





Review

One-Pot Multicomponent Polymerization, Metal-, and Non-Metal-Catalyzed Synthesis of Organoselenium Compounds

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Abstract: The one-pot multicomponent synthetic strategy of organoselenium compounds represents an alternative and robust protocol to the conventional multistep methods. During the last decade, a potential advance has been made in this domain. This review discusses the latest advances in the polymerization, metal, and metal-free one-pot multicomponent synthesis of organoselenium compounds.

Keywords: polymerization; organoselenium; one-pot multicomponent; metal-free-catalyzed



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1. Introduction

Organoselenium (OSe) compounds have recently gained considerable interest as a potential class of organic motifs due to their outstanding applications in synthetic organic and medicinal chemistry and their possible properties in materials science [1–4]. These are attributed to the exceptional properties of the selenium (Se) element. The latter is a non-metal present in almost living organisms as part of selenoproteins (e.g., thioredoxin reductases and glutathione peroxidase antioxidants enzymes) [5–9]. Accordingly, Se is crucial for protecting human cells from oxidative damage and the immune system's normal function [10–12]. Compared to sulfur (S), Se has a larger atomic radius (S: 1.02 Å vs. Se: 1.17 Å), lower electronegativity (S: 2.58 vs. Se: 2.55), higher polarizability (S: 2.9 Å vs. Se: 3.8 Å), and therefore Se is a likely better nucleophile than the S [5,8,13]. Accordingly, OSe compounds are known for their ability to react with O₂-free radicals and thus prevent the progression of oxidative stress-related diseases [3,6,10,14]. Furthermore, OSe compounds were also used in material science due to their semiconductor potential and therefore used in sodium-ion batteries, solar cells, and H₂ evolution catalysts [2,15–17]. Moreover, the Se center is present in many naturally occurring and bioactive interesting OSe compounds (Figure 1), such as the selenoaminoacids (e.g., selenocysteine (I), selenomethionine (II), and selenocystine (III)) [18–20]. Furthermore, ebselen (IV) is the most investigated Se compound with exciting GPX-like activity and has recently reached clinical phase III trials as a possible drug for Meniere's disease [11,21,22] (Figure 1). Moreover, ethaselen (V) entered trial phase II for non-small lung cancer treatment [23–26]. On the other hand, different OSe compounds have also manifested efficient catalytic activity for various organic reactions, such as the palladium-based OSe complex VI for the Heck reaction (Figure 1) [27].

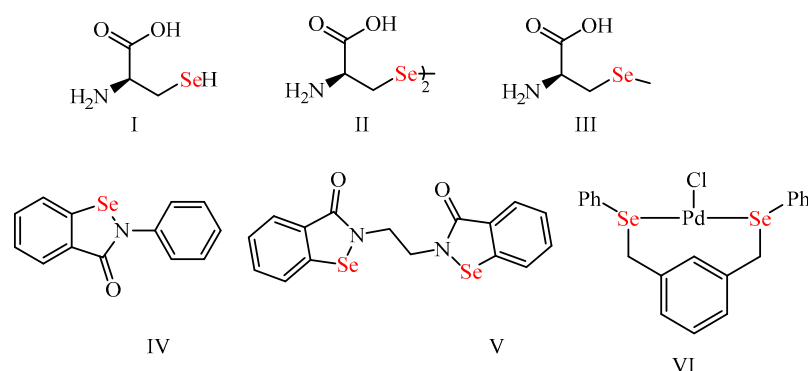


Figure 1. Organoselenium compounds (I–VI) with potential biological activities and diverse applications.

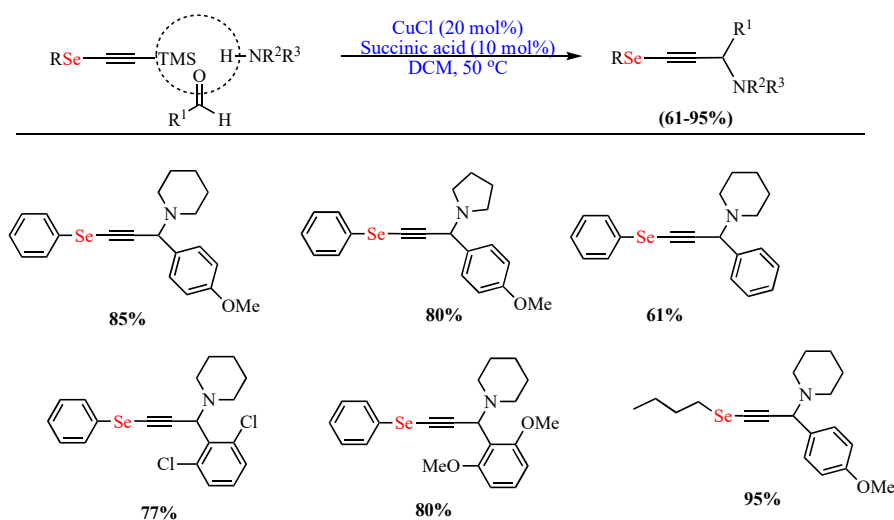
Given the exciting activities and the diverse applications of the OSe compounds, sustainable and efficient approaches for their preparation are in high demand. The synthesis of OSe compounds depends on their chemical structures (e.g., selenides, selenocyanates, diselenides) [26,28,29]. Standard methods include direct selenylation via reaction with proper Se reagents such as Na_2Se_2 and KSeCN . On the other hand, indirect selenylations include rearrangement of Se-containing precursors (e.g., isoselenocyanates) or multistep synthetic procedures using elemental Se together with organolithium or Grignard reagents and [2,13,24,30–35]. Despite being efficient, these classical strategies are relatively limited due to the challenges associated with the complicated synthetic procedure, regioselectivity, or harsh reaction conditions issues. Recently, various alternative reactions were developed as efficient and milder synthetic protocols within combinatorial chemistry (CC) [36–43]. The latter has emerged as a robust tool in medicinal chemistry [44,45]. It is now widely and consecutive covalent bonds formed between different building blocks [46]. Concurrently, drug candidates are discovered and selected by the screening of small molecule libraries for particular biological targets [47]. Despite the various strategies used in CC, multicomponent reactions (MCRs) are amongst the most investigated techniques for the efficient synthesis of chemical libraries [43,45]. MCRs have been known for over a century. They include generating skeletally diverse and complex molecular entities from more than two starting materials by straightforward chemical transformations employing comparatively mild conditions [37,48–50].

From an economical step and atom viewpoint, the MCR one-pot strategy would offer more robust access to OSe compounds. Though the MCRs have emerged as an efficient tool for constructing C–S bonds, similar approaches for synthesizing C–Se bonds have recently attracted more attention. We here want to summarize the recent developments of OSe compounds using the MCR one-pot approach to pave the way for medicinal chemists to have more accessible synthetic access to such a biologically relevant category of compounds. Specifically, we have structured this review based on the developments in metal-catalyzed and metal-free reactions in addition to the multicomponent polymerization synthesis of OSe compounds.

2. The One-Pot Multicomponent Combinatorial Synthesis of OSe Compounds

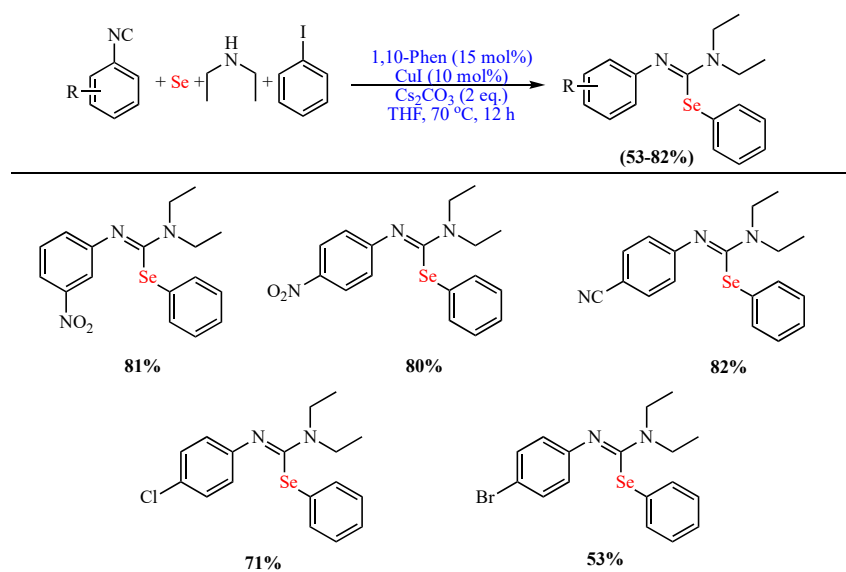
2.1. Metal-Catalyzed Synthesis of the OSe Compounds

In 2013, de Oliveira et al. reported the one-pot Cu-catalyzed (CuCl) synthesis of OSe propargylamines in excellent yields (up to 95%) via A³-coupling of trimethylsilyl Se-acetylene, *p*-methoxybenzaldehyde, and piperidine catalyzed in DCM as the solvent and in the presence of succinic acid additive at 50 °C (Scheme 1) [51].



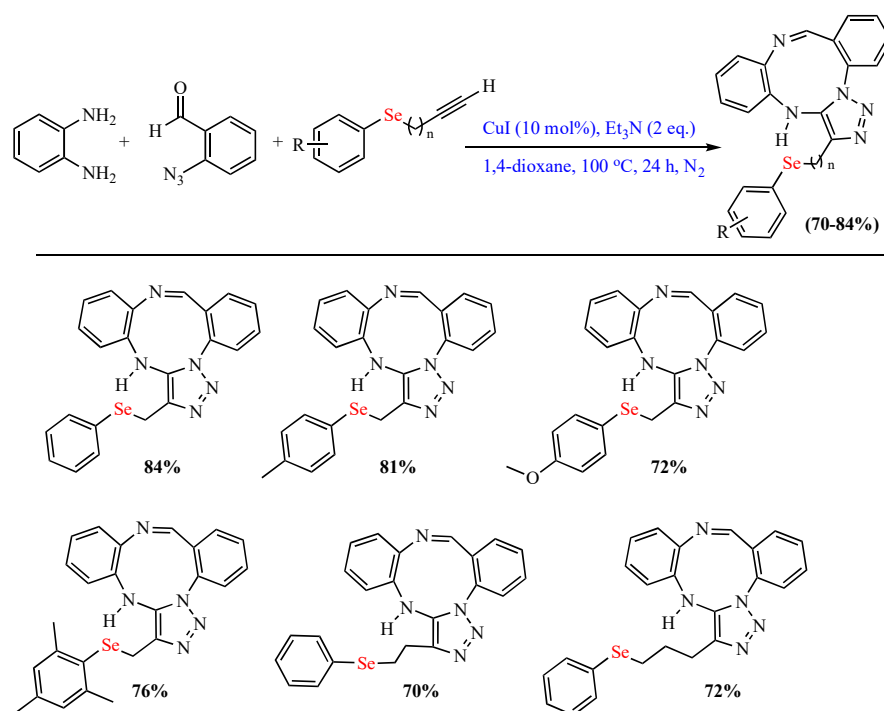
Scheme 1. Synthesis of OSe propargylamines.

In 2017, Liu et al. reported the synthesis of highly functionalized isoselenoureas through the Cu-catalyzed (CuI) 1,10-phenanthroline-promoted MCR of elemental Se, aryl iodides, isocyanides, and amines using Cs_2CO_3 as the base and THF as the solvent at 70 °C (Scheme 2) [52].



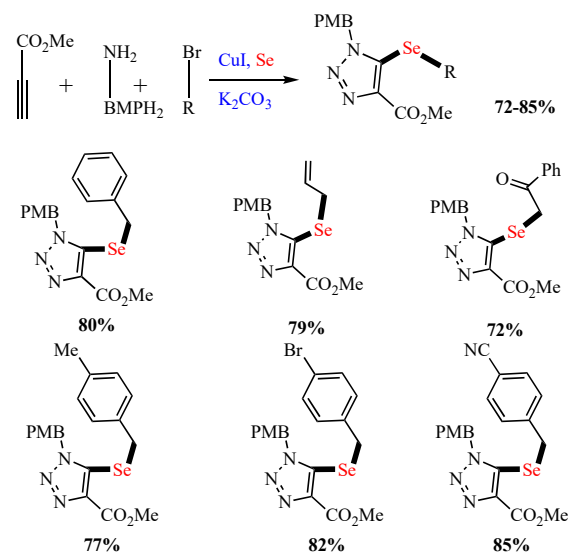
Scheme 2. Synthesis of functionalized isoselenoureas.

In 2018, Aquino et al. synthesized (arylselanyl)-alkyl-1,2,3-triazolo-1,3,6-triazonines via CuI-catalyzed MCR of 2-azidobenzaldehyde, 1,2-diaminobenzene, and various arylchalcogenyl alkynes in dioxane at 100 °C. The reaction included a wide variety of arylchalcogenyl alkynes (Scheme 3) [53].



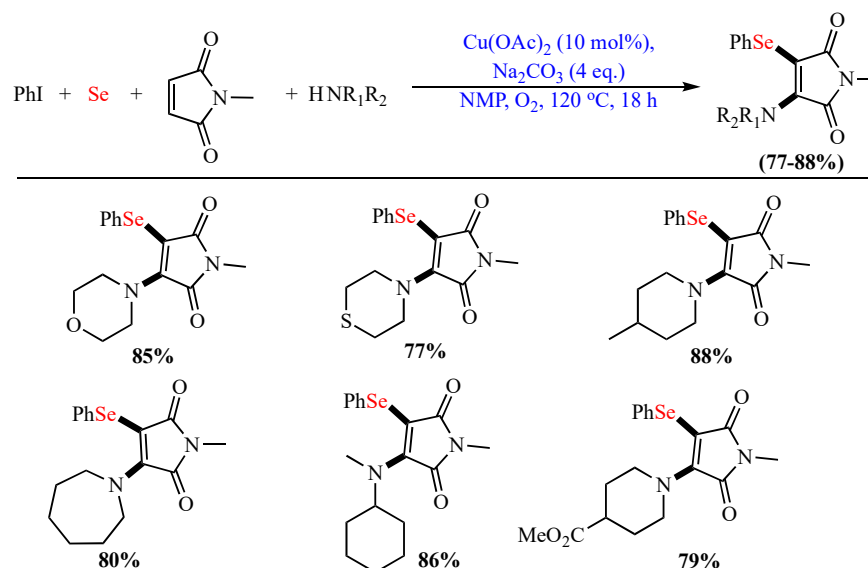
Scheme 3. Synthesis of (arylselanyl)-alkyl-1,2,3-triazolo-1,3,6-triazonines.

Zhang et al. reported the sequential multistep Cu-catalyzed (CuI) assembly of 5-selenotriazoles via the one-pot reaction of elemental Se, azide, alkyl halide, and alkyne. The selenylating agent and Cu(I) triazolides were generated in situ, and the reaction proceeded under mild conditions using readily available substrates with broad variety scope in high regioselectivity (Scheme 4) [54].



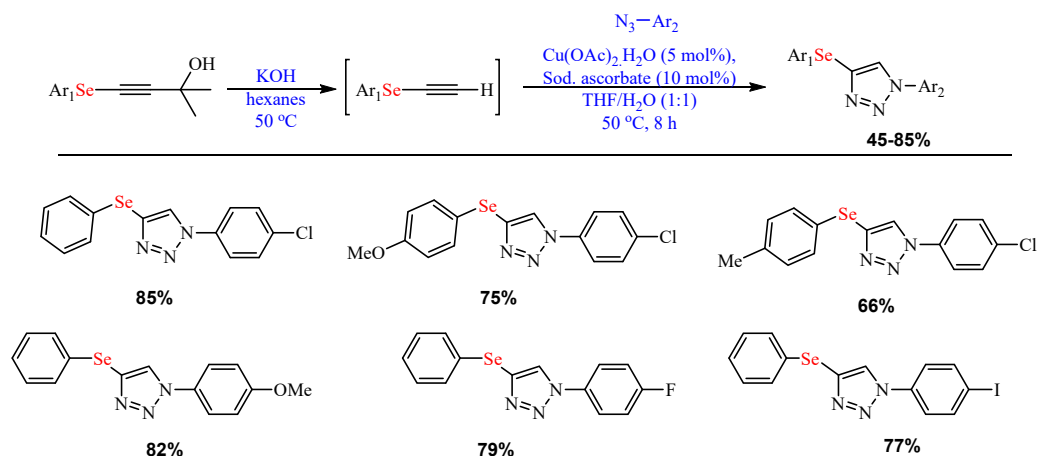
Scheme 4. Synthesis of 5-selenotriazoles.

In 2019, Gao et al. reported the Cu-catalyzed (Cu(OAc)₂) cross-coupling oxidative aminoarylselenation of maleimides using elemental Se, aryl iodides, and secondary amines. This reaction enabled the bifunctionalization of alkenes via the simultaneous one-pot construction of the C–N bond and C–Se bonds (Scheme 5) [55].



Scheme 5. Aminoarylselenation of maleimides.

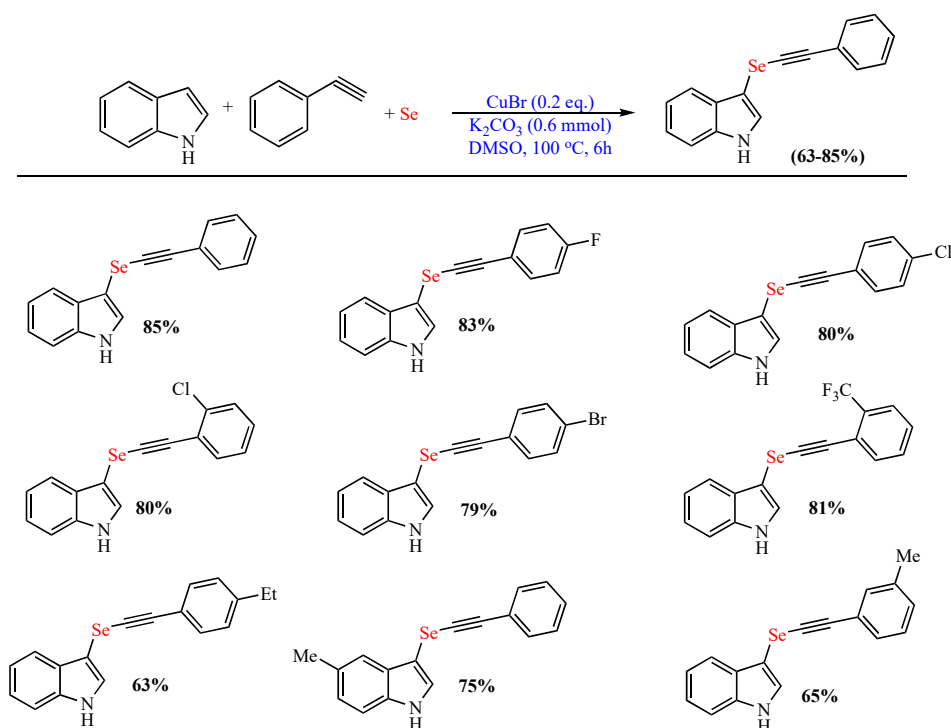
Recently, Begini et al. developed 4-arylselanyl-1*H*-1,2,3-triazoles from the one-pot Cu-catalyzed ($\text{Cu}(\text{OAc})_2$) reaction of selanylalkynylcarbinols and aryl azides in the presence of sodium ascorbate (10 mol%) in H_2O and THF (1:1) mixed solvent at 50°C (Scheme 6) [56].



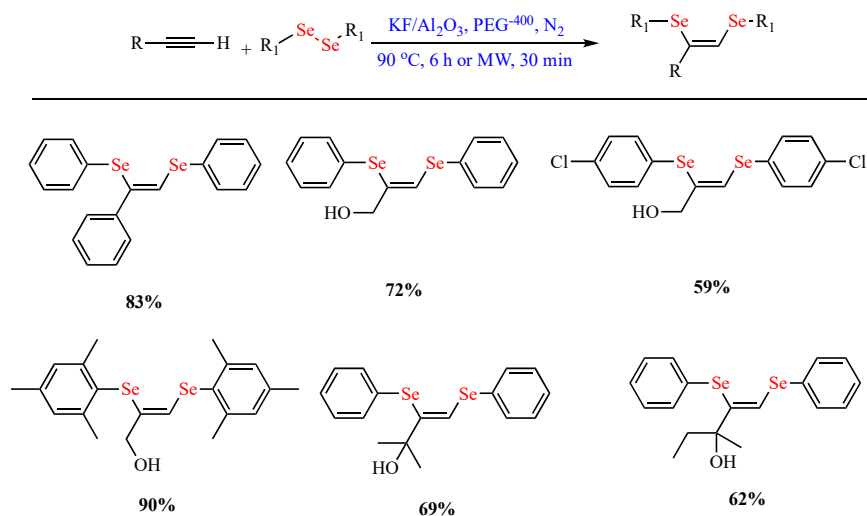
Scheme 6. Synthesis of 4-arylselanyl-1*H*-1,2,3-triazoles.

In 2021, Rather et al. disclosed the Cu-catalyzed (CuBr) synthesis of 3-((arylethynyl)selanyl)-1*H*-indoles in good yield (up to 83%) from elemental Se phenylacetylene and indole using K_2CO_3 as the base and DMSO as the solvent at 100°C . The strategy tolerates different indoles and phenylacetylene motifs and can be expanded to a gram scale without any difficulties (Scheme 7) [57].

Furthermore, Lara et al. reported the synthesis of (*Z*)-1,2-bis-arylselanyl alkenes by the one-pot reaction of terminal alkynes with diaryl diselenides using $\text{KF}/\text{Al}_2\text{O}_3$ and PEG-400 as a solvent in good yields. Interestingly, the reaction time was reduced from 6 h under conventional conditions to 30 min using microwave irradiation (Scheme 8) [58].

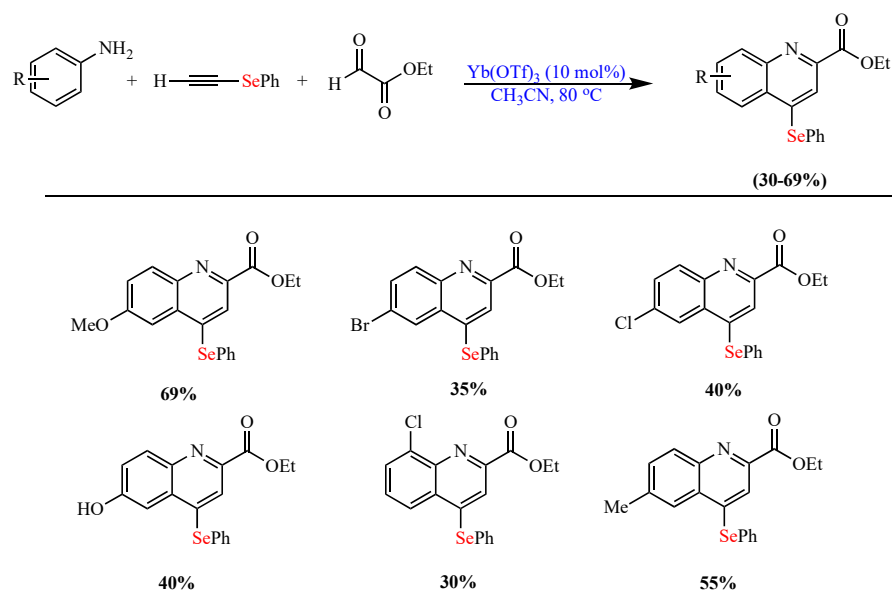


Scheme 7. Synthesis of 3-((arylethynyl)selenanyl)-1H-indoles.



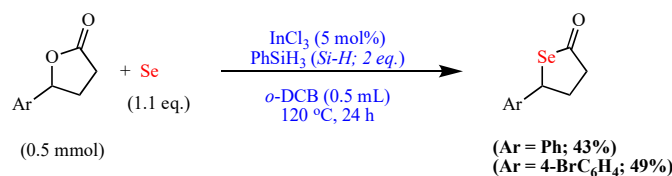
Scheme 8. Synthesis of (Z)-1,2-bis-arylselenanyl alkenes.

De Oliveira et al. reported the ytterbium(III)-catalyzed ($\text{Yb}(\text{OTf})_3$) synthesis of 2,4-disubstituted Se-quinoline derivatives via Povarov MCR between ethyl glyoxylate, *p*-anisidine, and ethynyl(phenyl)selane in CH_3CN as the solvent at 80 °C and in moderate yields (up to 69%) (Scheme 9) [59].



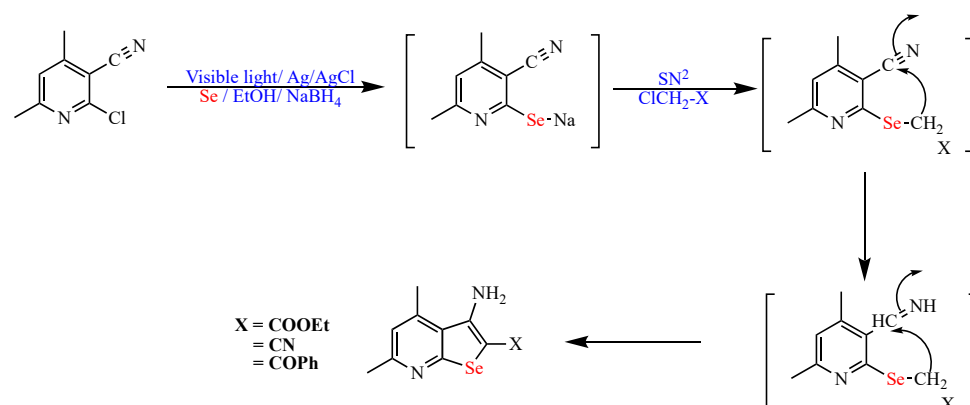
Scheme 9. Synthesis of 2,4-disubstituted Se-quinoline derivatives.

Moreover, Sakai et al. reported the indium-catalyzed ($\text{InCl}_3/\text{PhSiH}_3$) one-pot synthesis of selenolactones from elemental Se and lactones using *o*-dichlorobenzene as the solvent at 120°C for 24 h (Scheme 10) [60].



Scheme 10. Synthesis of selenolactones.

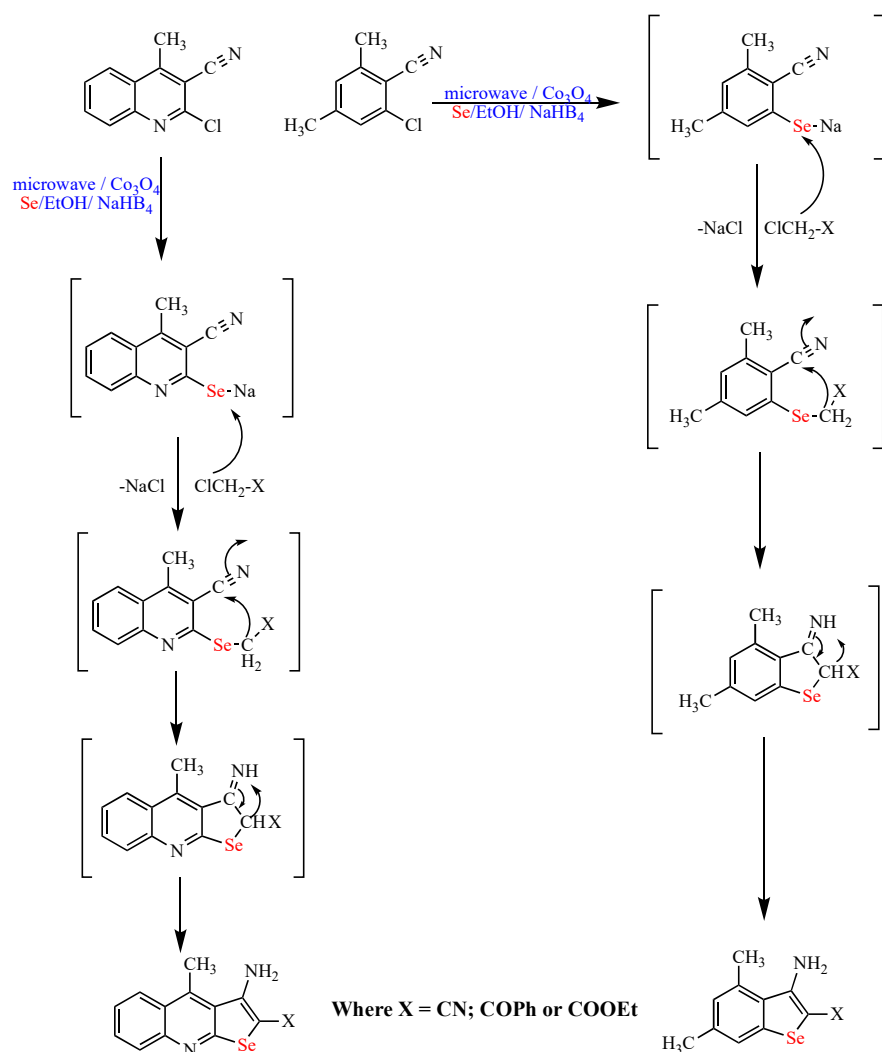
Recently, Attia et al. reported the one-pot synthesis of seleno [2,3-*b*]pyridine derivatives using Ag/AgCl nanoparticles under visible light irradiation. The reaction was carried out under mild conditions using visible light as the energy source, Ag/AgCl-nanoparticles, and EtOH as the solvent. It is worth noting that the Ag/AgCl-nanoparticles showed high catalytic activity and reusability potential up to five cycles in 94–91% isolated yields (Scheme 11) [61].



Scheme 11. Synthesis of seleno [2,3-*b*]pyridine derivatives.

Recently, the same group by Abdel-Hafez et al. reported the synthesis of selenopyridine and quinoline derivatives in excellent yields (up to 90%) and selectivity using Co_3O_4

nanoparticles heterogeneous catalyst under microwave irradiation and water as the solvent (Scheme 12) [62].



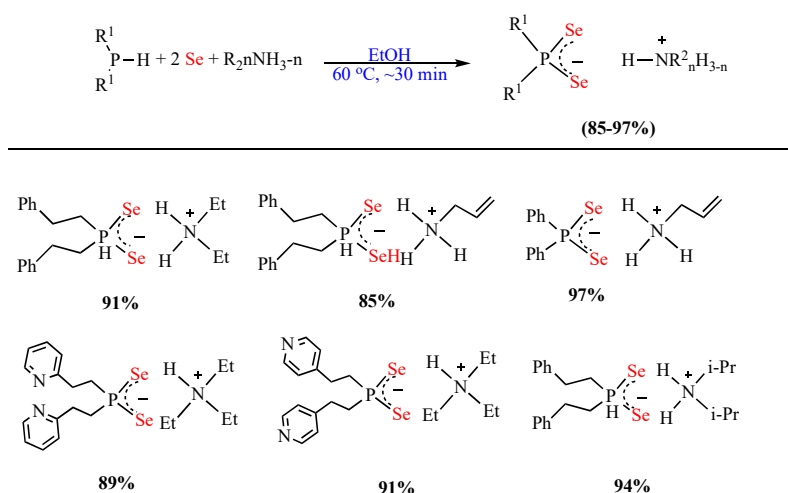
Scheme 12. Synthesis of selenopyridine and quinoline derivatives.

2.2. Metal-Free Synthesis of the OSe Compounds

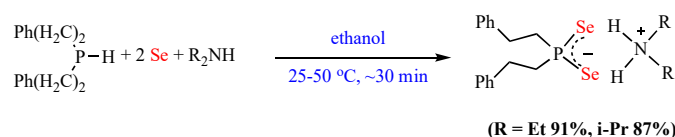
In 2010, Artem'ev et al. reported the MCR one-pot synthesis of alkylammonium diselenophosphinates in excellent yield (up to 97%) via reaction of elemental Se with amines (e.g., primary, secondary, or tertiary) and secondary phosphines in ethanol at 60 °C (Scheme 13) [63].

Furthermore, Artem'ev et al. also synthesized diselenophosphinates via a three-component reaction of secondary phosphine, Se powder, and amines in ethanol at 50–75 °C for 30 min (Scheme 14) [64].

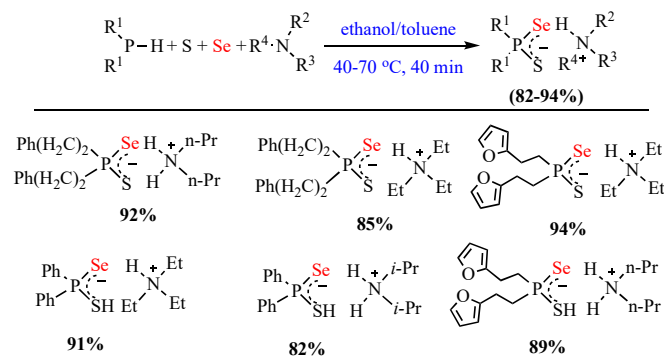
Additionally, Artem'ev et al. reported the one-pot multicomponent synthesis of mono-, di-, and trialkylammonium thioselenophosphinates in good yields (up to 94%) from secondary phosphanes, amines (primary, secondary, or tertiary), elemental S, and elemental Se (Scheme 15) [65].



Scheme 13. Synthesis of alkylammonium diselenophosphinates.



Scheme 14. Synthesis of diselenophosphinates.

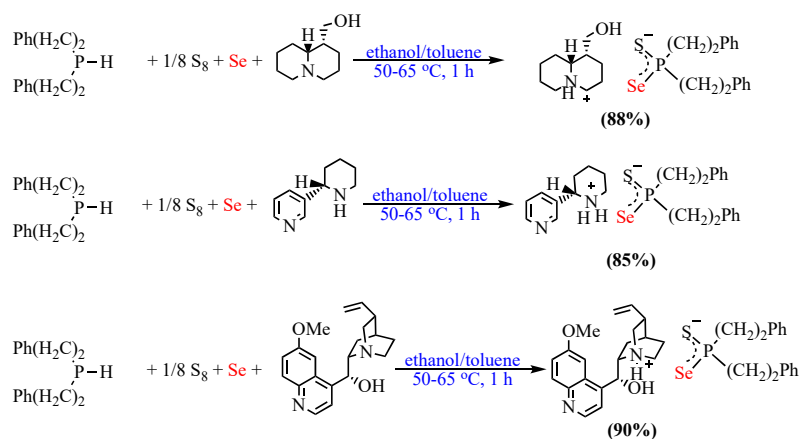


Scheme 15. Synthesis of mono-, di-, and trialkylammonium thioselenophosphinates.

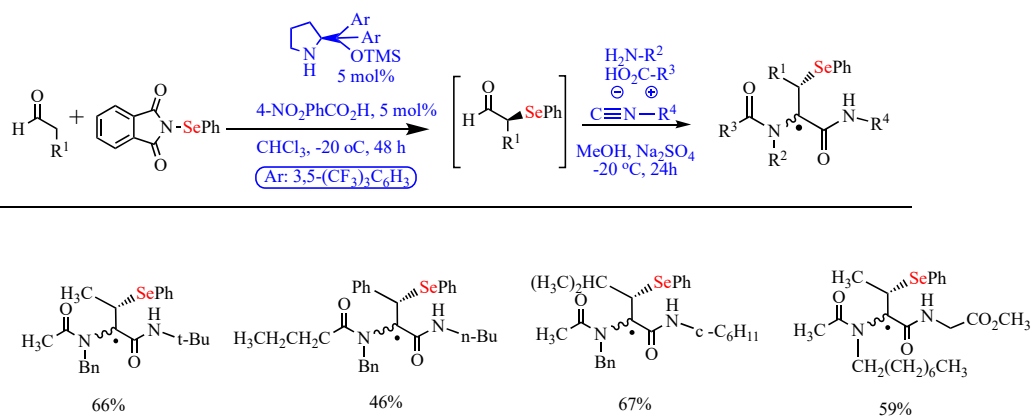
Despite the high yield and considerable success of the above reaction, it was limited to certain amines such as triethyl amine, dipropyl amine, and diisopropylamine. In 2012, Artem'ev et al. extended this reaction to natural alkaloids of different *N*-bases, namely, lupinine, anabasine, and quinine [66] (Scheme 16).

De La Torre et al. reported the metal-free synthesis of new selenocysteine-based peptoids and peptide-peptoid conjugates. The latter includes organocatalytic insertion of phenylselenium into the backbone of the aldehyde moiety using Jørgensen's catalyst, followed by a subsequent Ugi reaction (Scheme 17) [67].

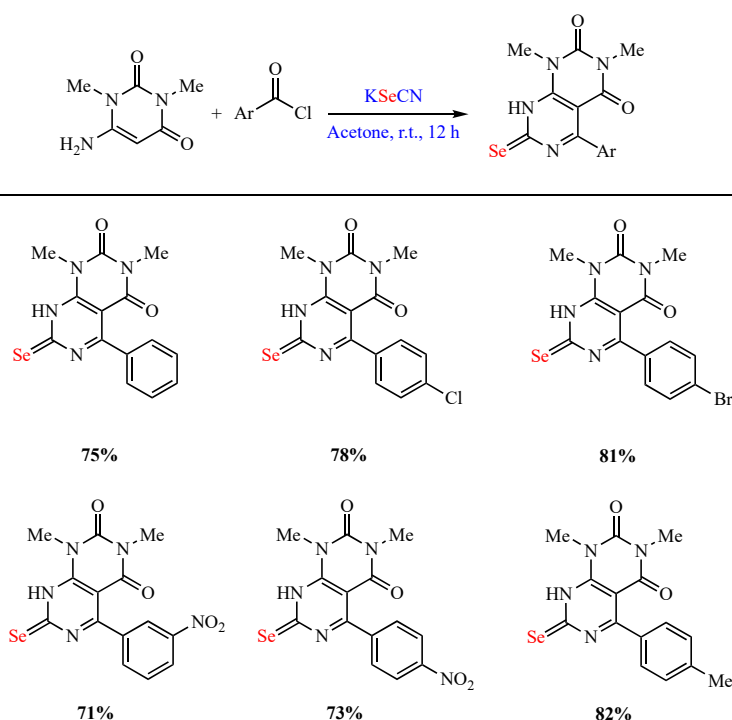
In 2018, Singh et al. reported the one-pot synthesis of 5-aryl-1,3-dimethyl-7-selenoxypyrimidino [4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-diones in good yields (up to 82%) by the reaction of aroyl chloride, KSeCN and 6-amino-*N,N'*-dimethyluracil in acetone (Scheme 18) [68].



Scheme 16. Synthesis of mono-, di-, and trialkylammonium thioselenophosphinates of lupinine, anabasine, and quinine.

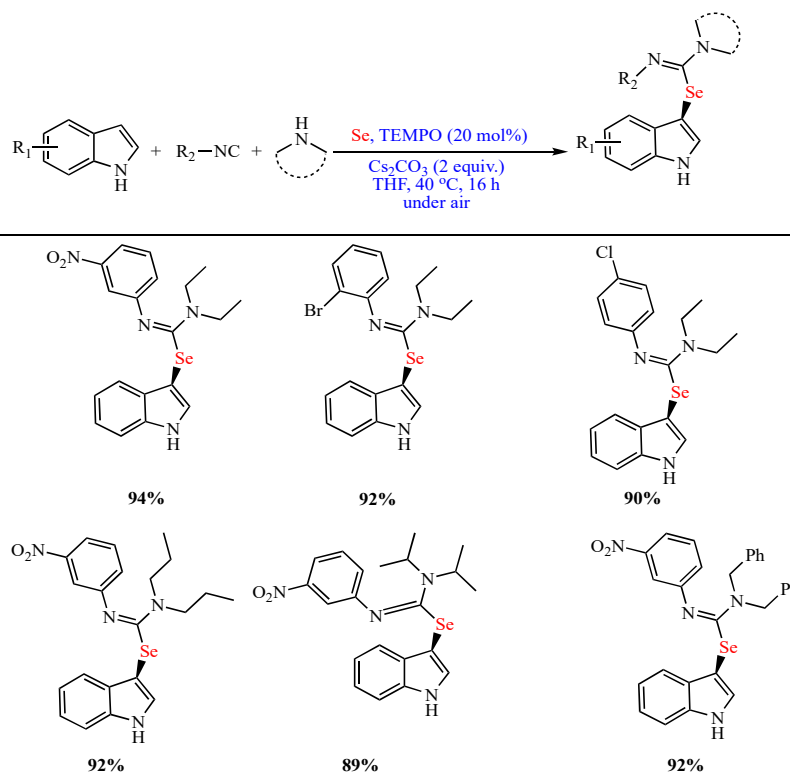


Scheme 17. Synthesis of selenocysteine-based peptoids and peptide-peptoid conjugates.



Scheme 18. Synthesis of 5-aryl-1,3-dimethyl-7-selenoxypyrimidino [4,5-d]pyrimidine-2,4(1H,3H)-diones.

Liu et al. reported the multicomponent Se functionalization of indoles at the C3 under transition metal-free conditions. The reaction was carried out using elemental Se, isocyanides, amines, and indoles. The reaction proceeded under mild conditions employing O_2 as the oxidant and TEMPO as the catalyst and encompassed a wide range of substrates in moderate to high yields (Scheme 19) [69].



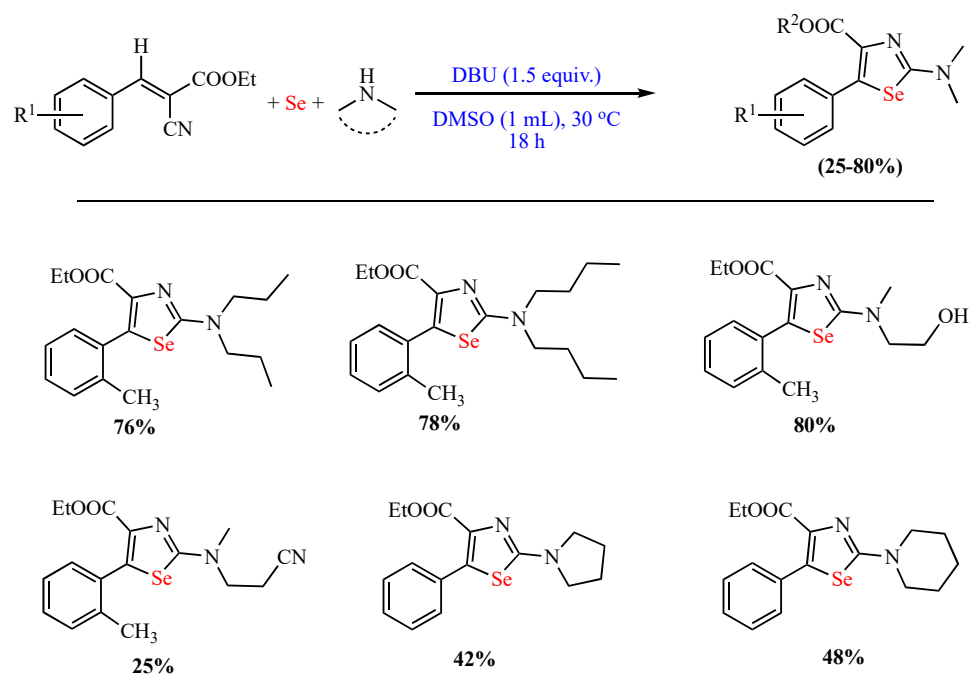
Scheme 19. Synthesis of Se functionalization of indoles.

In 2020, Liu et al. reported the one-pot synthesis of 2-amino-1,3-selenazoles with transition metal-free MCR of elemental Se, amines, and α,β -unsaturated isocyanides. The reaction of the elemental Se with isocyanide affords the corresponding isoselenocyanate, which undergoes intramolecular Michael cycloaddition followed by aromatization to provide 2-amino-1,3-selenazole in good yields (up to 80%) (Scheme 20) [70].

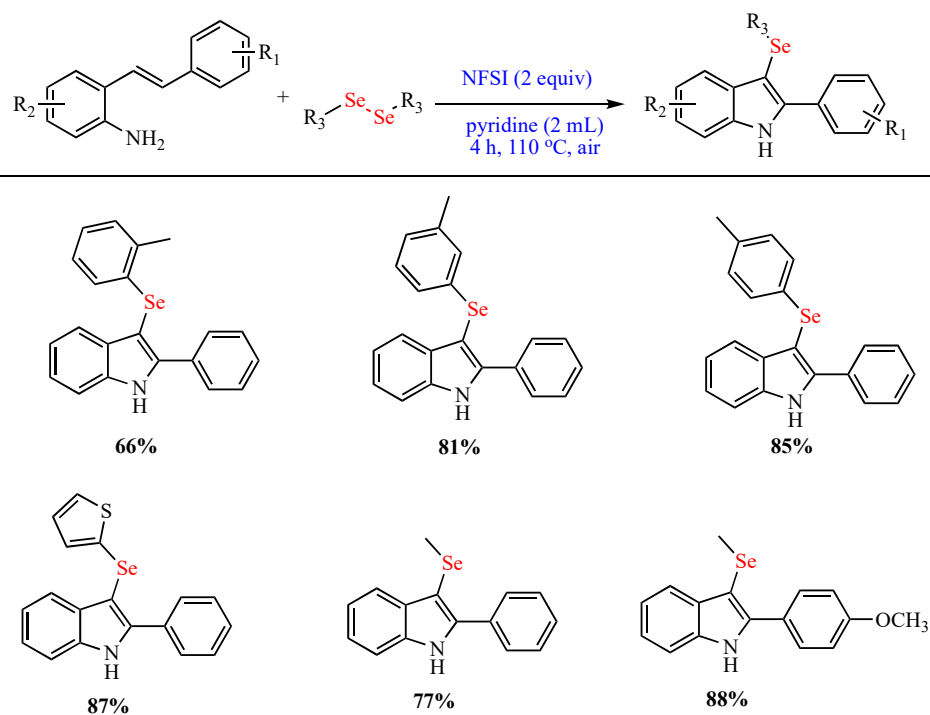
In 2020, Zhao et al. reported the organocatalytic (*N*-fluorobenzenesulfonimide) one-pot synthesis of 3-selenylindoles through intramolecular cyclization/selenylation of 2-vinylaniline in moderate to good yield (up to 88%). The reaction was smoothly furnished, employing wide substrates and good functional group transformations, and could also be tolerated to gram scale (Scheme 21) [71].

In 2022, Liu et al. reported the metal-free MCR synthesis of 3-alkylselenindole derivatives from elemental Se, indoles, and unactivated alkyl halides under mild conditions using *t*-BuONa as the base in CH_3CN as the solvent at 40 °C. The reaction encompassed wide functional group tolerance and can also be applied for a large scale (>10 g) in excellent yield (>90% yield) (Scheme 22) [72].

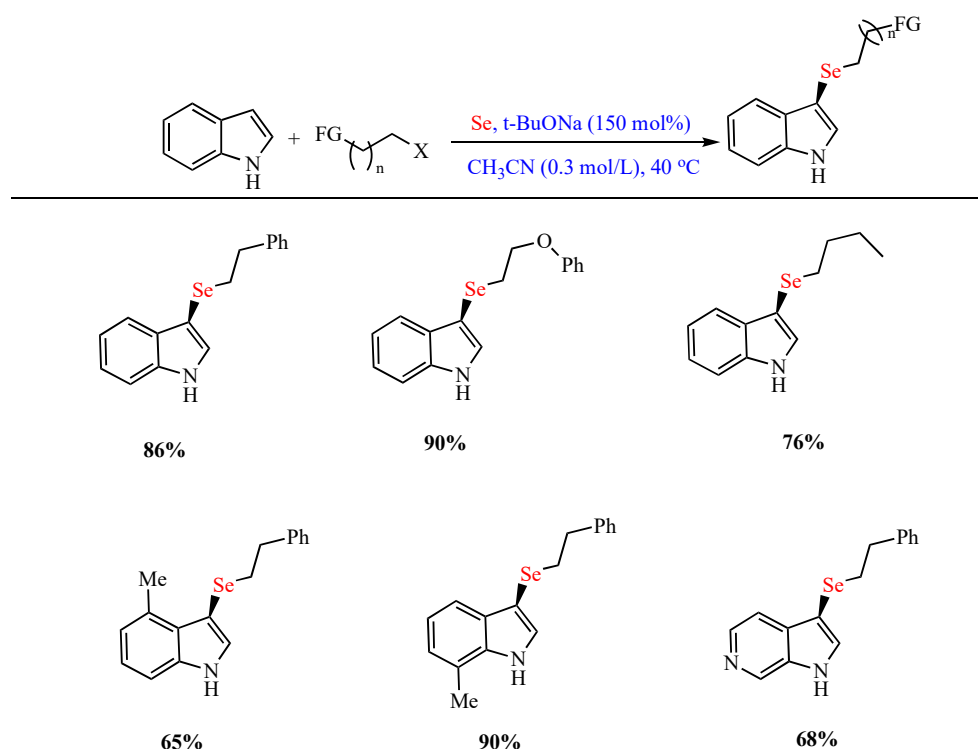
In 2021, Li et al. reported the synthesis of diselenocarbamates in good yields (up to 91%) via the one-pot MCR of elemental Se, amines, diselanes, and $CHCl_3$ using *t*-BuOK as the base and NMP as the solvent at 50 °C for 12 h (Scheme 23) [73].



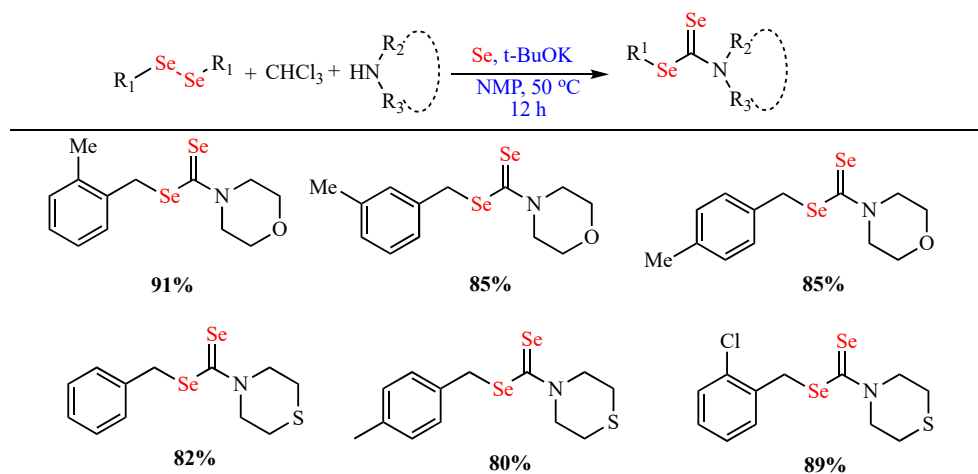
Scheme 20. Synthesis of 2-amino-1,3-selenazoles.



Scheme 21. Synthesis of 3-selenylindoles.

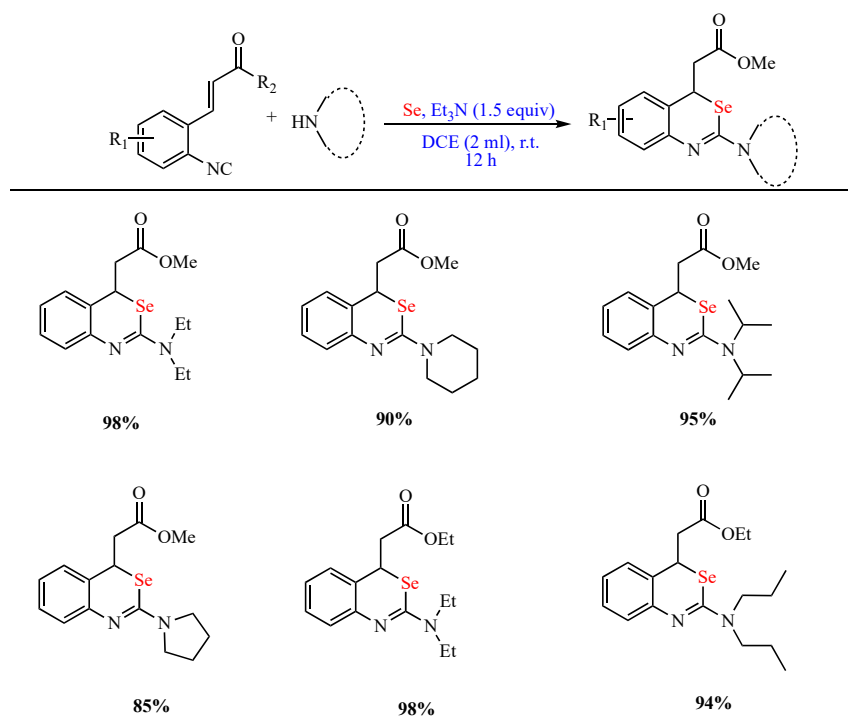


Scheme 22. Synthesis of 3-alkylselenindole derivatives.



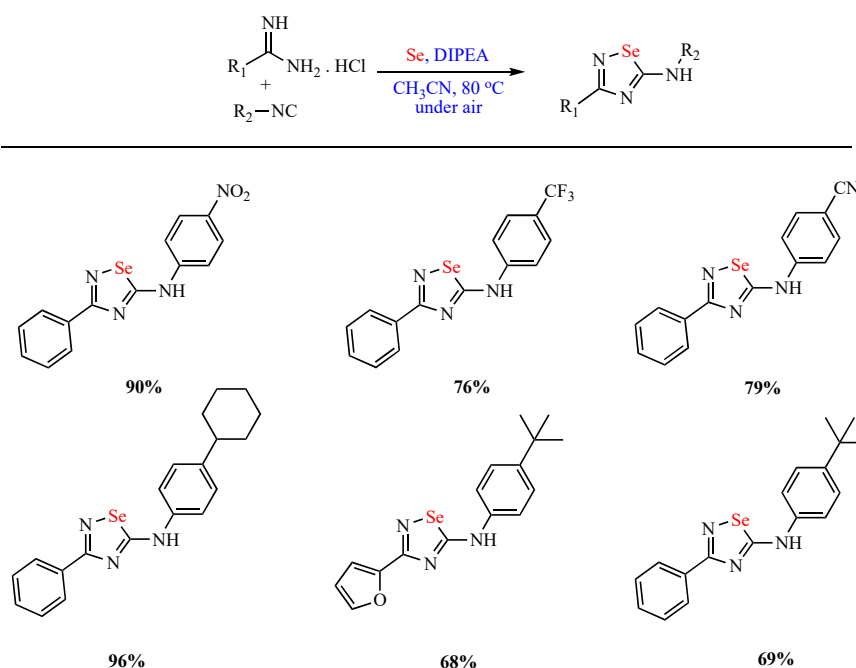
Scheme 23. Synthesis of diselenocarbamates.

Fang et al. developed the base promoted and metal-free cascade synthesis of 2-aminobenzo[d][1,3]selenazines via reaction of elemental Se, ortho-functionalized aryl isocyanides, and amines. The reaction proceeded under basic conditions via the in situ formation of isoselenocyanates from elemental Se and subsequent intramolecular Michael addition reactions (Scheme 24) [74].

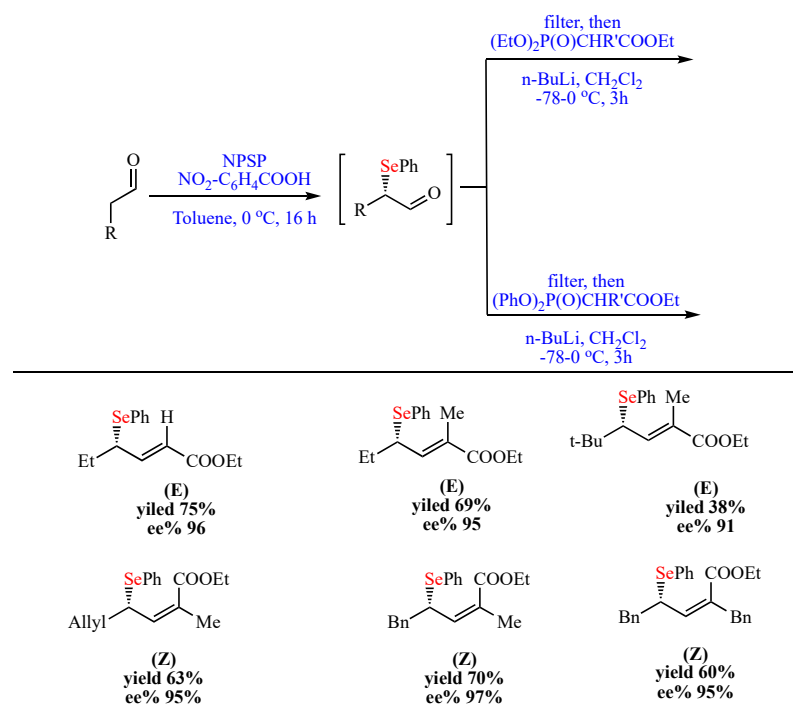


Scheme 24. Synthesis of 2-aminobenzo[d][1,3]selenazines.

Additionally, Fang et al. reported the metal-free preparation of 1,2,4-selenadiazol-5-amine derivatives in moderate to excellent yields (up to 96%) through the aerobic radical-cascade reactions of Se powder, isocyanides, and imidamides using O_2 as the green oxidant. It is worth noting that the reaction H_2O was the only byproduct obtained and the reaction encompassed good functional group tolerance and broad substrate scope. In addition, this protocol was applied for the late-stage functionalization of biologically active candidates (Scheme 25) [75].

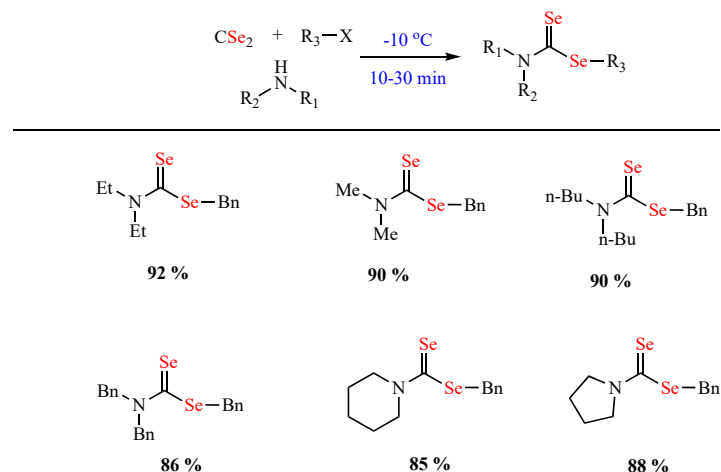


Scheme 25. Preparation of 1,2,4-selenadiazol-5-amine derivatives.



Scheme 28. Synthesis of trisubstituted allylic selenides.

Pan et al. reported the one-pot, metal-free, and solvent-free synthesis of diselenocarbamates from the reaction of CSe_2 , alkyl halides, and amines at $-10\text{ }^\circ\text{C}$ (Scheme 29) [79].

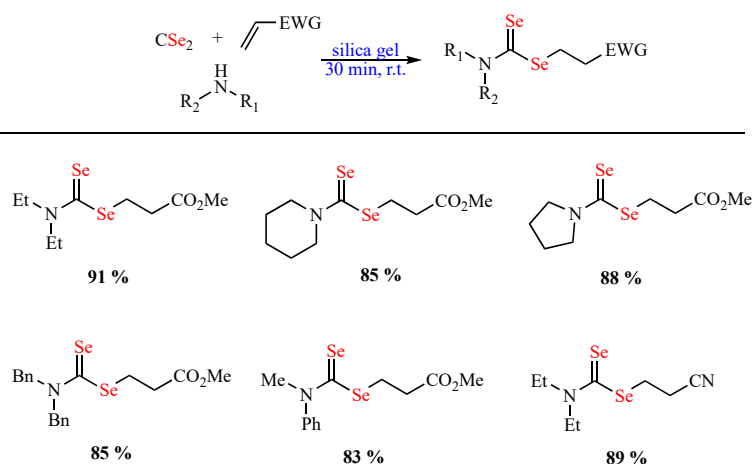


Scheme 29. Synthesis of diselenocarbamates.

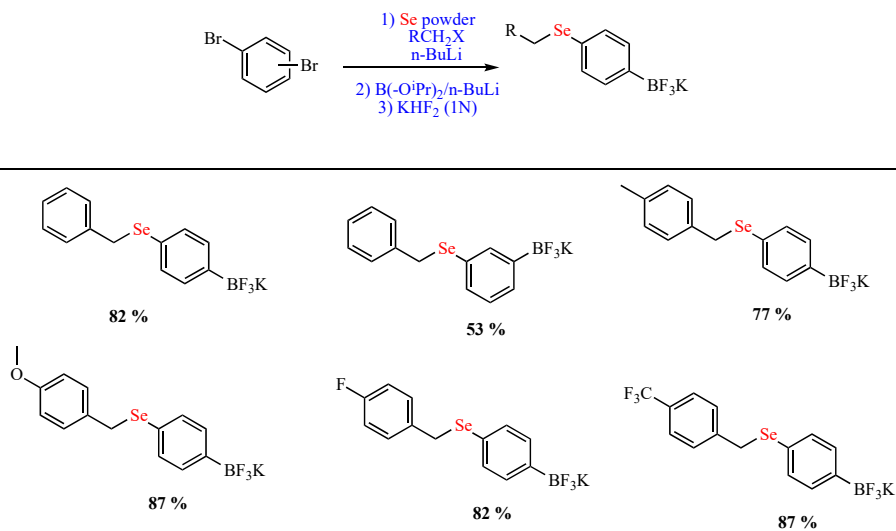
Furthermore, diselenocarbamates were synthesized from CSe_2 with aliphatic amines and alkenes as electron-deficient substrates via Michael-type addition using silica gel as the media (Scheme 30) [79].

Ahn et al. reported the one-pot preparation of organoselanyltrifluoroborates from Se powder, dihalobenzenes, and alkyl halides in 56–92% yields using $n\text{-BuLi}$ and boron isopropoxide at $-78\text{ }^\circ\text{C}$ (Scheme 31) [80].

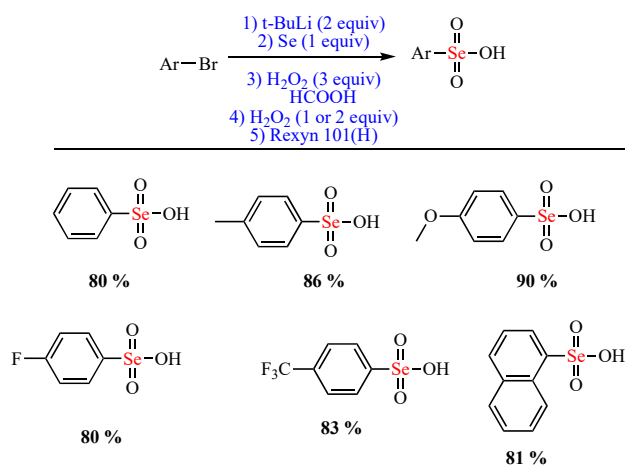
In 2021, Sands et al. reported the one-pot synthesis of structurally diverse selenonic acids in good yields (up to 90%) from elemental Se and aryl bromides. The reaction involves metalation using $t\text{-BuLi}$, selenation, and oxidation using H_2O_2 , followed by ion exchange using Rexyn 101(*H*) ion-exchange resin (Scheme 32) [81].



Scheme 30. Synthesis of diselenocarbamates.

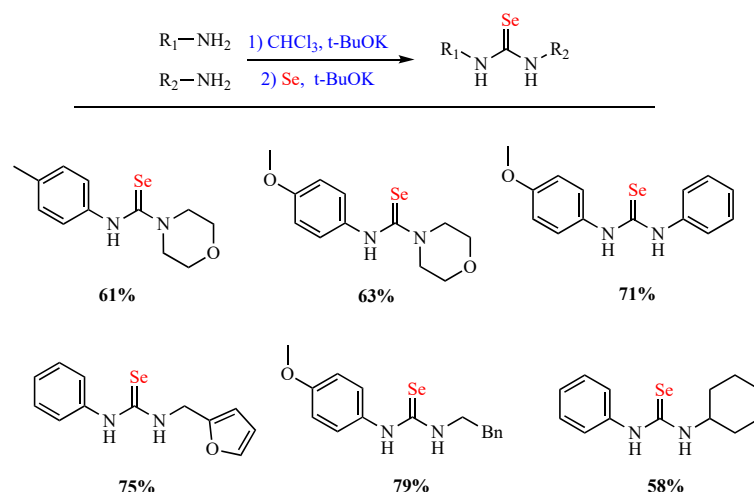


Scheme 31. Preparation of organoselanyltrifluoroborates.



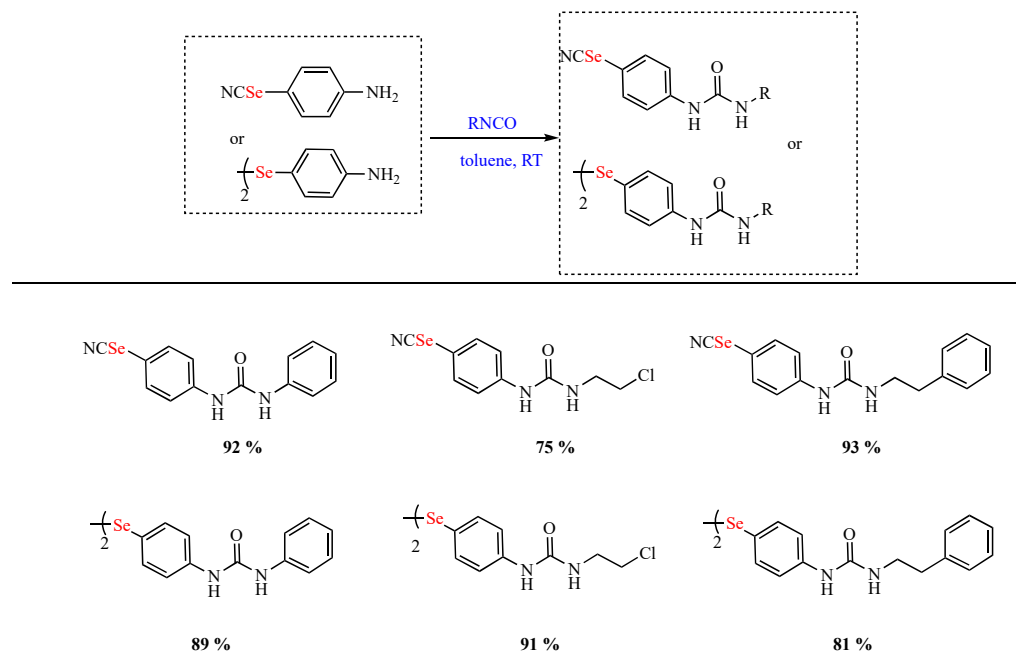
Scheme 32. Synthesis of structurally diverse selenonic acids.

In 2020, Wu et al. disclosed the one-pot multicomponent synthesis of unsymmetrical selenoureas and cycloselenoureas from selenium powder, $CHCl_3$, and two different amines using t -BuOH as the base at $50^\circ C$ for 3 h in moderate–good yields (up to 86%) (Scheme 33) [82].



Scheme 33. Synthesis of unsymmetrical selenoureas and cycloselenoureas.

In 2022, Shaaban and colleagues reported the development of urea-based selenocyanates and symmetrical diselenides in good yields (up to 93%) using 4-selenocyanatoaniline and 4,4'-diselenediyl dianiline, respectively, and commercially available isocyanates in toluene (Scheme 34) [83].



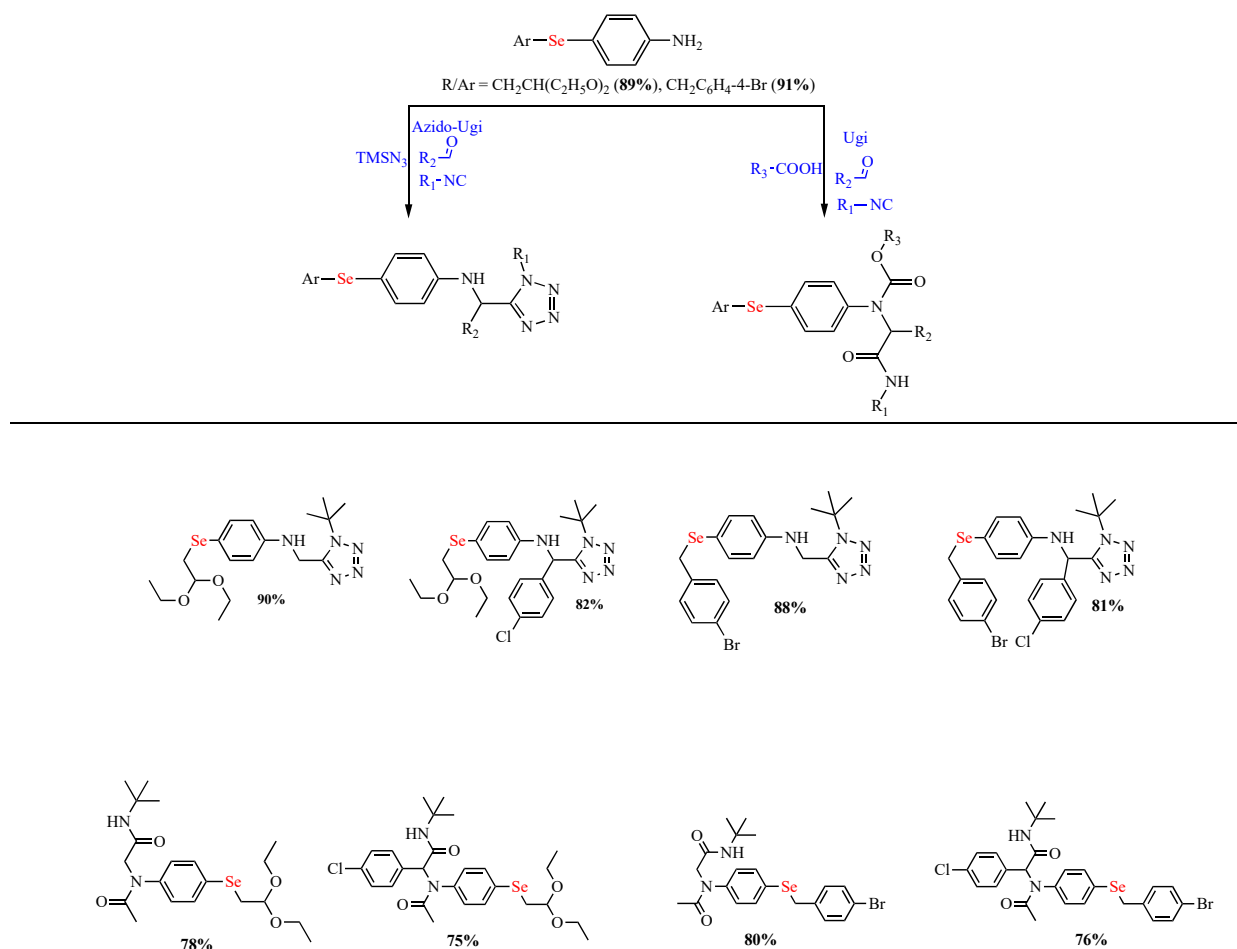
Scheme 34. Synthesis of urea-based selenocyanates and symmetrical diselenides.

In 2021, Shaaban et al. and his group developed of peptide-like and tetrazole-based redox-active multifunctional OSe compounds via multicomponent Ugi and azido-Ugi reactions. The reaction included novel Se-based aniline building blocks to incorporate the Se redox center into the backbone of the Ugi/Ugi-azide structurally diverse product's tail. Indeed, the reactions were carried out under mild conditions using DCM and MeOH as the solvent for the Ugi and Azido-Ugi reactions, respectively (Scheme 35) [12].

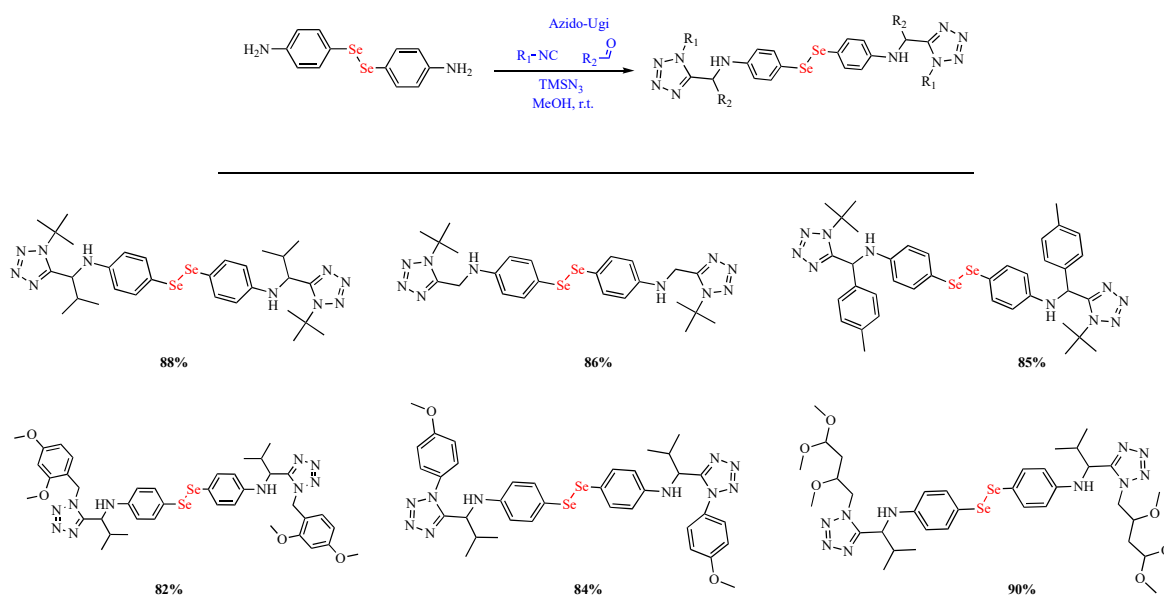
Furthermore, Shaaban et al. reported the combinatorial one-pot synthesis of tetrazole-based symmetrical diselenides and selenoquinones compounds via azido-Ugi and sequential nucleophilic substitution methodology (Scheme 36) [84].

Moreover, Shaaban et al. also reported the synthesis of different Se peptidomimetic compounds employing the Ugi isocyanide-based MCR using the Se-based isonitrile

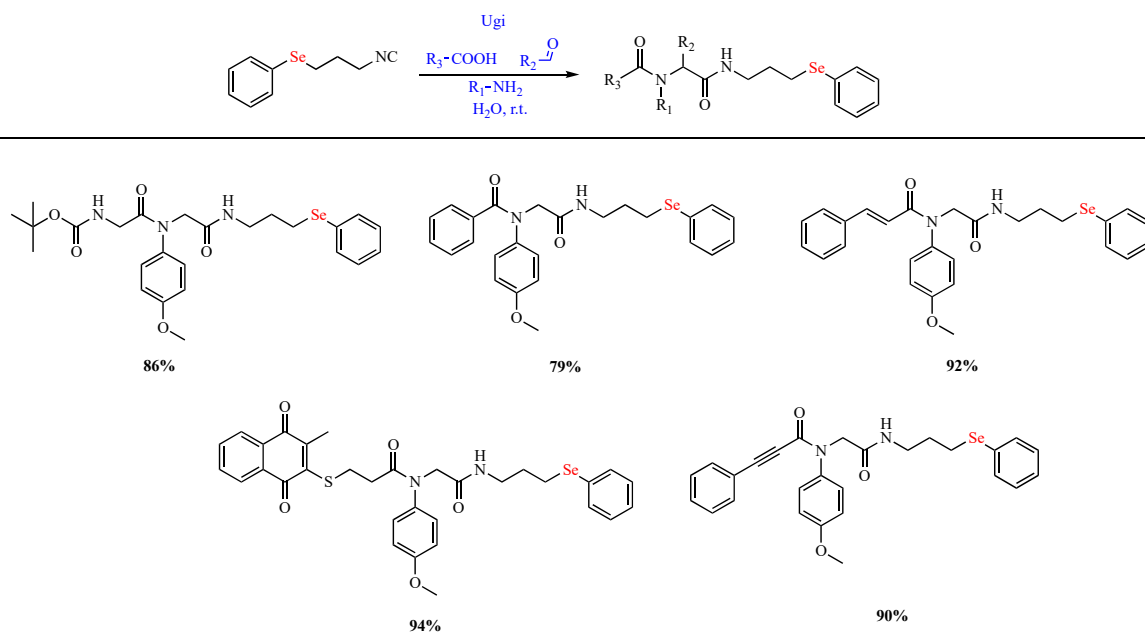
3-isocyanopropyl(phenyl)selane. The reaction was achieved under mild conditions using H₂O as the solvent in good yields (up to 94%) (Scheme 37) [85].



Scheme 35. Synthesis of peptide-like and tetrazole-based redox-active multifunctional OSe compounds.

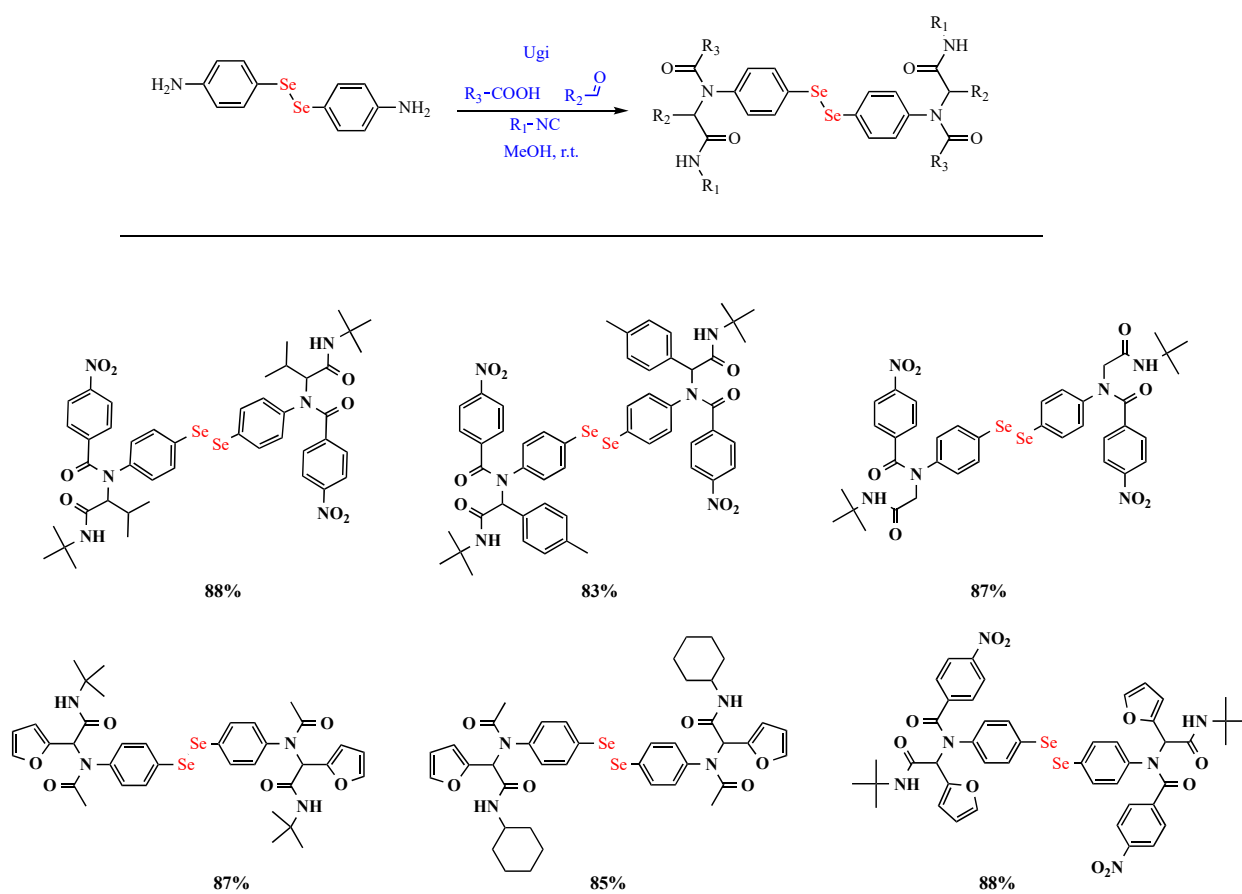


Scheme 36. Synthesis of tetrazole-based symmetrical diselenides and selenoquinones compounds.



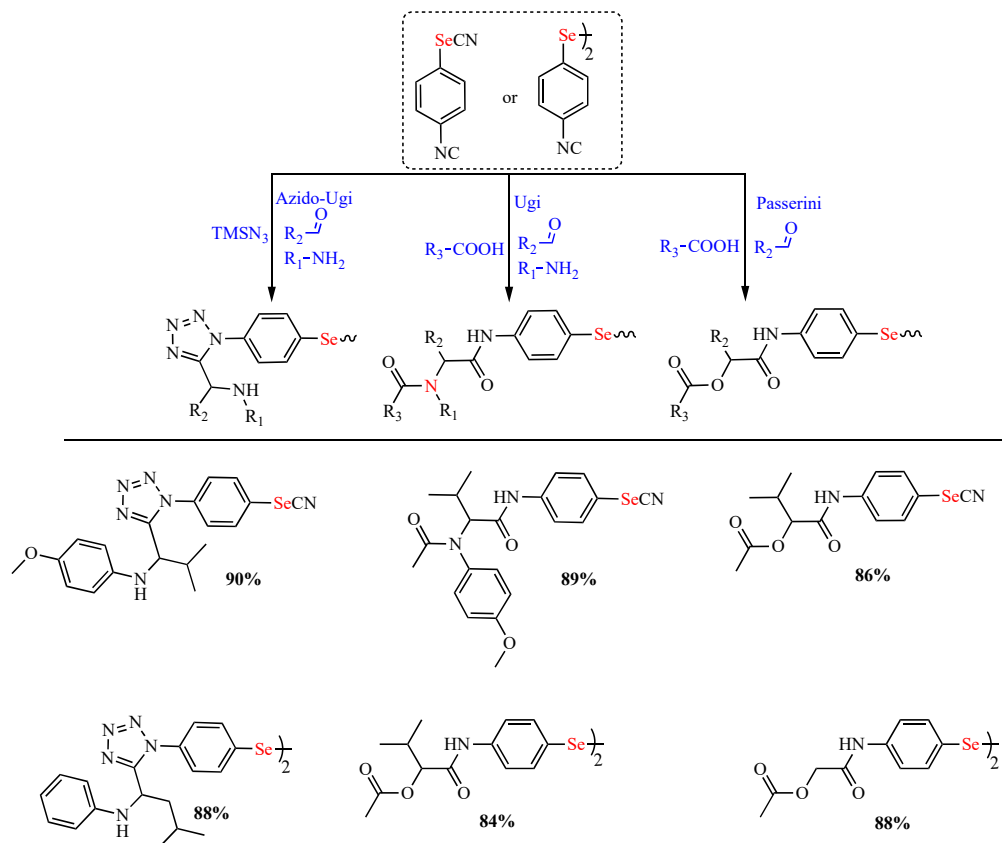
Scheme 37. Synthesis of different Se peptidomimetic compounds.

Additionally, Shaaban et al. reported the synthesis of symmetrical diselenide via one-pot Ugi using 4-(2-(4-aminophenyl)diselanyl)benzenamine as key synthon, which in turn allowed the access to the diselenide scaffolds (Scheme 38) [86].



Scheme 38. Synthesis of symmetrical diselenide.

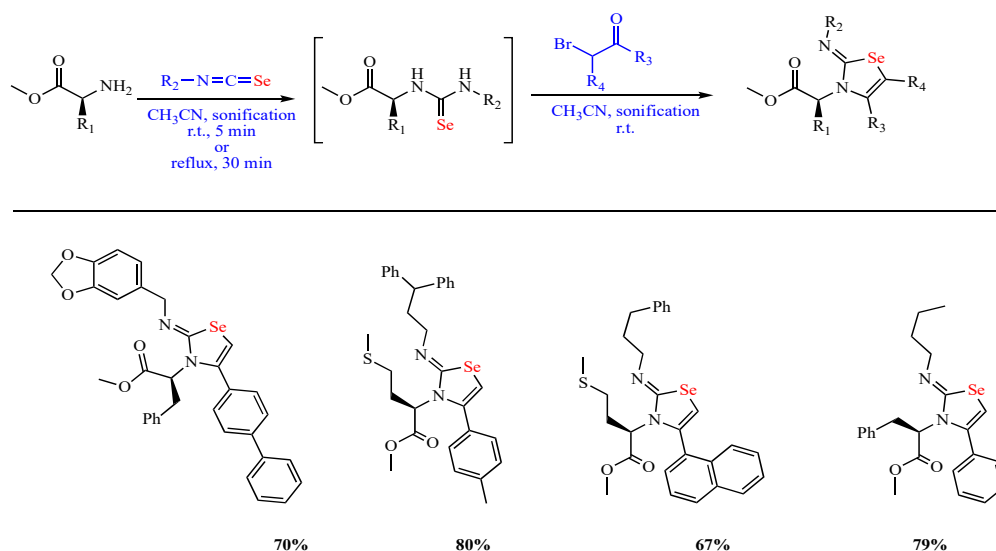
In 2021, Shaaban et al. reported the synthesis of new selenocyanate isocyanide and diselenide diisonitrile and explored their reactivities in Passerini, Ugi, and Azido-Ugi reactions. OSe-based pseudopeptides, peptidomimetics, and tetrazoles were obtained in good yields (up to 94%) (Scheme 39) [87].



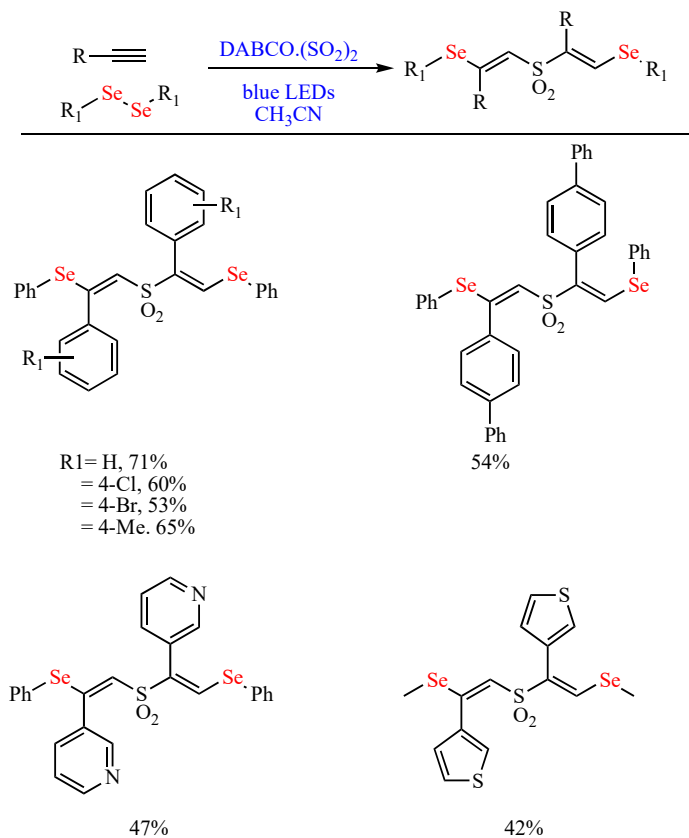
Scheme 39. The synthesis of new selenocyanate isocyanide and diselenide diisonitrile and explored their reactivities in Passerini, Ugi, and Azido-Ugi reactions.

Chang et al. reported the three components regioselective one-pot synthesis of chiral 2-iminoselenazolines by sonication from L-aminoester, isoselenocyanate, and α -bromoketone. In this reaction, selenazoles are obtained by Hantzsch reaction of selenoureas, generated in situ from the reaction of isoselenocyanate and L-amino esters, with α -bromoketones proceeded smoothly under ecofriendly conditions, i.e., at room temperature and under ultrasonication (Scheme 40) [88].

Chen et al. reported the construction of β -sulfonylviny selane bond via the visible-light mediated MCR cascade of diselenides, alkynes, and SO₂. In this reaction, novel class of β -sulfonylviny selanes in high selectivity for E configuration and in moderate yields (up to 71%) (Scheme 41) [89].



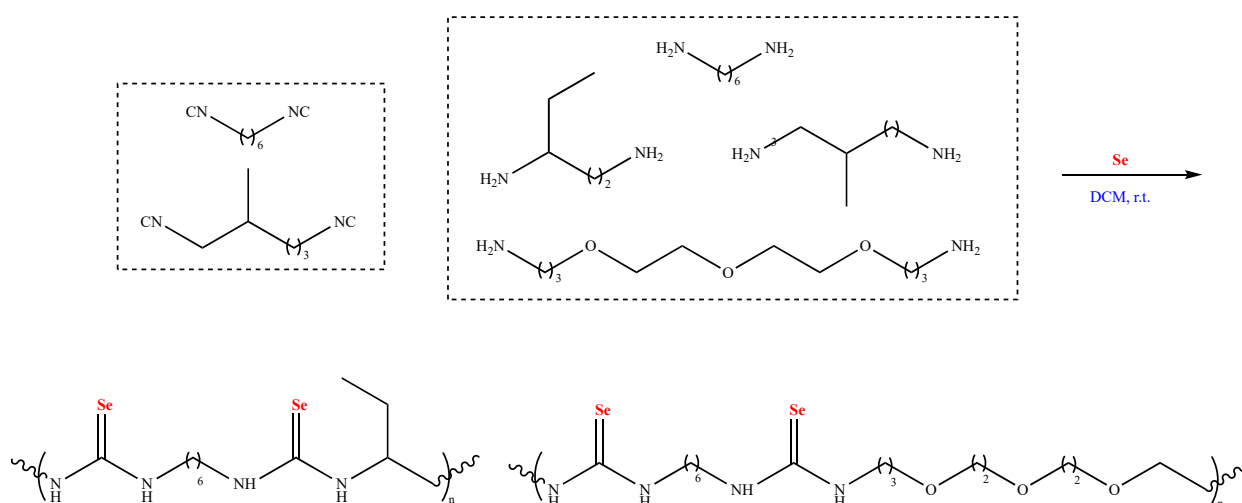
Scheme 40. Synthesis of chiral 2-iminoselenazolines.



Scheme 41. Synthesis of β -sulfonylvinylnelanes.

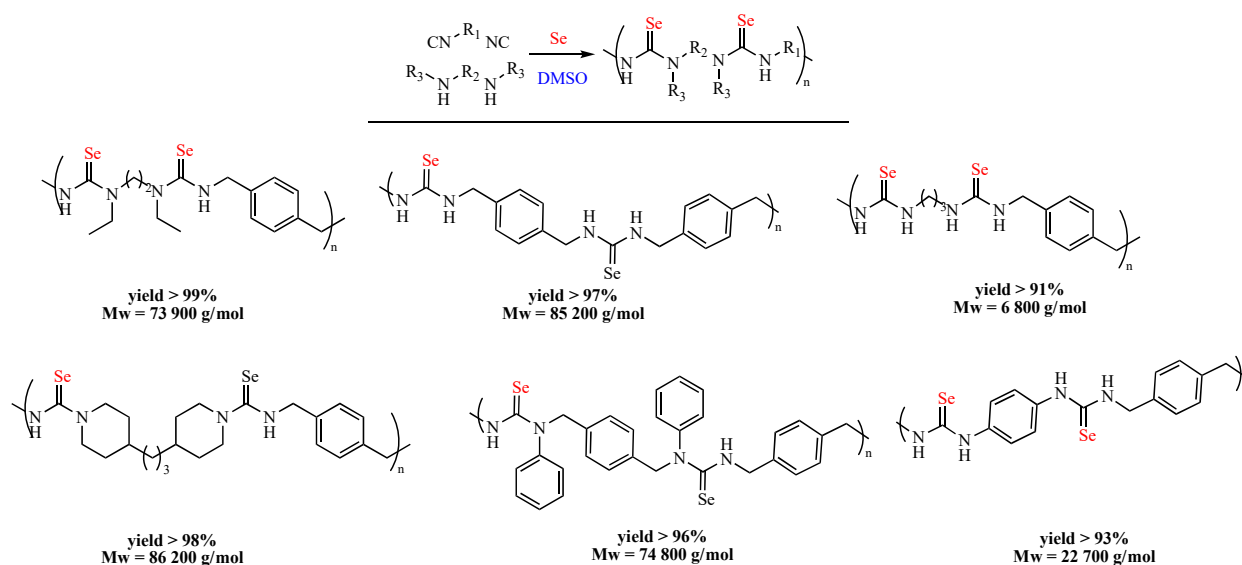
2.3. Multicomponent Polymerization Synthesis of OSe Compounds

In 2018, Tuten et al. reported the multicomponent polymerization reaction of elemental Se, amines, and isocyanides to form polyselenoureas in one step and at room temperature using DCM as the solvent (Scheme 42) [90].



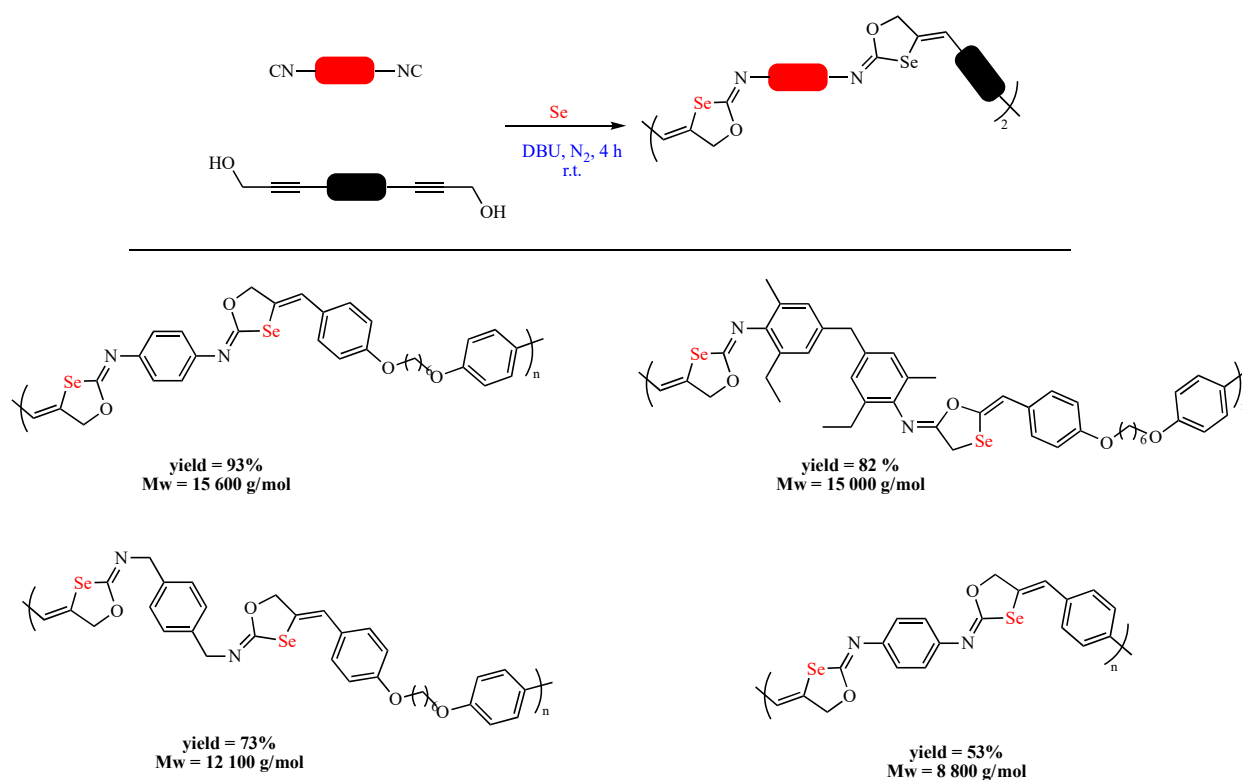
Scheme 42. The multicomponent polymerization synthesis of polyselenoureas.

In 2019, Wu et al. reported the synthesis of functionalized and structurally diverse polyselenoureas via catalyst-free and solvent-free MC polymerizations of elemental Se, diisocyanides, and aliphatic/aromatic diamines. It is worth noting that the obtained polyselenoureas encompassed enhanced thermal stability and solubility, long-term stability, and the potential extraction of gold ions (Au^{3+}) from mixed-metal ion solutions (Scheme 43) [91].



Scheme 43. Synthesis of functionalized and structurally diverse polyselenoureas.

In 2021, the same group by Tang et al. reported the synthesis of alicyclic poly(oxaselenolane)s at room temperature via metal-free multicomponent polymerizations of elemental Se dipropargyl alcohols and diisocyanides. It is worth noting that poly(oxaselenolane)s were obtained in high yields (up to 93%), high Se contents (up to 33.7 wt %), high molecular weights (up to 15 600 g/mol), and high thermal and chemical stability as well as excellent light refractivity, good solubility, and processability. Furthermore, the polymerization reaction encompassed a broad scope of the diisocyanides (e.g., benzyl and aromatic) as well as various dipropargyl alcohols (Scheme 44) [92].



Scheme 44. Synthesis of alicyclic poly(oxaselenolane)s.

3. Conclusions

In conclusion, the direct one-pot multicomponent synthesis of OSe compounds has emerged as a potential and atom-economic strategy. Furthermore, different metal-free, as well as metal-catalyzed, reactions evolved during the last decade. These approaches open new scopes for synthesizing OSe compounds, a group of compounds with attractive chemical, biological, and physical activities. Without a doubt, novel and improved strategies for synthesizing OSe compounds will also be released soon, addressing challenges such as site-selectivity, late-stage selenylation of natural products, and complex molecules.

Author Contributions: Conceptualization, S.S. and I.Y.; methodology, S.S. and I.Y.; software, I.Y. and S.S.; validation, M.G., H.M.A.E.-L. and M.M.K.; formal analysis, S.S. and I.Y.; investigation, S.S. and I.Y.; resources, M.G., H.M.A.E.-L. and M.M.K.; data curation, S.S. and I.Y.; writing—original draft preparation, S.S. and I.Y.; writing—review and editing, S.S. and I.Y.; visualization, M.G., H.M.A.E.-L. and M.M.K.; supervision, S.S. and I.Y.; project administration, S.S.; funding acquisition, M.G., H.M.A.E.-L. and M.M.K. All authors have read and agreed to the published version of the manuscript.

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