic aromatic substitution (Scheme 58, *part a*). Similarly, treatment of allyl phenyl ether with $SeCl_2$ provides the corresponding 1,4-benzoxaselenine **199** in 90% yield through the seleniranium cation **198** (Scheme 58, *part b*).[119]




**Scheme 56.** Synthesis of thiaselenanes **190**, **192** and diselenane **193** from propargyl bromide and chalcogen dihalides.

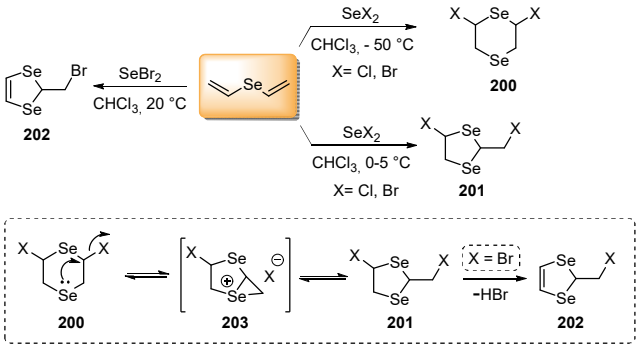



**Scheme 57.** Synthesis of selenomorpholine derivatives **194** and **195** from divinyl selenide **191**.




**Scheme 58.** Synthesis of benzoxaselenine **197** and **199** from selenirenium and seleniranium cation intermediates **196** and **198**.

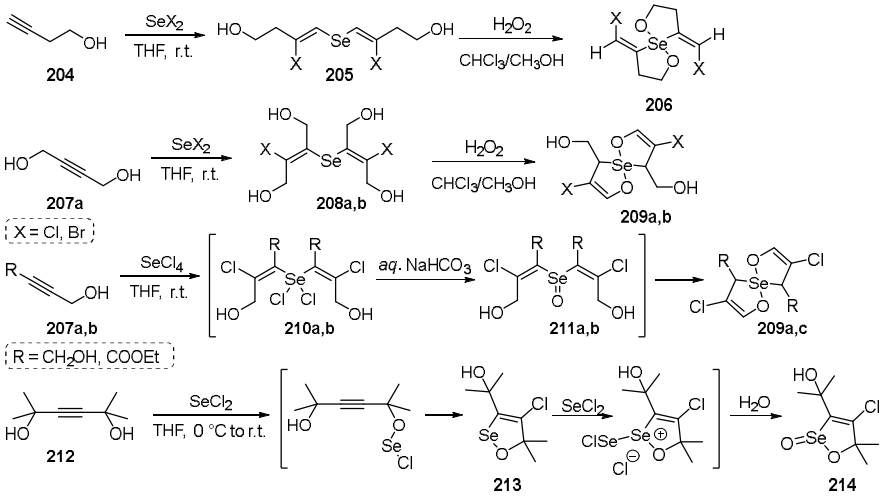
Cyclization reactions of divinyl selenide with selenium dihalides have been deeply investigated by Potapov and Amosova. Interestingly, the reaction temperature proved to play a crucial role in determining the structure of products. Indeed, while 1,4-diselenanes **200** were achieved at -50 °C, performing the reaction at higher temperatures (0 to 5 °C) provided 1,3-diselenolanes **201** (Scheme 59). Furthermore, 1,3-diselenole **202** was formed when divinyl selenide was treated with $SeBr_2$ at 20 °C. The mechanism proposed for the formation of such five-membered heterocycles involves the initial formation of halo-substituted 1,4-diselenanes **200** which undergo ring contraction through the seleniranum cation intermediate **203**. Finally, 1,3-diselenole **202** can be formed by dehydrobromination of **201** (Scheme 59).[120] Similar findings were also reported on the reactivity of divinyl sulfide with selenium dihalides.[121] Very recently, Amosova *et al.* exploited the reactivity of strained seleniranium intermediates **203** with nucleophiles for the synthesis of differently substituted selenium-containing six-membered heterocycles.[122]




**Scheme 59.** Synthesis of halogen-substituted selena-heterocycles **200**, **201**, **202** from divinyl diselenide.

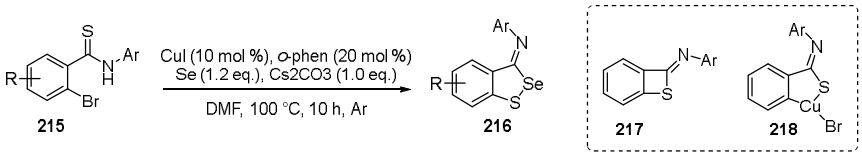
Potapov et al. also exploited the reactivity of selenenyl halides for the synthesis of natural-products-derived water-soluble 2*H*,3*H*-[1,3]-selenazolo[3,2-*a*]pyridin-4-ium systems through annulation reactions of 2-pyridinechalcogenyl halides with natural compounds such as eugenol, isoeugenol, and *trans*-anethole.[123]

The reactivity of selenium dichloride and dibromide with multiple bonds can also be harnessed for the synthesis of functionalised seleno-spiro compounds (Scheme 60).[124] Treatment of propargyl or homopropargyl alcohols with $SeCl_2$ or $SeBr_2$ affords the corresponding functionalised β-halo vinyl selenides; *in situ* oxidation to selenoxides and subsequent intramolecular cyclization leads to the formation of spirodioxyselenuranes. This methodology was applied to alcohols **204** and **207a** in order to access vinyl selenides **205** and **208**, efficiently converted into spiro derivatives **206** and **209a,b** upon reaction with hydrogen peroxide. On the other hand, selenoxide key intermediates **211** can also be formed by hydrolysis of unstable divinylselenium dichlorides **210**, conveniently prepared from alcohols and selenium tetrachloride. Notably, treatment of diol **212** with selenium dichloride afforded the cyclic seleninate **214** instead of the expected spirodioxyselenurane. The proposed reaction mechanism is reported in the Scheme 60. The steric hindrance of the four methyl groups hampers the addition to the triple bond and the reaction reasonably proceeds through the intermediate **213**.



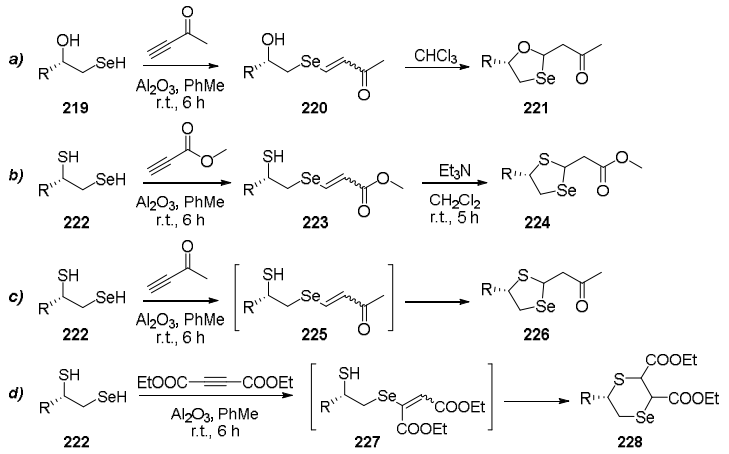

**Scheme 60.** Synthesis of functionalised seleno-spiro compounds **206**, **209**, **214** from propargyl or homopropargyl alcohols.

Wang et al. recently reported the synthesis of benzothiaselenoles **216** through the copper-catalysed reaction of 2-bromo-benzothioamides **215** with selenium (Scheme 61). The proposed reaction mechanism involves the formation of benzothietane-2-imine intermediates **217** *via* intramolecular copper-catalyzed Ullmann coupling reaction. An alternative path, proceeding through the five-membered cupracycle **218**, has also been proposed.[125]



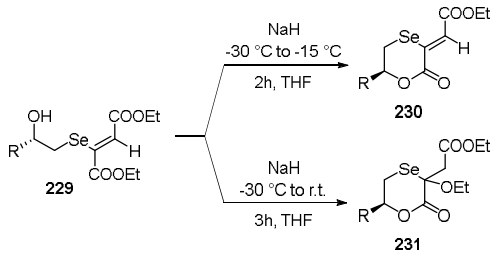

**Scheme 61.** Copper-catalysed synthesis of benzothiaselenoles **216**.

During the course of our study on the reactivity of selenosilanes with strained heterocycles, we also developed simple routes towards five-, six-, and seven-membered selenium-containing heterocycles.[126,127,128] In particular, we recently disclosed a convenient procedure to access a wide variety of functionalised alkyl selenols[129] which possess interesting biological properties[130] and behave as versatile intermediates for the synthesis of more complex molecules. For example, hydroxy substituted α,β-unsaturated γ-selenoketones **220**, easily prepared from β-hydroxy selenols **219** and 3-butyn-2-one through a seleno-Michael addition occurring mildly in the presence of $Al_2O_3$, proved to be rather unstable in slightly acidic solvents, such as chloroform, where an intramolecular oxa-Michael reaction led smoothly to the formation of the corresponding disubstituted 1,3-oxaselenolanes **221** (Scheme 62, *equation a*). Notably, the progress of the cyclization reaction could also be monitored by $^1$H NMR spectroscopy, using $CDCl_3$ as the solvent. Functionalised 1,3-thiaselenolanes **224** and **226** were also achieved from the corresponding β-mercapto selenols **222** and electron-poor alkynes. Intriguingly, while β-mercapto vinyl selenides **223** could be isolated and subsequently converted into **224** by a triethylamine-promoted intramolecular thia-Michael reaction (Scheme 62, *equation b*), α,β-unsaturated γ-selenoketones intermediates **225** were not isolated and the reaction of β-mercapto selenols **222** with 3-butyn-2-one under $Al_2O_3$ conditions led straightforwardly to **226** (Scheme 62, *equation c*). Similarly, trisubstituted thiaselenanes **228** were directly obtained from selenols **222** and a double activated Michael acceptor, such as the diethyl acetylenedicarboxylate, exploiting the reactivity of diester intermediates **227**, which easily undergo intramolecular thia-Michael reaction (Scheme 62, *equation d*).[128]




**Scheme 62.** Synthesis of selena-heterocycles through seleno-Michael reaction of functionalised alkyl selenols with electron-deficient alkynes.

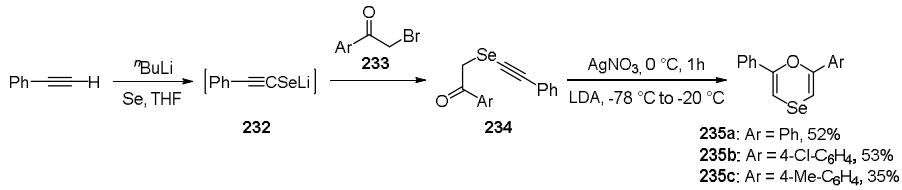
Hydroxy-substituted alkyl vinyl selenides bearing two ester groups could also be employed as precursors of biologically and synthetically valuable selenium-containing δ-lactones. Indeed, activated hydroxy vinyl selenides **229**, smoothly obtained from β-hydroxy selenols and acetylene dicarboxylate, underwent a NaH-promoted lactonization reaction to yield unsaturated 2-oxo-1,4-oxaselenanes **230**. Interestingly, the reaction temperature found to be a key parameter to isolate α,β-unsaturated derivatives **230**. Indeed, when the reaction of **229** with NaH was allowed to warm to room temperature, the exclusive formation of 2-oxo-1,4-oxaselenanes **231** was observed (Scheme 63). Reasonably, compounds **231** arise from the oxa-Michael addition of ethoxide anions, formed in the NaH promoted cyclisation of vinyl selenides **229** to α,β-unsaturated lactones **230**.[128]




**Scheme 63.** Synthesis of functionalised 2-oxo-1,4-oxaselenanes **230** and **231** from hydroxy-alkyl-vinyl selenides **229**.

The reactivity of selenols as efficient nucleophilic intermediates was also exploited by Xie *et al*. for the synthesis of selenazolidine-4-carboxylic acid derivatives as latent forms of selenocysteine.[131]

The synthesis of 1,4-oxaselenin derivatives was pursued by Koketsu *et al*. through the application of chalcogen insertion-based methodologies. Key 1-aryl-2-(phenylethynylselanyl)ethanone derivatives **234** were indeed prepared from alkynylselenolate **232** and phenacyl bromides **233**. Treatment of **234** with $AgNO_3$ and LDA provides access to disubstituted 1,4-oxaselenins **235** (Scheme 64).[132]



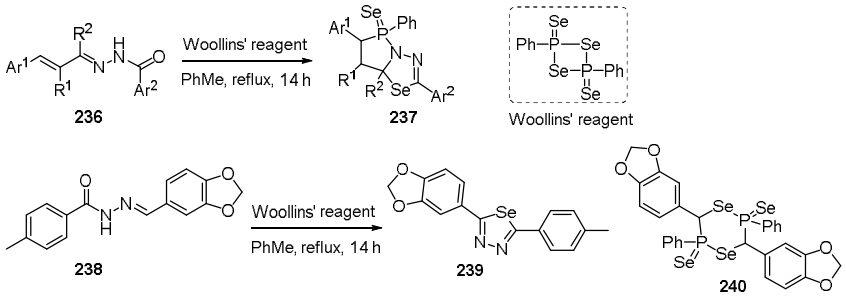

**Scheme 64.** Synthesis of 1,4-oxaselenin derivatives **235** from alkynylselenolates and phenacyl bromides.

Selenium-phosphorous-containg five- and six-membered heterocycles were prepared from amido-Schiff bases upon treatment with Woollins' reagent, which behaves as selenating-reductive cycloaddition reagent. Conjugated amido-Schiff bases **236** were converted into fused heterocycles **237**, bearing two five-membered rings. On the other hand, the reaction of Woollins' reagent with amido-Schiff base **238** afforded 1,3,4-selenadiazoles **239**, together with minor amounts of six-membered phosphorus-selenium heterocycle **240**, formed *via* a ring-expansion accompanied by an additional selenation/cyclization to the imine bond and carbonyl group (Scheme 65).[133]

**5. Conclusions and future outlook**

Selenium-containing heterocycles include several classes of ring systems with broad application in organic synthesis, catalysis, materials science, and medicinal chemistry. A number of practical and convenient methodologies for their synthesis have been developed over the recent years. Advances achieved in this field in the last two decades are reviewed and presented in this chapter. However, although the synthesis and the study of selena-heterocycles are attracting a steadily growing interest amongst organic and

medicinal chemists, several challenges remain ahead. The development of mild, green, and general routes amenable to labile yet valuable functional groups, as well as the synthesis of novel polyfunctionalised systems, characterized by high molecular complexity (measured by the extent of bond saturation and the number of stereogenic centers) are highly desirable targets in the current research.




**Scheme 65.** Woollins and co-workers' synthesis of selenium-phosphorous-containg five- and six-membered heterocycles.

**Acknowledgements**

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**References**

1. Lenardão, E. J.; Santi, C.; Sancineto, L. *New Frontiers in Organoselenium Compounds*, Springer, New York, **2018**.
2. Gao, M.; Wang, R.; Yu, F.; Li, B.; Chen, L. *J. Mater. Chem. B*, **2018**, *6*, 6637-6645.
3. a) Tanini, D.; D'Esopo, V.; Tatini, D.; Ambrosi, M.; Lo Nostro, P., Capperucci, A. *Chem. Eur. J*. **2020**, *26*, 2719-2725. b) Xu, H.; Cao, W.; Zhang, X. *Acc. Chem. Res*. **2013**, *46*, 1647-1658.
4. Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc*. **2005**, *127*, 14785-14803.
5. Gao, Y.; Wei, Y.; Ma, D. *Org. Lett*. **2019**, *21*, 1384-1387.
6. Tanini, D.; Capperucci, A. *New J. Chem*. **2019**, *43*, 11451-11468.
7. Braga, A. L.; Paixão, M. W.; Lüdtke, D.S.; Silveira, C.C.; Rodrigues, O. E. D. *Org. Lett*. **2003**, *5*, 2635-2638.
8. Patra, A. R.; Roy, S. S.; Basu, A.; Bhuniya, A.; Bhattachariee, A.; Hajra, S.; Sk, U. H.; Baral, R.; Bhattacharya, S. *Sci. Rep.* **2018**, *8*, 2194-2206.
9. Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev*. **2004**, *104*, 6255-6286 and references cited therein.
10. Jain, V. K.; Priyadarsini, K. I. *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments,* Royal Society of Chemistry, London, **2018**.
11. Tanini, D.; Lupori, B.; Malevolti, G.; Ambrosi, M.; Lo Nostro, P.; Capperucci, A. *Chem. Commun*. **2019**, *55*, 5705-5708.
12. a) Angeli, A.; Carta, F.; Donnini, S.; Capperucci, A.; Ferraroni, M.; Tanini, D.; Supuran, C. T. *Chem. Commun*. **2020**, *56*, 4444-4447. b) Angeli, A.; Tanini, D.; Nocentini, A.; Capperucci, A.; Ferraroni, M.; Gratteri, P.; Supuran, C. T. *Chem. Commun*. **2019**, *55*, 648-651.
13. Elsherbini, M.; Hamama, W. S.; Zoorob, H. H. *Coord. Chem. Rev*. **2016**, *312*, 149-177.
14. Elsherbini, M.; Hamama, W. S.; Zoorob, H. H. *Coord. Chem. Rev*. **2017**, *330*, 110-126.
15. Young, C. M.; Elmi, A.; Pascoe, D. J.; Morris, R. K.; McLaughlin, C.; Woods, A. M.; Frost, A. B.; de la Houpliere, A.; Ling, K. B.; Smith, T. K.; Slawin, A. M. Z.; Willoughby, P. H.; Cockroft, S. L.; Smith, A. D. *Angew. Chem. Int. Ed*. **2020**, *59*, 3705-3710.
16. Pascoe, D. J.; Ling, K. B.; Cockroft, S. L. *J. Am. Chem. Soc*. **2017**, *139*, 15160-15167.
17. Miao, Q.; Xu, J.; Lin, A.; Wu, X.; Wu, L.; Xie, W. *Curr. Med. Chem*. **2018**, *25,* 2009-2033

18. Di Leo, I.; Messina, F.; Nascimento, V.; Nacca, F. G.; Pietrella, D.; Lenardao, E. J.; Perin, G.; Sancineto, L. *Mini-Rev. Org. Chem*. **2019**, *16*, 589-601.
19. Angeli, A.; Tanini, D.; Viglianisi, C.; Panzella, L.; Capperucci, A.; Menichetti, S.; Supuran, C. T. *Bioorg. Med. Chem.* **2017**, *25*, 2518-2523.
20. Jin, Z.; Du, X.; Xu, Y.; Deng, Y.; Liu, M.; Zhao, Y.; Zhang, B.; Li, X.; Zhang, L.; Peng, C.; Duan, Y.; Yu, J.; Wang, L.; Yang, K.; Liu, F.; Jiang, R.; Yang, X.; You, T.; Liu, X.; Yang, X.; Bai, F.; Liu, H.; Liu, X.; Guddat, L. W.; Xu, W.; Xiao, G.; Qin, C.; Shi, Z.; Jiang, H, Rao, Z, Yang, H. *Nature*, **2020**, *582*, 289-293.
21. Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Discovery* **2007**, *6*, 881-890.
22. Gsanger, M.; Kirchner, E.; Stolte, M.; Burschka, C.; Stepanenko, V.; Pflaum, J.; Wurthner, F. *J. Am. Chem. Soc*. **2014**, *136*, 2351-2362.
23. Gao, F.; Cheng, Y.; Yu, Q.; Liu, S.; Shi, D.; Li, Y.; Wang, P. *Inorg. Chem*. **2009**, *48*, 2664-2669.
24. Abdel-Kader, M. H. *Photodynamic Therapy: From Theory to Application*, First Ed., Springer-Verlag, Berlin Heidelberg, **2014**.
25. Maity, P.; Kundu, D.; Roy, R.; Ranu, B. C. *Org. Lett*. **2014**, *16*, 4122-4125.
26. Alves, D.; Luchese, C.; Nogueira, C. W.; Zeni, G. *J. Org. Chem*. **2007**, *72*, 6726-6734.
27. Stein, A. L.; Bilheri, F. N.; Rosario, A. R.; Zeni, G. *Org. Biomol. Chem*. **2013**, *11*, 2972-2978.
28. Zeni, G.; Braga, A. L.; Stefani, H. A. *Acc. Chem. Res*. **2003**, *36*, 731-738.
29. Schumacher, R. F.; Rosario, A. R.; Leite, M. R.; Zeni, G. *Chem. Eur. J*. **2013**, *19*, 13059-13064.
30. Mohanakrishnan, A. K.; Amaladass, P. *Tetrahedron Lett*. **2005**, *46*, 7201-7204.
31. Sasaki, S.; Adachi, K.; Yoshifuji, M. *Org. Lett*. **2007**, *9*, 1729-1732.
32. Thomae, D.; Rodriguez Dominguez, J. C.; Kirsch, G.; Seck, P. *Tetrahedron,* **2008**, *64*, 3232-3235.
33. Thomae, D.; Kirsch, G.; Seck, P. *Synthesis,* **2008**, *2008*, 1600-1606.
34. Tanini, D.; Panzella, L.; Amorati, R.; Capperucci, A.; Pizzo, E.; Napolitano, A.; Menichetti, S.; d'Ischia, M. *Org. Biomol. Chem*. **2015**, *13*, 5757-5764.
35. Domazetovic, V.; Fontani, F.; Tanini, D.; D'Esopo, V.; Viglianisi, C.; Marcucci, G.; Panzella, L.; Napolitano, A.; Brandi, M. L.; Capperucci, A.; Menichetti, S.; Vincenzini, M. T.; Iantomasi, T. *Chem.-Biol. Interact*. **2017**, *275*, 13-21.
36. Liu, B.; Hu, Q.; Wen, Y.; Fang, B.; Xu, X.; Hu, Y. *Front. Chem.* **2019**, *2019*, *7*, 374.
37. Arsenyan, P. *Tetrahedron Lett*. **2014**, *55*, 2527-2529.
38. Amaresh, R. R.; Lakshmikantham, M. V.; Baldwin, J. W.; Cava, M. P.; Metzger, R. M.; Rogers, R. D. *J. Org. Chem*. **2002**, *67*, 2453-2458.
39. D'yakonov, V. A.; Ibragimov, A. G.; Khalilov, L. M.; Makarov, A. A.; Timerkhanov, R. K.; Tuktarova, R. A.; Trapeznikova, O. A.; Galimova, L. F. *Chem. Heterocycl. Compd*. **2009**, *45*, 317-326.
40. D'yakonov, V. A.; Tuktarova, R. A.; Tyumkina, T. V.; Khalilov, L. M.; Dzhemilev, U. M. *Russ. Chem. Bull. Inter. Ed*. **2010**, *59*, 1902-1908.
41. Klapotke, T. M.; Krumm, B.; Scherr, M. *Z. Anorg. Allg. Chem*. **2010**, *636*, 1955-1961.
42. Augustin, A. U.; Sensse, M.; Jones, P. G.; Werz, D. B. *Angew.Chem. Int.Ed*. **2017**, *56*, 14293-14296.
43. Date, S.; Hamasaki, K.; Sunagawa, K.; Koyama, H.; Sebe, C.; Hiroya, K.; Shigehisa, H. *ACS Catal*. **2020**, *10*, 2039-2045.
44. Sommen, G. L.; Linden, A.; Heimgartner, H. *Lett. Org. Chem*. **2007**, *4*, 7-12.
45. Leonard, K. A.; Hall, J. P.; Nelen, M. I.; Davies, S. R.; Gollnick, S. O.; Camacho, S.; Oseroff, A. R.; Gibson, S. L.; Hilf, R.; Detty, M. R. *J. Med. Chem*. **2000**, *43*, 4488-4498.
46. Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T. *Tetrahedron Lett*. **2002**, *43*, 7039-7041.
47. Kataoka, T.; Kinoshita, S.; Kinoshita, H.; Fujita, M.; Iwamura, T.; Watanabe, S.-I. *Chem. Commun.* **2001**, *43*, 1958-1959.
48. Kinoshita, H.; Osamura, T.; Kinoshita, S.; Iwamura, T.; Watanabe, S.-I.; Kataoka, T.; Tanabe, G. Muraoka, O. *J. Org. Chem*. **2003**, *68*, 7532-7534.
49. Abe, H.; Yamasaki, A.; Koshiba, N.; Takeuchi, Y.; Harayama, T. *Chem. Pharm. Bull*. **2001**, *49*, 1223-1225.
50. Sashida, H.; Ohyanagi, K.; Minoura, M.; Akiba, K.-Y. *J. Chem. Soc. Perkin Trans. 1,* **2002**, 606-612.
51. Sashida, H.; Kaname, M.; Nakayama, A.; Suzuki, H.; Minoura, M. *Tetrahedron* **2010**, *66*, 5149-5157.

52. Schneider, C. C.; Bortolatto, C.; Back, D. F.; Menezes, P. H.; Zeni, G. *Synthesis,* **2011**, *2011*, 413-418.
53. Staples, M. K.; Schiesser, C. H. *Chem. Commun.* **2010**, *46*, 565-567.
54. Lucas, M. A.; Nguyen, O. T. K.; Schiesser, C. H.; Zheng, S.-L. *Tetrahedron*, **2000**, *56*, 3995-4000.
55. Lucas, M. A.; Schiesser, C. H. *J. Org. Chem*. **1998**, *63*, 3032-3036.
56. Merino-Montiel, P.; López, Ó.; Fernández-Bolaños, J. G. *Tetrahedron,* **2012**, *68*, 3591-3595.
57. Sashida, H.; Nakayama, A.; Kaname, M. *Synthesis*, **2008**, *2008*, 3229-3236.
58. Capperucci, A.; Tanini, D. *Phosphorus Sulfur Silicon Relat. Elem*. **2015**, *190*, 1320-1338.
59. Degl'Innocenti, A.; Capperucci, A.; Acciai, M.; Tiberi, *Phosphorus Sulfur Silicon Relat. Elem.* **2009,** *184*, 1621-1626.
60. Martins, M. A.; Bastos, G. P.; Sinhorin, A. P.; Zimmermann, N. E.; Bonacorso, H. G.; Zanatta, N. *Synthesis,* **2002**, *2002*, 2220-2224.
61. Messali, M.; Abboudi, M.; Aouad, M. R.; Rezki, N.; Christiaens, L. E. *Org. Chem. Int*. **2011**, 1-7.
62. Luo, Z.; Sheng, J.; Sun, Y.; Lu, C.; Yan, J.; Liu, A.; Luo, H.-B.; Huang, L.; Li, X. *J. Med.Chem*. **2013**, *56*, 9089-9099.
63. Elsherbini, M.; Hamama, W. S.; Zoorob, H. H.; Bhowmick, D.; Mugesh, G.; Wirth, T. *Heteroatom Chem*. **2014**, *25*, 320-325.
64. Satheeshkumar, K.; Mugesh, G. *Chem. Eur. J.* **2011**, *17*, 4849-4857.
65. Balkrishna, S. J.; Bhakuni, B. S.; Chopra, D.; Kumar, S. *Org. Lett*. **2010**, *12*, 5394-5397.
66. Balkrishna, S. J.; Bhakuni, B. S.; Kumar, S. *Tetrahedron* **2011**, *67*, 9565-9575.
67. Nascimento, V.; Cordeiro, P. S.; Arca, M.; Marini, F.; Sancineto, L.; Braga, A.L.; Lippolis, V.; Iwaoka, M.; Santi, C. *New J. Chem*., **2020**, *44*, 9444-9451.
68. Singh, B. K.; Bairy, G.; Jana, R. *ChemistrySelect* **2017**, *2*, 9227-9232.
69. Zhou, Y.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta*, **2000**, *83*, 1576-1598.
70. Thomae, D.; Perspicace, E.; Xu, Z.; Henryon, D.; Schneider, S.; Hesse, S.; Kirsch, G.; Seck, P. *Tetrahedron*, **2009**, *65*, 2982-2988.
71. Yoshimatsu, M.; Yamamoto, T.; Sawa, A.; Kato, T.; Tanabe, G.; Muraoka, O. *Org.Lett*. **2009**, *11*, 2952-2955.
72. Geisler, K.; Langer, P.; Künzler, A.; Below, H.; Bulka, E.; Pfeiffer, W.-D. *Synthesis,* **2004**, *2004*, 97-105.
73. Koketsu, M.; Ando, H.; Sasaki, T.; Ishihara, H. *J. Heterocycl. Chem*. **2007**, *44*, 231-232.
74. Sengoden, M.; Vijay, M.; Balakumar, E.; Punniyamurthy, T. *RSC Adv.* **2014**, *4*, 54149-54157.
75. Koketsu, M.; Kiyokuni, T.; Sakai, T.; Ando, H.; Ishihara, H. *Chem. Lett*. **2006**, *35*, 626-627.
76. Sommen, G. L.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta*, **2007**, *90*, 1849-1855.
77. Sommen, G. L.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta*, **2008**, *91*, 209-219.
78. Sommen, G. L.; Linden, A.; Heimgartner, H. *Tetrahedron*, **2006**, *62*, 3344-3354.
79. Ueda, S.; Terauchi, H.; Suzuki, K.; Watanabe, N. *Tetrahedron Lett*. **2005**, *46*, 233-236.
80. Ueda, S.; Terauchi, H.; Suzuki, K.; Yano, A.; Matsumoto, M.; Kubo, T.; Minato, H.; Arai, Y.; Tsuji, J.-i.; Watanabe, N. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1361-1366.
81. Fujiwara, S.-I.; Shikano, Y.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem*. **2002**, *67*, 6275- 6278.
82. Asanuma, Y.; Fujiwara, S.-I.; Shin-ike, T.; Kambe, N. *J. Org. Chem*. **2004**, *69*, 4845-4848.
83. Sommen, G. L.; Linden, A.; Heimgartner, H. *Eur. J. Org. Chem*. **2005**, 3128-3137.
84. Sommen, G. L.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta,* **2006**, *89* 1322-1329.
85. Brown, G. A.; Anderson, K. M.; Murray, M.; Gallagher, T.; Hales, N. J. *Tetrahedron* **2000**, *56*, 5579-5586.
86. Chitra, S.; Paul, N.; Muthusubramanian, S.; Manisankar, P.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem*. **2011**, *46*, 5465-5472.
87. Pawar, M. J.; Burungale, A. B.; Karale, B. K. *Arkivoc* **2009**, *xiii*, 97-107.
88. Gopalakrishnan, M.; Thanusu, J.; Kanagarajan, V. *J. Korean Chem. Soc*. **2008**, *52*, 47-51.
89. Padmavathi, V.; Mahesh, K.; Venkata Subbaiah, D. R. C.; Padmaja, A. *Heteroatom Chem*. **2008**, *19*, 261-265.
90. Saravanan, S.; Athimoolam, S.; Muthusubramanian, S. *Arkivoc* **2007**, 22-33.
91. Bella, M.; Schultz, M.; Milata, V.; Konariková, K.; Breza, M. *Tetrahedron*, **2010**, *66*, 8169-8174.

92. Bella, M.; Schultz, M.; Milata, V. *Arkivoc* **2012**, 242-251.
93. Guan, Q.; Yang, F.; Guo, D.; Xu, J.; Jiang, M.; Liu, C.; Bao, K.; Wu, Y.; Zhang, W. *Eur. J.Med. Chem*. 2014, *87*, 1-9.
94. Labanauskas, L.; Dudutiene, V.; Matulis, D.; Urbelis, G. *Chem. Heterocycl. Compd*. **2009**, *45*, 1153-1154.
95. Hua, G.; Cordes, D. B.; Li, Y.; Slawin, A. M. Z.; Woollins, J. D. *Tetrahedron Lett*. **2011**, *52*, 3311-3314.
96. Hua, G.; Li, Y.; Fuller, A. L.; Slawin, A. M. Z.; Woollins, J. D. *Eur. J. Org. Chem*. **2009**, *2009*, 1612-1618.
97. Dotsenko, V. V.; Frolov, K. A.; Krivokolysko, S. G. *Chem. Heterocycl. Compd*. **2013**, *49*, 353-355.
98. Zhao, H. R.; Yu, Q. S. *Chin. Chem. Lett*. **2002**, *13*, 729-730.
99. Frolov, K. A.; Dotsenko, V. V.; Krivokolysko, S. G. *Chem. Heterocycl. Compd*. **2013**, *48*, 1886-1888.
100. Dyachenko, V. D.; Nikishin, A. A.; Chernega, A. N. *Chem. Heterocycl. Compd*. **2003**, *39*, 1153-1160.
101. Fang, Y.; Zhu, Z-L.; Xu, P.; Wang, S-Y.; Ji, S-J. *Green Chem*. **2017**, *19*, 1613-1618.
102. Koketsu, M.; Kiyokuni, T.; Sakai, T.; Ando, H.; Ishihara, H. *Chem. Lett*. 2006, *35*, 626-627.
103. Garud, D. R.; Koketsu, M. *Org. Lett*. **2008**, 10, 3319-3322.
104. Garud, D. R.; Ando, H.; Kawai, Y.; Ishihara, H.; Koketsu, M. *Org. Lett*. **2007**, *9*, 4455-4458.
105. Carland, M. W.; Martin, R. L.; Schiesser, C. H. *Tetrahedron Lett*. **2001**, *42*, 4737-4739.
106. Carland, M. W.; Schiesser, C. H. *Molecules* **2004**, *9*, 466-471.
107. Viglianisi, C.; Simone, L.; Menichetti, S. *Adv. Synth. Catal*. **2012**, *354*, 77-82.
108. Menichetti, S.; Capperucci, A.; Tanini, D.; Braga, A. L.; Botteselle, G. V., Viglianisi, C. *Eur. J. Org. Chem*. **2016**, 3097-3102.
109. Chu, C. K.; Ma, L.; Olgen, S.; Pierra, C.; Du, J.; Gumina, G.; Gullen, E.; Cheng, Y.-C.; Schinazi, R. F. *J. Med. Chem*. **2000**, *43*, 3906-3912.
110. Tanini, D.; Grechi, A.; Ricci, L.; Dei, S.; Teodori, E.; Capperucci, A. *New J. Chem*. **2018**, *42*, 6077-6083.
111. Bhabak, K. P.; Mugesh, G. *Chem. Eur. J*. **2008**, *14*, 8640-8651.
112. Back, T. G.; Kuzma, D.; Parvez, M. *J. Org. Chem*. **2005**, *70*, 9230-9236.
113. Back, T. G.; Moussa, Z.; Parvez, M. *Angew. Chem. Int. Ed*. **2004**, *43*, 1268-1270.
114. Back, T. G.; Moussa, Z. *J. Am. Chem. Soc*. **2003**, *125*, 13455-13460.
115. McNeil, N. M. R.; Matz, M. C.; Back, T. G. *J. Org. Chem*. **2013**, *78*, 10369-10382.
116. Toyoda, Y.; Koketsu, M. *Tetrahedron* **2012**, *68*, 10496-10501.
117. Martynov, A. V.; Larina, L. I.; Amosova, S. V. *Tetrahedron Lett*. **2012**, *53*, 1218-1221.
118. Martynov, A. V.; Makhaeva, N. A.; Amosova, S. V. *J. Sulfur Chem*. **2014**, 502-511.
119. Potapov, V. A.; Musalov, M. V.; Amosova, S. V. *Tetrahedron Lett*. **2011**, *52*, 4606-4610.
120. Amosova, S. V.; Penzik, M. V.; Albanov, A. I.; Potapov, V. A. *J. Organomet. Chem*. **2009**, *94*, 3369-3372.
121. Accurso, A. A.; Cho, S.-H.; Amin, A.; Potapov, V. A.; Amosova, S. V.; Finn, M. G. *J. Org. Chem*. **2001**, *76*, 4392-4395.
122. Amosova, S. V.; Filippov, A. A.; Makhaeva, N. A.; Albanov, A I.; Potapov, V. A. *Beilstein J. Org. Chem.* **2020,** *16,* 515-523.
123. Potapov, V. A.; Ishigeev, R. S.; Shkurchenko, I. V.; Zinchenko, S. V.; Amosova, S. V. *Molecules*, **2020**, *25*, 376.
124. Braverman, S.; Cherkinsky, M.; Kalendar, Y.; Jana, R.; Sprecher, M.; Goldberg, I. *Synthesis*, **2014**, *46*, 119-125.
125. Huang, M-Q.; Li, T-J.; Liu, J-Q.; Shatskiy, A.; Kärkäs, M. D.; Wang, X-S. *Org. Lett*. **2020**, *22*, 3454-3459.
126. Tanini, D.; Capperucci, A.; Degl'Innocenti, A. *Eur. J. Org. Chem*. **2015**, 357-369
127. Capperucci, A.; Tanini, D.; Borgogni, C.; Degl'Innocenti, A. *Heteroat. Chem.* **2014**, 25, 678-683.
128. Tanini, D.; Scarpelli, S.; Ermini, E.; Capperucci, A. *Adv. Synth. Catal*. **2019**, *361*, 2337-2346.
129. Tanini, D.; Tiberi, C.; Gellini, C.; Salvi, P. R.; Capperucci, A. *Adv. Synth. Catal*. **2018**, *360*, 3367-3375.

130. Tanini, D.; Capperucci, A.; Ferraroni, M.; Carta, F.; Angeli, A.; Supuran, C.T. *Eur. J. Med. Chem.* **2019**, *185*, 111811.
131. Xie, Y.; Short, M. D.; Cassidy, P. B.; Roberts, J. C. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2911-2915.
132. Koketsu, M.; Yang, H. O.; Kim, Y.M.; Ichihashi, M.; Ishihara, H. *Org. Lett*. **2001**, *3*, 1705-1707.
133. Hua, G.; Cordes, D. B.; Slawin, A. M. Z.; Woollins, J. D. *ACS Omega*, **2020**, *5*, 11737-11744.