SYNTHESIS OF N-, O-HETEROCYCLES FROM ALKENES AND DIORGANYL DISELENIDES

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Tales A. C. Goulart,* Roberto do Carmo Pinheiro,* Gilson Zeni

Laboratory of Synthesis, Reactivity, Pharmacological and Toxycological Evaluation of Organochalcogens, CCNE, UFSM, 97105-900 Santa Maria, Rio Grande do Sul, Brazil

(e-mail: talesqmc@gmail.com; docarmo.roberto@gmail.com)

Abstract. *Alkenes have played a crucial role in constructing a wide array of heterocycles in organic chemistry through various synthetic routes due to their reactivity. Among these processes, electrophilic cyclization using diselenides promotes the formation of new bonds. Incorporating selenium groups enhances synthetic versatility and enables further transformations, making these compounds attractive in synthetic chemistry. Moreover, organic selenium compounds are important in biological, material science, and pharmaceutical chemistry. This chapter explores the latest advances in cyclization reactions using alkenes and diorganyl diselenides to synthesize diverse N- and O-heterocycles, employing methodologies that involve transition metals, acid or base catalysis, and eco-friendly approaches such as visible light and electrochemical methods.*

Contents

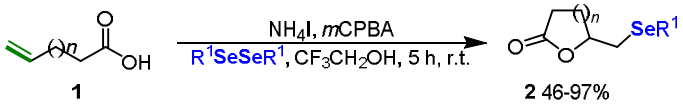
1. Introduction

Alkenes have been widely used to construct various heterocycles in organic chemistry through cyclization,[1,2] multicomponent reactions (MCRs),[3] cross-coupling,[4] and cycloaddition reactions.[5] Alkenes contain reactive π electrons that can be directly targeted by electrophiles or coordinate to transition metals, which results in the activation of the unsaturated carbon-carbon bond. Once the electrophile source activates the alkene or a catalyst species, its reactivity increases, and the carbon-carbon bonds are more likely to be attacked by nucleophiles.[6] These substrates are useful building blocks for constructing various heterocycles and polysubstituted alkanes in organic chemistry. Many synthetic approaches to the functionalization of alkenes involving C-C,[7] C-CF_3,[8] C-N,[9] C-O,[10] C-S,[11] and C-Se[12] bond formation have been reported in the literature. In this context, electrophilic cyclization reactions using diselenides also appear as powerful tools for functionalizing alkenes, promoting the formation of two new bonds, such as carbon-carbon/heteroatom-carbon and carbon-selenium.[13,14] It is also important to mention that once selenium groups have been incorporated into the desired molecules, future transformations at the incorporated selenium group are possible, making these compounds more attractive from the standpoint of synthetic chemistry.[15, 16] Additionally, organic selenium compounds are important structures in biological, material science, and pharmaceutical chemistry.[17,18,19] Not surprisingly, the number of reported methodologies using diselenides to

construct new heterocycles and promote the functionalization of alkenes and alkynes has increased over the past years.[20,21,22,23,24] Therefore, the main idea of this book chapter is to show and discuss the latest advances in cyclization reactions using alkenes with diorganyl diselenides to afford different N- and O-heterocycles.

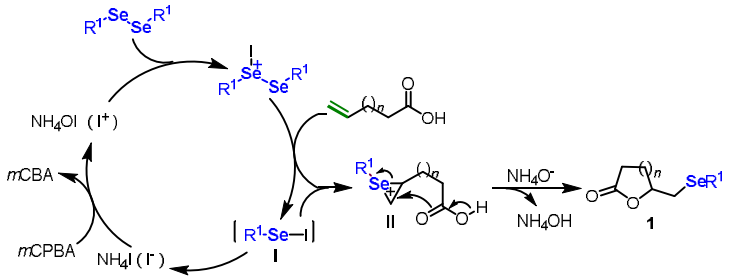
2. Synthesis of organoselenyl lactones *via* cyclization of alkenes under metal free conditions

Organoselenyl lactones **2** were synthesized in moderate to excellent yields by employing unsaturated carboxylic acids **1** and diorganyl diselenides. This reaction utilized *m*-chloroperoxybenzoic acid as the oxidizing agent and a catalytic amount of ammonium iodide (Scheme 1).[25]



Scheme 1. Synthesis of organoselenyl lactones **2**.

The same optimized conditions were successfully applied to afford the cyclic selenoether and tellurolactone products. In the mechanism, the authors proposed the *in situ* preparation of an electrophilic selenium species **I** through the reaction of diorganyl diselenide with ammonium iodide and *m*-chloroperoxybenzoic acid. Next, the desired product **2** was obtained through the carbon-carbon double bond activation by the electrophilic selenium species **I** followed by nucleophilic oxygen attack on selenonium intermediate **II** (Scheme 2).



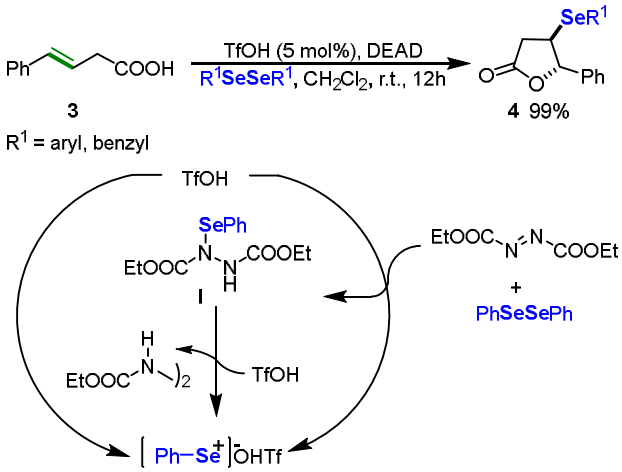
Scheme 2. Reaction mechanism for the formation of organoselenyl lactones **2**.

The cyclization of unsaturated carboxylic acids **3** with diorganyl diselenides was also investigated. However, when internal alkenes were used as substrates instead of terminal alkenes, the regiochemistry of the nucleophilic addition was altered, driven by the size of the carbon chain of the substrate. In this specific case, the electrophilic selenium species was prepared through the reaction of diethyl azodicarboxylate (DEAD) with diorganyl diselenides, yielding *N*-selenylhydrazine **I**, which the authors believe to be the key intermediate for the transformation into organoselenyl lactones **4** (Scheme 3).[26] The methodology was also applied to diorganyl disulfides and the coupling reactions involving diorganyl diselenides and boronic acids.

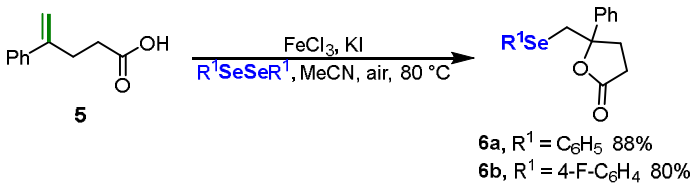
3. Synthesis of organoselenyl lactones *via* cyclization reactions using ferric chloride

The annulation of unsaturated carboxylic acids **5** with diorganyl diselenides to produce lactone derivatives **6** was also investigated using ferric chloride (III) as a catalyst, with KI as the iodine source under aerobic atmosphere. Following these conditions, the aryseleno-substituted γ-lactones **6** were obtained in high yields (Scheme 4).[27] This synthetic methodology showed high atomic efficiency, as only 0.5 equiv. of diorganyl diselenides are required to promote cyclization and introduce the arylselenium group into the heterocycle. Control experiments and radical trapping studies performed by the authors suggested that the reaction might proceed through a radical/nucleophilic addition mechanism. While the reactive selenium

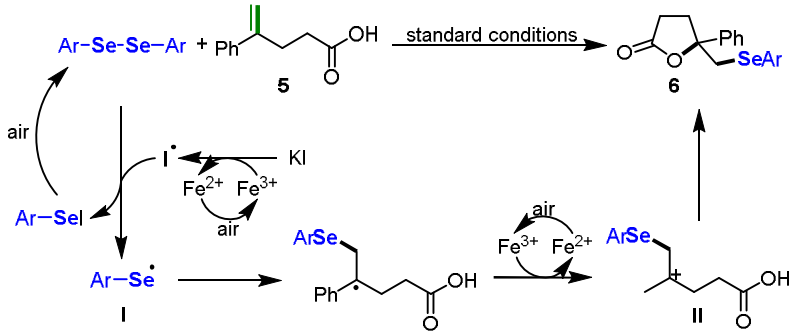
species **I** formation occurs *via* a radical pathway involving the direct participation of $FeCl_3$, the cyclization of the intermediate **II** follows an ionic process (Scheme 5).



Scheme 3. Synthesis of organoselenyl lactones **4**.



Scheme 4. Synthesis of aryseleno substituted γ-lactones **6**.

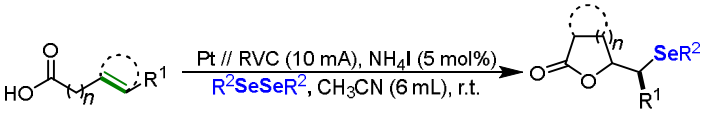


Scheme 5. Reaction mechanism for the formation of aryseleno substituted γ-lactones **6**.

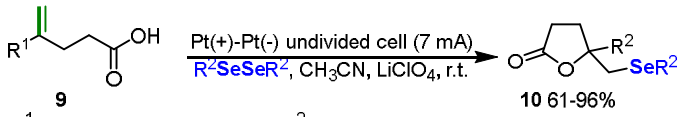
4. Synthesis of organoselenyl lactones promoted by electrochemical processes

Recently, an electrochemical synthesis protocol to access organoselenyl-substituted lactones **8** was reported. In this study, the cyclization of unsaturated carboxylic acids **7** with diorganyl diselenides was successfully developed using an undivided cell with a platinum plate anode, a reticulated vitreous carbon cathode, and ammonium iodide as the electrolyte, yielding organoselenyl lactones **8** in 52% to 92% yields (Scheme 6). Selenoetheres could also be synthesized by applying the same reaction conditions to unsaturated alcohols instead of unsaturated carboxylic acids.[28] Another method for producing organoselenyl lactones *via*

an electrochemical process employed an undivided cell, platinum plate anode, platinum plate cathode, and $LiClO_4$ as the electrolyte. In this related study, unsaturated carboxylic acids **9** containing electron-withdrawing or electron-donating aryl, naphthyl, benzoyl, and heteroaryl groups, as well as diaryl and dialkyl diselenides, afforded organoselenyl lactones **10** in moderate to high yields (Scheme 7).[29] Control experiments suggested that the reaction mechanisms could involve ionic and radical pathways.



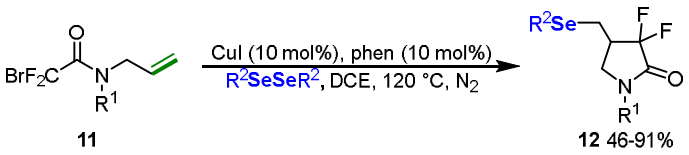
Scheme 6. Synthesis of organoselenyl lactones **8**.



Scheme 7. Synthesis of organoselenyl lactones **10**.

5. Synthesis of organoselenyl lactams/oxazolines *via* radical-promoted cyclization of alkenes

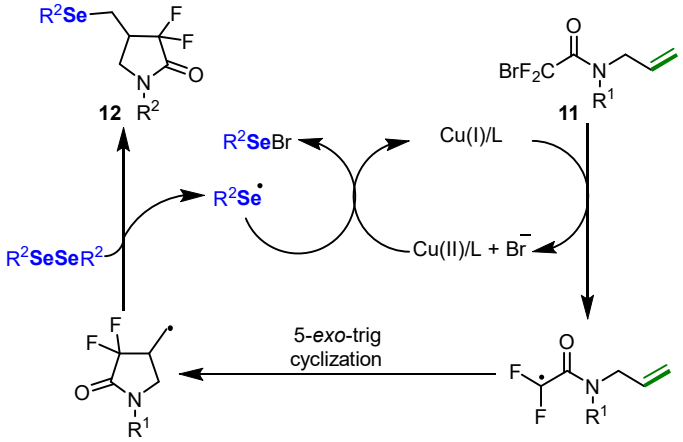
Other unsaturated carboxylic acid derivatives, such as unsaturated amides **11**, were also explored and proved suitable substrates for cyclization promoted by diorganyl diselenides. The desired organoselenyl lactams **12** were obtained using bromodifluoroacetamides and diorganyl diselenides as substrates under copper catalysis with phenanthroline as the ligand. Under these conditions, unsaturated acetamides with various *N*-substituents proceeded efficiently, giving the respective organoselenyl lactams **12** in good yields (Scheme 8).[30]



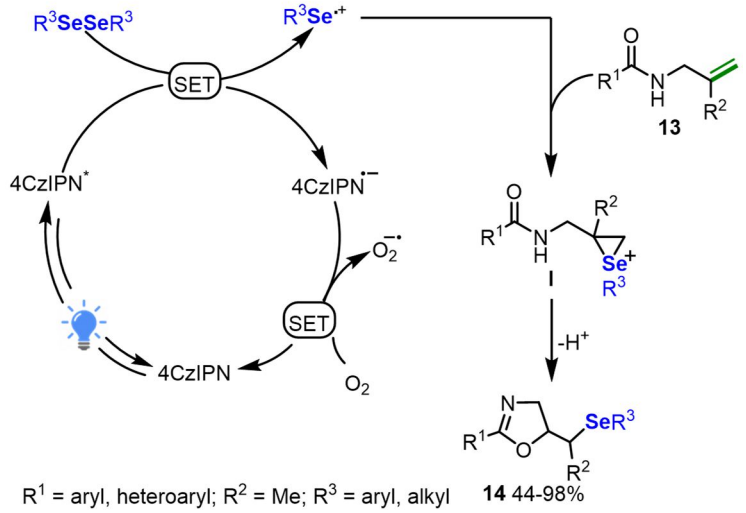
Scheme 8. Synthesis of organoselenyl lactams **12**.

The mechanism proposed by the authors indicates that the involvement of both radical and ionic organoselenium species is crucial for this synthetic protocol, being essential for functionalizing the heterocycles and reducing Cu(II) to Cu(I) (Scheme 9).

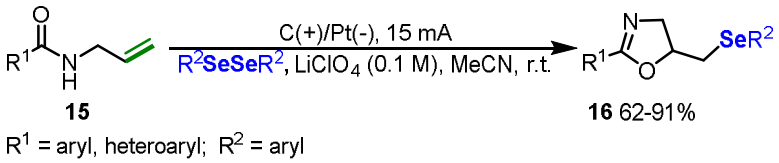
When photoredox catalysis was used instead of copper-catalyzed conditions for unsaturated acetamides **13**, oxazolines **14** were produced in excellent yields. Under these conditions, visible light facilitates the intramolecular nucleophilic attack of oxygen on the organoselenonium cation, forming organoselenyl oxazolines **14** (Scheme 10).[31] A similar outcome was observed when an electrochemical chalcogenation process with unsaturated acetamides **15** was used. In this electro-oxidative chalcogenation/cyclization, the authors discovered that using an undivided cell with graphite electrodes and an acetonitrile solution containing 0.1 M $LiClO_4$ as the electrolyte resulted in higher yields of organoselenyl oxazolines **16** (Scheme 11).[32] Mechanistic studies suggested the involvement of both radical and ionic pathways in product formation. The reaction conditions were also suitable for organosulfur isoxazolines from oximes and diorganyl disulfides as organohalogen sources.



Scheme 9. Reaction mechanism for the formation of organoselenyl lactams **12**.



Scheme 10. Reaction mechanism for the formation of organoselenyl oxazolines **14**.

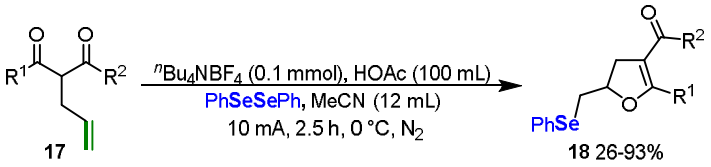


Scheme 11. Synthesis of organoselenyl oxazolines **16**.

6. Synthesis of organoselenyl dihydropyrans *via* electrochemical cyclization of alkenes

Cyclizing olefinic carbonyl compounds with diorganyl diselenides using unsaturated ketones as substrates provides a different approach for synthesizing organoselenyl heterocycles. Propane-1,3-dione **17** with diorganyl diselenides under electrochemical oxidative conditions formed the desired organoselenyl dihydrofuran derivatives **18** in moderate to good yields (Scheme 12).[33] This eco-friendly approach tolerated unsaturated ketones with electron-donating or electron-withdrawing groups at R^1 and R^2 positions. However,

only diphenyl diselenides were investigated in the reported work without exploring other diorganyl diselenides with different substituents. Additionally, organoselenyl isoxazolines were obtained when the authors applied these conditions to unsaturated acetamides.

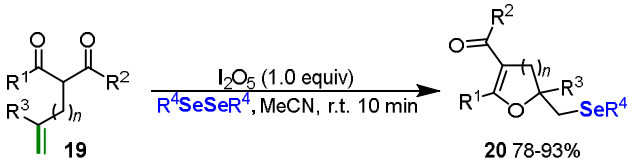


R^1 = aryl, alkyl; R^2 =aryl, alkyl, MeO, EtO, *t*-BuO, CN, Ts

Scheme 12. Synthesis of organoselenyl dihydrofuran derivatives **18**.

Oxidative electrochemical cyclization of unsaturated ketones **19** with diorganyl diselenides and I_2O_5 provides a powerful method to get both organoselenyl dihydrofuran and organoselenyl dihydropyran derivatives **20** in high yield. Unsaturated ketones **19** can serve as reactive substrates for oxidative electrochemical cyclization and nucleophilic cyclization promoted by an electrophilic selenium species. Consequently, under the reported conditions, the desired products **20** were formed in good yields and within 10 min. at room temperature (Scheme 13).[34] The conditions also proved effective for other unsaturated carbonyl compounds, including sulfonamides, *N*-Boc acrylamides, carboxylic acids, and aromatic amides, resulting in the formation of organoselenyl oxazolines, organoselenyl isoxazolidines, organoselenyl oxazolidinones, organoselenyl, and organoselenyl imidazolines.

The authors investigated the reaction mechanism and proposed that an organoselenenyl iodine species is the key intermediate, promoting cyclization and functionalizing the heterocycle.



R^1, R^2 = alkyl, aryl; R^3 = H, Me,CO_2Et

R^4 = alkyl, aryl, benzyl, heteroaryl; n = 1, 2

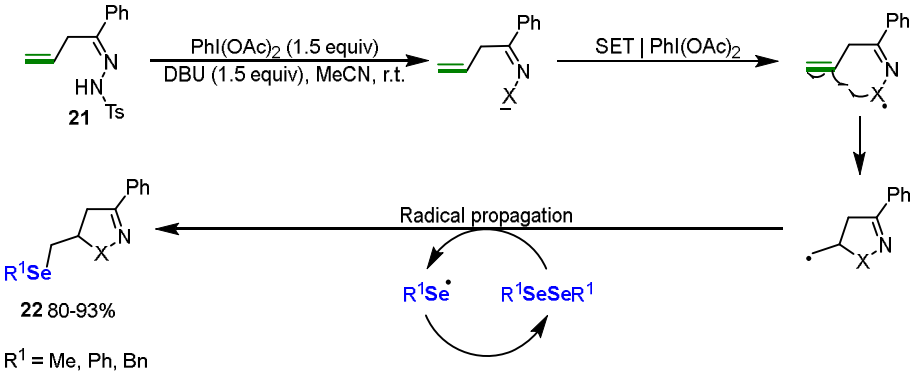
Scheme 13. Synthesis of organoselenyl dihydropyran derivatives **20**.

7. Synthesis of selenyl *N*-, *O*-heterocycles promoted by hydrazones, benzimidates, and oximes

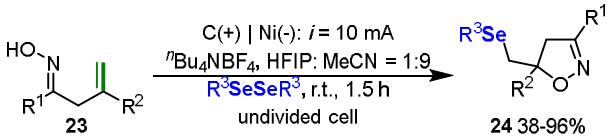
Unsaturated hydrazones, benzimidates, and oximes have been used as substrates in cyclization reactions mediated by diorganyl diselenides under either radical or electrophilic conditions. For instance, the cascade cyclization/organoselenylation of unsaturated hydrazones **21** was employed with diorganyl diselenides and phenyliodine(III) diacetate (PIDA) as the oxidant, yielding organoselenyl pyrazoles **22** (Scheme 14).[35] The mechanistic study revealed that the reaction proceeds *via* a radical pathway; however, diorganyl diselenides do not promote the cyclization reaction. During this process, the organoselenyl group is incorporated into the pyrazole ring during the propagation step. Additionally, an example of a radical pathway was demonstrated in the electrochemical oxidative tandem cyclization of unsaturated oximes **23** with diorganyl diselenides, producing organoselenyl isoxazoline derivatives **24** (Scheme 15).[36] The authors proposed that the organoselenyl radical activates the double bond and contributes to the heterocycle's functionalization. Similarly, the mixture of Oxone® and diorganyl diselenides provided excellent results in forming the same class of compounds.[37]

Alongside the radical pathway, organoselenyl isoxazolines **26** were synthesized using an electrophilic approach involving organoselenium compounds. This method generated reactive organoselenyl chlorides in situ by reacting $PhICl_2$ with diorganyl diselenides. The subsequent reaction of these organoselenyl chlorides

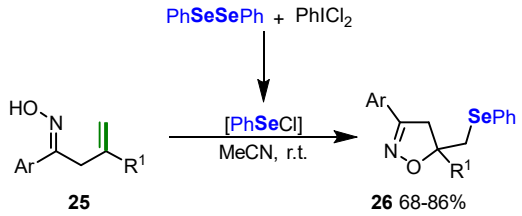
with unsaturated oximes **25** resulted in the formation of organoselenyl isooxazolines **26**, initiated by the activation of the double bond followed by nucleophilic cyclization and ring functionalization (Scheme 16).[38] Moreover, the electrophilic cyclization of unsaturated benzimidates **27** to afford organoselenyl oxazines **28** was achieved using diorganyl diselenides as the organoselenium source and $PhICl_2/Cu_2O$ as the catalysts (Scheme 17).[39]



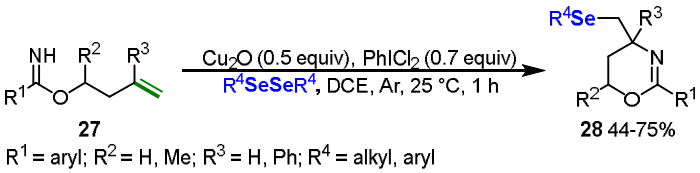
Scheme 14. Reaction mechanism for the formation of organoselenyl pyrazoles **22**.



Scheme 15. Synthesis of organoselenyl isoxazoline derivatives **24**.



Scheme 16. Synthesis of organoselenyl isooxazolines **26**.

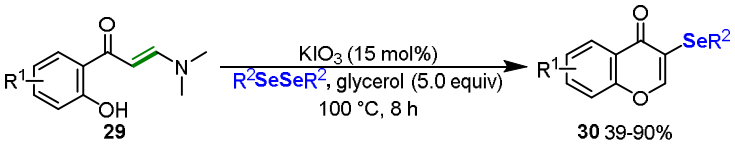


Scheme 17. Synthesis of organoselenyl oxazines **28**.

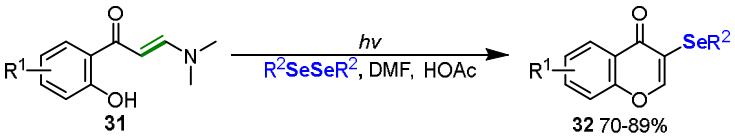
8. Synthesis of organoselenyl chromenones *via* cyclization reaction of enaminones

Aryl derivatives with unsaturated alkyl carbonyl compounds, are excellent substrates for organoseleno cyclization. The research conducted by Braga's laboratory introduced a more environmentally friendly protocol for synthesizing organoselenyl chromenones **30** through the organoseleno cyclization of

2-hydroxyphenyl enaminones **29** (Scheme 18).[40] Their study rigorously investigated optimal reaction conditions, identifying a KIO_3/glycerol mixture as the most efficient catalytic system for yielding products **30** in high yields. Notably, the methodology was significantly enhanced by reducing the amount of diorganyl diselenides to half the molar equivalent, promoting atom economy and sustainability. Additionally, these reaction conditions were successfully applied to diorganyl disulfides as well. Visible light and diorganyl diselenides were employed using a similar methodology to promote the organoseleno cyclization of 2-hydroxyphenyl enaminones **31** in the mild conditions. This methodology resulted in the formation of organoselenyl chromenones **32**, with yields ranging from 70% to 89% (Scheme 19).[41] The control experiments conducted by the authors demonstrated that the reaction initially involves an organoselenyl radical, which is subsequently transformed into an electrophilic species, thereby resulting in the cyclization of the enaminones **31** and the functionalization of the chromenones ring.



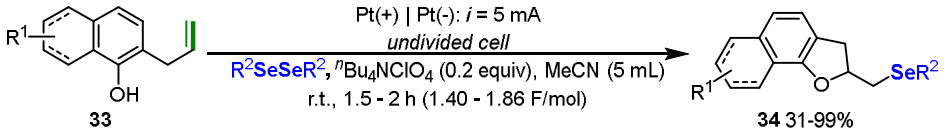
Scheme 18. Synthesis of organoselenyl chromenones **30**.



Scheme 19. Synthesis of organoselenyl chromenones **32**.

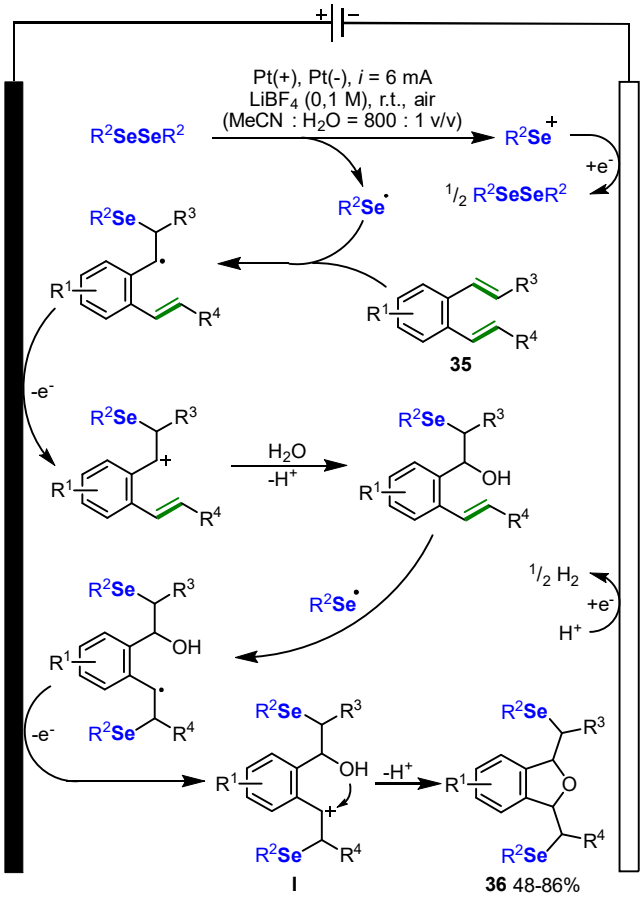
9. Synthesis of organoselenyl benzofuran derivatives *via* electrochemical reactions

Electrochemical synthesis was developed as an alternative eco-friendly methodology for the selenofunctionalization of aryl alkenes using allyl naphthol **33** and phenol derivatives. This method yielded the corresponding organoselenyl dihydrofurans **34** using catalytic amounts of *n*-Bu_4NClO_4 as the electrolyte and Pt electrodes in an undivided cell (Scheme 20).[42]



Scheme 20. Synthesis of organoselenyl dihydrofurans **34**.

In the extension of this methodology, allyl phenol derivatives were cyclized to form organoselenyl dihydrobenzofurans *via* an electrophilic organoselenium species, prepared *in situ* through the reaction of diorganyl diselenides with Oxone®.[43] Benzyl alcohols, generated *in situ via* anodic oxidation of alkenes, are excellent nucleophiles in the organoseleno cyclization of *o*-divinylbenzenes **35**. In this case, the initial formation of organoselenyl radical species, which add to the double bond, leaves the benzyl alcohol.[44] The nucleophile attacks the intermediate carbocation **I**, forming seleno-dihydroisobenzofurans **36** (Scheme 21).



R^1 = H, Me, halogens, MeO; R^2 = aryl, Me; R^3 = R^4 = CO_2Me, CO_2Et, CO_2Bn, MeCO, EtCO, CN

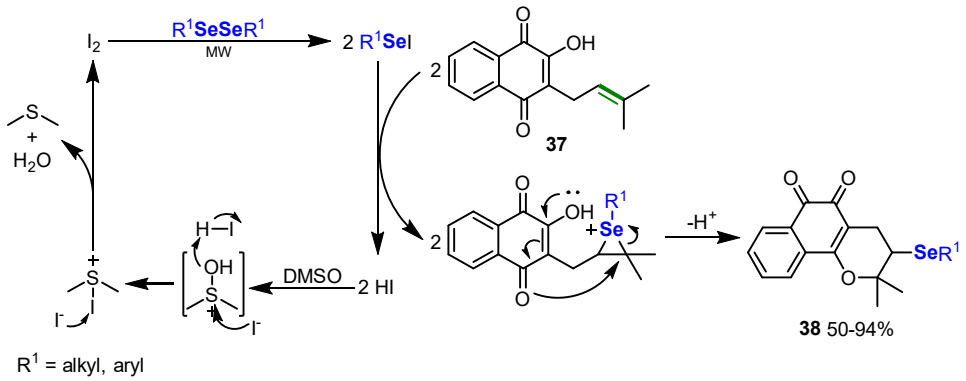
Scheme 21. Reaction mechanism for the formation of seleno-dihydroisobenzofurans **36**.

10. Organoselenyl halides promoting cyclization reactions

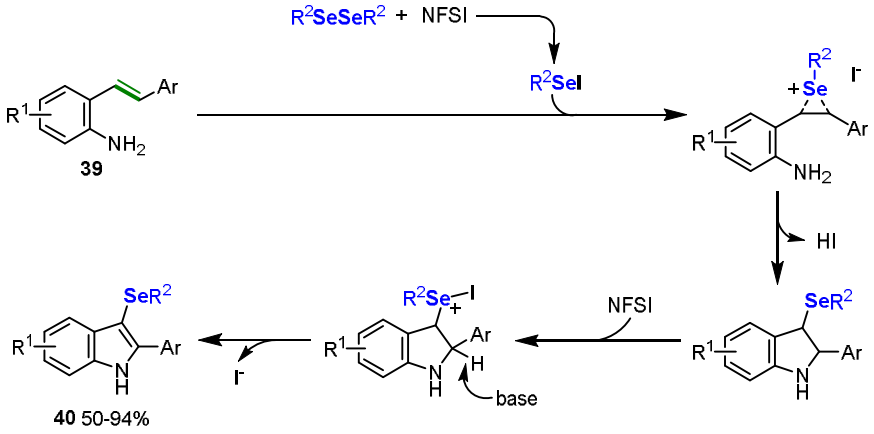
The development of strategies for preparing certain electrophilic species presents a significant challenge in organoselenium chemistry due to the inherent instability of these compounds. In this context, Braga developed a catalytic system composed of diorganyl diselenides, molecular iodine, and DMSO to form organoselenyl iodine *in situ*.[45] The authors used this strategy to prepare organoselenium-containing lapachones, evaluating the potential of diorganyl diselenides containing different substituents in the reaction with the I_2/DMSO system for preparing electrophilic species of organoselenium. The reaction of these species with lapachol **37** led to the formation of organoselenyl lapachone derivatives **38** under mild conditions and within a short reaction time (Scheme 22).[46,47] Furthermore, these compounds are promising candidates for anticancer drug development and demonstrate activity against trypomastigotes when subjected to biological activity evaluation. Braga's group expanded these concepts by introducing electrochemistry into this organoseleno cyclization and extensively studied the range of reaction conditions, applying them to different quinones.[48]

The cyclization and functionalization of aromatic amines and their derivatives have been achieved using the organoselenyl cyclization conditions. In this context, 2-vinylanilines **39** were reacted with diorganyl

diselenides and *N*-fluorobenzenesulfonimide (NFSI), resulting in the formation of 3-organoselenyl-indoles **40** with moderate to good yields (Scheme 23).[49]



Scheme 22. Reaction mechanism for the formation of organoselenyl lapachone derivatives **38**.

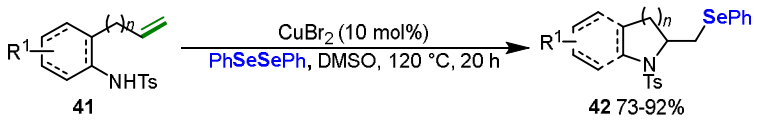


Scheme 23. Reaction mechanism for the formation of 3-organoselenyl-indoles **40**.

This methodology demonstrates that the electrophilic species of organoselenium, which promotes cyclization, is prepared *in situ* by reacting diorganyl diselenides with NFSI. The organoselenenyl iodide acts as a carbon-carbon double bond activator, facilitating nucleophilic attack by the nitrogen atom and yielding the products. A critical aspect of this reaction is that the presence of a base in the reaction medium prevents the reduction of the double bond, thereby facilitating the formation of the indoline ring. However, when NTs-2-alkenylanilines **41** were employed as substrates in reactions conducted with diorganyl diselenides and copper bromine as the catalyst, the resulting products are organoselenyl indolines or organoselenyl quinolines **42**, facilitated by double bond reduction (Scheme 24).[50]

11. Organoseleno cyclization of 2-alkenylbenzamides

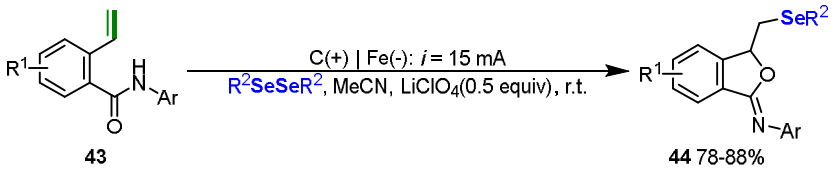
In contrast to *N*-Ts-2-alkenylanilines, where the nitrogen atom behaved as the nucleophilic center, unsaturated benzamide derivatives exhibited the carbonyl oxygen as the nucleophile. Within this context, the reaction of 2-vinylbenzamides **43** with diorganyl diselenides in a continuous electrochemical microreactor gave the iminoisobenzofurans **44** in good yields and high chemoselectivity (Scheme 25).[51]



41 **42** 73-92%

R^1 = H, Cl, Me, MeO; n = 1, 2

Scheme 24. Synthesis of organoselenyl indolines **42**.

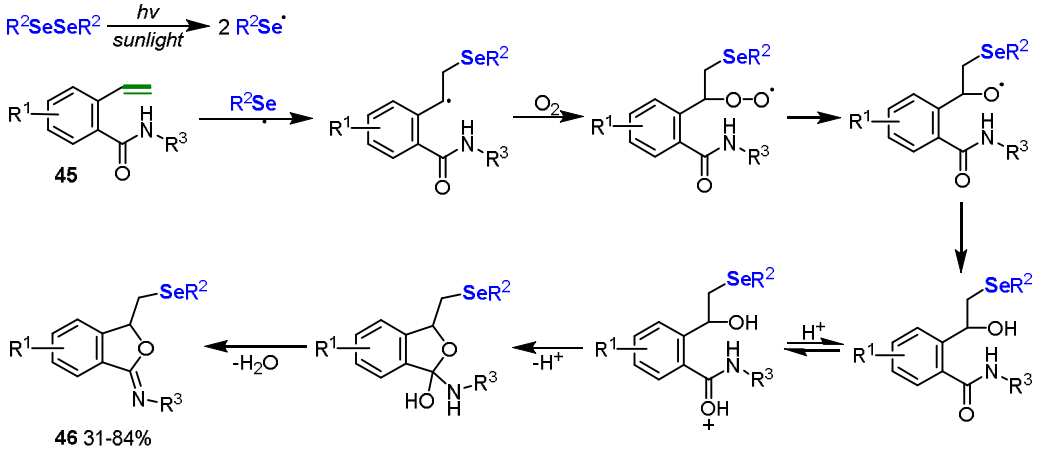


43 **44** 78-88%

R^1 = H, Me, Cl; R^2 = alkyl, aryl

Scheme 25. Synthesis of iminoisobenzofurans **44**.

The same research group also reported a sunlight-promoted aerobic selective organoseleno cyclization of 2-vinylbenzamides **45**. The authors observed that TFA significantly influenced chemoselectivity as the catalyst or Na_2CO_3 as the base.[52] When 2-vinylbenzamides were treated with TFA in acetonitrile under sunlight at room temperature, the iminoisobenzofurans **46** products of *O*-cyclization, were exclusively obtained (Scheme 26). On the other hand, when a base like Na_2CO_3 was added to 2-vinylbenzamide **47**, only *N*-cyclization products **48** were obtained in moderate yields (Scheme 27).

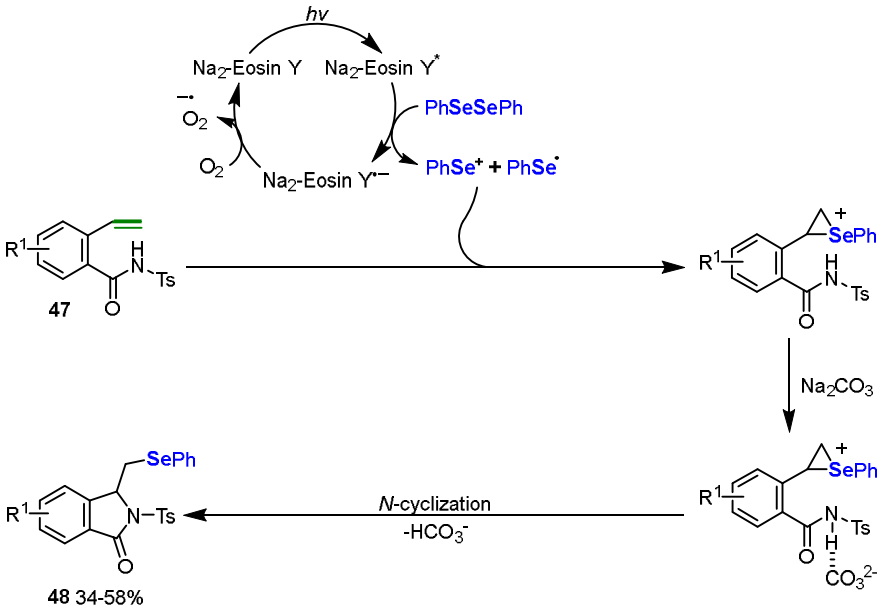


45 **46** 31-84%

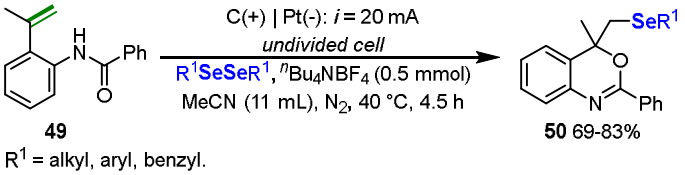
R^1 = H, Me, Cl; R^2 = alkyl, aryl; R^3 = Me, $ArSO_2$, $MeSO_2$, $EtSO_2$, MeO, *i*-PrO, *t*-BuO, BnO

Scheme 26. Reaction mechanism for the formation of iminoisobenzofurans **46**.

Organoseleno cyclization using electrochemical oxidative conditions was described for unsaturated benzamides **49**. In this case, a nucleophilic oxygen attacks the double bond; then, the electrochemical process generates organoselenyl radicals that add directly to the carbon-carbon double bond to form organoselenyl benzoxazines **50** (Scheme 28).[53] One year later, the same group reported the synthesis of iminoisobenzofurans **52** *via* an organoseleno cyclization of benzamides **51**. The carbonyl group is bonded directly to the central ring in this context.



Scheme 27. Reaction mechanism for the formation of iminoisobenzofuran tosylisoindolinones **48**.



Scheme 28. Synthesis of organoselenyl benzoxazines **50**.

The authors, in the same way as before, studied the mechanism for the reaction and proposed an organoselenyl radical species as an activator of the double bond, thereby facilitating an *O*-nucleophilic attack that results in the formation of the five-membered ring (Scheme 29).[54]

12. Synthesis of organoselenyl thiazine *via* electro-oxidative reaction

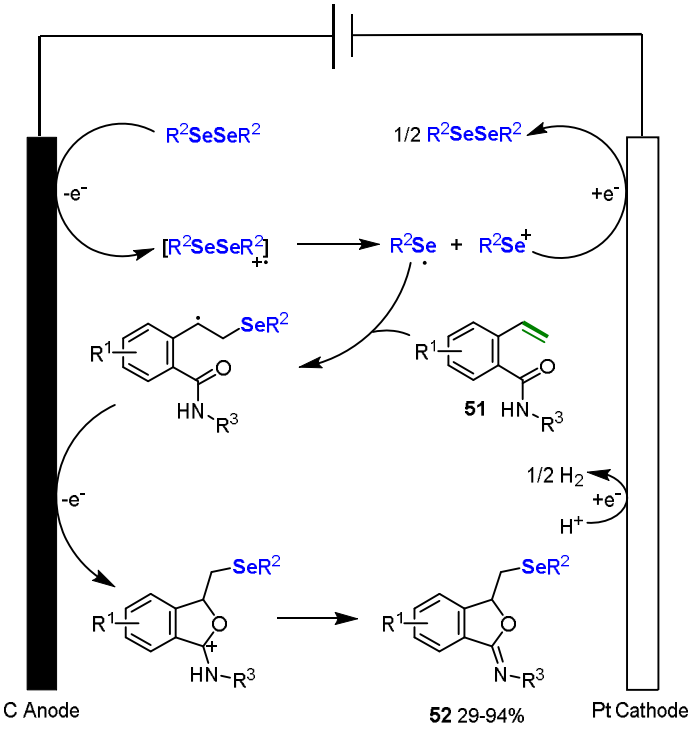
Organoselenyl thiazine derivatives **54** can be easily formed by cyclization of allylthiobenzoimidazoles **53** promoted by organoselenium (Scheme 30).[55]

Under these conditions, the organoselenonium cation was generated *in situ* through the electro-oxidative reaction of diorganyl diselenides. Experimental efforts aimed at optimizing reaction conditions demonstrated that electrolysis produced superior results using an undivided cell equipped with a graphite anode and a platinum plate cathode in a process employing $LiClO_4$ as the electrolyte, and acetonitrile as the solvent at room temperature in an open tube. Remarkably, the method demonstrated pronounced regioselectivity, yielding exclusively the 6-*endo-trig* product (Scheme 30).

13. Synthesis of organoselenyl oxindoles and quinolinones promoted by electrochemical processes

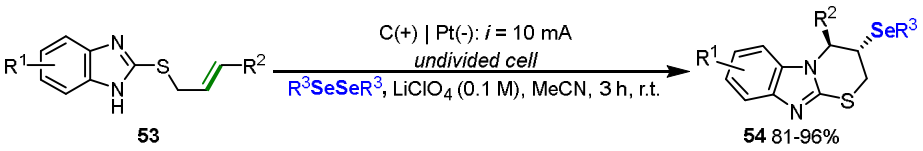
Carbon from aromatic systems is frequently employed as nucleophiles or radicals in organoseleno cyclization reactions. An example includes the development of tandem cyclization of unsaturated arylamides **55**, facilitated by diorganyl diselenides under conditions of electrochemical oxidation, to synthesize

organoselenyl oxindoles **56** (Scheme 31).[56] The undivided cell featuring a graphite rod cathode, Pt plate anode, and Bu_4NPF_6 as the electrolyte in acetonitrile solvent proved to be optimal conditions, typically resulting in high product yields. Terminal alkenes were effectively cyclized under these conditions, yielding the products through an exclusive 5-*exo-trig* mechanism. Furthermore, the authors also described that the reaction could be performed through a one-pot, two-step synthesis starting with anilines and acryloyl chloride for the *in situ* generation of acrylamides.



R^1 = H, Me, MeO; R^2 = alkyl, aryl, benzyl; R^3 = H, alkyl, aryl

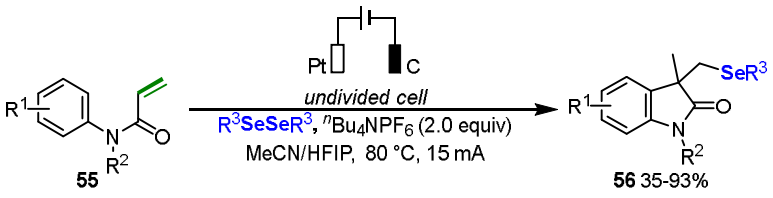
Scheme 29. Reaction mechanism for the formation of iminoisobenzofurans **52**.



R^1 = H, Me, Br, Cl, F, MeO; R^2 = alkyl, aryl; R^3 = aryl, benzyl

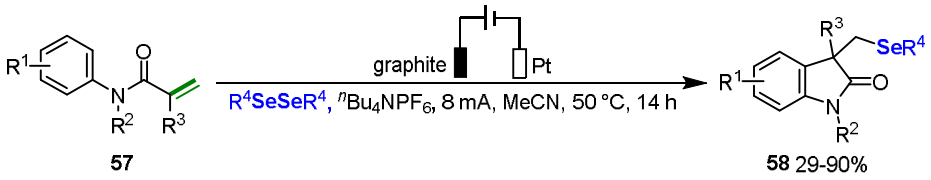
Scheme 30. Synthesis of organoselenyl thiazine derivatives **54**.

Under comparable electrochemical oxidation conditions employing an undivided cell with a graphite anode and a platinum cathode, unsaturated arylamides **57** were likewise converted into organoselenyl oxindoles **58** (Scheme 32).[57] The innovation of this work was the generality of the reaction conditions, which can be applied not only to unsaturated arylamides featuring a terminal double bond but also to internal alkenes **59**. In this case, quinolinones **60** were obtained only by 6-*endo-trig* mode with yields from 30% to 78% (Scheme 33). Moreover, the same reaction conditions lead to the cyclization of unsaturated benzamides and benzoic acids, yielding the corresponding iminoisobenzofurans and lactones as products.



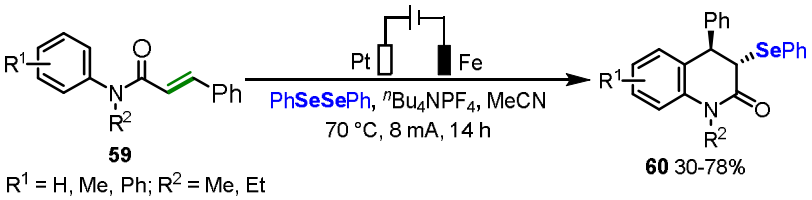
R^1 = H, Me, MeO, halogens, F_3C; R^2 = Me, Ph; R^3 = alkyl, aryl, heteroaryl

Scheme 31. Synthesis of organoselenyl oxindoles **56**.



R^1 = H, Me, OMe, halogen, MeCO, CN; R^2 = aryl, alkyl, benzyl; R^3 = Me, Ph; R^4 = aryl, alkyl

Scheme 32. Synthesis of organoselenyl oxindoles **58**.

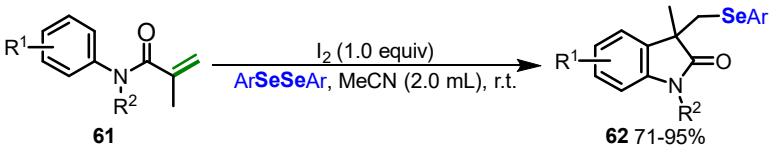


R^1 = H, Me, Ph; R^2 = Me, Et

Scheme 33. Synthesis of quinolinones **60**.

14. Synthesis of organoselenyl oxindoles *via* radical species of diorganyl diselenides

Electrochemical oxidation conditions, as described above, can generate organoselenyl radical species from diorganyl diselenides in the cyclization of unsaturated arylamides, and halogens can also achieve this transformation. An example described in 2022 detailed a cascade cyclization reaction of unsaturated arylamides **61** with diselenides, promoted by iodine oxidation, resulting in the formation of organoselenyl oxindoles **62** (Scheme 34).[58] In this study, an investigation was conducted using varying key parameters to determine optimal reaction conditions. These parameters were successfully applied to several arylamides, resulting in the formation of products with high yields. The authors suggested a radical mechanism for product formation. Nevertheless, the potential formation of organoselenyl halides from the reaction of diorganyl diselenides and halides suggests that an ionic pathway cannot be entirely dismissed. Furthermore, the reaction conditions were effectively adapted for diorganyl disulfides.

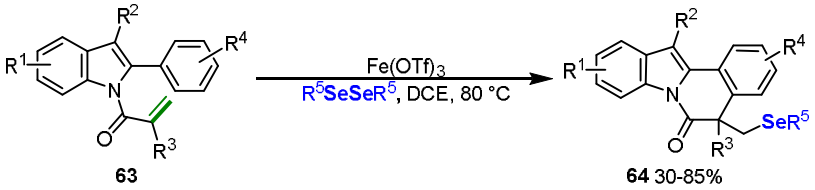


R^1 = halogens, ester, ether, alkyl; R^2 = alkyl, aryl, benzyl

Scheme 34. Synthesis of organoselenyl oxindoles **62**.

15. Synthesis of organoselenyl indolo-isoquinolinones and organoselenyl benzoazepines *via* electrophilic organoselenium species

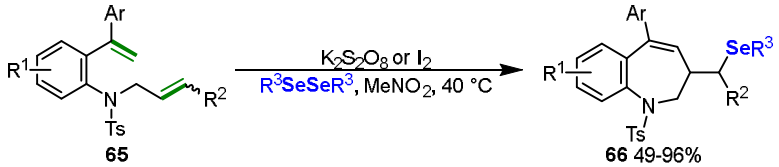
Electrophilic organoselenium species have also been involved in the synthesis of organoselenyl indolo-isoquinolinones **64** *via* $Fe(OTf)_3$-promoted cascade selenylation/cyclization of 2-arylindoles **63** with diorganyl diselenides (Scheme 35).[59] This methodological enhancement entails the creation of two new bonds (C-Se and C-C) simultaneously under ambient conditions, achieving the functionalized product in a single procedural step. The mixture of iron salts with diorganyl diselenides in these reactions results in an electrophilic organoselenium species, which activates the indole double bond, leading to cyclization through nucleophilic attack. Another methodology involving electrophilic organoselenium species was described for cyclizing benzenesulfonamides **65**, leading to organoselenyl benzoazepines **66** in good yields (Scheme 36).[60] The control experiments conducted by the authors indicated the involvement of the organoselenium species in both cyclization and functionalization steps.



63 **64** 30-85%

R^1 = H, Me MeO, halogens; R^2 = aryl, alkyl; R^3 = Me, Ph; R^4 = H, Me, MeO, F; R^5 = aryl

Scheme 35. Synthesis of organoselenyl indolo-isoquinolinones **64**.



65 **66** 49-96%

R^1 = H, Me, MeO, Br, Cl, F; R^2 = H, Me; R^3 = alkyl, aryl, heteroaryl

Scheme 36. Synthesis of organoselenyl benzoazepines **66**.

16. Conclusion

Because of their significant biological relevance and exceptional versatility, diorganyl diselenides have been used in organic synthesis to form numerous molecules. In addition to diorganyl diselenides, alkenes constitute one of the most versatile classes of organic compounds. Their reactivity has been extensively explored through several combinations, producing numerous new classes of compounds over the years. The combination of these important classes of compounds has proven effective in synthesizing several functionalized heterocycles. This book chapter covers the recent methodologies for synthesizing different product classes by applying transition metals, acid or base catalysis, and eco-friendly approaches such as visible light and electrochemical methods. Furthermore, the biological activities of some synthesized products were evaluated, revealing varying degrees of activity influenced by the selenium content in their structural formation.

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