

MINI-REVIEW ARTICLE

Synthesis of Aryl/Heteroaryl Selenides Using Transition Metals Catalyzed Cross Coupling and C–H Activation

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Abstract: Aryl and heteroaryl selenides are an important class of organic compounds and their synthesis has been widely studied all over the world in the last two decades. Transition metals catalysed cross-coupling and directed C–H activation in unactivated arenes in the presence of diselenides/aryl selenols are found to be the most important tools for their synthesis. In recent years different transition metal catalysts were found to be effective to perform C–Se cross-coupling in both aryl and heteroaryl rings. The present review article covers all the recent advances made in the last ten years in the field of the synthesis of aryl and heteroaryl selenides through homogeneous and heterogeneous transition metals catalyzed cross-coupling reactions and directed selenylation *via* C–H bond activations.



Dr. Debasish Kundu

Keywords: Cross-coupling, C-H activation, transition metal, selenides, homogeneous and heterogeneous catalysis, organic compounds.

1. INTRODUCTION

In the last two decades, researchers have witnessed the different transition metals catalyzed cross-coupling reactions as powerful organic synthetic methods for the generation of several biologically important molecules and natural products based on Carbon-heteroatom bonds. The diaryl diselenide compounds are attracting considerable attention from organic chemists due to their potential biological activities (*e.g.*, anticancer, antitumor, antiviral, antimicrobial, antioxidant and antithyroid) [1-9]. They also exhibit tremendous catalytic activity in modern organic synthesis [10]. Diselenides, which mostly serve as a valuable source of organoselenium reagents, allows the inclusion of selenium moieties into the aromatic rings of organic molecules for the successful implementation in the generation of C–Se bonds [11]. A number of sustainable, new, and greener methodologies have been reported in the literature to prepare unsymmetrical diaryl selenides. Although C–Se cross-coupling reactions under conventional pathways suffer from several drawbacks such as the use of expensive and toxic solvents, longer reaction times, stoichiometric or greater quantity of metallic reagents, and high reaction temperature [12-19]. Selenation *via* C–H activation has been introduced as a sustainable alternative for this purpose.

Due to the much lower toxicity, availability, and acceptable stability of selenium, diselenides have received significant attention because they have been postulated as one of the most attractive sources of selenium as well as important selenylating agents in the cross-coupling reactions with pre-functionalized reactants like haloarenes, aryl boronic acids, diazonium salts and aryl amines to

synthesize unsymmetrical selenides [20-26]. The preparation of diaryl selenides from organoboron compounds is traditionally less explored compared to aryl halides. Based on the earlier reports of an ever-increasing number of groups, the researchers were intrigued by the chemistry of Se–Se bond in diselenides because it can generate nucleophiles (RS^-), electrophiles (RS^+) or radicals (RS^\cdot) which underwent various nucleophilic, electrophilic as well as photochemical transformations.

Cross-coupling reactions *via* transition metals catalysis have emerged as an interesting and appropriate technique for the synthesis of organoselenides [27-34]. Synthesis of highly potent diaryl selenides through such a concise and convenient catalytic route has motivated the area of research at its vital stage of development. Over the past few years, significant developments in C–Se cross-coupling chemistry have been successfully achieved by employing transition metals like copper, silver, iron, nickel, palladium, indium, *etc.*, but catalytic systems consisting of some transition metals are not highly desirable and anticipated due to their tremendous cost, toxicity, and low turnover number. Although, the metal-assisted transformations are highly efficient, regio- and stereoselective leading to a decrease in the production of waste, the costly and toxic heavy metal complexes go through difficulties in the separation of soluble metal catalysts from the reaction centre. A number of specialized works toward the metal-free synthesis of diaryl selenides are available in the literature [35-39], but our current research focuses on the applicability of transition metals to catalyze their synthesis.

In recent times, selenylation reactions of activated $C(sp^2)$ –H bonds by transition metals catalysis have gained growing importance regarding photochemical transformations in modern organic chemistry. Transition metals-assisted aromatic C–H oxygenation [40-42], amination [43-45], and halogenation [46-48] reactions have been successfully achieved by researchers in synthetic

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chemistry. Synthesis of diaryl diselenide scaffolds through conventional techniques emphasized harsh reaction conditions, functional group incompatibility, and high reaction temperature, and thus offering low reaction yields. However, the direct conversion of activated C–H bonds to C–Se functionality through transition metals catalysis has proved a powerful strategy to realize enormous promising transformations as these catalytic reactions require mild reaction conditions, step and atom economic approach, environmentally green and sustainable protocols [49-53]. These catalytic methodologies made the synthetic pathways more sustainable due to the low waste production [54-58]. The ease of C–H bond cleavage is facilitated by close contact between the transition metal centre and the inert C–H bond. The compounds, having scope for more than one C–H activation, were also studied and regioselective C–H functionalization in such cases was also achieved [59-66].

The authors herein intended to design a current comprehensive and organized overview of the selective C–Se bond formation *via* three eco-friendly and greener techniques, (i) transition metals catalyzed cross-coupling reactions of aryl halides and diaryl diselenides (ii) transition metals promoted cross-coupling interactions between aryl boronic acids and diaryl diselenides, (iii) direct selenylation of activated C–H bond functionalities of arenes and (iv) Role of dual transition metals catalytic systems in C–Se cross-coupling. In the present review work, the catalytic methods employed herein are subjected to be convenient, eco-friendly and atom-economical, which mostly involve the use of commercially available, non-expensive, non-toxic reagents and environmentally benign solvents.

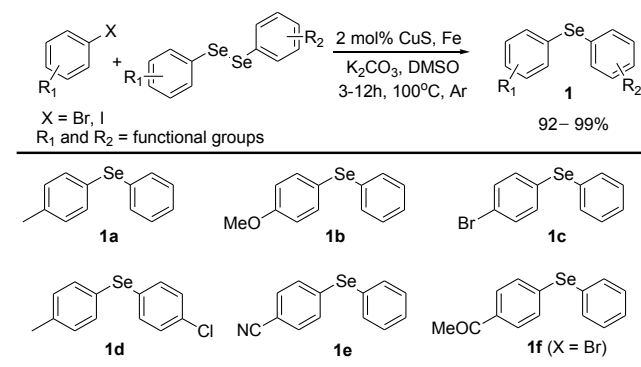
2. C-SE CROSS-COUPLING BETWEEN ARYL HALIDES AND DIARYL DISELENIDES

Due to nontoxicity, low cost, and easy accessibility, aryl halides with wider functionalities served as excellent substrates in effective cross-coupling reactions [67-68]. Owing to the better leaving group aptitude of iodide compared to chloride and bromide, aryl iodides are highly capable of forming C–Se bonds. Cross-coupling reactions of aryl halides with diselenides are generally accomplished by nucleophilic displacement reactions leading to the construction of C–Se bonds. The couplings of aryl halides and diaryl diselenides were achieved by both homogeneous and heterogeneous metal catalytic systems. The homogeneous system consisted of ligands and in spite of showing high catalytic activity, they were not recoverable and reusable, unlike heterogeneous catalysis.

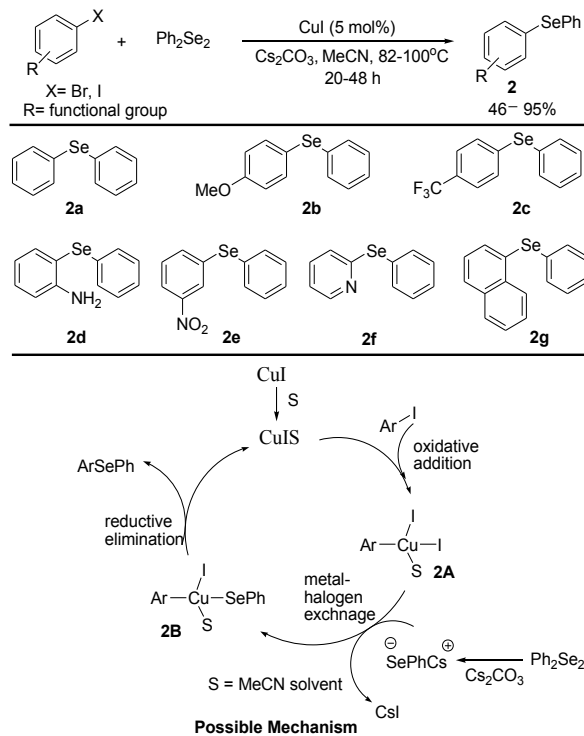
In the last decade ligand free-transition metals catalysed cross-coupling has attracted the attention of synthetic chemists due to the low cost, easy separation of product from the reaction medium and higher atom economy. Li and co-workers [69] introduced CuS-catalysed coupling between aryl halides and diaryl diselenides in DMSO solvent at 110°C with remarkably excellent yields (Scheme 1). The reaction required K_2CO_3 as a base. The cross-coupling interaction was found to be accelerated in the presence of iron powder. The reaction was found to be equally efficient in presence of electron-donating and electron-withdrawing groups in the benzene ring of aryl halides. The authors have established that iron is not only reducing CuS to form an active catalyst Cu_2S but the oxidized form of iron *i.e.*, Fe_xO_y acted as support against catalyst agglomeration in the DMSO solvent.

In 2011, Sekar *et al.* [70] introduced an external ligand-free heterogeneous copper (I) iodide-mediated catalytic procedure to design a wide collection of selenides from the cross-coupling interaction of aryl halides with diphenyl diselenide at moderate temperature (< 100°C). Under the optimized reaction protocol, aryl halides

with well-tolerated electron-donating and electron-withdrawing functional groups were efficiently coupled with diphenyl diselenide to render the desired selenides in moderate to good yields (Scheme 2). Interestingly aryl bromides were found to undergo coupling under copper-free conditions *via* the S_NAr path, however, the yield was found to be enhanced in presence of a Cu-catalyst. The authors proposed an oxidative addition-reduction elimination mechanistic path for the mentioned reaction where Cu(I), the active catalyst, underwent oxidative addition with aryl halides to form **2A**. A metal halogen exchange led to the attachment of the selenium centre with copper to form **2B** and lastly the desired product was furnished *via* reductive elimination.



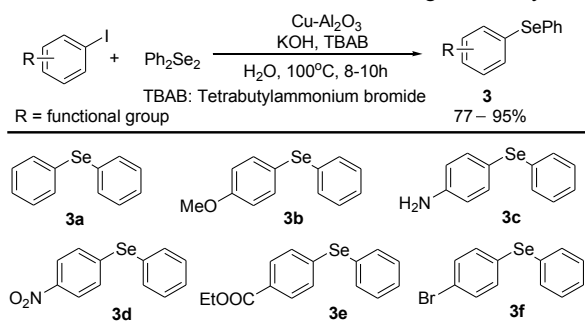
Scheme 1. Preparation of unsymmetrical selenides *via* homogeneous CuS/Fe catalysis.



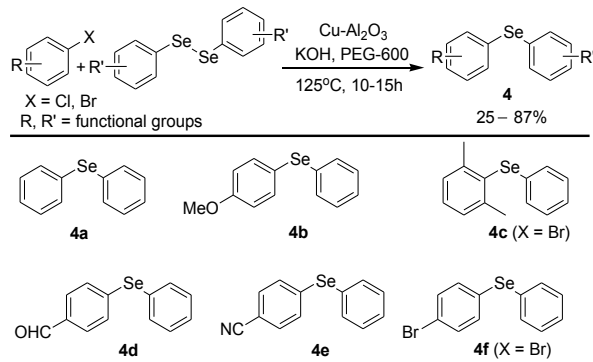
Scheme 2. Heterogeneous CuI catalyzed the synthesis of different diaryl selenides.

In 2013, Ranu and co-workers [71] developed a sustainable heterogeneous catalytic procedure for C–Se cross-coupling between aryl halides and diaryl/heteroaryl diselenides *via* alumina supported Cu(II) catalyst in water and PEG-600. The catalytic system was capable to synthesize a variety of aryl and heteroaryl selenides in good to excellent yields with a very high functional group compatibility. Apart from aryl iodides and bromides, aryl chlorides, bearing

electron-withdrawing groups in the aromatic ring were found to undergo C–Se coupling under this catalytic system. The solvent-mediated halo-selective selenylations of aryl iodides in the H₂O and aryl bromides in PEG-600 by diaryl selenide catalyzed by Cu–Al₂O₃ are depicted in Scheme 3 and Scheme 4, respectively. The catalytic system was found to be recyclable up to seven times without any significant loss of activity. The authors have proposed a metal-assisted nucleophilic substitution mechanism for this reaction where Cu-centre remains in a +2 oxidation state throughout the cycle.



Scheme 3. Heterogeneous Cu–Al₂O₃ promoted selenylation of aryl iodides.

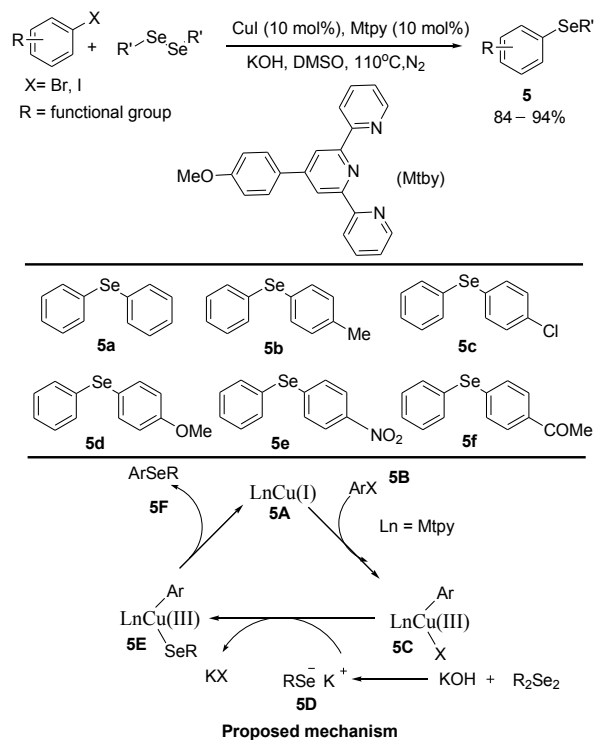


Scheme 4. Heterogeneous Cu–Al₂O₃ promoted selenylation of aryl bromides.

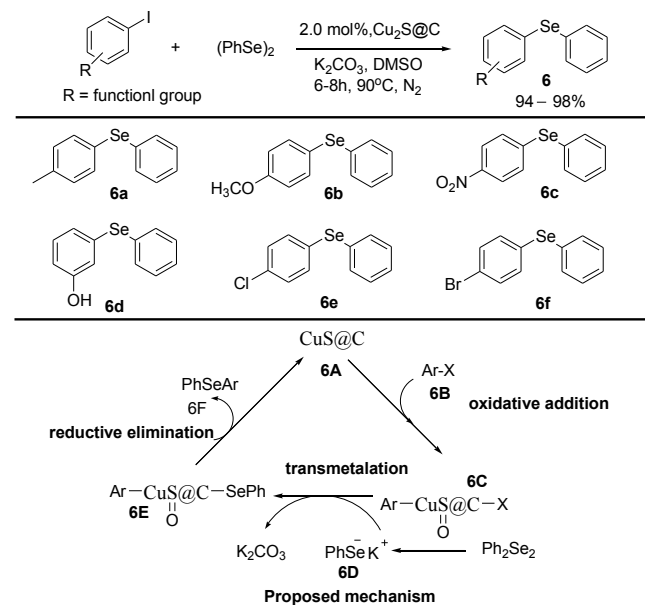
Movassagh and Hosseinzadeh [72] have reported a nitrogen-based bidentate ligand 4'-(4-methoxyphenyl)-2,2':6',2''-terpyridine (Mtby) which can assist CuI catalyzed C–Se cross-coupling between aryl iodides/bromides and diaryl diselenides (Scheme 5). The reaction was performed by using KOH as a base under a nitrogen atmosphere. A library of diaryl selenides was synthesized with a high functional group tolerance in excellent yields. The authors proposed an oxidative addition and reductive elimination mechanistic path for the reaction. The Cu(I)-ligand complex **5A** underwent oxidative addition with aryl halide (**5B**) to form Cu(III)-intermediate **5C**. Transmetalation between potassium aryl selenide (**5D**) and **5C** led to the formation of intermediate **5E** which then underwent reductive elimination to release the desired product **5F** via the regeneration of an active catalyst **5A** for the next cycle.

Ionic liquid-mediated synthesis of diaryl selenides, catalysed by copper sulphide-based carbon, was explored by Kim *et al.* [73]. The heterogeneous catalyst (Cu₂S@C) was efficient enough to perform C–Se cross-coupling in aryl iodides under ligand-free conditions (Scheme 6). The advantage of this catalyst was reflected by its recovery, reusability, and recyclability after several runs. The reaction was successful with both electron-donating and withdrawing functional groups in the aromatic ring of aryl iodides. The reaction showed excellent chemoselectivity while reacting diselenides with iodo-chloroarenes and iodo-bromoarenes, where chlorine and bromine in the aromatic ring remained unreacted. Oxidative addition of

aryl halide (**6B**) with active catalyst (**6A**) led to the formation of intermediate **6C** which underwent transmetalation with **6D** to form **6E**. Finally, the reductive elimination of **6E** led to the formation of product **6F**.



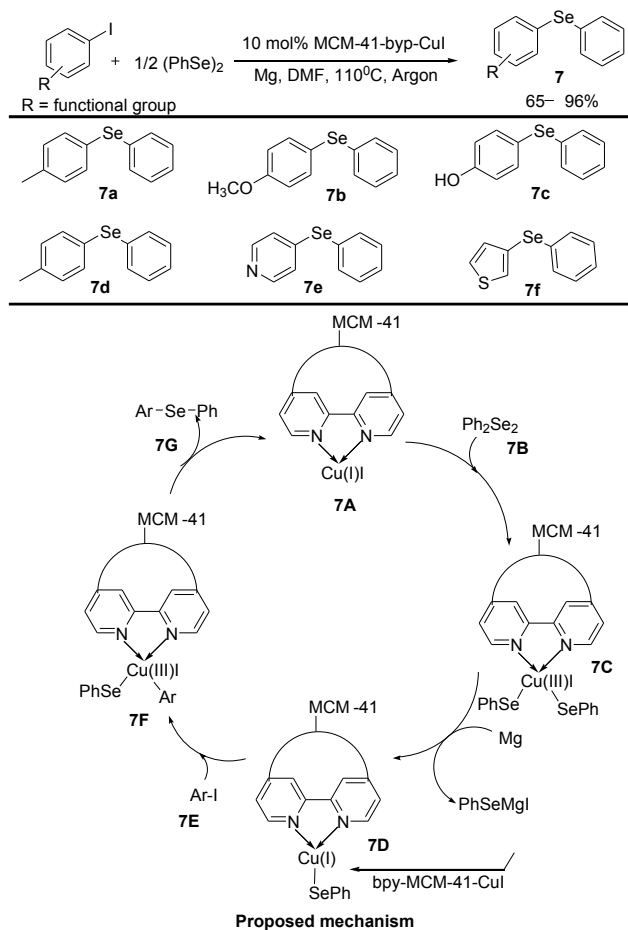
Scheme 5. Homogeneous Mtby-ligand-based Cu-catalyzed C–Se cross-coupling.



Scheme 6. Heterogeneous Cu₂S@C assisted cross-coupling of substituted aryl halides with diphenyl diselenide.

Zhao and co-workers have explored bipyridine functionalized MCM-41 modulated Cu(I) heterogeneous catalyst, [74] as a clean and eco-friendly catalyst for the synthesis of diaryl selenides by C–Se cross-coupling between a variety of diaryl diselenides and several aryl iodides at 110°C in DMF solvent (Scheme 7). Large numbers of diaryl selenides were synthesized by keeping both electron-

rich and electron-deficient functional groups in the aromatic ring in good to excellent yields. Heterocyclic iodides such as pyridinyl iodides, thiophenyl iodides also underwent coupling with diselenides under the standardized reaction conditions. The bipyridine chelated MCM-41 supported Cu(I) catalyst (**7A**) underwent oxidative addition with diselenide (**7B**) to form Cu(III) intermediate **7C** and subsequently it was converted to **7D** by reacting with Mg. **7D** underwent oxidative addition with aryl iodide (**7E**) and subsequent reductive elimination led to the formation of product (**7F**).



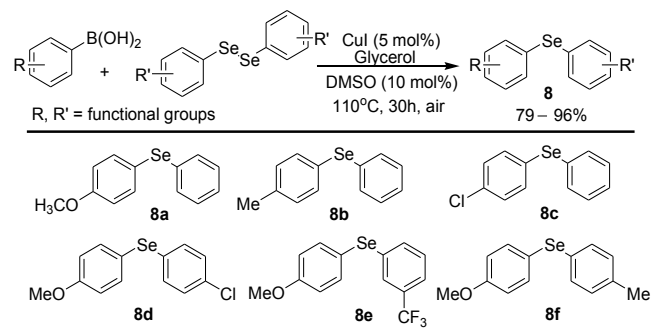
Scheme 7. Heterogeneous cross-coupling of aryl iodide and diaryl diselenide catalyzed by MCM-41-byp-Cu

3. CROSS-COUPLING OF ORGANOBORONIC ACID AND DIARYL DISELENIDES

Organoboron compounds are generally known as potential Lewis acids due to their electron-deficient character [75-77]. Organoboronic acids with a well-functional group tolerance are found to be excellent and suitable coupling partners for transition metals catalyzed cross-coupling transformations owing to their acceptable stability, commercial availability, nontoxicity and moderate chemical reactivity under different synthetic protocols. Organoboronic acids are well explored as coupling partners in the C-heteroatom bond formations *via* Cham-Evans-Lam type coupling and therefore in recent years, several metal-catalysed protocols have been developed for the synthesis of diaryl/heteroaryl selenides from aryl and heteroaryl boronic acids.

The use of green and recyclable solvents always attracted the attention of organic chemists due to their nontoxicity, recyclability, easy accessibility and biodegradability [78]. In this context, in

2012, Ricordi *et al.* [20] developed a convenient and green synthetic protocol to prepare unsymmetrical diaryl selenides through ligand-free CuI-promoted cross-coupling interaction of diaryl diselenide with aryl boronic acid in the presence of glycerol as solvent and DMSO as additive under 100°C heating condition (Scheme 8). Boronic acids containing both electron-rich and electron-deficient groups served as outstanding coupling partners to afford good to excellent yields under this homogeneous catalytic system.



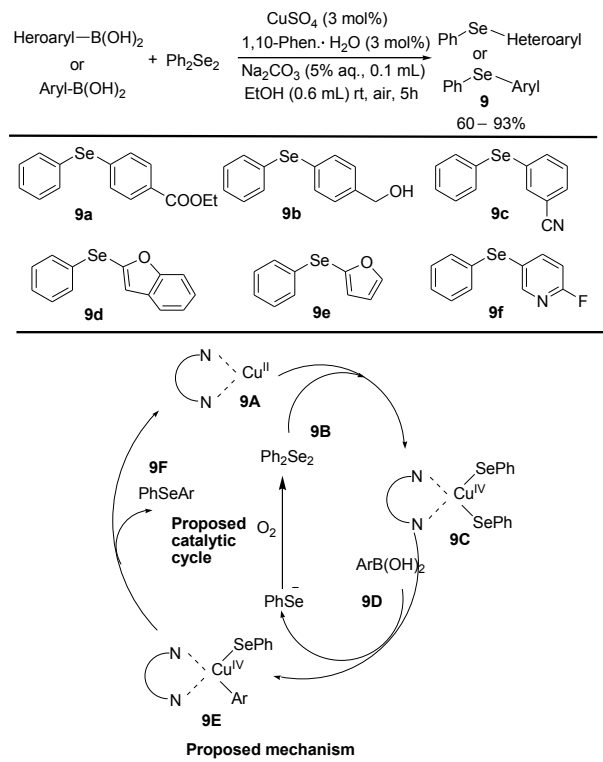
Scheme 8. Homogeneous CuI catalyzed cross-coupling between diselenides boronic acids.

In 2013, Zheng and co-workers [22] reported the coupling of aryl and heteroaryl boronic acids with diphenyl diselenides by using CuSO₄ as a catalyst and 1,10 phenanthroline as a ligand (Scheme 9) in eco-friendly ethanol solvent at room temperature. The reaction showed excellent functional group tolerance *e.g.* -methyl, -methoxy, -fluoro, -chloro, -cyano, *etc.* in the aromatic ring. Apart from these, heteroaryl boronic acids such as furyl, benzofuryl and pyridyl boronic acids were successfully employed for the synthesis of aryl-heteroaryl selenides under the reaction conditions in good yields. However, the authors failed to produce any conversion to the product. The authors have proposed a Cu(II)-Cu(IV) oxidative addition of active catalyst **9A** with diphenyl diselenides (**9B**) to produce intermediate **9C**, which then reacted with boronic acid (**9D**) to form intermediate **9E** at the expense of PhSe⁻ which under atmospheric O₂ formed diselenide. Reductive elimination from intermediate **9E** led to the formation of product **9F**.

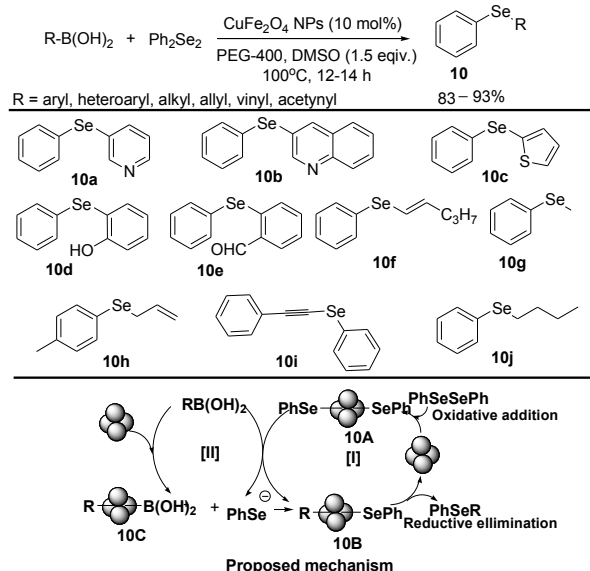
Kundu *et al.* in the same year reported magnetically separable heterogeneous CuFe₂O₄ nanoparticle catalysed C–Se cross-coupling of boronic acids and diselenides in green PEG-400 solvent under 100°C heating (Scheme 10) [24]. The most important achievement of this methodology was the successful implementation of aryl, heteroaryl, alkyl, allyl, vinyl and acetynyl boronic acids as coupling partners with diaryl diselenides. Thus a library of aryl selenides and heteroaryl selenides *e.g.*, pyridinyl, thiophenyl and quinolinyl selenides were successfully synthesized in excellent yields. The authors proposed the simultaneous operation of two catalytic cycles toward the formation of the product. In Cycle I, the oxidative addition of diselenide with nanoparticle produced **10A**, whereas intermediate **10C** is produced in cycle II *via* a reaction between the nanoparticle and boronic acid. Finally, transmetalation from cycles I and II produced intermediate **10B** which upon reductive elimination led to the formation of the product. The catalyst was easily separable from the reaction medium and was found to be recyclable up to 5 times without any significant loss of activity.

A heterogeneous catalytic system bearing copper (II) catalyst adsorbed on the spongy surface of nitrogen-containing a covalent imine network substance (Cu^{II}-CIN-1) was explored by Roy and coworkers [79] to perform the cross-coupling between aryl boronic

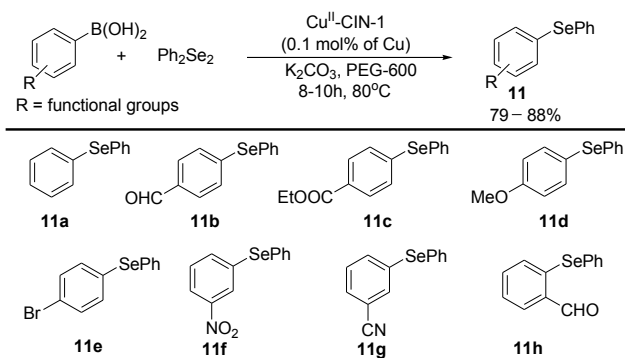
acids and diphenyl diselenide in polyethylene glycol (PEG-600) (Scheme 11). The large surface area and a large number of active sites enabled a catalytic system to perform this reaction at 80°C to produce an excellent yield of products. Aryl boronic acids having both electron-donating and withdrawing groups in the *-ortho*, *-meta* and *-para* position of aromatic ring successfully underwent coupling with diphenyl diselenides to produce a library of diaryl selenides in excellent yields. The authors, by performing several experiments, have established that the reactions went through heterogeneous catalysis and no leaching of metal occurs during or after the reaction from the supported catalytic system.



Scheme 9. Homogeneous Cu-1,10 Phen- catalyzed coupling of diphenyl diselenide and aryl boronic acid.

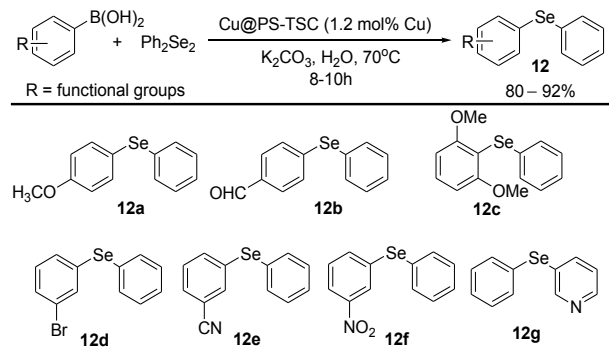


Scheme 10. Magnetically separable heterogeneous CuFe_2O_4 nanoparticles catalyzed cross-coupling of organoboronic acid and diphenyl diselenide.



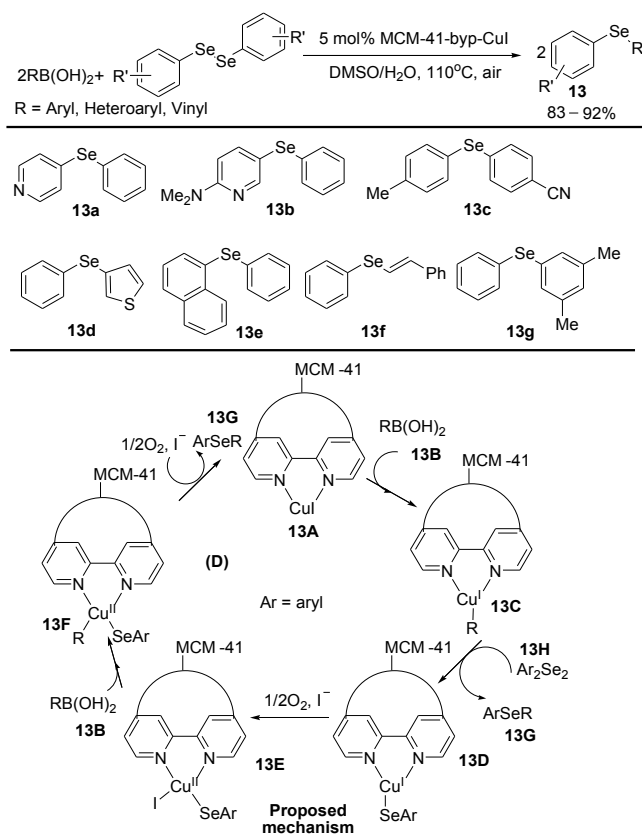
Scheme 11. Heterogeneous Cu^{II} -CIN-1 assisted phenyl selenylation of aryl boronic acid.

Islam *et al.* [80] developed heterogeneous polystyrene anchored Cu@PS-TSC catalyst (PS: polystyrene and TSC: thiosemicarbazone ligand) for performing cross-coupling of boronic acids with diphenyl diselenides under mild conditions (Scheme 12). Aryl boronic acid with various electron donating and electron withdrawing functionalities like $-\text{OMe}$, $-\text{NO}_2$, $-\text{CHO}$, $-\text{CN}$, $-\text{Br}$, *etc.* interact efficiently with diphenyl diselenide to furnish the desired selenylated products in excellent yields. The significant advantage of this protocol was the use of water as a solvent and the high recyclability of the catalyst.



Scheme 12. Heterogeneous Cu@PS-TSC promoted selenylation of aryl boronic acid with Ph_2Se_2 .

Cai *et al.* [81] developed a recyclable and reusable MCM-41-immobilized bipyridine copper (I) [$\text{MCM-41-bpy-Cu}^{\text{I}}$] a heterogeneous catalyst for the construction of C–Se bonds through the coupling of organoboronic acids with diaryl diselenide in DMSO–water solvent (Scheme 13). This was a silica-supported 2,2'-bipyridine chelated heterogeneous copper(I) complex applied for a large array of aryl, heteroaryl and vinyl boronic acids to produce a library of aryl and heteroaryl selenides in good to excellent yields. The authors also focussed on the reusability and recoverability of the catalyst without the loss of catalytic activity even after several runs. The catalyst was characterised by several experimental techniques such as HR-TEM, ICP-MS, FT-IR and TGA studies. According to the proposed mechanism, the active catalyst **13A** underwent a reaction with boronic acid (**13B**) to form intermediate **13C**. The reaction between **13C** with diselenide (**13H**) produced the desired product (**13G**) through the formation of intermediate **13D** which then underwent oxidation to form $\text{Cu}(\text{II})$ intermediate **13F**. **13E** again reacted with another equivalent of boronic acid to form intermediate **13F**. Reductive elimination from **13F** followed by oxidation led to the formation of another equivalent of the product (**13G**) with regeneration of active $\text{Cu}(\text{I})$ catalyst **13A**.

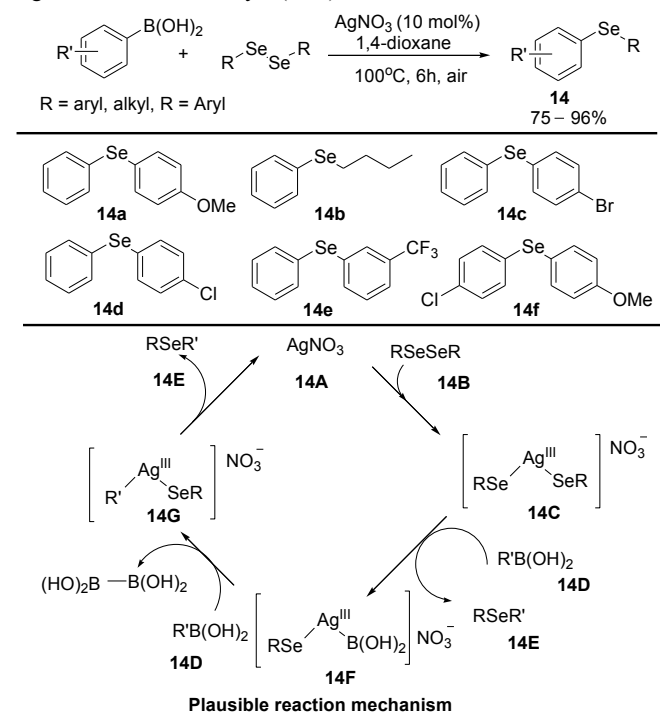


Scheme 13. Heterogeneous MCM-41-bpy-CuI catalyzed cross-coupling between diaryl selenide and aryl boronic acid.

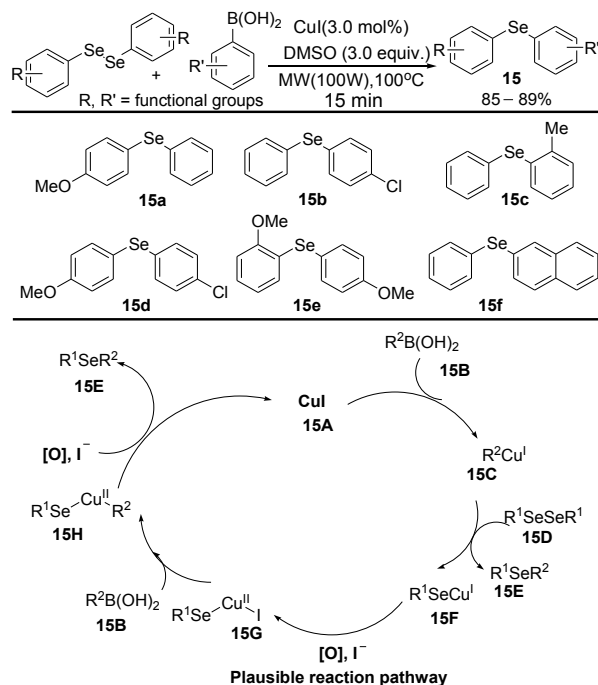
In 2016, Alves and co-workers [82] introduced AgNO_3 as a catalyst for performing the cross-coupling between organoboronic acids and diselenides in 1,4-dioxane under 100°C heating conditions (Scheme 14) without using any DMSO. This pioneering work of ligand-free Ag catalysed cross-coupling was successfully applied by the authors for the synthesis of a library of diaryl and aryl-alkyl selenides in good to excellent yields. Both electron-donating and withdrawing groups in the aromatic ring of boronic acids were found to be equally effective while performing this reaction under standardized conditions. The mechanism started with the oxidative addition of Ag(I) catalyst **14A** with diselenide (**14B**) to form Ag(III) intermediate **14C**. The reaction of organoboronic acid (**14D**) with **14C** led to the formation of intermediate **14F** via the formation of 1 equivalent of product **14E**. **14F** then reacted with another equivalent of boronic acid (**14D**) to produce intermediate **14G** which subsequently underwent reductive elimination to form another equivalent of product **14E**.

Microwave-assisted solvent- and ligand-free C–Se cross-coupling of diselenides and aryl boronic acids for the synthesis of unsymmetrical organoselenides was developed by Braga *et al.* in 2017 [25]. The optimized reaction proceeded well when aryl boronic acid (0.5 mmol) was efficiently coupled with diaryl diselenide (0.25 mmol) in the presence of CuI catalyst (3.0 mol %) at 100°C under microwave for a very short reaction time of 15 min (Scheme 15). Apart from synthesizing a bunch of diaryl selenides, the authors also explored this reaction for the synthesis of diaryl tellurides and sulphides. The reaction was also successful with dialkyl diselenide. A decrement in reaction yield was observed while performing the reaction under an oxygen atmosphere instead of an inert atmosphere. The outcome of the reaction remained unaffected while performing the reaction in presence of TEMPO. The mecha-

nism was proposed based on several experiments. The organocupper intermediate (**15C**), produced from CuI (**15A**) and organoboronic acid (**15B**), led to the formation of desired product **15E** and intermediate **15F** after reacting with diselenide (**15D**). **15F** then underwent oxidation to produce Cu(II)-intermediate (**15G**) which upon reacting with another equivalent of boronic acid (**15B**), produced **15H**. Finally, **15H** underwent reductive elimination followed by oxidation to produce the desired product (**15E**) again with the regeneration of the catalyst (**15A**).

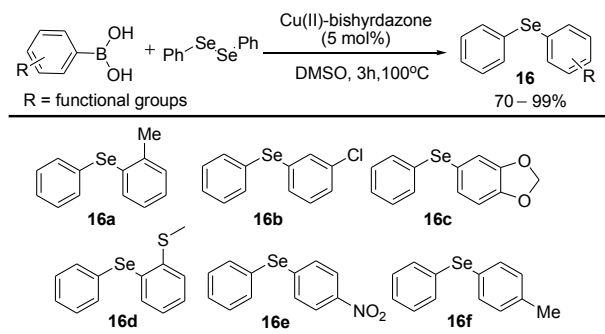


Scheme 14. Synthesis of differently substituted diorganyl selenides using a homogeneous Ag-catalytic system.



Scheme 15. Homogeneous Cu-catalysed microwave-assisted C–Se coupling.

The cross-coupling reaction between diaryl diselenides and differently substituted aryl boronic acids using less expensive transition metals like iron, copper, and nickel in combination with tridentate or tetradentate ligands such as salophane, isonicotinohydrazide, bishydrazone, bisbenzimidazolyl pyridine was investigated by Burang *et al.* in 2018 [83]. Among these metals, copper was found to be the most efficient catalyst. The Schiff base Cu(II)-bishydrazone has been chosen as it covers the production of a wide range of diaryl selenides in good to excellent yields within a shorter reaction time (Scheme 16).



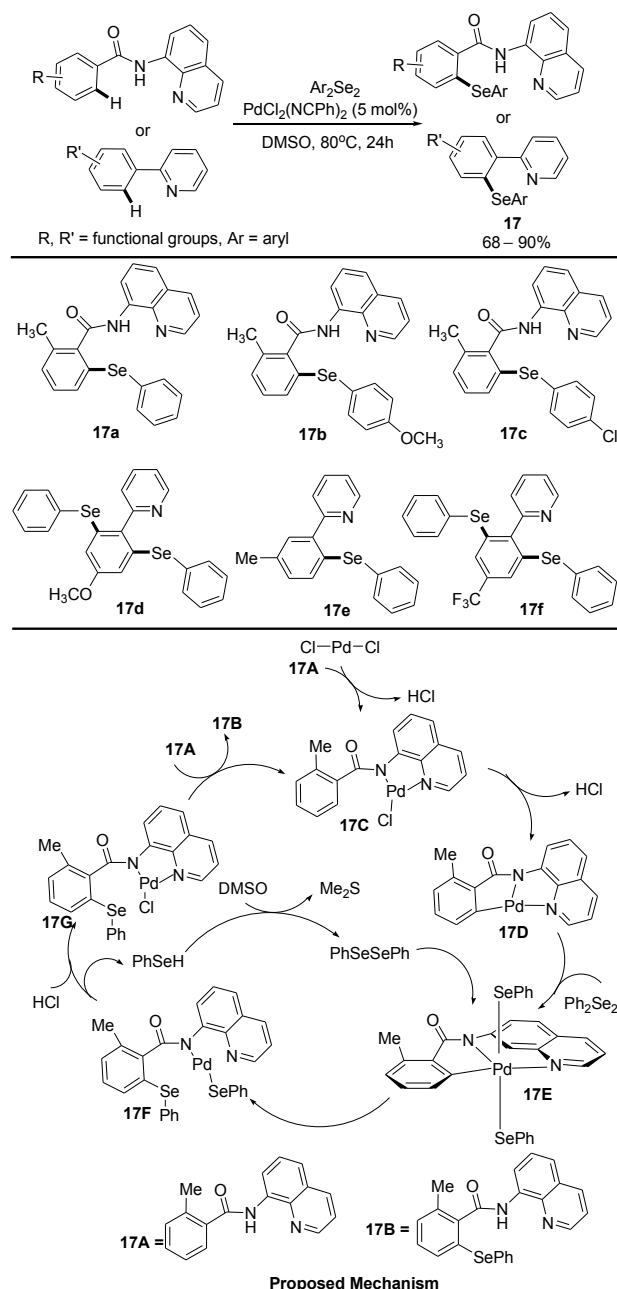
Scheme 16. Homogeneous Cu(II)-bishydrazone catalyzed cross-coupling of aryl boronic acid with diphenyl diselenide.

4. SELENIATION VIA C–H BOND ACTIVATION UNDER HOMOGENEOUS METAL-BASED CATALYSIS

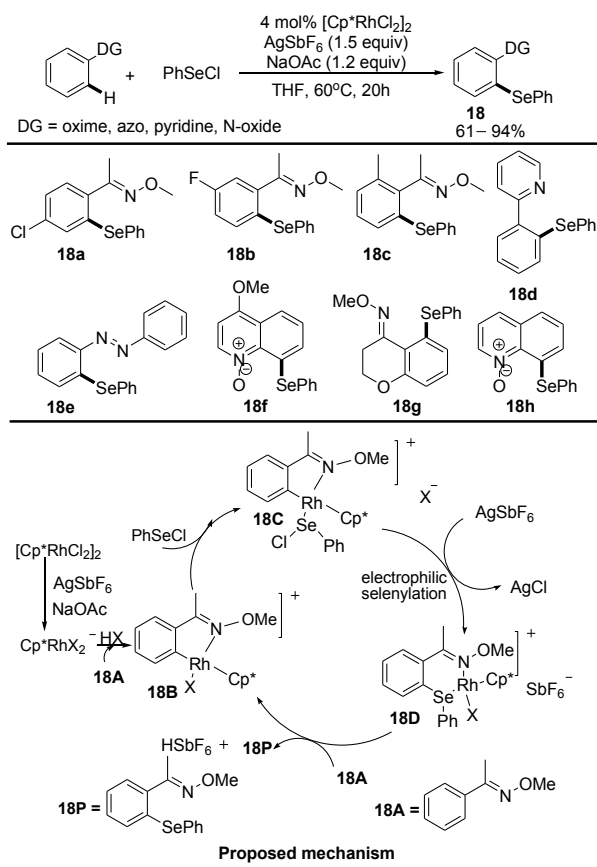
Transition metals catalyzed directed C–H activation have achieved attractive success in the last decade in the field of the formation of carbon-heteroatom bonds in aromatic rings. Higher atom economy in comparison to the cross-coupling reactions made this methodology more acceptable for organic chemists. In recent times, several transition metal catalytic systems have been explored for performing directed C–H selenation in aromatic rings. Palladium metals have recognized themselves to be the most efficient catalysts for their excellent activity for the C(sp²)–H bond activations. In this context, Iwasaki and co-workers [49] reported chelate-assisted Pd(II) promoted C(sp²)–H bond activation of arenes with the assistance of directing groups like 8-amidoquinoline and 2-phenyl pyridine. PdCl₂(NCPH)₂ was investigated to be the suitable catalyst for performing the reaction in DMSO (Scheme 17). In the case of C–H selenylation of benzamides furnished diselenated product. However, the introduction of a methyl group in the *-meta* position of the aromatic ring resulted in the formation of a monoselenated product due to the steric hindrance of the methyl group in metal chelation in the *-ortho* position. The same scenario was observed in the case of C–H selenation of 2-aryl pyridines. The authors proposed the mechanistic path on the basis of several experimental outcomes. Substrate **17A** underwent chelation with PdCl₂ via amide and quinolone nitrogen centre to form intermediate **17C** which was then converted into **17D** at expense of HCl. Then **17D** underwent oxidative addition with diselenide to form **17E** which then transfer one selenium centre from metal to activated *ortho*-carbon of the aromatic ring to form **17F**. Then intermediate **17G** is produced *via* the removal of PhSeH which in the reaction medium formed Ph₂Se₂ again. The final product **17B** was released from **17G** *via* chelation of the metal centre with another substrate to form **17C** again for the next cycle.

In 2015, Wan and Li *et al.* introduced rhodium (III) catalytic system for the N-directed *ortho*-selenylation *via* C–H activation. Several N-directing groups such as oxime, pyridine, azo, and N-oxide were utilised to perform *ortho*-Selenylation in aromatic rings

by using PhSeCl as a source of selenium [84]. The reaction proceeded smoothly in the presence of AgSbF₆ as an additive and NaOAc as a base under mild heating at 60°C in THF (Scheme 18). The scope of this reaction was explored for different substituted oximes, quinolone-N-Oxides, azoarenes and 2-aryl pyridines which furnished the desired *ortho*-selenated product in good to excellent yields. The reaction showed a primary kinetic isotopic effect (K_H/K_D = 2.3) for deuterium-substituted aryl oximes and this fact indicated the involvement of *ortho*-metal chelation in the rate-determining step. The rodocatalytic intermediate **18B** is produced *via* substrate (**18A**) chelation to the active catalyst. Chelation of *ortho*-carbon to Rh-centre *via* nucleophilic displacement chloride led to the intermediate **18C** which then underwent Ag-assisted chloride abstraction to form **18D**. The final product was released from **18D** *via* the chelation of another substrate to regenerate **18B** for the next cycle.



Scheme 17. Chelate assisted Pd catalyzed C(sp²)–H selenation of arenes.



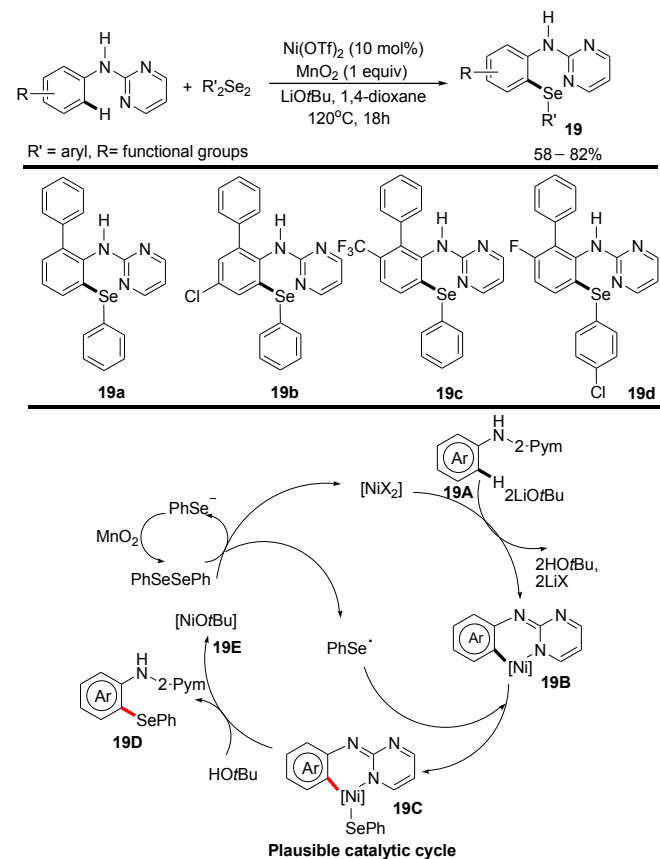
Scheme 18. Rh(II) catalyzed N-directed C–H selenylation in arenes with PhSeCl.

In recent years Nickel catalysts appeared as an effective catalytic system for performing C(sp²)–H activation in the aromatic ring to insert different heteroatom-based functional groups. Ni-catalysts are also demanding especially due to their eco-friendly behaviour, less economy, easy accessibility, and lower toxicity [85-87]. In 2015, Ackermann *et al.* [26] successfully achieved nickel-catalysed pyrimidine-N-directed *ortho*-C–H selenation in an aromatic ring of 2-pyrimidyl anilines using MnO₂ as an additive at 120°C (Scheme 19). Reaction under ligand-free conditions, high regioselectivity and compatibility with various functional groups are the main advantages of this protocol. A library of *ortho*-Seleno-substituted 2-pyrimidyl aniline derivatives was registered with good yields. The reaction was also successful with disulfides performing C–H thiolation in the same compounds.

The authors proposed the mechanism where a base-assisted interaction of substrate **19A** with the catalyst led to the formation of intermediate **19B** which then underwent selenation to form **19C**. Finally, the product **19D** was released *via* the interaction of **19C** with ^tBuOH and the metal-base complex **19E** was formed. The catalyst regeneration from **19E** was assisted by diselenide to continue the next cycle. MnO₂ acted as an oxidizing agent which regenerated diselenide from selenyl anion.

Copper-catalysed N-directed *ortho*-C–H selenation in aryl and heteroaryl rings was successfully introduced by Baidya and co-workers by using silver carbonate as an additive [88] (Scheme 20). The Library of aryl and heteroaryl substituted 8-aminoquinoline amide derivatives underwent coupling with diaryl/heteroaryl diselenides to produce the desired *ortho*-selenated derivatives in good to excellent yields. The reaction furnished monoselenated

products when either one *ortho*-position was blocked or there was a bulky substituent in one *meta* position to retard *ortho*-chelation. In the mechanism, the interaction of substrate (**20A**) with Cu(II) led to the formation of intermediate **20B** which upon C–H activation produced **20C**. Then oxidation of **20C** by diselenide led to the formation of intermediate **20D** which underwent reductive elimination to form the monoselenated product (**20E**). The monoselenated product then participated in the next cycle to form diselenated product (**20F**).

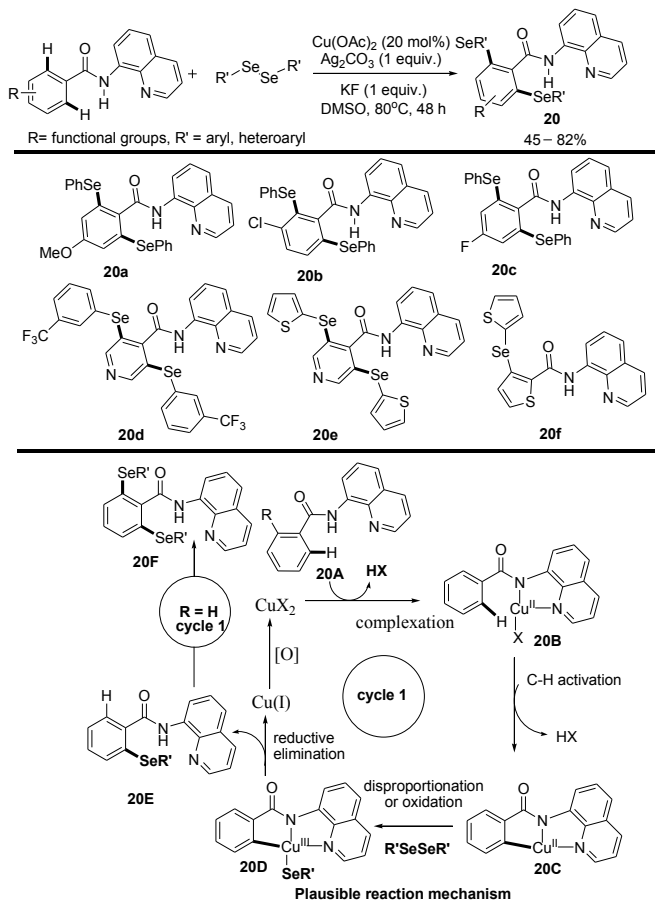


Scheme 19. Ni(II) promoted C–H selenylation of pyramidal assisted aniline.

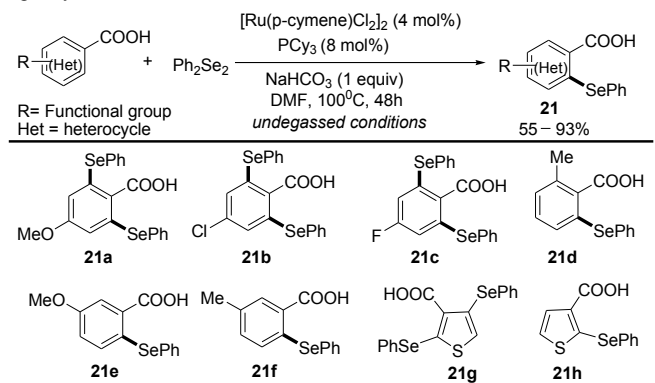
The same research group in 2017 [89] reported Ru(II) catalyzed direct C–H selenylation of heteroaromatic and aromatic carboxylic acids at *ortho* position by diaryl diselenide. Careful optimization of the protocol suggested that the selenylation reaction progressed smoothly in the presence of tricyclohexylphosphine (PCy₃) ligand, NaHCO₃ base in DMF solvent at 100°C, leading to the formation of di-*ortho*-selenated products in good to excellent yields (Scheme 21). However just like the previous protocols, here also monoselenated products were obtained when one of the *ortho*-positions was blocked or the presence of a bulky substituent in the *meta* position. The reactions were found to undergo smoothly in presence of different radical scavengers.

Pyrazolones are potential nonsteroidal anti-inflammatory drugs (NSAIDs) particularly used as pharmaceutical agents in clinical practice [90, 91]. Ackermann and co-workers [92] applied silver catalyst for the first time for performing selective C–H selenylation of the functionalized pyrazolone derivatives with diaryl diselenide in toluene at 100°C (Scheme 22). This O-directed C–H activation showed excellent regioselectivity. In the case of C–C bond formation with vinyl esters, C–H activation was achieved at the –

ortho position of the aryl ring. However, the silver catalyzed C—H selenation was achieved in the pyrazolone ring at the *ortho*-position to the carbonyl group. A library of seleno-substituted pyrazolones was synthesized in moderate to good yields by this protocol.



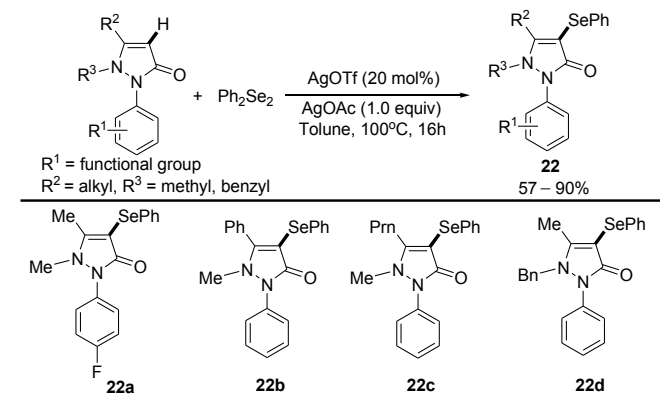
Scheme 20. Selenylation of 8-aminquinoline assisted (hetero) arenes with diphenyl diselenide.



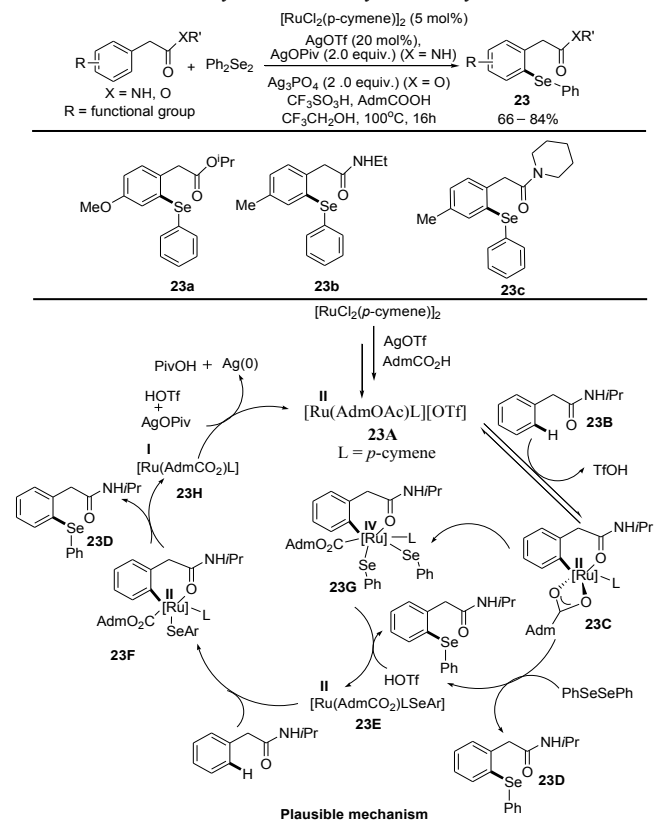
Scheme 21. Ru(II) promoted C—H selenylation of hetero (aromatic) carboxylic acids.

In 2019, Ma *et al.* [93] reported Ru(II) catalyzed N- and O-directed C—H selenylation of aryl acetic amides and esters respectively through weakly distal coordination in the presence of trifluoromethanesulfonic acid and 1-adamantane acetic acid at 100°C in trifluoromethyl ethanol solvent (Scheme 23). In presence of silver triflate (AgOTf), O-directed C—H selenation was achieved by using Ag₃PO₄ as oxidant, whereas N-directed C—H selenation was successful with AgOPiv (silver pivalate) as oxidant. The reaction delivered wide substrate scope, regioselectivity, and excellent func-

tional group compatibility. The active catalyst **23A** is formed by chloride abstraction by AgOTf. Reversible C—H bond activation *via* weak coordination produced **23C** rutheno cycle which reacted with diselenide to form intermediate **23E**. Alternatively, the oxidative addition of diselenide with **23C** led to the formation of Ru(IV) intermediate **23G** which upon reductive elimination formed the desired product and intermediate **23E**. Then **23E** participated in a second C—H bond activation to produce intermediate **23F** which further underwent reductive elimination to form the desired product. Finally Ru(I) intermediate **23H** underwent oxidation by AgOPiv to regenerate the active catalyst.



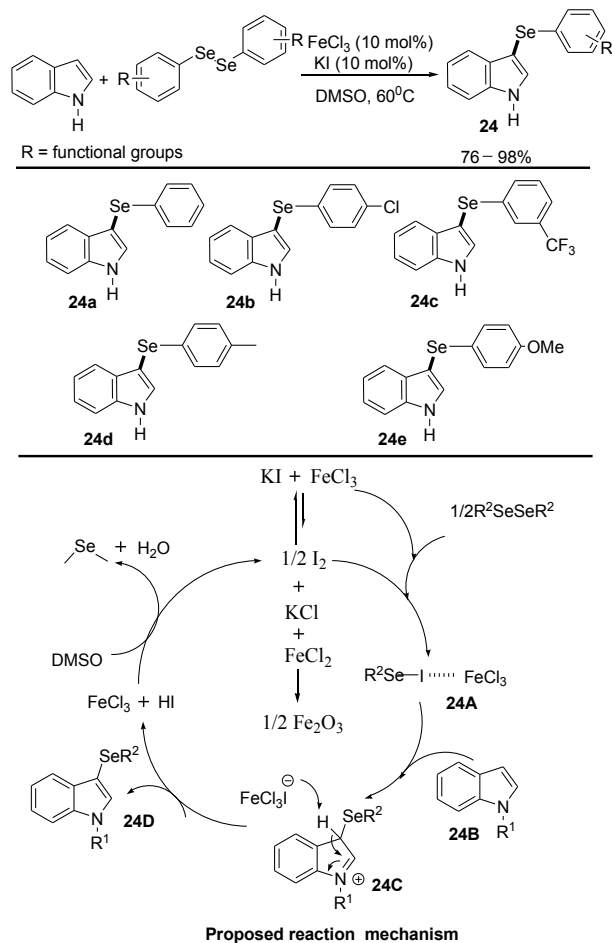
Scheme 22. Silver Catalyzed C—H Selenylation of Pyrazolones.



Scheme 23. Scope of C—H selenylation of aryl acetic amides and esters.

Chalcogenylindoles are important targets in organic synthesis due to their extensive therapeutic values against several critical diseases [94-99]. In this perspective, Rampon *et al.* [100] suggested iron-assisted C-3 selenylation of indole using diaryl diselenide in the presence of KI as an additive at 60°C (Scheme 24). A library of 3-selenyl indoles was synthesized in excellent yields using different

substituted diaryl diselenides. In the mechanism, FeCl₃ oxidized iodide to iodine which then underwent Fe (III) assisted substitution with diselenides to form intermediate **24A**. The substrate **24B** then reacted with **24A** to form intermediate **24C** which then underwent metal-assisted nucleophilic displacement at the 3-position of the indole ring to provide the desired product **24D** at the expense of catalyst and HI. Oxidation of HI to iodine was performed by DMSO for starting of the next cycle.

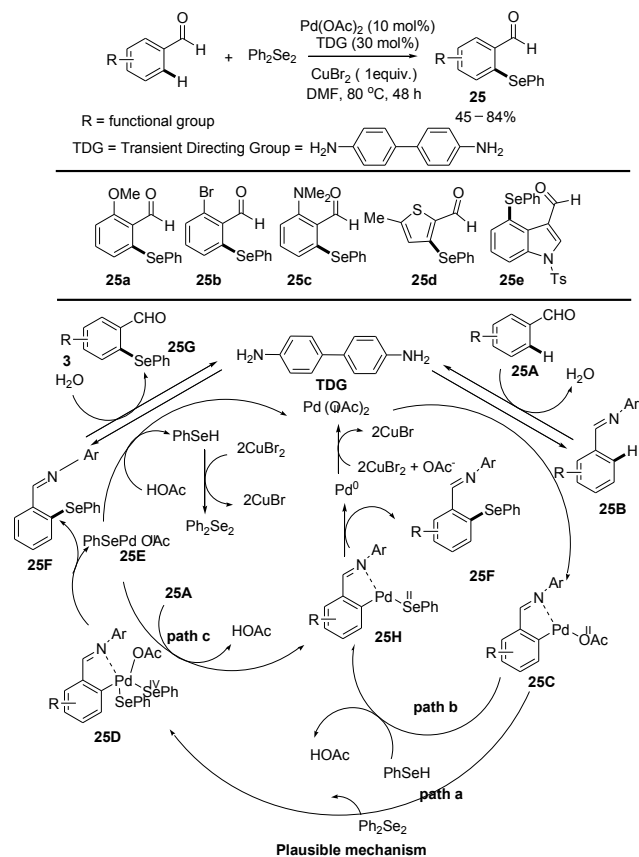


Scheme 24. Iron(III) catalyzed C-3 selenylation of indole.

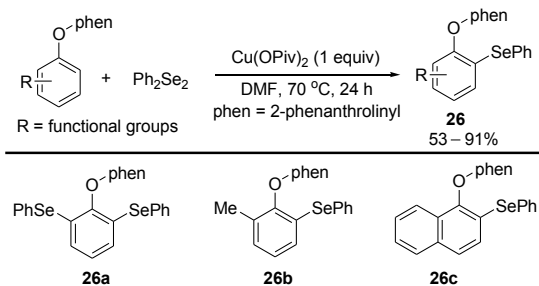
Recently Zhang *et al.* reported an interesting concept of using a transient directing group for performing Pd-catalysed *N*-directed C–H selenation of aromatic and heteroaromatic aldehydes at the *ortho*-position by using diaryl diselenides as selenium source (Scheme 25) [101]. The reaction required the use of 1 equivalent of CuBr₂ as an oxidizing agent for the regeneration of the catalyst. Aromatic aldehydes with mainly electron-donating groups were found to be reactive under the standardized reaction conditions. Thiophenyl aldehyde and 3-formyl indoles also produced a good yield of products, however, the reaction failed completely to initiate any conversion to the product in furan and pyrrole systems.

The mechanism was proposed based on several experimental techniques. The reaction of aldehyde **25A** with TDG led to the formation of **25B** which in presence of Pd-catalyst underwent C–H activation to form the palladacycle intermediate **25C**. Then **25C** underwent oxidative addition with diselenides to form Pd (IV) intermediate **25D** which upon reductive elimination formed intermediate **25E** via releasing desired *O*-selenated aryl imine (**25F**). **25F** upon reacting with water provided the *O*-selenated aryl aldehyde

25G. Regeneration of active catalyst from **25E** was assisted by AcOH at the expense of PhSeH. In another path **b**, intermediate **25C** underwent a reaction with PhSeH, generated in the path **a**, to form intermediate **25H** which again led to formation of *O*-selenated aryl imine **25F** via Pd(II)-Pd(0) reductive elimination. Oxidation of Pd(0) to Pd (II) was achieved by CuBr₂ to initiate the next cycle.



Scheme 25. Pd catalyzed TDG mediated *ortho*-selenylation of benzaldehyde.

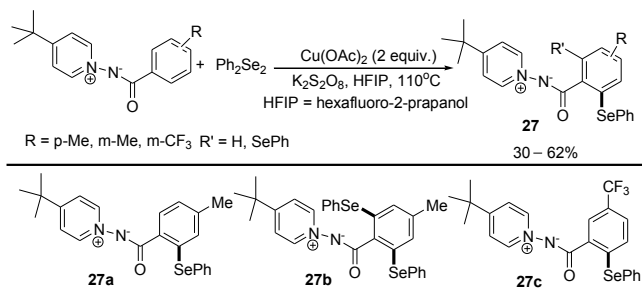


Scheme 26. Copper-assisted *N*-directed C–H Selenation of phenols.

Recently, Miaura *et al.* explored phenanthroline bidentate auxiliary as an efficient directing group for performing *ortho*-C–H selenation of phenols by using homogeneous Cu(OPiv)₂ as an effective metal source (Scheme 26) [55]. The reaction was highly regioselective and the desired selenated products were obtained in good to excellent yields.

Dauglis *et al.* recently introduced *N*-aminopyridinium ylide as an efficient directing group for Cu-promoted aromatic C–H selenation by using diaryl diselenides (Scheme 27) [102]. The reaction required the use of 2 equivalent copper acetate in presence of K₂S₂O₈ as an oxidizing agent in a hexafluoro-2-propanol solvent. The reactions were high yielding and showed excellent functional

group compatibility in the aromatic ring. The authors also explored the scope of this reaction with disulfides for performing C–H sulfonation under similar conditions.



Scheme 27. Copper-assisted C–H selenylation of N-aminopyridinium ylide.

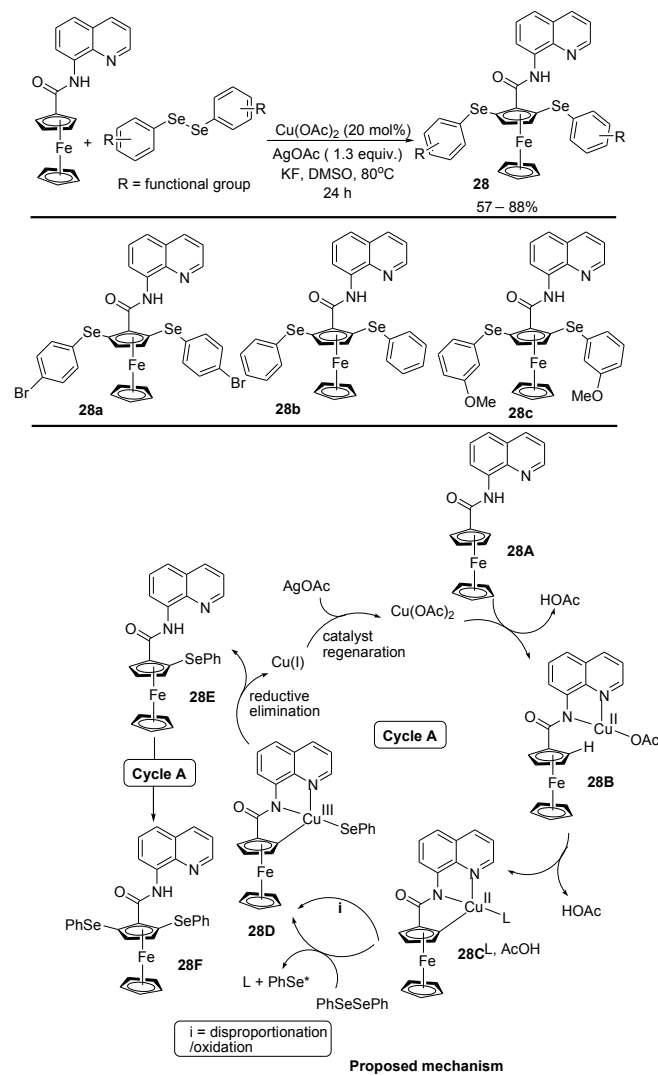
Kumar and co-workers nicely designed 8-aminoquinoline as directing group for performing Cu-catalysed C–H selenation in the aromatic ring of ferrocenamide (Scheme 28) [103]. The reaction required the use of silver acetate and KF as an additive and 80°C heating in DMSO solvent. The reactions resulted in diselenation in the two *ortho*-positions w.r.t. the directing group. A library of desired products was obtained in good to excellent yield by using different aryl substituted diaryl diselenides. The authors also applied this C–H activation technique to introduce the C–S and C–Te bonds in the ferrocene ring successfully. The authors proposed the mechanism of this reaction on the basis of several evidential facts. The reaction of Copper acetate catalyst with substrate ferrocenamide **28A** led to the formation of intermediate **28B** which upon releasing AcOH, formed **28C**. Interaction of **28C** with diselenide led to the formation of intermediate **28D**, where the Cu–Se bond was accompanied by oxidation of Cu(II) to Cu(III). Finally, reductive elimination from intermediate **28D** led to the formation of the monoselenated product **28E** via forming Cu(I) which then underwent oxidation by silver acetate to regenerate the active catalyst Cu(OAc)₂. **28E** then formed the desired diselenated product **28F** by participating in the next catalytic cycle.

5. HOMOGENEOUS DUAL TRANSITION METALS CATALYSED C–Se CROSS-COUPLING UNDER LIGAND-FREE CONDITIONS

In 2020, Kundu and co-workers have introduced an innovative Cobalt/Copper dual catalytic system to perform C–Se cross-coupling under ligand-free conditions under microwave heating (Scheme 29) [104]. Co(acac)₂ and CuI both were used as a catalyst in a 5 mol% amount to perform cross-coupling between aryl iodides/bromides with diaryl diselenides under microwave heating. The reaction required DMSO as a solvent and KOH as a base and it was also found to be completed under a very short reaction time. The reaction was initiated by an *in situ* reductions of Co(II) to Co(I) which then underwent oxidative addition with aryl iodides to form intermediate **29A**. On the other side, the interaction of CuI with diaryl diselenide in presence of KOH led to the formation of intermediate **29B**. Transfer of selenium species from Cu(I) to Co(III) occurred *via* transmetalation between **29A** and **29B** to form **29C** which underwent reductive elimination to form the desired diaryl selenide product. A large array of aryl bromides and iodides were found to undergo coupling with diselenides successfully to produce the desired product in good to excellent yields.

The same group in 2021 developed a Ni/Cu dual catalytic system for the synthesis of diaryl selenides by performing coupling of diselenides with aryl halides (Scheme 30) [105]. Ni(acac)₂ and CuI were used as catalysts to perform the C–Se coupling under ligand-

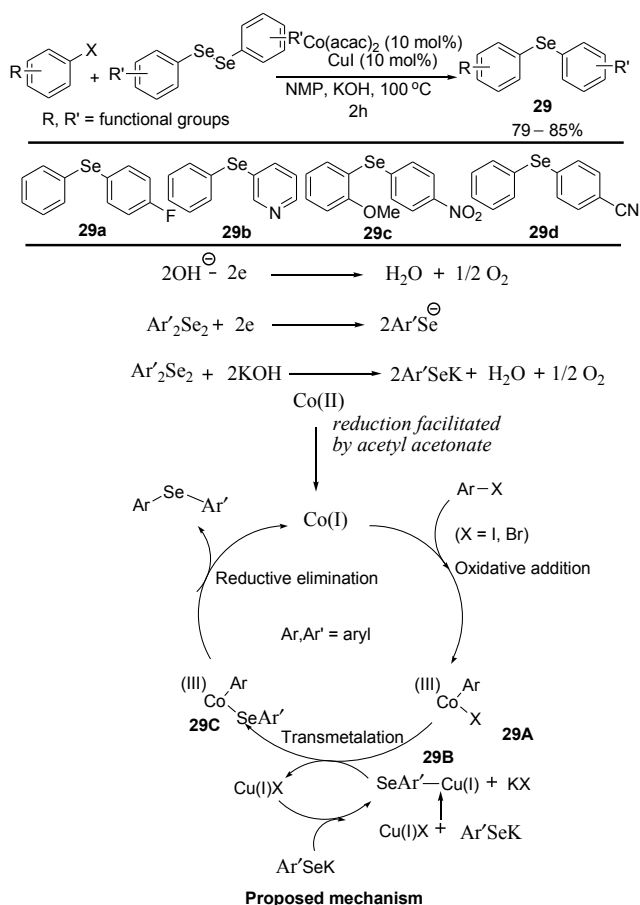
free conditions. The reaction was reported to follow a similar kind of mechanism involving Ni(0)/Ni(II) oxidative addition followed by transmetalation from Cu(I). Finally, reductive elimination led to the formation of the product.



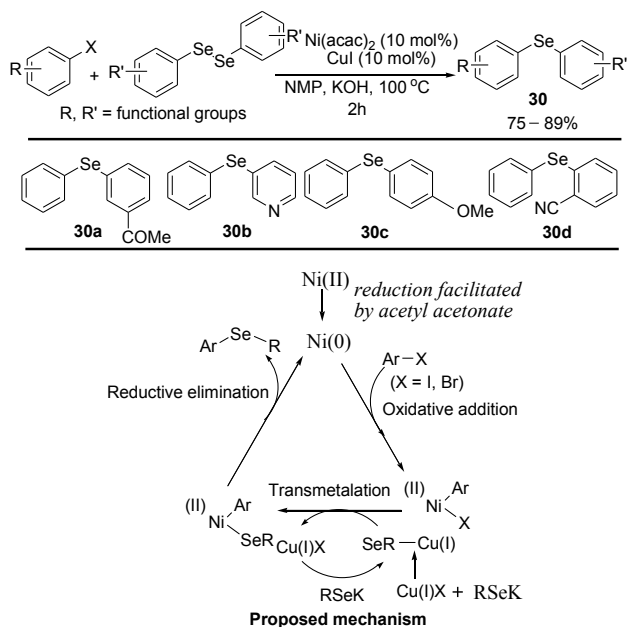
Scheme 28. 8-Aminoquinoline directed Cu-catalysed C–H selenation in ferrocenamide.

CONCLUSION

The present review article summarizes and deliberates the methodologies employed in transition metals catalysed the construction of C–Se bonds through cross-coupling of diaryl diselenides with aryl halides and aryl boronic acids and *via* C–H bond activation. The application of different transition metals such as Cu, Fe, Ni, Co, Pd, Ru, Rh *etc.* in both homogeneous and heterogenous forms are discussed with their mechanistic cycles towards the formation of organoselenides. In the case of cross-coupling with aryl halides and aryl boronic acids, both homogeneous and heterogenous metal catalysis were found to be equally active, however, the recyclability of catalysts was an important merit of heterogenous catalysts. Through these two types of cross-coupling reactions, C(sp²)–Se bond formations were achieved in the aromatic ring, heterocycles, vinyl and styryl positions. On the other side, direct C–H activation was mainly performed *via* homogeneous catalytic systems where oxygen or nitrogen directing groups were generally used. The C–H selenations were generally achieved at the *ortho*



Scheme 29. Co/Cu-dual catalyzed C–Se cross-coupling under ligand-free conditions.



Scheme 30. Ni/Cu-dual catalyzed C–Se cross-coupling.

position of aromatic and heteroaromatic ring w.r.t. the directing group. In spite of a large number of successes in the selenylation in the aromatic ring, there are also many scopes that are still unexplored, e.g. C–H selenation at *-meta* and *-para* position in the

aromatic ring, designing newer directing groups, etc. The application of heterogeneous catalysts is still to be explored in C–H selenation reactions. We strongly believe that this review will encourage synthetic chemists to explore the mentioned points. In summary, this review will draw a sharp interest in the researchers in designing new organoselenium compounds.

LIST OF ABBREVIATIONS

?? = ????????????????

?? = ????????????????

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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