

Recent Advances in Light-Induced Selenylation

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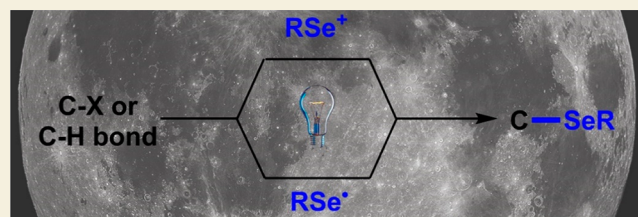
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ABSTRACT: Selenium-containing organic molecules have recently found a plethora of applications, ranging from organic synthesis to pharmacology and material sciences. In view of these concepts, the development of mild, efficient, and general protocols for the formation of C–Se bonds is desirable, and light induced approaches are appealing ways. The aim of this Review is to provide the reader with the most recent examples of light promoted selenylation processes.

KEYWORDS: C–Se bond formation, diazonium salts, diselenides, multicomponent reactions, selenylation, photochemistry, photocatalysis, radicals, visible light



1. INTRODUCTION

Interest in the presence of selenium-based functional groups in an organic molecule is currently increasing, and several selenoorganics have found application as building blocks in synthesis.^{1–4} Indeed, apart from some promising applications in material science,^{5–11} selenium containing compounds are widely investigated in the pharmaceutical industry, showing a broad range of bioactivities (e.g., as antimicrobials, antivirals, or antitumoral agents).^{12–22} Figure 1 collects some examples of Se-containing bioactive molecules, in most cases characterized by the aryl selenoether scaffold tethered to a (hetero)aromatic ring.^{23–32} In particular, arylselenide **II** exhibits activity against mood and neurodegenerative dis-

eases,^{27,28} indole **III** is an antiproliferative and a Tubulin inhibitor,²³ compound **IV** has been proposed as an antitumor agent,²⁴ quinoline **V** is an anti-inflammatory derivative,²⁶ naphthol **VI** shows activity as a 5-LOX (lipoxygenase) inhibitor,²⁴ compound **VII** is active against SARS-CoV-2,³² and diselenide **IX** has broad and potent anti-HIV activity (Figure 1).^{29–31}

In view of these concepts, the adoption of mild routes to the formation of Se–X bonds is desirable in the frame of green and mild approaches. The use of a photochemical reaction to promote a selenylation event is an appealing choice.

Scheme 1 collects the main routes for the light induced introduction of a selenium-containing substituent in an organic compound. Usually, the selenylating agent is a diselenide RSeSeR (mostly R is an aryl group). Due to the $n \rightarrow \sigma^*$ transition, diselenides show an absorption tail in the visible region ($\lambda < 500$ nm).³³ The excitation of these compounds can occur via direct visible light irradiation or by the help of a photocatalyst (PC) and causes the homolytic cleavage of the Se–Se bond to form RSe• (Scheme 1a, path *i*).³⁴ Such an intermediate may be easily oxidized by molecular oxygen to generate the corresponding cation (path *ii*). The latter intermediate may be alternatively formed by photocatalyzed oxidation of RSeSeR followed by the cleavage of the resulting radical cation (paths *iii*, *iv*). Both RSe• and RSe⁺ are reactive species that easily added to C=C or triple C–C bonds as well as heteroaromatic rings. The selenylation may take place even

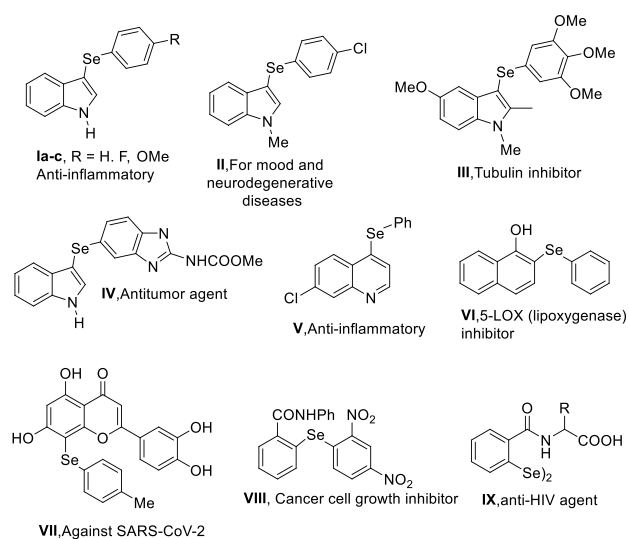
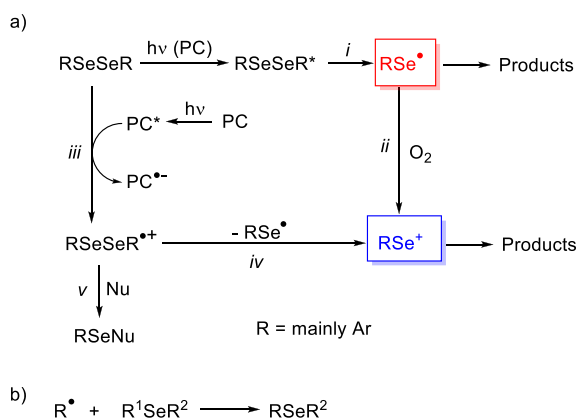


Figure 1. Bioactive selenides and diselenides.

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Scheme 1. Main Photochemical/Photocatalyzed Strategies for Selenylation Reactions



by interaction of $RSeSeR^{\bullet\bullet}$ with a nucleophilic species (path v).

An alternative approach involved the light promoted generation of a carbon centered radical R^{\bullet} that upon addition to a selenylating agent R^1SeR^2 led to the installation of a C–Se bond in a given compound (Scheme 1b).

The aim of the present Review is to collect recent photochemical/photocatalyzed routes in selenylation reactions mainly devoted to the forging of Se–C bonds.³⁵

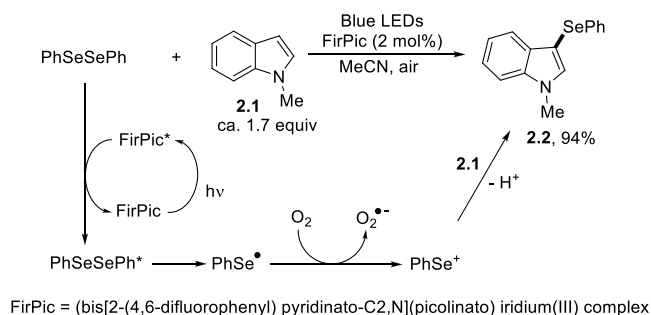
2. FORMATION OF $C(sp^2)$ –SE BOND

Most of the reactions belonging to this class are related to the synthesis of aryl selenides as detailed below.

2.1. Formation of an Ar–Se bond

As previously mentioned, diselenides ($RSeSeR$) are the elective selenylating agents, since they are stable and easy to handle. The direct introduction of a RSe group onto a (hetero)-aromatic ring by using $RSeSeR$ upon visible light exposure or under oxidative conditions has been developed for the first time only in 2017, and it is based on the use of the bis[2-(4,6-difluorophenyl)pyridinato-C2,N](picolinato) iridium(III) complex (FirPic) as the photocatalyst. The excited FirPic is first responsible for the cleavage of the Se–Se bond. Oxidation of the so-generated RSe^{\bullet} radical by molecular oxygen results in the formation of the electrophilic $RSe^{\bullet+}$ species, that is in turn trapped by the (hetero)arene. By adopting this strategy, a wide range of arenes as well as of nitrogen and sulfur based heterocycles have been successfully functionalized also on a multigram scale.³⁶ Scheme 2 illustrates the easy derivatization of the electron-rich *N*-methylindole **2.1**.

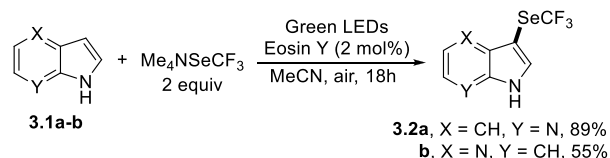
Scheme 2. Photocatalyzed Preparation of 3-Selenylindoles



Blue light absorption of $RSeSeR$ caused the direct homolysis of the Se–Se bond to form arylselenyl radicals (RSe^{\bullet}) which are in turn used for the photocatalyst-free synthesis of 3-selenylindoles. These 3-chalcogenylindoles exhibit significant activity as antitumorals and as inhibitors of tubulin polymerization. The protocol, that occurs in ethanol as the benign medium, has also been applied to the preparation of different diarylselenides in the reaction with electron-rich aromatics (e.g., anilines and phenols) in good to excellent yields.³⁷ A similar approach for the chalcogenation of (hetero)arenes has been developed in *tert*-butanol by using a white light LED as the energy source. The formation of an exciplex between the (hetero)arene and $PhSeSePh$ has been envisaged in this case.³⁸ A metal-free selenylation may also take place making use of Rose Bengal (RB) that has the role of photooxidizing the (hetero)aromatic to its radical cation that in turn reacted with $PhSeSePh$.³⁹

An alternative way to have access to a substituted selenyl radical is by having recourse to an organic dye in the role of PhotoOrganoCatalyst (POC).⁴⁰ The metal-free, green light promoted C–H trifluoromethylselenolation of heteroarenes has been optimized in the presence of Eosin Y as the photoredox catalyst and nucleophilic Me_4NSeCF_3 as the trifluoromethylselenating agent. Eosin Y was engaged in a reductive quenching cycle by reaction with Me_4NSeCF_3 functioning as the electron donor ($E_{ox} = +0.72$ V vs SCE) with the concomitant release of the CF_3Se^{\bullet} intermediate that was prone to functionalize 4- and 7-azaindoles (**3.1a,b**, Scheme 3). The success of the introduction of this fluorinated

Scheme 3. Trifluoromethylselenylation of 4- and 7-Azaindoles

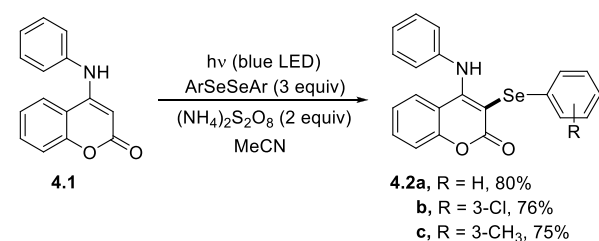


substituent was attributed to the choice of the POC that is able in the excited state to selectively oxidize Me_4NSeCF_3 rather than any heteroaromatic to be functionalized. The reaction has also been optimized under continuous flow conditions.⁴¹

An arylselenyl group was easily installed under photochemical oxidative conditions into 4-anilino coumarins (e.g., **4.1**), compounds that exhibit a promising antimicrobial activity (Scheme 4).⁴²

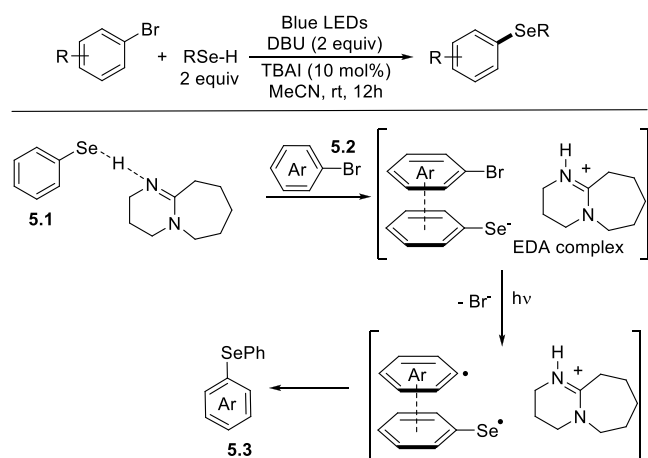
The introduction of a RSe group into a (hetero)aromatic compound may likewise take place by an ipso-substitution

Scheme 4. Metal-Free, Blue-Light Driven Arylation of 4-Anilino Coumarins



reaction on an aryl halide. Diaryl selenides are thus accessible on a gram scale via the formation of an electron donor–acceptor (EDA) complex. In this case, an aryl halide **5.2** (including chlorides) reacted with a selenol **5.1** in the presence of an organic base (e.g., DBU). Intermolecular charge transfer occurring upon visible light exposure generates, along with a halide anion, the selenyl/aryl radical pair, and the desired product **5.3** was then obtained by radical–radical coupling (Scheme 5).⁴³

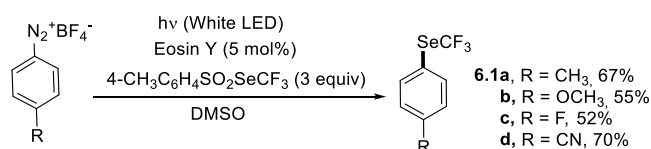
Scheme 5. Selenylation via an EDA Complex



A related reaction has been reported for the UV light mediated coupling of aryl halides (iodides and bromide) with diselenides in argon saturated acetonitrile, in the presence of DBU. A 300 W Hg lamp was adopted as the light source, and, again, a selenyl radical was suggested as the intermediate.⁴⁴

In the past decade, trifluoromethyl tolueneselenosulfonate (TsSeCF₃) has been successfully employed as shelf stable reagent in trifluoromethylselenations taking place under photoredox catalyzed conditions.⁴⁵ Such derivative has been applied to the visible light driven synthesis of trifluoromethylselenolated arenes **6.1a–d** and perfluoroalkylselenolated derivatives under metal-free conditions, by using Eosin Y as the photoredox catalyst (Scheme 6). The formation of the Ar–Se

Scheme 6. Visible-Light Photoredox Catalyzed Trifluoromethylselenation of Aryldiazonium Salts

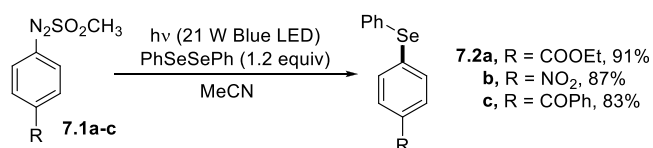


bond relies on the aryl radical addition onto TsSeCF₃.⁴⁶ A related approach has been exploited for the selenodifluoromethylation of anilines. In the latter case, the anilines were converted in situ to the corresponding arenediazonium salt that engaged a photoredox catalyzed reaction with difluoromethyl tolueneselenosulfonate.⁴⁷

Aryl radicals may be alternatively generated from bench stable derivatives of aryldiazonium salts. This is the case of arylazo sulfones **7.1a–c** that upon visible light exposure underwent a homolytic cleavage of the N–S bond,⁴⁸ and the resulting aryl radical has been used for the preparation of a wide range of unsymmetrical (hetero)aryl selenides **7.2a–c**

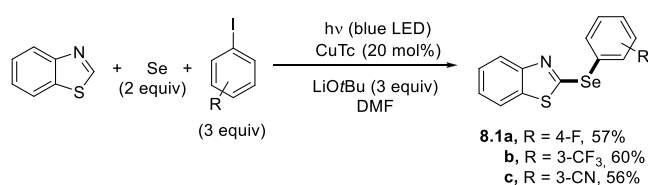
and tellurides under photocatalyst- and metal-free conditions (some examples in Scheme 7).^{49,50}

Scheme 7. Photocatalyst-Free Preparation of Arylselenides via Arylazo Sulfones



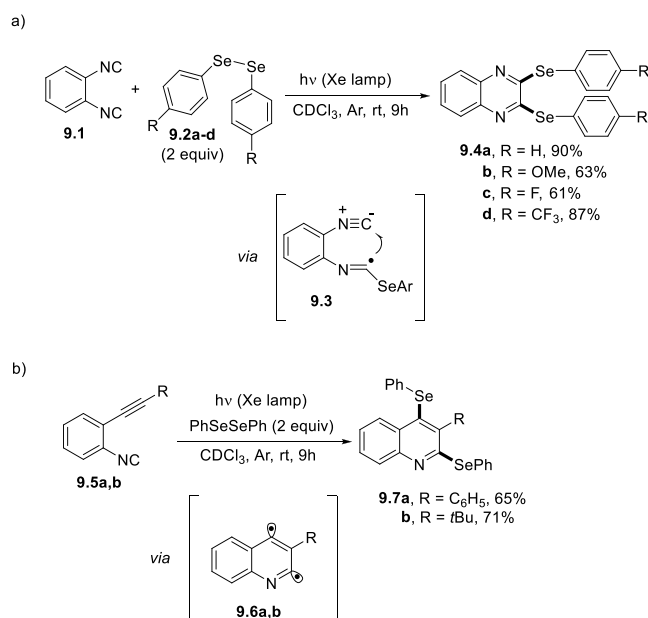
Differently substituted arylchalcogenated azoles **8.1a–c** have been prepared via a three-component approach, by using aryl iodides, azoles, and nonvolatile elemental chalcogens (S, Se) as the starting substrates with the help of copper(I) thiophene-2-carboxylate (Cu–Tc) as the catalyst (Scheme 8).⁵¹

Scheme 8. Three-Component Preparation of 2-Selanylbenzothiazoles



The formation of the Ar–Se bond may likewise take place with the concomitant formation of the (hetero)aromatic ring. This is the case of the biselenative cyclization of *o*-diisocyanoarenes (Scheme 9a). The irradiation of diaryl (**9.2a–d**) or dialkyl diselenides with a Xe lamp generates selenyl radicals that were smoothly added to an isocyanide group of an *o*-diisocyanoarene (**9.1**) to form an imidoyl radical (**9.3**) that cyclized onto the other isocyanide group. The resulting imidoyl radical intercepted another molecule of

Scheme 9. Photoinduced Preparation of (a) 2,3-Bis(selanyl)Quinoxalines and (b) 2,4-Bis-chalcogenated Quinolines

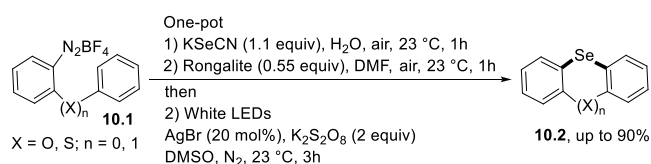


diselenide to give 2,3-bis(selenyl)quinoxalines **9.4a–d** in a good yield.⁵² In a similar way, 2-chalcogenated quinolines **9.7a,b** have been obtained from the corresponding *o*-alkynylaryl isocyanides **9.5a,b** via the intermediacy of 2,4-dehydroquiniline diradical intermediates **9.6a,b** in what it is considered a sort of light-induced aza-Bergman-type cyclization (Scheme 9b).⁵³

Another example of construction of a nitrogen based heterocycle involved the synthesis of a series of selenyl-substituted pyrimido[1,2-*b*]-indazoles in moderate to satisfactory yields via visible light induced cascade three component reaction of 3-aminoindazoles, ynals, and diselenides. The addition of the diselenide radical cation onto the triple bond has been envisaged as the key step.⁵⁴

Selenaheterocycles have attracted attention since their potential employment as organic semiconductors in the preparation of organic light-emitting diodes (OLEDs) as well as of organic field-effect transistors (OFETs).^{55,56} A one-pot route to this synthetic target is depicted in Scheme 10.

Scheme 10. Photochemical Route to Selenaheterocycles



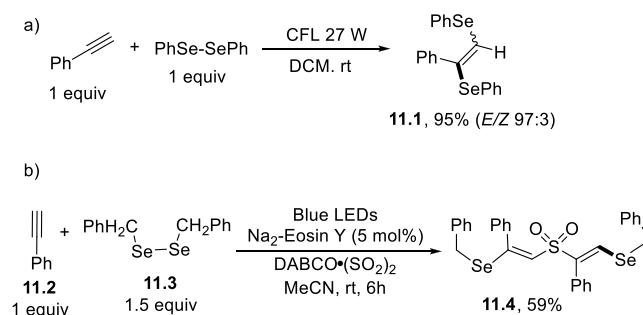
Aryldiazonium salts **10.1** were first treated with KSeCN to give the corresponding aryl selenocyanates that upon treatment with Rongalite (HOCH₂SO₂Na) led to diaryl diselenides. Crude diselenides were then treated with a silver catalyst in the presence of K₂S₂O₈ (as a sacrificial oxidant) upon visible light irradiation to form selenaheterocycles **10.2** with the intermediacy of an arylselenyl radical.⁵⁷

2.2. Formation of a Vinyl–Se Bond

Apart from their extensive use as synthetic precursors of enediynes and polyfunctionalized olefins, 1,2-bis-organylselenyl alkenes were found to exhibit antinociceptive and antioxidant activities.⁵⁸ Thermal preparation of such derivatives commonly requires harsh conditions as well as transition metal catalysts and reductants, but photochemical approaches to 1,2-bis-organylselenyl olefins occur at room temperature and under additive-free conditions. The strategy involves the white light irradiation of a mixture of an arylacetylene and a diaryl diselenide in DCM to promote the efficient formation of **11.1** as the *E*-stereoisomer, due to the occurrence of PhSe• addition on the triple C–C bond followed by photoisomerization (Scheme 11a).⁵⁹ A protocol for the photoinduced selenophosphination of alkynes in the presence of diphosphines and diselenides under UV light irradiation was proposed, and it led to the one-pot forging of a vinyl-P and a vinyl-Se bond.⁶⁰ The photochemical 1,2-selenosulfonylation of alkynes was also promoted by the presence of catalytic amounts of Co(II) salts or metallic Cu starting from PhSeSO₂Ph.⁶¹

The vinyl radical intermediate was exploited in a multi-component cascade reaction for the synthesis of β -sulfonylvinylselenanes (Scheme 11b). Despite the reaction possibly working under uncatalyzed conditions, in some cases, the presence of a photocatalyst (e.g., Na₂-Eosin Y) was found to be beneficial. Thus, the irradiation of a mixture of Na₂-Eosin Y (5 mol %), phenylacetylene **11.2**,

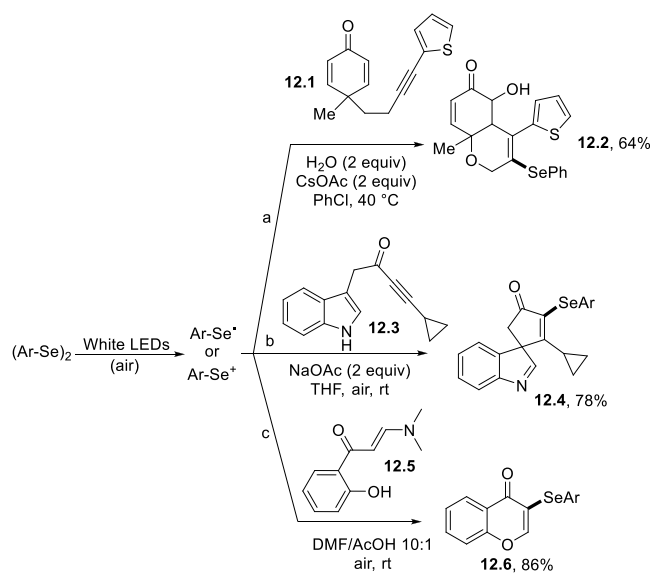
Scheme 11. Synthesis of (a) 1,2-Bis-organylselenyl Alkenes and (b) β -Sulfonylvinylselenanes



DABCO·(SO₂)₂, and diselenide **11.3** led to the liberation of PhCH₂Se• and a vinyl radical from it upon addition to **11.2**. The vinyl radical in this case reacted with sulfur dioxide, allowing for the concomitant formation of C–Se and C–S bonds in compound **11.4** (mainly in the *E*-configuration).⁶²

The addition of a photogenerated selenyl radical onto a triple bond (in alkyne-tethered cyclohexadienone **12.1**) has also been exploited for the preparation of 5-hydroxy-3-selenyl-4*a*,8*a*-dihydro-2*H*-chromen-6(*5H*)-ones (e.g., **12.2**), with some of them exhibiting a potent cancer cell-growth inhibition activity (Scheme 12, path a). Compound **12.2** has been formed

Scheme 12. Different Approaches for the Forging of a Vinyl–Se Bond for the Synthesis of (a) 5-Hydroxy-3-selenyl-4*a*,8*a*-dihydro-2*H*-chromen-6(*5H*)-ones, (b) 3-Selenospiroindolenine, (c) 3-Selenyl-4*H*-chromen-4-ones



by a nucleophilic substitution with water in the presence of CsOAc on the diselenide intermediate.⁶³ An interesting route to spirocyclic dienones has been likewise devised by the addition of photogenerated PhSe• to aromatic homologated-ynones that caused a dearomative selenylative carbo-spirocyclization to give selenylatedenones.⁶⁴

Anticancer agents bearing a 3-selenospiroindolenine core (e.g., **12.4**) have been prepared via spirocyclization of an indolyl-ynone (**12.3**) upon addition of PhSe• (again formed by photolysis of the Se–Se bond) on the alkyne moiety that triggered the cyclization process (Scheme 12, path b).⁶⁵

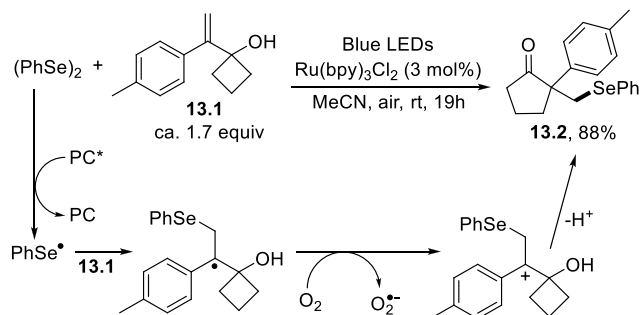
2-Hydroxyphenyl enaminone **12.5** has been employed for the preparation of 3-selenyl-4*H*-chromen-4-one **12.6** (Scheme 12, path c).⁶⁶ The PhSe• radical photogenerated in the first step of the reaction is oxidized by oxygen to the corresponding phenylselenyl cation (PhSe⁺) that prompted added to the C=C bond of **12.5** to generate a selenium ion. An intramolecular nucleophilic addition of the OH group followed by dimethylamine loss released the desired **12.6** that can be smoothly converted into the corresponding selenyl pyrimidines via treatment with benzamides. Compound **12.5** was used as well as starting compound for the synthesis of trifluoromethylselenylated heterocycles. Thus, blue light irradiation of trifluoromethyl tolueneselenosulfonate liberated a CF₃Se radical that initiated the trifluoromethylselenolation event.⁶⁷

Visible light irradiation of diaryl selenides in the presence of alkyne derived 1,6-enynes resulted in a radical addition/cyclization/selenation sequence where two arylselenide units were incorporated in the final, polyfunctionalized product having a five-membered heterocyclic ring.⁶⁸

3. FORMATION OF C(sp³)–Se BOND

The typical approach for the installation of a C(sp³)–Se bond is the addition of a selenium containing species to a C=C bond. As an example, β -selenylated cyclic ketone **13.2** has been obtained from 1-(1-arylvinyl)cyclobutanol **13.1** in the presence of Ru(bpy)₃Cl₂ as the photosensitizer. Energy transfer from excited Ru(bpy)₃^{2+*} to PhSeSePh caused the release of PhSe•, that was in turn intercepted by the olefin moiety. Oxidation of the so-generated carbon centered radical followed by semipinacol rearrangement through 1,2-alkyl migration and deprotonation led to the ring expanded product **13.2** in good to excellent yields (Scheme 13).⁶⁹ However, the

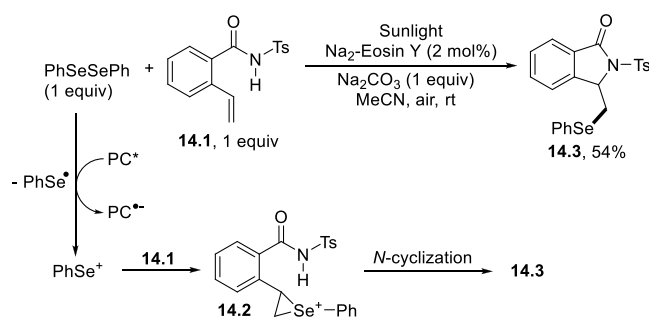
Scheme 13. Photosensitized Conversion of 1-(1-Arylvinyl)cyclobutanol into β -Selenylated Cyclic Ketones



oxidation of PhSe• to the cation followed by addition onto **13.1** was not excluded as an alternative path. The light induced α -selenolation of ketones was as well as achieved in the presence of pyrrolidine as the organocatalyst. In the latter case, PhSe• readily attacked to the in situ formed enamine.⁷⁰

Exposure to natural sunlight of a mixture of a vinyl benzamide (**14.1**) and a diphenyl selenide in air saturated acetonitrile resulted in the formation of selenated heterocycles. Interestingly, the chemoselectivity of the reaction can be directed by tuning the reaction conditions. Indeed, iminoisobenzofurans are obtained in the presence of an acid catalyst (trifluoroacetic acid), while when the same process is performed in the presence of a base (Na₂CO₃), isoindolinones (**14.3**) are exclusively obtained via a N-cyclization (Scheme 14).⁷¹ In each case, Na₂-Eosin Y acted as the photocatalyst and

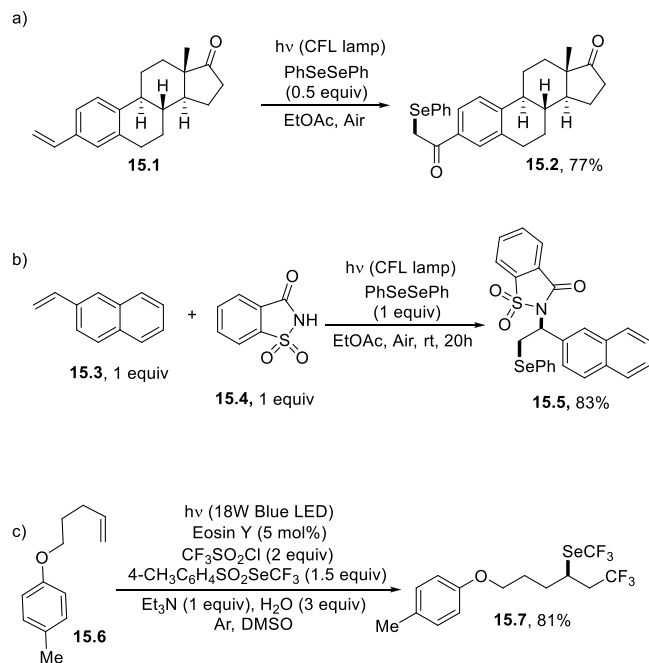
Scheme 14. Sunlight Photocatalyzed Preparation of Isoindolinones



the aryl-stabilized seleniranium ion **14.2** was invoked as the intermediate. A set of differently substituted seleno oxazolines was prepared via photoredox catalyzed selenyl cation induced cyclization of *N*-allylamides.⁷² A blue light induced tandem C–Se and C–O or C–N bond formation was applied to the multistep synthesis of natural alkaloid (\pm)- γ -lycorane. The presence of CBr₄ assured the formation of the diselenide radical cation that promotes the construction of a perhydroindole ring.⁷³

The visible light induced oxidative selenation of styrenes as a route to α -selenoaryl and α -selenoalkyl ketones has been recently reported. The reaction took place in ethyl acetate and was exploited for the functionalization of styrene-functionalized biomolecules (e.g., for the estrone derivative **15.1**, Scheme 15a). The carbonyl group was formed by oxygen

Scheme 15. Functionalization of (a) Styrenes, (b) 2-Vinyl Naphthalenes, and (c) Simple Alkenes



addition onto the benzyl radical intermediate.⁷⁴ The same research group optimized the visible or sunlight driven three-component aminoselenation of alkenes with sulfonimides (e.g., saccharin **15.4**) and diselenides via a seleniranium ion (see an example in Scheme 15b).⁷⁵

A three component strategy was adopted for the transition metal-free synthesis of *N*-(arylthio/seleno)ethyl sulfoxidimines

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