SYNTHESIS OF FUNCTIONALIZED HETEROCYCLIC COMPOUNDS DRIVEN BY VISIBLE-LIGHT PHOTOCATALYSIS

DOI: http://dx.medra.org/10.17374/targets.2022.25.480

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Abstract. *The employment of visible-light has emerged as a powerful, selective, and sustainable tool for the construction and functionalization of heterocyclic systems. This review highlights the recent progress in protocols to obtain benzothiazoles, triazoles, and selenoindoles mediated by light providing overviews of their synthetic scope. In addition, the mechanisms involved are discussed.*

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1. Introduction

The scientific community adopted light-induced reactions as an innovative opportunity across a broad range of areas (pharmaceuticals, agrochemicals, animal health products, *etc.*).[1,2,3,4] The use of light-irradiation over the last decade allowed access to a wide variety of heterocyclic compounds, perhaps inaccessible through other methods.[5,6,7] Although not all organic compounds are capable of absorbing light, because the molecules need chromophores that can handle these processes, the synthetic community has been developing novel protocols to tackle this drawback.[1,5] In this sense, photocatalysis arises as a promising solution to drive reactions that are difficult, sometimes even impossible, to carry out by thermal activation.[3] The use of visible-light (λ=400-700 nm) provides several advantages over the use of ultraviolet light. Besides, UV light frequently induces unselective reactions and requires the use of specialized light sources and photoreactors. Instead, visible-light can be considered as a mild and environmentally friendly reagent, with high energy efficiency, simplicity, and financial cost.[8]

When a reaction mixture is irradiated with visible-light, the addition of organic dyes, transition metal complexes, or semiconductors is required to absorb the light, as the typical organic molecules are transparent to such irradiation. These species absorb the radiation and induce chemical reactions transferring their excitation energy *via* electron transfer (ET) (photoredox catalysis), or hydrogen atoms (hydrogen atom transfer photocatalysis), or collision (energy transfer, photosensitization).[1] In the absence of any extra-added photocatalyst, examples of transformations are limited to organic substrates whose absorption falls within the visible wavelength range or the formation of an electron donor-acceptor complex which is able to absorb.[9] To achieve effective visible-light absorption, charge separation, and charge transfer, a vast number of photocatalytic materials have been synthesized and studied in several organic transformations. The

progress in the field of photocatalysis has enabled the development and application of novel photocatalysts for the synthesis and functionalization of heterocyclic compounds.[10]

Also, several technological innovations have rendered selective, more reproducible, and scalable photoinduced reactions. Light Emitting Diodes (LEDs) were quickly identified as desirable lighting sources due to being energy-efficient and long lasting. Moreover, the evolution of photoreactors for both batch- and flow-mode represent a huge promise for the field.[8]

This review summarizes the advances in the visible-light-induced synthesis and functionalization of certain important heterocycles. Based on our recent contributions, we describe three families: bezothiazoles, triazoles, and selenoindoles. Particular emphasis is also placed on the recent developments of the visible-light photocatalytic synthetic protocols discussing useful and readily accessible literature. Additionally, this review offers a critical assessment of some mechanistic insights into photochemical reactions, which provide methodologies to further explore synthetic approaches for heterocyclic compounds.

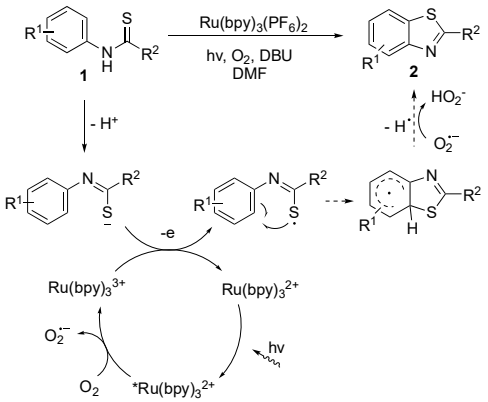
2. Benzothiazoles

Benzothiazole is a benzo-fused heterocycle that is present in many naturally occurring products and has been used as an antimicrobial, antitumor, anticonvulsant, and neuroprotective agent.[11] There are numerous synthetic methodologies in the literature to obtain this important class of heterocyclic compounds, but in recent years emphasis has been placed on the development of new methodologies based on photocatalysis, which involves greener reaction conditions. Among the methods based on the use of light, the most prominent are the employment of direct $C(_{sp}{}^2)$–H activation using UV or visible-light to form intramolecular C-S bonds. This approach implies the intermolecular cyclization reaction between 2-aminothiophenols and different reagents, where aldehydes are the most frequently used, and cascade radical cyclization reactions of 2-isocyanoaryl thioethers. Some of these methodologies are described below.

2.1. Synthesis by C–H activation and $C(_{sp}{}^2)$–S formation

Over the past decade, radical chemistry, specifically photoredox catalysis, has risen as a popular and powerful tool for C–H functionalization. In particular, the employment of direct $C(_{sp}{}^2)$−H activation/intramolecular C–S bond formation has been studied for the synthesis of 2-substituted benzothiazoles. Peñéñory *et al.* reported a ground-breaking work which developed the cyclization of thiobenzanilide **1** for the synthesis of 2-substituted benzothiazoles **2** induced by a stoichiometric amount of *p*-chloranil under a medium-pressure Hg lamp irradiation at 80 °C in toluene or 1,2-dichloroethane. In this work, the authors proposed that, in non-polar solvents, the *p*-chloranil triplet generated by UV radiation acts as a hydrogen atom acceptor, to generate the sulphur-centred radical of the substrate, which, after an intramolecular cyclization and re-aromatization, generates the corresponding benzothiazole reaching acceptable to very good benzothiazole yields.[12]

Li *et al.* reported a methodology for the cyclization of **1** to obtain **2** by photoredox catalysis, using $Ru(bpy)_3{}^{2+}$ as photocatalyst in the presence of 1,8-diazabicycloundec-7-ene (DBU) as a base in an oxygen atmosphere. According to the mechanism, in a first step, the excited photocatalyst ($Ru(bpy)_3{}^{2+}$*) is oxidized to $Ru(bpy)_3{}^{3+}$ by molecular oxygen, while the latter is turned into the $O_2{}^{\bullet-}$ upon ET (Scheme 1). The sulphur-centred anion of **1** generated by organic base DBU, forms a sulphur radical by a single ET to $Ru(bpy)_3{}^{3+}$, regenerating $Ru(bpy)_3{}^{2+}$ and closing the photoredox cycle. This radical finally produced **2** after intramolecular cyclization, and $O_2{}^{\bullet-}$ assisted re-aromatization. By this methodology, **2** were obtained from moderate to excellent yields. This mild reaction condition tolerates many functional groups.[13] Using also a ruthenium-based photocatalyst, Gustafson *et al.* described a methodology to obtain benzothiazoles based on a photocatalytic oxidative C−H thiolation. This methodology involves the use of **1** as a substrate, $Ru(bpy)_3Cl_2$ as a photocatalyst, sodium persulfate as an oxidizing agent, and pyridine as a base under blue LED irradiation. The mechanism suggests that the excited state of the photocatalyst activates the persulfate producing the sulphate radical ($SO_4{}^{\bullet-}$) which is a powerful oxidizing agent together with Ru^{3+}, the latter being responsible for oxidizing the sulphur of the thiobenzanilide to form its radical cation, which then undergoes an intramolecular cyclization. In the next step, re-aromatization takes place to give the product of interest. This methodology allows obtaining 2-alkyl or 2-aryl benzothiazoles from moderate to good yields.[14]



Scheme 1. Photocatalyzed synthesis of **2** with $Ru(bpy)_3^{2+}$ and proposed mechanism.

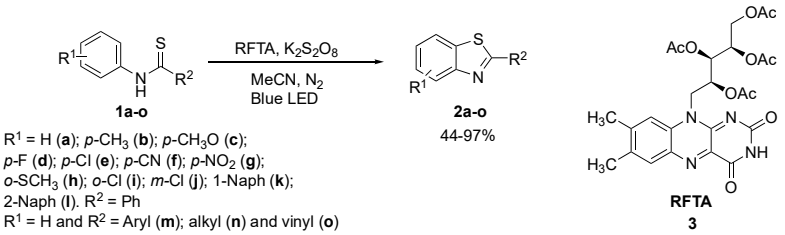
Lei *et al.* reported a photoredox catalysis methodology using the combination of a photocatalyst with a proton reducing catalyst, namely ($Ru(bpy)_3(PF_6)_2$) and ($Co^{III}(dmgH)_2(4\text{-}NMe_2\text{-}C_5H_4N)Cl$), under weak alkaline conditions, starting from **1** under blue LED irradiation, using sodium glycinate as a base in stoichiometric quantities and DMAP in sub-stoichiometric amount, in an argon atmosphere to obtain **2** under oxidant-free conditions with concomitant generation of H_2. This methodology achieves excellent results with either electron-rich or electron-poor substituents; however, the presence of a strong π-donating group (−OMe) or a strong electron-withdrawing group ($-CF_3$) on the *N*-aryl ring decreases the reactivity. These catalytic systems can be scaled up to gram scale, with excellent yield.[15]

Srivastava and co-workers developed the synthesis of 2-aminobenzothiazoles starting from arylthiourea, using Eosin Y (EY) as a photocatalyst, green LEDs as light source, and *N,N*-diisopropylethylamine as an organic base, in aerobic conditions. This procedure gives the desired product in good to excellent yields and tolerates considerable functional group variations including electron-withdrawing and electron-donating substituents. Moreover, this methodology gave excellent yield when the reaction started directly from arylisothiocyanate and a secondary amine in a one-pot procedure.[16]

Xu and co-workers developed a visible-light-driven methodology for C−H thiolation that does not require the use of a photosensitizer, metal catalyst, or base. The procedure is based on the intramolecular cyclization of **1** through a reverse Hydrogen-Atom Transfer (RHAT) process. Light-activated thiobenzanilide suffers a RHAT process in the presence of 2 equivalents of TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxide), to produce the corresponding sulphur radical, which undergoes an intramolecular cyclization to finally produce benzothiazole. This methodology affords the formation of benzothiazoles with electron-rich, -neutral, and -withdrawing groups in good to excellent yields.[17]

More recently, our group developed the synthesis of 2-substituted benzothiazoles **2a-o** through an efficient photochemical approach for visible-light-driven aromatic C−H thiolation reactions of thiobenzanilides **1a-o**, using riboflavin 2′,3′,4′,5′-tetraacetate (RFTA) **3** as a photocatalyst and persulfate as a sacrificial oxidizing agent under nitrogen atmosphere. The advantages of this approach include the use of a natural organic dye, riboflavin, as a photocatalyst, the absence of transition-metal complexes and bases, and the use of blue light to promote the reaction to obtain the corresponding benzothiazoles in good to excellent yields (Scheme 2). Also, the methodology tolerates both electron-donating and electron-withdrawing substituents and represents the first methodology that successfully produced nitro-substituted 2-phenylbenzothiazole under photochemical approaches. Moreover, some 2-alkylbenzothiazoles were obtained in moderate to very good yields and a double-cyclization product was reported in 41% yield.[18]

Upon some mechanistic studies, the authors suggested that ET occurs from **1** to the excited state of RFTA, to produce the radical cation of thiobenzanilide together with the radical anion $RFTA^{\bullet-}$. In a second step, the deprotonation of the radical cation of thiobenzanilide is assisted by the radical anion $RFTA^{\bullet-}$, which, after cyclization and further re-aromatization by oxidant potassium persulfate, afforded the desired benzothiazole.[18]



Scheme 2. Photocatalyzed synthesis of 2-substituted benzothiazoles **2a-o** with RFTA **3**.

The synthesis of **2** was developed by Zhou *et al.* using the heterogeneous photocatalysis graphitic carbon nitride (g-C_3N_4) as a catalyst in air atmosphere and blue LED irradiation.[19] Similarly to RFTA,[18] this methodology presents excellent isolated yields and compatibility of different functional groups, including *p*-nitro containing thiobenzanilide **1g**, which is a challenging substrate.[19]

2.2. Synthesis starting from 2-aminothiophenols

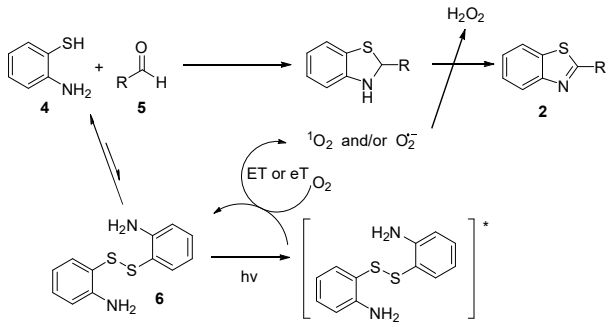
The photocatalyzed reaction of 2-aminothiophenols **4** with different reagents is one of the most studied methodologies to obtain benzothiazoles due to its simplicity, mild reaction conditions, and the commercial availability of starting materials.

Sharma *et al.* reported the synthesis of benzothiazoles using a decarboxylative cross-coupling reaction between α-keto acids and 2-aminothiophenols in the presence of H_2O_2 as an oxidant, air atmosphere, and blue LED irradiation, without any photocatalyst. Mechanistic studies propose the formation of an electron donor-acceptor complex (EDA complex) between the α-keto acid and the 2-aminothiophenol. This EDA complex, irradiated with blue light and in the presence of an oxidizing agent such as H_2O_2, further undergoes decarboxylation and, after several rearrangements, the desired benzothiazole is obtained. By modifying the substituents present in both α-keto acid and **4**, a wide family of benzothiazoles were obtained, bearing both donor and acceptor substituents, as well as benzothiazoles unsubstituted at the C2 position. The authors describe a metal-free and photocatalyst-free photooxidative synthesis of benzothiazoles.[20] Also described in bibliography, there are methodologies where the formation of a disulphide intermediate acts as a photosensitizer.[21,22] The synthesis of benzothiazoles from **4** and aldehydes **5** under aerobic conditions and blue LED irradiation was reported by Yan and co-workers. The authors propose the formation of an imine which, in presence of O_2 and upon irradiation, is oxidized to the corresponding disulphide. In a second step, light promoted homolytic fragmentation of the disulphide, generating a thiyl radical which, after intramolecular cycloaddition and oxidation, affords the final product. The scope of the reaction included the use of different 2-aminothiophenols with methoxyl, methyl, fluoro, chloro, and bromo substituents to obtain benzothiazoles in good yields.[21] In further studies, Cho *et al.* explored the mechanism of this reaction between **4** and **5** that precede using water as a solvent in an air atmosphere with blue LED irradiation, to obtain the corresponding benzothiazole. Mechanistic studies show that 2-aminothiophenol disulphide **6** is formed under irradiation and is the species that works as a photosensitizer in the benzothiazole formation reaction (Scheme 3). Regarding the scope, the mild reaction conditions tolerate various functional groups, affording a wide variety of **2** with very good to excellent yields (70-95%).[22]

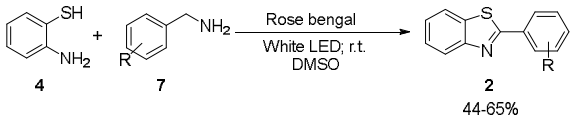
Another intermolecular cyclization methodology includes the use of photoredox catalysts under visible-light irradiation, using organic catalysts, transition-metal complex, and semiconductor materials.

Cho *et al.* employed $Ru(bpy)_3Cl_2$ as a photoredox catalyst, starting from **4** and **5** in the presence of oxygen under blue LED irradiation. The authors propose that, in the first step, the corresponding benzothiazoline is formed as an intermediate, and this part of the reaction proceeds in absence of photocatalyst and light. The formation of benzothiazole occurs through a reaction of α-amino C−H oxidation of benzothiazoline catalysed by $Ru(bpy)_3Cl_2$, which involves O_2 reduction followed by ET from benzothiazoline. The use of different aldehydes leads to the formation of 2-alkyl and 2-aryl benzothiazoles with excellent yields, using mild reaction conditions and with minimal amounts of photocatalyst (0.1 mol%), which allows minimizing toxic waste formation.[23] Similarly, Sun *et al.* developed an efficient and green method for the synthesis of benzothiazoles *via* light-induced condensation cyclization using fluorescein as a

photocatalyst, and methanol as solvent in air atmosphere. This methodology tolerates a series of substituents, such as electron-withdrawing and electron-donating groups, on the aromatic ring of the aldehyde as well as the 2-aminothiophenol moiety, keeping the performance of the reaction. As in the previous case, once the benzothiazoline is formed, the photocatalytic cycle between this species and fluorescein/O_2 under irradiation takes place, to give the corresponding benzothiazole.[24] Similarly and starting from these precursors, Tran *et al.* synthesized derivatives of benzothiazoles using EY as photocatalyst with very good to excellent yields and mild reaction conditions.[25] At the same time, Chandru Senadi and co-workers developed a similar methodology using Rose Bengal as a photocatalyst in the presence of **4** and benzylamines **7** (Scheme 4). In this case, the photocatalyst plays a fundamental role, since it acts in a first stage to transform benzylamine into aldehyde, which couples *in situ* with **4** to form benzothiazoline, and in the presence of Rose Bengal gives the corresponding 2-arylbenzothiazoles **2**. This mild, metal-free methodology, that avoids the use of less stable aldehyde derivatives, is compatible with electron-donating as well as electron-withdrawing functionalities to afford benzothiazoles in moderate yields (41-65%).[26]



Scheme 3. Mechanism proposed by Cho *et al.*



Scheme 4. Photocatalyzed synthesis of **2** with Rose Bengal.

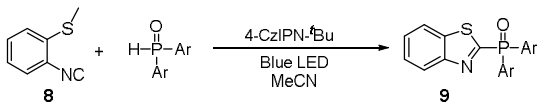
Other types of catalysts used are tetrazine[27] and pyrazine[28] derivatives, which show visible-light absorption and have been used as photoredox catalytic systems for the synthesis of **2** starting from aldehydes and **4**. Both catalysts demonstrated excellent catalytic activity in the presence of both alkyl and aryl aldehydes with different substituents, under mild conditions, and in excellent reaction yields.

In recent years, the use of semiconductors as photocatalysts for heterogeneous catalysis reactions has attracted much attention, since its easy separation and reuse constitutes a powerful tool to achieve complex chemical transformations. As a result, this type of heterogeneous catalyst has been employed for the synthesis of benzothiazole due to the great interest in the development of new methodologies to obtain this interesting heterocycle. In this sense, Biswas *et al.* developed the synthesis of benzothiazoles starting from 2-aminothiophenols together with aryl, and alkyl aldehydes using mesoporous CdS nanosphere as heterogeneous photocatalyst under visible-light irradiation. CdS nanospheres exhibited excellent catalytic performance and were easy to separate for their further reuse. The experimental results showed a loss of catalytic performance after the fourth cycle due to significant agglomeration of the material.[29] Also, Rai *et al.* employed as heterogeneous photocatalyst $Cu/Cu_2O@g\text{-}C_3N_4$ for the synthesis of 2-aryl benzothiazoles *via* condensation of structurally different aldehydes with *o*-aminothiophenol. The authors, who proposed a simple methodology under mild reaction conditions, in aqueous medium, white LED irradiation, reported very good reaction yields (80-94%). Moreover, the catalyst was able to be reused for five recycling cycles without significant loss of its activity, making this protocol a greener alternative method.[30] Chikate *et al.*

reported the use of CdSe nanocomposites as a photocatalyst for the synthesis of 2-substituted benzothiazoles. These nanocomposites were prepared by molecular self-assembly of CdSe nanoparticles within the layers of montmorillonite (MMT) through intercalation, forming lamellar structures. The methodology utilizes aliphatic, aromatic, and heterocyclic aldehydes and 2-aminothiophenol to obtain benzothiazoles with excellent yields (up to 98%) under visible-light irradiation. The use of this combination of materials showed a synergistic interaction between CdSe sites and MMT support within the nanocomposite structure, giving even higher yields than the separate materials. Moreover, the catalytic activity was marginally reduced during five successive cycles even after prolonged exposure to light, making this a robust material for photocatalysis.[31]

2.3. Synthesis starting from 2-isocyanoaryl thioethers

Another photoinduced synthetic methodology to obtain benzothiazoles involves the use of 2-isocyanoaryl thioethers **8** as precursors. This method has been widely used to obtain benzothiazoles with functionalities of interest in position 2, such as perfluorinated substituents, phosphine oxides, among others, given the interest in these derivatives of benzothiazoles and their applications; and the chance of incorporating different heteroatoms to this fascinating structure. Zhang *et al.* synthesized 2-CF_2/CF_3-containing benzothiazoles with excellent yields through a visible-light-induced radical cascade cyclization of **8**, using iridium salts (*fac*-Ir(ppy)$_3$) as photocatalyst and sodium sulphite as a reducing agent to regenerate Ir^{3+} and close the catalytic cycle.[32] Also, Yu *et al.* developed an efficient fluoroalkylation/cyclization methodology by reacting commercially available fluoroalkyl radical sources, like perfluoroalkyl iodide, tetramethylethane-1,2-diamine (TMEDA), and structurally simple **8** under blue-light irradiation giving access to diverse, biologically potential, 2-fluoroalkylbenzothiazoles. The perfluoroalkyl radicals required for the radical-cascade cyclization reaction are generated from the irradiation of the perfluoroalkyl iodide-TMEDA EDA complex. This methodology allows 2-fluoroalkylbenzothiazoles with very good performance. Another advantage is that, starting from 2-isocyanoaryl selenoethers, and under the same reaction conditions, the authors obtain the interesting 2-perfluoroalkylbenzoselenazoles.[33] In a more recent study, the authors developed a photocatalyst, namely 2,4,5,6-tetrakis(3,6-di-*tert*-butyl-9*H*-carbazol-9-yl)-isophthalonitrile (4CzIPNtBu), for the cascade cyclization reaction of **8** initiated by phosphorus-radicals to obtain 2-phosphorylated benzothiazoles **9** (Scheme 5). The products of interest were obtained in moderate to very good yields, under mild reaction conditions and blue LED irradiation.[34]



Scheme 5. Photocatalyzed synthesis of 2- phosphorylated benzothiazoles **9** with 4CzIPNtBu.

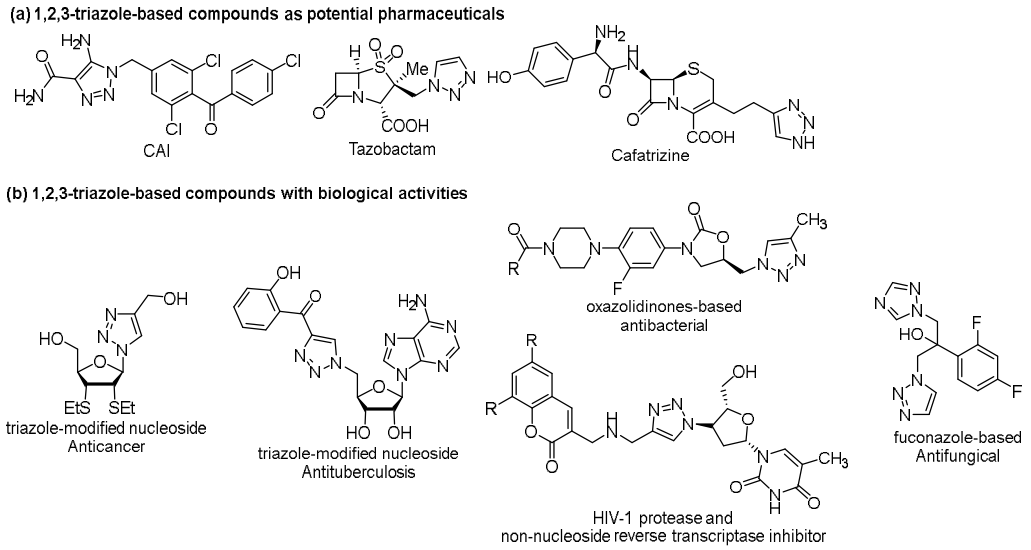
Recent reports use a similar catalyst (1,2,3,5-tetrakis-(carbazol-9-yl)-4,6-dicyanobenzene, 4CzIPN) to obtain ether-functionalized benzothiazoles starting from 2-isocyanoaryl thioethers and ethers with moderate yields and mild reaction conditions. This methodology allows the corresponding benzoselenazoles with moderate yields.[35]

3. Triazoles

Triazoles are five-membered heterocycles containing two carbon and three nitrogen atoms. Because of their structure, it is possible to propose two triazole isomers depending on the relative position of the nitrogen atoms: 1,2,3-triazole and 1,2,4-triazole. Due to its high relevance in medicinal chemistry, materials science, and polymer chemistry, in this section we will account for 1,2,3-triazole.

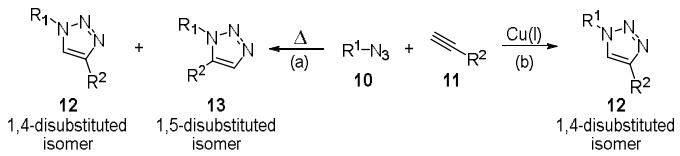
Triazoles are exceptionally stable under many reaction conditions such as acidic and basic, as well as oxidative and reductive media, due to their aromatic character. Furthermore, they are relatively resistant to metabolic degradation.[36] Triazoles have a particularly high dipole moment -around 5D- and participate in intermolecular hydrogen bond and dipole-dipole interactions.[37] Due to their structural characteristics, they resemble the amide bonds and are excellent candidates as linkers for different conjugates.[38,39]

Triazoles are not usually found in nature, however, their core is present in molecules with interesting biological activities (Scheme 6).[40] Just a few triazole derivatives are actually commercially available or in advanced clinical trials. Among them, we can mention the anticancer carboxyamidotriazole (CAI), the β-lactam antibiotics Tazobactum, and the cephalosporin Cefatrizin (Scheme 6a). Other examples with biological properties such as anticancer, antifungal, and antibacterial, HIV inhibitors, antituberculosis, among others (Scheme 6b) are currently under study. The biological potential of triazole-containing compounds is unlimited.



Scheme 6. Biological active triazole-containing molecules.

The most important reaction for the 1,2,3-triazoles formation is known as Huisgen cycloaddition, where an organic azide **10** reacts with an alkyne **11**. Although this reaction was discovered by the early 20th century, its mechanism was revealed by Huisgen's group in the 1960s.[41] The synthetic potential of the azide-alkyne cycloaddition (AAC) reaction is surprising, since a great structural variety can be obtained by the substituents modification on the organic azide or alkyne. Despite this, for about forty years the reaction lacked selectivity since a mixture of 1,4 **12** and 1,5 **13** regioisomers was always obtained (Scheme 7a). In the early 2000s, the Sharpless[42] and Meldal[43] groups found almost simultaneously that Cu(I) salts were able to accelerate the reaction rate up to 10 million times. In addition, the advantage of using Cu(I) did not affect the reaction rate only, but also gave access towards the 1,4-regioisomer exclusively, under mild reaction conditions (Scheme 7b). This reaction, called Cu(I) catalysed azide-alkyne cycloaddition (CuAAC), is currently the most used for the synthesis of 1,4-disubstituted 1,2,3-triazoles, and its application reaches almost all branches of chemistry: the discovery of new drugs,[44] biochemistry,[45] polymer and dendrimer chemistry,[46] and materials science.[47]



Scheme 7. AAC reactions regioselectivity under thermal and Cu(I)-catalysed conditions.

CuAAC reaction is included within the group of reactions that Sharpless defines as *click*.[44] Among the main features of this reaction we can mention: simple procedures, broad synthetic scope with excellent yields and specificity; in addition, the products are easy to isolate; no secondary or dangerous by-products to the environment and health are generated; readily available and easy-to-handle starting materials are used; and, in many cases, mild reaction conditions can be set and water or alcohol can be employed as benign solvents.

Organic chemists succeeded in proving that just the Cu(I) species has catalytic activity in the CuAAC reactions to obtain 1,4-disubstituted 1,2,3-triazoles.[48] Fortunately, copper is a low-toxic and abundant element on earth compared to other transition metals used as catalysts. Also, cooper allows the development of environmentally friendly methodologies and, above all, very inexpensive. The sources of copper that have been used in the CuAAC reactions are really varied. For example, elemental copper was incorporated as wire[49] or as nanoparticles[50]. A mixture of Cu(0) and Cu(II) has also been used to generate the active species by a comproportionation reaction.[51] Other methodologies use Cu(I) directly, but due to its sensitivity to oxidation conditions, an inert oxygen-free atmosphere is essential. In these cases, a ligand-based on nitrogen must be added to stabilize Cu(I) and prevent it from oxidation or disproportionation.[52] The *in situ* production of Cu(I) from a suitable Cu(II) source is the simplest and most convenient procedure, since Cu(II) salts are easy-to-handle, cost-effective, and, moreover, their hydrates are highly stable to air and humidity. These methods ensure a high and constant concentration of Cu(I) throughout the reaction. The most widely used catalyst system is $CuSO_4$ and sodium ascorbate as a copper source and reducing agent, respectively. Although the oxidation and deactivation are not ruled out in aqueous and aerobic media, the amount of the reducing agent is normally used up to five times equivalents against the metal cation, thus overcoming this limitation. Despite all these advantages, reducing agents such as sodium ascorbate have been shown to have a negative impact on biological systems, affecting for example, protein chains[53] and even the DNA structure.[54] To compensate for these drawbacks, protocols where the active Cu(I) is generated *in situ* by the photo-reduction of Cu(II), have been successfully developed. With this new concept in hand, the application of the CuAAC reactions is not only possible in biological environments but also extended to materials science given their perfect spatial and temporal control of these methodologies.

For many years, scientists have been interested in light as an efficient energy source to induce chemical reactions.[55] The main advantage of using photochemical methods is the possibility to reach reactive intermediaries and chemical transformations that would be impossible to achieve in the absence of light.[56,57,58] The use of visible-light to promote organic transformations has developed in an unbridled way in recent decades, mainly due to the awareness on the part of the scientific community to promote energy efficiency.[59] Visible-light has relatively low energy, which allows exciting a specific population of molecules simultaneously, favouring the selectivity of the reaction, as well as the possibility of using sunlight as an inexhaustible energy source.

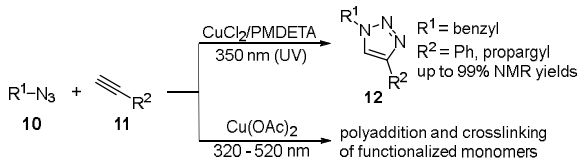
In the next section, we will review how organic chemists are using visible-light to promote triazole generation reactions in a more practical and environmentally friendly way. Among these approaches, we will find that many of them use copper to promote CuAAC reactions, but others that do not depend on this transition metal will also be shown. Finally, functionalization on triazole rings using visible-light will be also described.

3.1. Visible-light promoted copper(I)-catalysed azide-alkyne cycloaddition

The use of light for the generation of the Cu(I) active species can be carried out by direct photolysis of Cu(II) through photon absorption by a Cu(II)/ligand complex that triggers a photoinduced ET reaction (Scheme 8). This approach was applied for the first time by Yagci and Tasdelen, using a photochemical protocol based on $CuCl_2$ and *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDETA) and it allowed that an organic azide **10** reacts with an alkyne **11** to obtain the triazole **12**.[60] Although the irradiation wavelength used (350 nm) is not in the visible range, this work represented a significant advance in the application of click chemistry in biological systems sensitive to certain commonly used reducing agents.

Later on, Schubert's group succeeded to access to the active Cu(I) species from Cu(II) acetate, after having tested many other Cu(II) sources and ligands.[61] This new protocol uses irradiation in the UV-vis range between 320 and 520 nm (Xe lamp). In addition, this system was used with the aim of carrying out

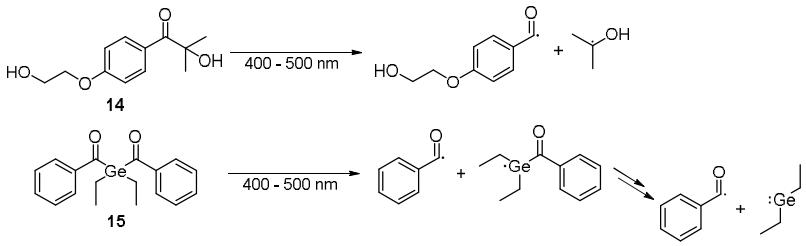
polymerization reactions using polyfunctional monomers, to generate linear and cross-linked polymers with interesting physical and mechanical properties. The direct photolysis disadvantage is that these complexes frequently absorb at short wavelengths, so high-energy irradiation sources are necessary, and the use of visible-light is limited.



Scheme 8. CuAAC-triggered by direct photolysis.

Indirect photolysis is another efficient method for Cu(II) photoreduction which generates reducing radical intermediates. In these approaches, a photolabile molecule is irradiated with UV or visible-light in order to generate radicals which are able to reduce Cu(II) triggering the CuAAC reactions. The first example was reported by Bowman *et al.*[62] They used the well-known Irgacure® **14**, a radical initiator normally used for radical polymerization reactions, as a reducing radicals precursor molecule (Scheme 9). Employing this new approach, it was possible to synthesize polymers starting from functionalized monomers with azide and alkyne groups with perfect spatial and temporal control. Despite its potential application in several fields of chemistry, its robustness, and control, the use of energetic wavelengths between 400 and 500 nm continues to be required.

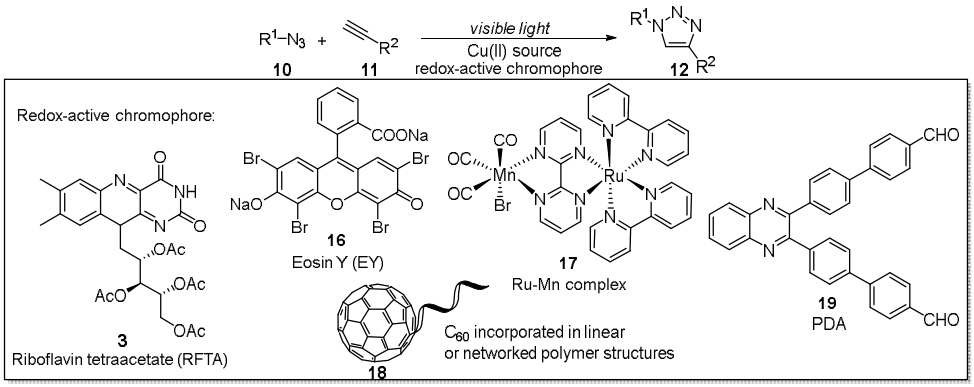
In order to use visible-light for the photostimulated CuAAC reaction, Yagci and co-workers reported a germanium-based photoinitiator **15** (dibenzoyldiethylgerman, DBDEG) (Scheme 9), which was able to efficiently generate Cu(II) reducing radical species.[63] This system was not only successfully applied in obtaining simple triazoles **12**, but also in some macromolecular reactions including polymer end-group functionalization, block copolymer formation, and step-growth polymerization.



Scheme 9. Indirect photolysis, reducing Cu(II) radicals generation.

On the other hand, Vicent *et al.* were able to use sunlight efficiently to achieve a photoinduced CuAAC reaction.[64] In this case, a Cu(II) complex with non-aromatic amino ligands was used in presence of ketoprofen, a benzophenone with a carboxylic group which is able to coordinate to a metal centre. Basically, the benzophenone ability to generate radical anions was exploited as a strong reducing agent when the complex is irradiated with visible-light.[65] The photogeneration of the Cu(I) active species was demonstrated by obtaining mono-, di- and tetrasaccharides linked through triazole units in very good yields, low catalyst loading, and short reaction times.

Visible-light-photoinduced CuAAC reactions can also be carried out using the organic molecules, transition metal complexes, or semiconductor materials shown in Scheme 10 as photocatalysts, which are able to generate exciting reducing species or intermediates to achieve active Cu(I) species from Cu(II). The first example was reported by König and Ritter,[66] who used riboflavin tetraacetate **3** as a redox-active chromophore, which gives the reduced species when irradiated with blue light and in the presence of any sacrificial donor such as triethylamine (TEA). This reduced species is returned to its initial state by an ET reaction to Cu(II) to give Cu(I), the active species in CuAAC.



Scheme 10. Redox-active chromophores used in visible-light promoted CuAAC reactions.

Later, Argüello *et al.* reported the use of other organic dyes, such as EY **16**, which is able to assist the photoreduction of Cu(II) and its application in the synthesis of triazoles by CuAAC.[67] This protocol uses green LED as an irradiation source, water as a solvent, and a very low catalyst load; where triazoles are produced from very good to excellent isolated yields. They propose a one-pot approach, and the metallic catalyst can be reused up to three times without considerable loss of efficiency. Unlike König's work, the presence of sacrificial reducing agents was not necessary since the dye excited species has the reduction potential necessary to afford the metal cation reduction reaction. Inspired by this observation, an in-depth mechanistic study was reported by Argüello, Marin, and co-workers, where the performances of the photoinduced CuAAC reactions in the presence of some sacrificial electron donors were studied.[68] While for EY, the reduction of Cu(II) to Cu(I) occurs by EY excited triplet state (^{3}EY*), for RFTA, the presence of a sacrificial amine was crucial to generate RFTA$^{\bullet-}$ or RFTAH$^{\bullet}$ which reduces the active species precursor cation.

Jain's group succeeded in synthesizing a complex based on Ru and Mn **17**, which absorbs in a wide range of the visible spectrum and, by irradiation with white light, is able to reduce Cu(II) to Cu(I). The novel complex was applied in a photo-triggered CuAAC reaction using ethanol as a green solvent and in very good to excellent triazole reaction yields.[69] The use of triethylamine as a sacrificial reducing agent was also required. In the proposed mechanism, when the complex is excited with visible-light, TEA gives an electron to Ru, and this reduced species spontaneously transfers one electron to the Mn, which ends up reducing Cu(II) to Cu(I).

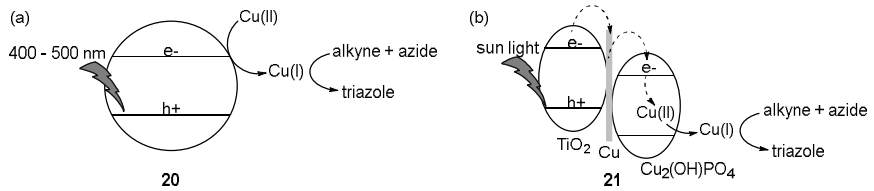
Yagci *et al.* were able to demonstrate that fullerene and its derivatives **18** can also carry out photo-triggered CuAAC reactions. In this approach, visible-light, in a range between 400 nm and 500 nm, was used to electronically excite C_{60} and to promote the photoreduction of Cu(II).[70] The C_{60} molecule could be incorporated into linear and cross-linked polymer chains to obtain homogenous and heterogeneous photocatalysts, respectively, in order to promote the formation of triazoles present in small molecules and polymers.

Very recently, Bhalla *et al.* have synthesized a pyrazine derivative assembly (PDA) **19** which, when combined with Cu(II) ions under visible-light-photostimulated conditions, generates triazoles by a one-pot approach. In this photo-triggered CuAAC reaction neither reducing nor stabilizing agents are necessary.[71]

Yagci was also able to demonstrate that semiconductors can be used to promote Cu(II) photoreduction using visible-light. ZnO nanoparticles **20** were used in the presence of $CuCl_2$ and PMDETA in acetonitrile (Scheme 11a). When the reaction mixture was irradiated, the semiconductor generated the exciton, which is able to transfer an electron to Cu(II), generating the Cu(I) species which catalyses the cycloaddition reaction giving triazoles in very good yields.[72]

More recently, Karthikeyan, Aman *et al.* reported the synthesis of triazoles using TiO_2-$Cu_2(OH)PO_4$ **21** as an efficient nano-photocatalyst under solvent-free conditions. This procedure uses sunlight as a source of irradiation, which stimulates the formation of the TiO_2 exciton, and transfers an electron from its

conduction band to the Cu(II) unit. Then, these excited electrons transfer to the Cu(II) unit through *in situ* created metallic copper and Cu(I) is transiently generated as the active species that catalyses the triazoles production in very good yields (Scheme 11b).[73]



Scheme 11. Excitons mediated CuAAC reactions.

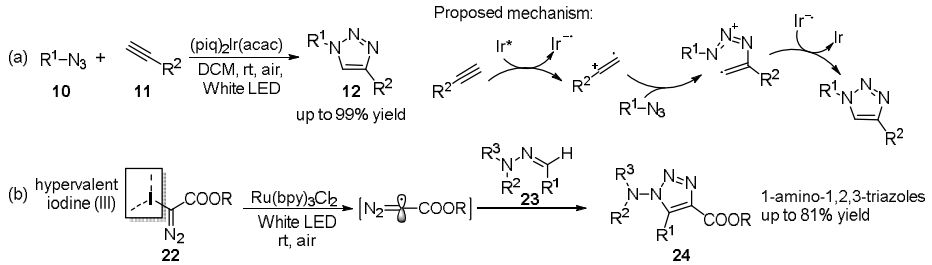
EY **16** was also used in a protocol proposed by Singh *et al.* for the synthesis of triazoles through a one-pot reaction involving a mixture of Cu(I) salt, benzyl epoxide or halide, alkyne, and azide salt. Unlike the previous examples, the photocatalyst assists the reaction between an epoxide or a benzyl halide and the azide anion, to obtain an organic azide, which reacts with the activated alkyne by Cu(I) in order to give the triazole by cycloaddition reaction.[74]

3.2. Visible-light assisted copper-free triazole synthesis

Not only copper has the leading role in azide-alkyne cycloaddition reactions. In addition, quite a few photochemical approaches have been developed where the photocatalyst assists the cycloaddition up-on visible-light absorption, generating reactive species that give the desired triazoles (Scheme 12).

Zheng *et al.* developed a protocol that uses a photoactive Ir complex which is able to oxidize the alkyne **11** to its radical cation under white LED irradiation. Then, the radical cation reacts with the organic azide **10** by a radical cycloaddition reaction, which gives rise to the triazole formation **12** and the concomitant regeneration of the photocatalyst.[75] This approach ensures very high regioselectivity comparable to the classical CuAAC. This work represents the first example of a copper-free azide-alkyne regioselective photoinduced cycloaddition reaction (Scheme 12a).

Wang, Li, and co-workers propose a more sophisticated approach to obtain 1-amino-1,2,3-triazoles **22**, using the ruthenium complex $Ru(bpy)_2Cl_2$ as a photocatalyst.[76] In this protocol, hydrazones **23** react with hypervalent iodine diazo reagents *via* a visible-light-induced [3+2] cyclization reaction. The electronically excited photocatalyst transfers an electron to the hypervalent iodine reagents to give the diazo radical intermediate, which reacts with the hydrazone to give the 1-amino-1,2,3-triazole **24** by a radical cycloaddition reaction (Scheme 12b).



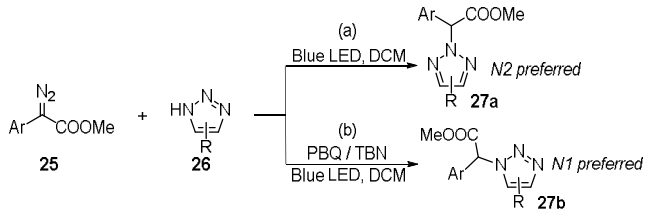
Scheme 12. a. Ir complex; b. Ru complex mediated visible-light-assisted copper-free triazole synthesis.

3.3. Visible-light-driven triazole functionalization

So far, we have explained how the cycloaddition reaction between an alkyne and an organic azide occurs to generate substituted triazoles controlled by the reactant structure and its reaction mechanism. Next, two protocols capable to derivatize already formed triazoles using visible-light and α-diazoacetates are now presented (Scheme 13).

Jurberg and co-workers demonstrated that visible-light is able to photolyze aryldiazoacetates **25** to generate a carbene intermediate, which can act as a nucleophile and adds to the triazole ring **26**. This reaction generates the corresponding insertion product followed by a proton abstraction.[77] The procedure was carried out in dichloromethane (DCM) as a solvent and a good selectivity towards the *N2* triazole **27a** could be observed (Scheme 13a).

Yang and Ma reported a complementary and photocatalyzed approach. In this work, several benzotriazoles were functionalized with α-diazoacetates in the presence of catalytic amounts of the *p*-benzoquinone (PBQ)/*tert*-butylnitrite (TBN) as a catalytic system.[78] The tentative mechanism proposes a hydrogen atom transfer reaction between benzotriazole and the excited *p*-benzoquinone, and the concomitant coupling between this radical and the carbene produced by the α-diazoacetate photolysis. This metal-free reaction is highly selective towards the *N1* triazole **27b** ring and can be carried out under mild reaction conditions affording very good triazole yields (Scheme 13b).

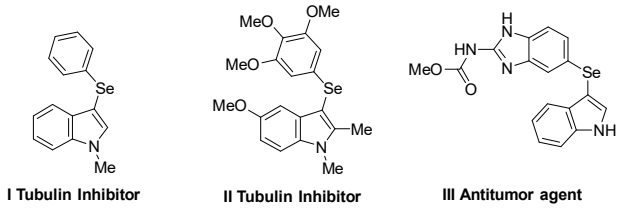


Scheme 13. Triazole functionalization by photostimulated approaches.

4. Selenoindoles

The synthesis of organoselenium compounds is a topic of great interest to the scientific community because these structures are present in a wide range of molecules of value, both biological, pharmaceutical, agrochemical, and in material science.[79,80] The demand for these structures has led to a deep development and study in the formation of C-Se bonds.

In particular, the formation of selenoindoles aims to harmonize the qualities of the indole ring,[81] which is a recurring motif in countless molecules of biological importance and technological applications, with the insertion of an organochalcogen. Starting from the premise that both the indole nucleus and the organoselenium compounds have interesting properties, it can be hypothesized to obtain a synergistic effect that would potentially enrich their properties and present unique attributes. Some structures with biological activity turn out to be antioxidant agents I,[82] tubulin inhibitors II,[83] and antitumor agents III[84] (Scheme 14).



Scheme 14. Biological active organoselenium molecules.

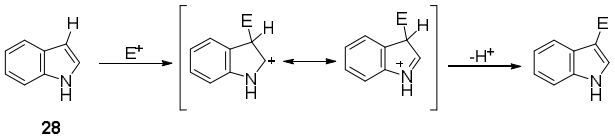
Today, there is a wide variety of synthetic methodologies to obtain this type of compounds; however, they resort to oxidizing agents[85], metallic catalysis using Pd[86] or Ru[87] nanospheres, and Lewis's acids such as $FeCl_3$.[88] The main difficulties faced by these synthetic designs consist of the use of high temperatures, economically expensive starting materials, the presence of metals, and a large excess of reagents. With the awareness of environmental issues and the development of more sustainable processes, photochemistry once again appears as a viable alternative, combined with the possible compatibility of green solvents.

The main goal of this section is to outline photochemical reactions available to obtain 3-selenoindoles. To this end, it is necessary to mention that starting materials are easily available, for example: indole is a

commercially available heterocycle, and the source of chalcogen; in addition, the selected bibliography makes special emphasizes on the use of aryl or alkyl diselenides, which give atomic economy to the chemical system, also giving the possibility "of customizing" these compounds because their syntheses are widely known.[89,90]

4.1. Indole ring reactivity

In the analysis to obtain 3-selenoindoles, the starting reagents need to be analysed. For its part, indole **28** is very reactive by the aromatic electrophilic substitution at the C3 position of the pyrrolic ring. This property is due to its enamine character where the positive charge can be delocalized at the nitrogen atom, stabilizing the Wheland´s intermediate. Subsequently, proton loss recovers the aromaticity of the indole ring, obtaining the functionalized product (Scheme 15).

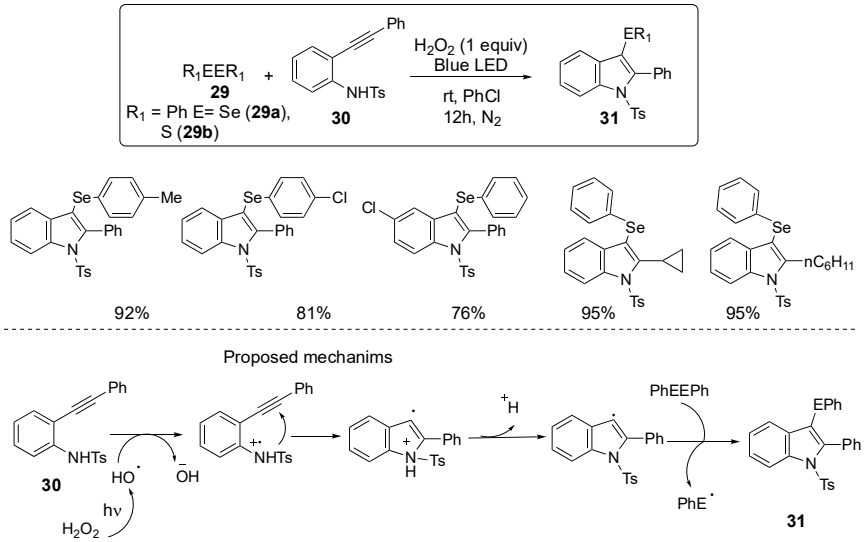


Scheme 15. S_EAr for indole rings, C3 functionalization.

In addition, indole reactivity is not only unique to S_EAr, but it can also receive radicals or participate as a nucleophile through the use of strong bases. Moreover, indole has the particularity of being a reducing agent (electron donor), being an extremely versatile compound in organic synthesis.

4.2. Synthesis of 3-selenoindoles by direct irradiation

Diselenides, particularly present the possibility of breaking the dichalcogen bond to obtain two radicals, which will become reactive intermediates. As an example, Shi and Wang[85] reported a reaction protocol where LED light, hydrogen peroxide, diphenyldiselenide **29a** and a functionalized aniline **30** produces 3-seleindoles **31** (Scheme 16).

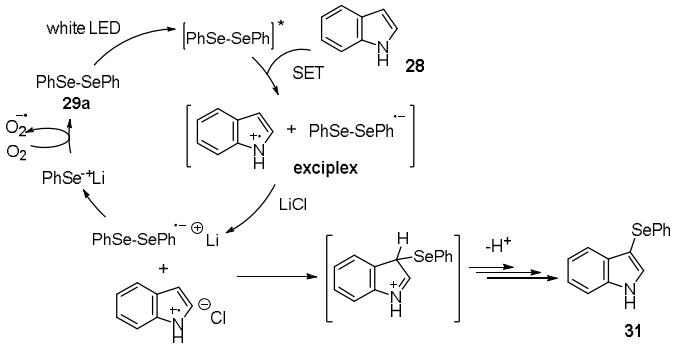


Scheme 16. Synthesis of 3-selenoindoles, cycling, and functionalization of indoles.

The authors' proposal is based on the photoinduced breaking of the peroxide bond generated radicals ˙OH which, through an ET, achieves a cyclization of **30** in the first instance, forming an indole ring with a

carbon radical at position 3. The developed methodology was extended to diselenide compounds. Finally, this radical reacts with the chalcogen **29** obtaining the final product **31** and a radical centred on the chalcogen that can react again. The main advantage of this work consists of the initial reagents and the formation of the indole ring. However, conditions such as halogenated solvent together with the need of an inert atmosphere do not respond to green chemistry grounds (Scheme 16).

In 2017, Kumaraswamy and collaborators[91] planned the generation of the indole radical cation by irradiation with visible-light (white LED) to pursue an ET reaction mechanism. The methodology developed tolerates a wide number of functionalities and more than 20 organoselenium molecules can be obtained from indole functionalization as well as anilines, pyrroles, and thiophenes substrates. Within the reaction conditions, the use of LiCl as an additive is mentioned; this salt is in charge of stabilizing the nucleophilic species of selenium. The reaction mechanism proposed in their work consists of the formation of the excited diphenyldislenide **29a**, which is reduced by indole **28** through Single ET, mediated by an exciplex. Finally, LiCl allows the charge separation, favouring the formation of the desired product **31**. The relevance of this methodology lies in its high atomic economy, great performances with various substrates, and its interesting mechanistic proposal (Scheme 17).



Scheme 17. Kumaraswamy´s mechanism proposal.

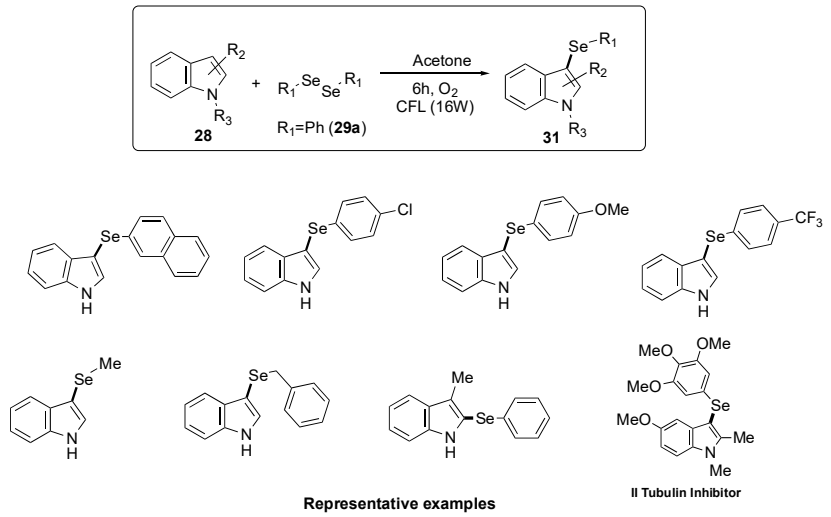
Later on, Kumar *et al.*[92] reported the use of visible-light as an energy source to obtain 3-organochalcogen indoles **31** in the presence of oxygen, without additives. The main advantage of this system lies in its high atomic economy, excellent yields, and great compatibility of functional groups. This work reports the access to a large number of compounds, presenting more than 20 examples with various functionalities, including electron-withdrawing, electron donor groups, and halogens. A particularity of this reaction system is the possibility of obtaining 2-selenoindoles when the C3 position is blocked (Scheme 18).

Regarding the study of the reaction mechanism, the authors affirm that the use of compact fluorescent lamps (16W) is capable of exciting indole **28** and thus facilitates its oxidation in the presence of oxygen. In this case, the indole structure allows the formation of a radical cation, generating a radical centred at position C3, which can abstract the chalcogen moiety from its respective dimer **29**, finally giving selenoindoles products **31** through deprotonation. It is interesting to mention that the synthesis protocol allows access to sulphur and selenium compounds (Scheme 19).

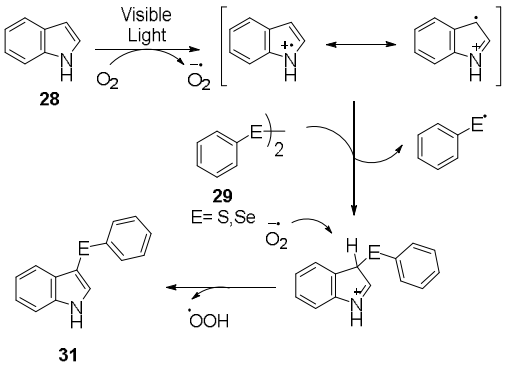
In agreement with previous studies, Heredia and Argüello[93] propose a green synthetic route to obtain 3-selenoindoles **31** using ethanol as solvent under blue LED irradiation. Several indoles **28** and **29a** were studied. Among the virtues of the chemical system developed, the following can be stressed: its high atomic economy, versatility, and robustness of the method that can be appreciated by its compatibility with aromatic, benzyl, and aliphatic substrates. In addition, kinetic and non-kinetic evidence is presented on the reaction mechanism, among which we can mention laser flash photolysis (LFP), fluorescence, and UV-vis experiments (Scheme 20).

Inside the mechanistic study, the authors compare the possible reactive pathways and, through experimental results, present a new proposal, where **29a** is photolyzed generating two selenium centred radicals. The difference of this path lies in the immediate addition of this mentioned reactive species to the

aromatic system, which generates a new radical species **A**/(PhSe•) cantered on a carbon atom. A vital change underlies here because there are now two possible routes for the rearomatization of the ring: one is the abstraction of the hydrogen atom by selenium radical (coming from the PhSeSePh photolysis), the other one being oxidation to form a carbocation (also known as Wheland's intermediate). Consequently, through a proton abstraction, 3-selenoindoles **31** are obtained (Scheme 21).



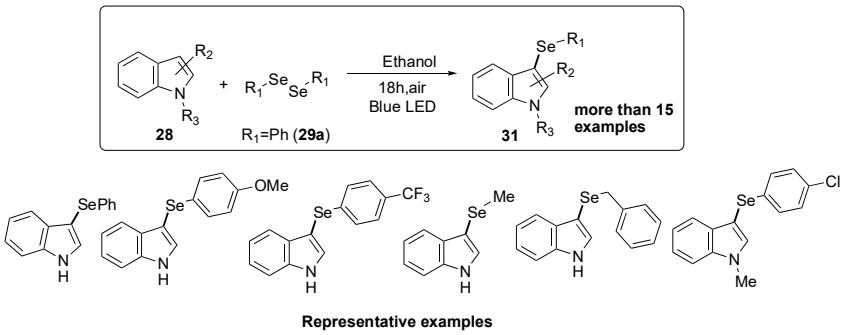
Scheme 18. Kumar´s 3-selenoindoles synthesis.



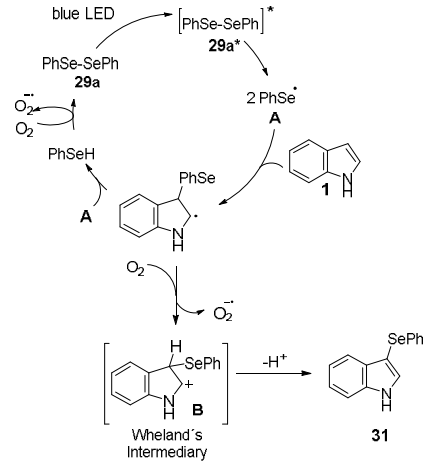
Scheme 19. Kumar´s mechanisms by excited indole.

Oksdath-Mansilla *et al.*[94] reported the synthesis of 3-selenoindoles **31** in flow, through a multi-step synthesis. Here, the synthesis can be divided into two processes, the first of which is the reduction of aryl selenocyanates **32** using Rongalite **33** as a reducing agent (the authors call this process "dark" because it is not photo dependent) to obtain diaryldiselenides **29**. The second process is the functionalization of indoles **28** after visible-light activation of the former compound, the diaryldiseleniede, under continuous flow conditions. In this report, good reaction yields were reported for various compounds (Scheme 22).

The value of this work lies in the compatibility of thermal and light reactions, added to the advantages of continuous flow chemistry, among which the following can be mentioned: reduction of the reaction time (compared to the batch conditions reported by Argüello[93], the reaction time is reduced by a factor of 9), and the possibility of scaling up where 1 gram of 3-phenylselenoindole could be obtained.



Scheme 20. Heredia's photoinduced 3-selenoindoles synthesis.



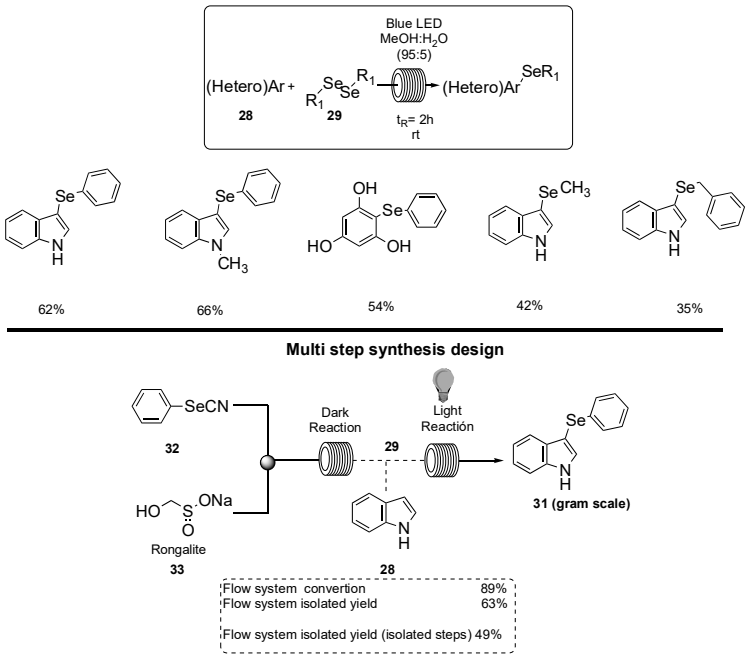
Scheme 21. Mechanism proposal of PhSe• radical indole insertion.

4.3. Synthesis of 3-selenoindoles using photocatalysis

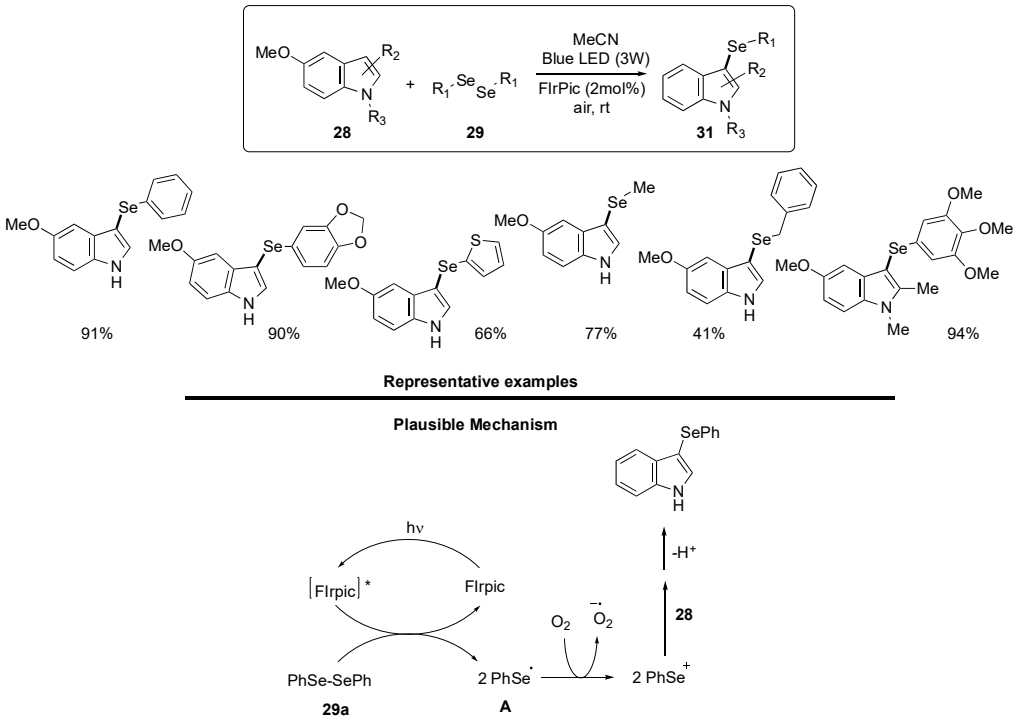
Herein, we revised the most recent works to obtain 3-selenoindoles **31** *via* photolysis or direct irradiation. Photoredox catalysis is widely known as a powerful tool in organic synthesis.[95] Regarding this matter, Zhang *et al.*[96] reported the formation of these compounds using an organometallic Iridium complex (FIrPic).

The designed methodology is robust because it can functionalize different aromatic compounds such as indole, thiophene, pyrrole, *etc.* Likewise, the mechanism proposed by the authors involves an energy transfer process between the photocatalyst and **29a** and the formation of the electrophilic species of selenium (PhSe•), which is formed in the presence of oxygen by irradiation with visible-light (Scheme 23). After that, the electrophilic selenium is added to the indolic ring **28**.

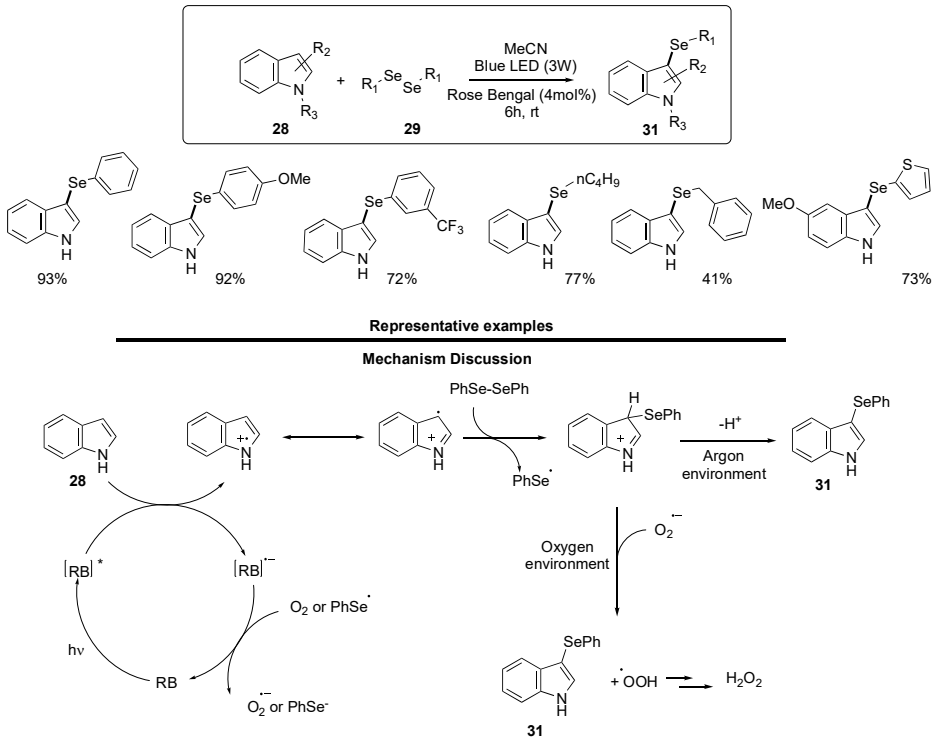
In 2018, Braga[97] reported a transition metal-free synthetic method using Rose Bengal (RB) as a photocatalyst to obtain 3-selenoindoles **31** (Scheme 24). It should be noted that this method is not exclusive for indoles **28**, the authors extend this methodology to imidazoles and electron-rich arenes as well. The synthesis is broadly compatible with various functionalities for both electron-donor and electron-withdrawing substituents. Moreover, it extends to aliphatic, benzylic, and aryl chalcogenated dimers **29**. The authors suggest a radical mechanism based on various mechanistic tests performed, where it can be mentioned the use of a radical scavenger like TEMPO. In turn, they exhibit two possible mechanistic pathways; this is because their protocol is compatible with aerobic and anaerobic environments (argon atmosphere).



Scheme 22. Continuous flow synthesis reported by Oksdath-Mansilla.



Scheme 23. Zhang´s synthesis to obtain 3-selenoindoles employing Ir complex.



Scheme 24. Braga´s photocatalytic synthesis to obtain 3-selenoindoles.

Progress within photocatalysis to obtain this type of organoselenium compounds is scarce. However, the designed methodologies cover a wide spectrum of substrates and reaction conditions, maintaining green chemistry principles and optimization of all resources as a beacon for further studies.

4.4. Synthesis of fluorinated 3-selenoindoles

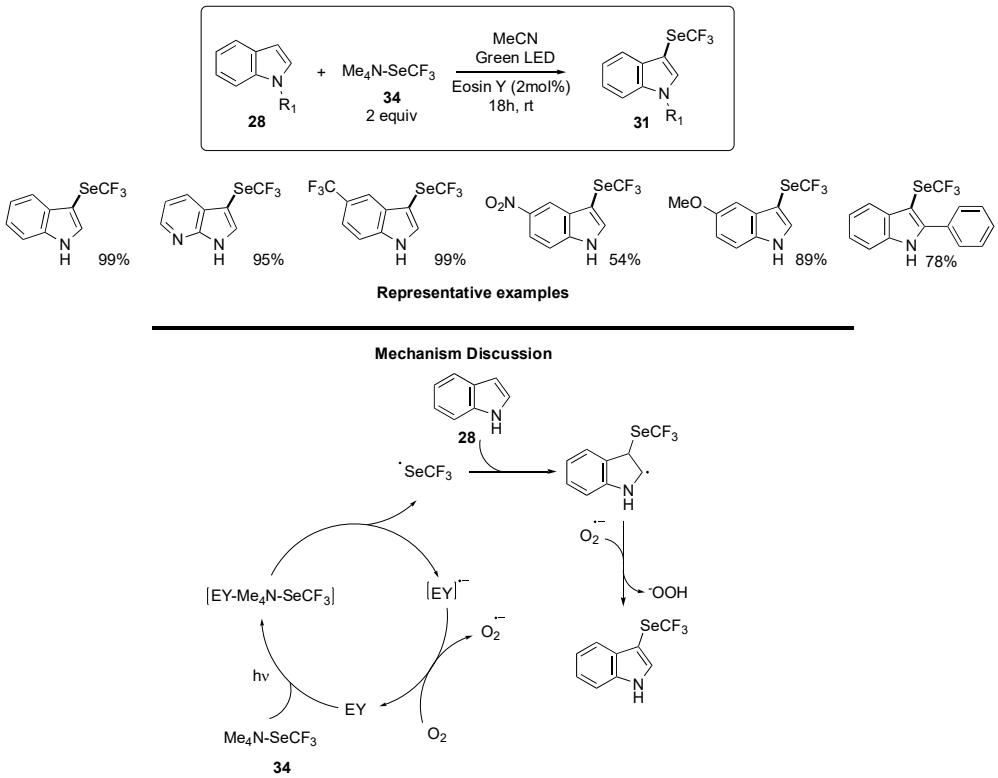
The organofluorine compounds in the presence of the selenium atom resulted in a very interesting combination. Perfluorinated compounds are widely known for their characteristics and utilities in various areas of science.[98] Magnier *et al.*[99] propose the use of a quaternary salt that contains the $SeCF_3$ group, and it is known that the radical species can be formed by means of an ET between tetramethylammonium-$SeCF_3$ **34**, and EY as a photocatalyst under green light irradiation. The methodology proposed by the authors is broadly compatible with indoles **28** that have electron withdrawing, and electron donor functionalities, and can be extended to pyrroles. Regarding the reaction mechanism, they suggest an association between the photocatalyst EY which, after ET, forms the radical $^{\bullet}SeCF_3$, that is subsequently inserted into the indole ring, finally giving 3-$SeCF_3$ indole systems **31** (Scheme 25).

5. Conclusions

In conclusion, this review has summarized recent advances in the synthesis of different heterocyclic compounds using visible-light. The examples include the production of benzothiazoles, triazoles, and selenoindoles scaffolds, which are known to have a wide range of applications. This represents a great challenge from the green chemistry point of view. Here, we have attempted to present most of the related methods recently reported in the literature.

The incredible evolution and the easy accessibility to LED technology have resulted in the development of new ways for the efficient synthesis of heterocycles. Consequently, several research teams have reported novel methodologies. Moreover, the use of continuous flow reactors appears to be a promising

competitive procedure compared to classical batch reaction, allowing more effective light absorption, which leads to improved reaction time, yields, and an easy scale-up.



Scheme 25. Synthesis of 3-selenoindoles using perfluorinated substrates.

We are looking forward to the novel development of synthetic methods using photochemical tools within the upcoming years. There are still a lot of systems to explore in order to make these reactions environmentally friendly and to obtain biologically active heterocycles. The task of discovering new heterocyclic systems with novel properties, inaccessible by other methodologies, remains open to the scientific community.

Acknowledgement

This work was supported by Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Secretaría de Ciencia y Tecnología de la Universidad Nacional de Córdoba (SeCyT-UNC) and Ministerio de Ciencia, Tecnología e Innovación Productiva (MinCyT) Argentina. I. D. L gratefully acknowledges the receipt of a fellowship from CONICET.

References

1. Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 10034-10072.
2. Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102-113.
3. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322-5363.
4. Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, *116*, 9850-9913.
5. Rossi, R.; Bardagi, J.; Buden, M. *Curr. Org. Synth.* **2017**, *14*, 398-429.
6. Xuan, J.; Lu, L. Q.; Chen, J. R.; Xiao, W. J. *Eur. J. Org. Chem.* **2013**, *2013*, 6755-6770.

7. Hu, X. Q.; Liu, Z. K.; Xiao, W. J. *Catalysts* **2020**, *10*, 1-26.
8. Buglioni, L.; Raymenants, F.; Slattery, A.; Zondag, S. D. A.; Noël, T. *Chem. Rev.* **2022**, *122*, 2752-2906.
9. Crisenza, G. E. M.; Mazzarella, D.; Melchiorre, P. *J. Am. Chem. Soc.* **2020**, *142*, 5461-5476.
10. Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. *Acc. Chem. Res.* **2016**, *49*, 1911-1923.
11. Dhadda, S.; Raigar, A. K.; Saini, K.; Manju; Guleria, A. *Sustain. Chem. Pharm.* **2021**, *24*, 100521.
12. Rey, V.; Soria-Castro, S. M.; Argüello, J. E.; Peñéñory, A. B. *Tetrahedron Lett.* **2009**, *50*, 4720-4723.
13. Cheng, Y.; Yang, J.; Qu, Y.; Li, P. *Org. Lett.* **2012**, *14*, 98-101.
14. Dinh, A. N.; Nguyen, A. D.; Aceves, E. M.; Albright, S. T.; Cedano, M. R.; Smith, D. K.; Gustafson, J. L. *Synlett* **2019**, *30*, 1648-1655.
15. Zhang, G.; Liu, C.; Yi, H.; Meng, Q.; Bian, C.; Chen, H.; Jian, J. X.; Wu, L. Z.; Lei, A. *J. Am. Chem. Soc.* **2015**, *137*, 9273-9280.
16. Srivastava, V.; Singh, P.; Singh, P. P. *Croat. Chem. Acta* **2015**, *88*, 227-233.
17. Xu, Z. M.; Li, H. X.; Young, D. J.; Zhu, D. L.; Li, H. Y.; Lang, J. P. *Org. Lett.* **2019**, *21*, 237-241.
18. Bouchet, L. M.; Heredia, A. A.; Argüello, J. E.; Schmidt, L. C. *Org. Lett.* **2020**, *22*, 610-614.
19. Bai, J.; Yan, S.; Zhang, Z.; Guo, Z.; Zhou, C.-Y. *Org. Lett.* **2021**, *23*, 4843-4848.
20. Monga, A.; Bagchi, S.; Soni, R. K.; Sharma, A. *Adv. Synth. Catal.* **2020**, *362*, 2232-2237.
21. Ye, L.; Chen, J.; Mao, P.; Mao, Z.; Zhang, X.; Yan, M. *Tetrahedron Lett.* **2017**, *58*, 874-876.
22. Hwang, H. S.; Lee, S.; Han, S. S.; Moon, Y. K.; You, Y.; Cho, E. J. *J. Org. Chem.* **2020**, *85*, 11835-11843.
23. Yu, C.; Lee, K.; You, Y.; Cho, E. J. *Adv. Synth. Catal.* **2013**, *355*, 1471-1476.
24. Sun, W.; Chen, H.; Wang, K.; Wang, X.; Lei, M.; Liu, C.; Zhong, Q. *Mol. Catal.* **2021**, *510*, 111693.
25. Le, H. A. N.; Nguyen, L. H.; Nguyen, Q. N. B.; Nguyen, H. T.; Nguyen, K. Q.; Tran, P. H. *Catal. Commun.* **2020**, *145*, 106120.
26. Palani, P.; Chithiraivel, V.; Chandru Senadi, G. *Mater. Today Proc.* **2022**, in press https://doi.org/https://doi.org/10.1016/j.matpr.2021.06.312.
27. Samanta, S.; Das, S.; Biswas, P. *J. Org. Chem.* **2013**, *78*, 11184-11193.
28. Dadwal, S.; Kumar, M.; Bhalla, V. *J. Org. Chem.* **2020**, *85*, 13906-13919.
29. Das, S.; Samanta, S.; Maji, S. K.; Samanta, P. K.; Dutta, A. K.; Srivastava, D. N.; Adhikary, B.; Biswas, P. *Tetrahedron Lett.* **2013**, *54*, 1090-1096.
30. Singh, P. K.; Bhardiya, S. R.; Asati, A.; Rai, V. K.; Singh, M.; Rai, A. *ChemistrySelect* **2020**, *5*, 14270-14275.
31. Wade, A. R.; Pawar, H. R.; Biware, M. V; Chikate, R. C. *Green Chem.* **2015**, *17*, 3879-3888.
32. Yuan, Y.; Dong, W.; Gao, X.; Xie, X.; Zhang, Z. *Org. Lett.* **2019**, *21*, 469-472.
33. Liu, Y.; Chen, X.-L.; Sun, K.; Li, X.-Y.; Zeng, F.-L.; Liu, X.-C.; Qu, L.-B.; Zhao, Y.-F.; Yu, B. *Org. Lett.* **2019**, *21*, 4019-4024.
34. Liu, Y.; Chen, X.-L.; Li, X.-Y.; Zhu, S.-S.; Li, S.-J.; Song, Y.; Qu, L.-B.; Yu, B. *J. Am. Chem. Soc.* **2021**, *143*, 964-972.
35. Xie, X.-Y.; Li, Y.; Xia, Y.-T.; Luo, K.; Wu, L. *Eur. J. Org. Chem.* **2021**, *2021*, 4273-4277.
36. Ferreira, S. B.; Sodero, A. C. R.; Cardoso, M. F. C.; Lima, E. S.; Kaiser, C. R.; Silva, F. P.; Ferreira, V. F. *J. Med. Chem.* **2010**, *53*, 2364-2375.
37. Whiting, M.; Muldoon, J.; Lin, Y.-C.; Silverman, S. M.; Lindstrom, W.; Olson, A. J.; Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; Elder, J. H.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 1435-1439.
38. de Miguel, G.; Wielopolski, M.; Schuster, D. I.; Fazio, M. A.; Lee, O. P.; Haley, C. K.; Ortiz, A. L.; Echegoyen, L.; Clark, T.; Guldi, D. M. *J. Am. Chem. Soc.* **2011**, *133*, 13036-13054.
39. Zheng, T.; Rouhanifard, S. H.; Jalloh, A. S.; Wu, P. Click Triazoles for Bioconjugation. In *Click Triazoles*; Košmrlj, J., Ed.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2012, 163-183.
40. Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* **2011**, *6*, 2696-2718.
41. Huisgen, R.; Szeimies, G.; Möbius, L.. *Chem. Ber.* **1967**, *100*, 2494-2507.
42. Rostovtsev, V. V; Green, L. G.; Fokin, V. V; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599.
43. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064.

44. Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128-1137.
45. Yang, M.; Li, J.; Chen, P. R. *Chem. Soc. Rev.* **2014**, *43*, 6511-6526.
46. Astruc, D.; Liang, L.; Rapakousiou, A.; Ruiz, J. *Acc. Chem. Res.* **2012**, *45*, 630-640.
47. Bryant, J. J.; Bunz, U. H. F. *Chem. Asian J.* **2013**, *8*, 1354-1367.
48. Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457-460.
49. Molteni, G.; Bianchi, C. L.; Marinoni, G.; Santo, N.; Ponti, A. *New J. Chem.* **2006**, *30*, 1137-1139.
50. Lipshutz, B. H.; Taft, B. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 8235-8238.
51. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210-216.
52. García-Álvarez, J.; Díez, J.; Gimeno, J.; Suárez, F. J.; Vincent, C. *Eur. J. Inorg. Chem.* **2012**, *2012*, 5854-5863.
53. Zhan, W.; Barnhill, H. N.; Sivakumar, K.; Tian, H.; Wang, Q.. *Tetrahedron Lett.* **2005**, *46*, 1691-1695.
54. Liu, P.-Y.; Jiang, N.; Zhang, J.; Wei, X.; Lin, H.-H.; Yu, X.-Q. *Chem. Biodivers.* **2006**, *3*, 958-966.
55. Roth, H. D. *Angew. Chem. Int. Ed.* **1989**, *28*, 1193-1207.
56. J, T. N.; Gary, S. *Science* **1975**, *187*, 303-312.
57. Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052-1103.
58. Albini, A. F. M. *Handbook of Synthetic Photochemistry*; Albini, A., Fagnoni, M., Eds.; Wiley, 2009.
59. Anastas, P. T. . W. J. C. *Green Chemistry : Theory and Practice*; Anastas, P. T., Warner, J. C., Eds.; Oxford University Press: New York, 1998.
60. Tasdelen, M. A.; Yagci, Y. *Tetrahedron Lett.* **2010**, *51*, 6945-6947.
61. Sandmann, B.; Happ, B.; Vitz, J.; Hager, M. D.; Burtscher, P.; Moszner, N.; Schubert, U. S. *Polym. Chem.* **2013**, *4*, 3938-3942.
62. Adzima, B. J.; Tao, Y.; Kloxin, C. J.; DeForest, C. A.; Anseth, K. S.; Bowman, C. N. *Nat. Chem.* **2011**, *3*, 256-259.
63. Arslan, M.; Yilmaz, G.; Yagci, Y. *Polym. Chem.* **2015**, *6*, 8168-8175.
64. Beniazza, R.; Lambert, R.; Harmand, L.; Molton, F.; Duboc, C.; Denisov, S.; Jonusauskas, G.; McClenaghan, N. D.; Lastécouères, D.; Vincent, J.-M. *Chem. Eur. J.* **2014**, *20*, 13181-13187.
65. Harmand, L.; Lambert, R.; Scarpantonio, L.; McClenaghan, N. D.; Lastécouères, D.; Vincent, J.-M. A *Chem. Eur. J.* **2013**, *19*, 16231-16239.
66. Ritter, S. C.; König, B. *Chem. Commun.* **2006**, *2006*, 4694-4696.
67. Castro-Godoy, W. D.; Heredia, A. A.; Schmidt, L. C.; Argüello, J. E. *RSC Adv.* **2017**, *7*, 33967-33973.
68. Martínez-Haya, R.; Heredia, A. A.; Castro-Godoy, W. D.; Schmidt, L. C.; Marin, M. L.; Argüello, J. E. *J. Org. Chem.* **2021**, *86*, 5832-5844.
69. Kumar, P.; Joshi, C.; Srivastava, A. K.; Gupta, P.; Boukherroub, R.; Jain, S. L. *ACS Sustain. Chem. Eng.* **2016**, *4*, 69-75.
70. Taskin, O. S.; Yilmaz, G.; Yagci, Y. *ACS Macro Lett.* **2016**, *5*, 103-107.
71. Kumar, S.; Kumar, M.; Bhalla, V. *Chem. Asian J.* **2021**, *16*, 3944-3950.
72. Yetiskin, O.; Dadashi-Silab, S.; Khan, S. B.; Asiri, A. M.; Yagci, Y. *Asian J. Org. Chem.* **2015**, *4*5, 442-444.
73. Kiranmye, T.; Vadivelu, M.; Magadevan, D.; Sampath, S.; Parthasarathy, K.; Aman, N.; Karthikeyan, K. *ChemistrySelect* **2021**, *6*, 1210-1215.
74. Mishra, A.; Rai, P.; Srivastava, M.; Tripathi, B. P.; Yadav, S.; Singh, J.; Singh, J. *Catal. Letters* **2017**, *147*, 2600-2611.
75. Wu, Z.-G.; Liao, X.-J.; Yuan, L.; Wang, Y.; Zheng, Y.-X.; Zuo, J.-L.; Pan, Y. *Chem. Eur. J.* **2020**, *26* 25, 5694-5700.
76. Dong, J.-Y.; Wang, H.; Mao, S.; Wang, X.; Zhou, M.-D.; Li, L. *Adv. Synth. Catal.* **2021**, *363*, 2133-2139.
77. Stivanin, M. L.; Fernandes, A. A. G.; da Silva, A. F.; Okada Jr, C. Y.; Jurberg, I. D. *Adv. Synth. Catal.* **2020**, *362*, 1106-1111.
78. Yang, J.; Duan, J.; Wang, G.; Zhou, H.; Ma, B.; Wu, C.; Xiao, J. *Org. Lett.* **2020**, *22*, 7284-7289.
79. Nogueira, C. W.; Rocha, J. B. *J. Braz. Chem. Soc.* **2010**, *2010*, 2055-2071.
80. Lovato, F. L.; Teixeira da Rocha, J. B.; Dalla Corte, C. L. *Chem. Res. Toxicol.* **2017**, *30*, 1134-1144.

81. Pelkey, E. T.; Gribble, G. W.; Badenock, J. C.; Barden, T. C.; Berthel, S. J.; Firooznia, F.; Fu, L.; Kester, R. F.; Kishbaugh, T. L. S.; Li, J. J.; Russel, J. S.; Sundberg, R. J.; Wu, Y.-J. *Heterocyclic Scaffolds II: Reactions and Applications of Indoles*; 2010.
82. Kumar, S.; Yan, J.; Poon, J.-F.; Singh, V. P.; Lu, X.; Karlsson Ott, M.; Engman, L.; Kumar, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 3729-3733.
83. Kuršvietienė, L.; Mongirdienė, A.; Bernatonienė, J.; Šulinskienė, J.; Stanevičienė, I. *Antioxidants* **2020**, *9*, 80-91.
84. Guan, Q.; Han, C.; Zuo, D.; Zhai, M.; Li, Z.; Zhang, Q.; Zhai, Y.; Jiang, X.; Bao, K.; Wu, Y.; Zhang, W. *Eur. J. Med. Chem.* **2014**, *87*, 306-315.
85. Chen, Y.; Cho, C.-H.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 6802-6811.
86. Vásquez-Céspedes, S.; Ferry, A.; Candish, L.; Glorius, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 5772–5776.
87. Lin, M.; Kang, L.; Gu, J.; Dai, L.; Tang, S.; Zhang, T.; Wang, Y.; Li, L.; Zheng, X.; Zhu, W.; Si, R.; Fu, X.; Sun, L.; Zhang, Y.; Yan, C. *Nano Res.* **2017**, *10*, 922-932.
88. Sperança, A.; Godoi, B.; Menezes, P. H.; Zeni, G. R. *Synlett* **2013**, *24*, 1125-1132.
89. Oliveira, A. R. M. de; Piovan, L.; Simonelli, F.; Barison, A.; Santos, M. de F. C.; de Mello, M. B. M. *J. Organomet. Chem.* **2016**, *806*, 54-59.
90. Mathis, C. A.; Wang, Y.; Holt, D. P.; Huang, G.-F.; Debnath, M. L.; Klunk, W. E. *J. Med. Chem.* **2003**, *46*, 2740-2754.
91. Kumaraswamy, G.; Ramesh, V.; Gangadhar, M.; Vijaykumar, S. *Asian J. Org. Chem.* **2018**, *7*, 1689-1697.
92. Rathore, V.; Kumar, S. *Green Chem.* **2019**, *21*, 2670-2676.
93. Lemir, I. D.; Castro-Godoy, W. D.; Heredia, A. A.; Schmidt, L. C.; Argüello, J. E. *RSC Adv.* **2019**, *9*, 22685-22694.
94. Heredia, A. A.; Soria-Castro, S. M.; Castro-Godoy, W. D.; Lemir, I. D.; López-Vidal, M.; Bisogno, F. R.; Argüello, J. E.; Oksdath-Mansilla, G. *Org. Process Res. Dev.* **2020**, *24*, 540-545.
95. Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075-10166.
96. Zhang, Q.-B.; Ban, Y.-L.; Yuan, P.-F.; Peng, S.-J.; Fang, J.-G.; Wu, L.-Z.; Liu, Q. *Green Chem.* **2017**, *19*, 5559-5563.
97. Saba, S.; Rafique, J.; Franco, M. S.; Schneider, A. R.; Espíndola, L.; Silva, D. O.; Braga, A. L. *Org. Biomol. Chem.* **2018**, *16*, 880-885.
98. Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881-1886.
99. De Zordo-Banliat, A.; Barthélémy, L.; Bourdreux, F.; Tuccio, B.; Dagousset, G.; Pégot, B.; Magnier, E. *Eur. J. Org. Chem.* **2020**, *2020*, 506-509.