Light-Induced Domino and Multicomponent Reactions: How to Reach Molecular Complexity without a Catalyst

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Achieving high molecular complexity can be not trivial, but the exploitation of domino reactions provides an atom- and step-economical method to reach this target. Over the past decades, a lot of efforts have been put on the development of photocatalytic cascades employing both metal-based and purely organic catalysts. Despite the effectiveness of these protocols, catalyst- and additive-free light-induced domino reactions are gaining momentum thanks to their efficiency, operational simplicity and sustainability. The increasing number of papers published on this field in the last years is a proof of the appeal of these transformations. In this Review, we discuss domino and multicomponent reactions mediated by light with a focus on photocatalyst- and additive-free processes. The most recent advances in the synthesis of complex nitrogen-, oxygen-, sulphur- and selenium-heterocycles together with multicomponent cascades are analysed with an emphasis on both experimental and mechanistic studies.

1. Introduction

The development of efficient approaches for the combination of chemicals under catalyst- and solvent-free conditions has attracted much attention in recent years. Methodologies where there is no use of catalysts and/or other additives represent an appealing approach both for the academic and industrial research since they allow the minimization of waste, operational simplicity, ease of purification thus the reduction of the cost of the entire process.[1]

Visible light-initiated chemical reactions have emerged as a powerful tool in synthetic chemistry for improving efficiency as well as devising mechanistically interesting novel synthetic routes to target molecules, barely possible by traditional thermal reactions.[2] Nowadays, the focus of new synthetic strategies has moved towards the development of milder and greener reaction conditions allowing for the construction of complex molecular scaffolds in a more environmentally friendly way.

Photo-assisted organic chemistry combines modern synthetic methods development and boundless opportunities for integrating the newly elaborated methodology into photochemical sequences for building molecular complexity. This can be applied to visible light photocatalysis, but especially to photoinduced cascade and domino reactions yielding complex poly-heterocyclic molecular architectures via simple experimental procedures.[3] Achieving high molecular complexity can be not trivial, but the exploitation of domino or tandem reactions provides an atom- and step-economical method to reach this target. Over the past decades, a lot of efforts have been dedicated to the development of photocatalytic cascades employing both metal-based and purely organic catalysts.[4] Also multicomponent reactions (MCRs), an important subclass of tandem/domino reactions, allow three or more simple precursors to be employed in a single synthetic operation without isolating the intermediates with high atom economy operational simplicity.[5]

Despite the efficiency of these protocols, catalyst- and additive-free light-induced domino reactions are still in their infancy and nowadays their blossoming is demonstrated by the increasing number of papers published on this topic in the last two years.

A fundamental prerequisite for light mediated transformations to proceed in the absence of a catalyst is the presence of a chromophoric unit able to absorb light at the irradiation wavelength. Different strategies can be exploited for the reaction initiation. In catalyst-free conditions, these mainly rely on: i) the direct excitation of one of the starting materials which can be subsequently exploited for the generation of another reactive radical via energy transfer (ET) or single electron transfer (SET), ii) homolysis of labile bonds, iii) the formation of charge-transfer complexes or exciplex manifolds, and/or iv) the irradiation of Electron-Donor-Acceptor (EDA) complex intermediates. In some cases, the solvent can support the reaction by radical relay or hydrogen transfer. The choice of the wavelength employed is certainly linked to the reactive species which is going to absorb the light. This can be seen certainly as a limitation for these transformations which is avoided in the presence of the photocatalyst. Recently, the availability of low cost and monochromatic light sources such as LEDs is pushing towards a preferable employment of safer and easier to handle visible-light. Although, UV-irradiation can still be a valuable alternative to construct high-valuable molecular structures considering the actual possibility to control and tune also UV-light avoiding the formation of complex mixtures of products.

This review will deal with the recent progresses towards photocatalyst- and additive-free processes, mediated by light, with a special focus on domino/tandem and multicomponent reactions. The contributions to the field of the last five years will be analysed, although in a not comprehensive manner. Recent advances in the production of nitrogen-, oxygen-, sulphur- and selenium-heterocycles will be reviewed, in addition to protocols affording not cyclic compounds by MCR domino processes. Synthetic strategies, exploiting exciplex manifolds in [2 + 2]-heterocycloadditions mediated by visible light and involving carbonyl partners, has been reviewed by Franceschi et al. in early 2023 therefore it will not be the subject of this work.[6] Concerning the classification of the reactions presented according to a domino, tandem or a multicomponent process, we employed the definition used in the original paper. For a more
detailed definition of domino/tandem reactions in organic synthesis see the paper from Tietze.[7,8]

2. Oxygen Heterocycles

Among the pharmaceuticals approved by the U.S. Food and Drug Administration (FDA), oxygenated derivatives are ranked as the second most abundant type of heterocycles finding application in the treatment of a plethora of medical conditions.[9] Exhibiting a wide range of biological and pharmacological activities, it is not surprising that the preparation of oxygenated heterocycles has attracted the attention of synthetic chemists, more and more interested in developing milder and more ecofriendly methodologies to obtain these complex structures. Among them, visible light-mediated processes are gaining momentum, in particular those allowing the construction of substituted rings in a domino fashion and in the absence of the catalyst. In this section, we will analyse the most recent photo-induced strategies to construct five and six-membered rings containing at least one oxygen atom.

2.1. Five-membered rings

Benzofuran and dihydrobenzofuran derivatives are biologically relevant heterocycles.[10] Among the most recent photo-mediated methodologies reported for their preparation in the last five years, in 2022, Liu, Tang et al. developed a divergent synthesis of carbonylated 3 and hydroxylated benzofurans 4 via a metal- and catalyst-free radical annulation of 1,6-ynes 1 in the presence of bromomalonates 2 under irradiation at 405 nm (Scheme 1).[11] In this case, an energy transfer (ET) was exploited to generate alkyl and bromine radicals through the homolysis of the bond C–Br of bromomalonate 2, a rarely followed pathway.[12] The solvent played a crucial role for the divergence of the reaction allowing the carbonylated products 3 to be obtained in MeOH, while the hydroxylated benzofurans 4 were preferentially formed in non protic solvents such as toluene. As the scope of products 3 is concerned, aryl alkynes 1 containing an aromatic ring substituted with both electron-withdrawing (EWG) and electron-donating (EDG) groups as R1, were well tolerated (45–85% yield) as well as a methyl or fluorine atom in the ortho or meta positions (58 and 72% yield respectively). A thienyl alkyne gave the desired product in 70% yield, while alkyl alkynes were not suitable for the reaction. The scope in the R2 group was explored only for carbonylated benzofurans. The employed malonates 2 were, generally, methyl or ethyl esters bearing as R2 group a halogen or a methyl substituent. The scope in the hydroxylated benzofurans 4 was less wide (6 vs 23 examples) and the yields were lower (35–52%) than compounds 3.

The reaction mechanism was supported by NMR studies, control experiments, UV/VIS absorption spectroscopy and emission quenching experiments. As summarized in Scheme 2, the 1,6-yn e 1 is able to absorb the light going to a singlet state (1* S1) which upon intersystem crossing (ISC) proceeds to its triplet excited state (1* T1). Having a relatively long lifetime,
intermediate $1^*$ ($T_1$) can give an ET with bromomalonate 2. The latter in its excited state gives C–Br homolysis generating alkyl a and bromine radicals as demonstrated by emission quenching experiments. Thus, the formed alkyl radical a can attack the 1,6-enzyme 1 in the ground state starting a cascade reaction. The 5-exo-dig cyclization is followed by the fast capture of the vinyl radical c by Br• to give intermediate d which was detected by NMR. From the common intermediate d, the reaction can follow two different pathways. In MeOH, the presence of residual water triggers the enol e formation via a visible light-promoted SNAr process, followed by aromatization and the loss of H$_2$ (proved by deuteriation experiment). Alternatively, in toluene, intermediate d can directly give aromatization to f. During the work-up the labile bromine atom is substituted with an OH group to give the compound 4 (Scheme 2).

The activation of the starting-material through ET was exploited also by Li et al. for the synthesis of sulfonyl-functionalised dihydrobenzofuranes 7 (Scheme 3).[13] 2-Alkynylarylethers 5 and sulfonyl chlorides 6 were employed as the substrates under irradiation with a 3 W blue LED or sunlight. This additive and photocatalyst-free cascade relies also on a solvent-radical relay strategy in which both the biomass-derived solvent 2-MeTHF and the light are essential to afford the product. The scope of the reaction was not influenced by the presence of substituents on the 2-alkynylarylethers 5 and no direct correlation between yields and both electronic effects or position of the groups was observed by the authors. On the contrary, for aromatic sulfonyl chlorides 6, the presence of an ortho substituent caused a slight decrease in yield, while 2-naphthalene- and thiophene-sulfonil chlorides were suitable. No reaction was observed substituting the oxygen with a nitrogen atom in compound 5.

On-off experiments confirmed the light to be essential for reactivity, even though the solvent can support the reaction for a certain time by radical relay. This point was further confirmed by GC-MS analysis which allowed to determine the formation of 2-chloro-2-methyltetrahydrofuran f and 2-chloro-5-methyltetrahydrofuran f, proving the existence of α-oxo radicals e/e' able to abstract the chlorine atom from the sulfonil chloride 6 to generate the corresponding sulfonyl radical a. The latter can be also formed by an ET from the excited state of the 2-alkynylarylether 5, the only species able to absorb light between 400 and 500 nm. The formation of an Electron-Donor Acceptor (EDA) complex was excluded because any change in the UV-Vis spectrum of 5 was observed upon the sulfonyl chloride 6 addition. Once the sulfonyl radical a is formed, it can easily attack the triple bond of the alkyne in its ground state to give a high reactive alkenyl radical b. Thus, a cascade process is

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**Scheme 1.** Divergent synthesis of carbonylated 3 and hydroxylated 4 benzofurans.

**Scheme 2.** Proposed mechanism for the divergent synthesis of carbonylated 3 and hydroxylated 4 benzofurans.
started by an intramolecular 1,5-hydrogen atom transfer (1,5-HAT) to give c, followed by 5-exo-trig cyclization. The formed radical d is able to abstract a hydrogen atom from the solvent, releasing the sulfonylated dihydrobenzofuranes 7 and the α-oxo radicals e/e’.

2-Alkynylarylethers 5 were exploited by Shen et al. as well to develop a new protocol for obtaining difluoroamidosulfonylated dihydrobenzofuranes 9 (Scheme 4).[14] The protocol relies on a three component radical cascade including a bicyclization and the formation of a charge-transfer (CT) complex (Scheme 5). DABCO(SO$_2$)$_2$ was employed as sulfur dioxide surrogate, while N-allylbromodifluoroacetamides 8 were used as synthons for the second ring bearing a nitrogen atom and a CF$_2$ group. Sodium hydrogencarbonate was employed as the base and DMA/H$_2$O as the solvents. Considering the scope, the electronic properties of substituents on the benzene ring of N-allylbromodifluoroacetamide derivatives 8 seemed not to influence the

Scheme 3. Visible light-mediated tandem radical addition/1,5-hydrogen atom transfer/cyclization of 2-alkynylarethers 5 with sulfonyl chlorides 6.


Scheme 5. Proposed mechanism for the three-components radical cascade bicyclization.
yields. The reaction was extended to di-substituted derivatives and to longer chains, while cyclopentyl and pyridyl substrates were unreactive. A significant effect on the reactivity was demonstrated by the $R_2^2/R_3^3$ groups, present on 2-alkynylarylethers $5$, causing a decrease in yields while increasing their steric hindrance.

The reaction mechanism was elucidated by control experiments and UV-Vis spectroscopy (Scheme 5). The formation of a CT-complex between the acetamide $8$ and DABCO($SO_2$)$_2$ was confirmed by a change on the absorbance of $8$ upon the addition of the $SO_2$ surrogate. Once the complex is formed, illumination with a blue light induces a SET to give the difluoroalkyl radical $a$ and a cationic tertiary amine radical together with $SO_2$. A 5-exo-trig cyclization allows the first ring closure giving the radical intermediate $b$ which, reacting with $SO_2$, produces the sulfonyl radical derivative $c$. The latter can react with the triple bond of the 2-alkynylarylether $5$ forming the vinyl radical $d$. After a 1,5-HAT, delivering radical $e$, a second 5-exo-trig cyclization allowing the closure of the oxygenated ring. The product is finally formed by hydrogen transfer from the solvent.

Another appealing strategy for the production of oxygenated compounds was recently developed by Corti et al. (Scheme 6). In this case, valuable 2,3-dihydrobenzofurans $12$ were obtained in a single step, from low to good yields (29–69%), from 2-allylphenols $10$ which were photochemically activated by the addition of a base, such as 1,1,3,3-tetramethylguanidine (TMG), to generate the corresponding phenolate anions $10^-$. Thus, upon irradiation with a blue LED the phenolate anion can absorb the light becoming a strong reducing agent in its excited state. A SET between $10^*$ and the $\alpha$-iodo sulfone $11$ can generate the electron-deficient radical $a$ upon C–I cleavage. The formation of this radical $a$ triggers a cascade process consisting in its addition to the 2-allylphenol $10$ double bond thus entering in a tandem atom transfer radical addition (ATRA). A final nucleophilic substitution delivered the product $12$. Besides aryl- and alkyl-substituted $\alpha$-iodo sulfones $11$, also perfluorohexyl iodide, tetrabromomethane and bromo(trichloro)methane can be used as the radical precursors. Interestingly, employing the latter halogenated compounds the reaction proceeds via EDA complex forming 2,3-dihydrobenzofurans $12$ bearing a gem-dibromoalkene or a gem-dichloroalkene fragment. As the 2-allylphenols $10$ scope is concerned, phenols substituted with ester, halides (Br, Cl), cyano, aldehyde, ketone and ether moieties were tested. The highest yields were obtained with phenols bearing an EWG in the para-position.

### 2.2. Six-membered rings

Among oxygenated heterocycles, coumarin and chromone structures are present in a variety of biological active compounds or natural products. In the last years, because of the mild reaction conditions, visible light-induced cyclization has been largely exploited. Interestingly, tailoring of the starting-material structures allows for diverse and site selective functionalization of the newly formed ring. For example, 3-bromocoumarins $15$ can be obtained by the methodology reported by Yan et al. in 2023. In this case, alkynoates $13$ were employed as the starting-material in the presence of CBr$_4$ as bench stable and easy to handle brominating reagent in DMF under blue LED illumination. Interestingly, the solvent has a central role in mediating this tandem radical brominative addition/cyclization generating, upon interaction with CBr$_4$ under irradiation, a
bromine radical and the radical intermediate d (Scheme 7). The formation of Br• after addition to the α-position of the triple bond, as previously described, generates a reactive vinyl radical a which can undergo a 5-exo-trig-spiro-cyclization, followed by 1,2-migration to release c. The re-aromatization of c, to give the 3-bromocoumarin 15, is made possible by the interaction of c with the radical intermediate d.

A good substrate scope was demonstrated for this reaction. In general, yields higher than 80% were obtained changing the R² group while keeping R¹ as a hydrogen atom. As the R¹ group is concerned, good yields were obtained with para-substituted aromatic rings with both EDG and EWG (66–99% yields) except for Cl, which led to by-products formation. No reaction was observed when R¹ was a NO₂ group independently from its position. A slight decrease in yield was obtained with di-substituted aromatic rings.

A different approach to obtain 3-cyanoalkyl coumarins 18 was developed by Hu et al. (Scheme 8). In this case, α-hydroxycinnamic esters 16 were employed both as the starting-materials and as the precursors for an internal photosensitizer, while O-perfluoropyridin-4-yl oximes 17, bearing a well-designed leaving group, were used as radical precursors for the cyanoalkyl moiety. The presence of a base, e.g. K₂CO₃, argon atmosphere and blue light were essential to have reactivity. The base, in fact, is necessary to deprotonate the α-hydroxycinnamic ester 16, releasing the phenolate anion 16*. Upon the base addition, the solution became yellow, thus the phenolate ion can absorb the blue light going to an excited-state 16*, whose emission is quenched by the oxime 17. The reductive N–O bond cleavage of oxime releases an unstable iminyl radical a. Its transposition to the central cyanoalkyl radical b was proved by TEMPO trapping experiments. In the last steps of the reaction mechanism, intermediate 16* is captured by radical b to form intermediate c which upon cyclization forms d. The latter so-formed radical gives a SET followed by deprotonation to release the final 3-cyanoalkyl coumarin 18 (Scheme 8). Regarding the scope, 27 products were reported with yield ranging from 24 to 85%. A gram scale synthesis was also performed, however with a diminished yield (46% vs 68%). The reaction, in general, can tolerate both EWG and EDG on the oxime, with moderate yields in the presence of heteroatoms. Regarding the substitution pattern on α-hydroxycinnamic esters 16, strong EWG such as NO₂ were not suitable while halogens, alkyl and alkyloxy groups gave from high to high yields. A poor scope was demonstrated for the R² group being limited to either a hydrogen or a methyl group.

Based on the decarboxylative coupling cyclization of enaminones 19 with N-arylglycine 20, in 2022, the groups of Xie and Le proposed a catalyst- and additive-free synthesis of 3-amino alkyl chromones 21 (Scheme 9). This reaction was mediated by blue light, under air in a mixture of THF/H₂O. The electronic properties of the R² group of enaminones 19 had no effects on the conversion with yields for products 21 between 65 and 73%. The poorest result was obtained with NO₂ group, in fact the yield dropped to 40%. N-arylglycine 20 with EWG gave lower yields than those substituted with EDG. The steric hindrance on the nitrogen atom had a huge impact on the reaction.

The key event in the mechanism of this decarboxylative coupling cyclization is the excitation of the enaminone 19 (Scheme 9). In its excited state, in fact, it is able to interact with O₂ to form singlet oxygen O₂*. Once O₂* is formed, it can interact with the N-arylglycine 20 causing its decarboxylation and the generation of the superoxide radical. The α-amino radical a is oxidized and deprotonated to form imine b. Its attack on the enaminone ground state gives an iminium intermediate c, which can engage a sequence of intramolecular
cyclization/elimination to form the desired 3-amino alkyl chromones 21.

In 2019, the group of Xu developed a novel radical strategy to introduce selenyl and hydroxyl groups in the same molecular scaffold under metal-free conditions.\(^\text{[21]}\) The formation of three new bonds and three stereocenters was realized via a multi-component tandem cyclization/substitution reaction employing water, diselenides 23 and alkyne-tethered cyclohexadienones 22 as starting-materials (Scheme 10). The presence of a catalytic amount of a base, e.g. CsOAc, PhCl as the solvent and the illumination with a white LED at 40°C were necessary for the formation of the product 24. The scope consisted in 21 5-hydroxy-3-selenyl-4a,8a-dihydro-2\(H\)-chromen-6(5\(H\))-ones 24 with yields ranging from 40 to 88%. Regarding the substituents on the alkyne-tethered cyclohexadienone 22, there was a good variability on the \(R_1\) group, while \(R_2\) was limited to methyl, ethyl or phenyl groups. Phenyl or substituted phenyl groups were well accepted on 23.

The proposed reaction mechanism was supported by TEMPO trapping and deuteration experiments. In the presence of TEMPO, the reaction yield decreased from 75 to 10% under standard condition, suggesting the involvement of a radical pathway. In the presence of only 1 equivalent of CsOAc, product 24 and intermediate d were isolated in a 1:1 mixture. Compound d evolved to the product under the standard conditions suggesting it to be an intermediate in the reaction mechanism. Moreover, employing \(\text{H}_2^{18}\text{O}\), the labelled product was obtained. Rationalizing these results, the authors suggested the following mechanism: the irradiation with white light is able to break the Se-Se bond releasing two PhSe* radicals which can attack the triple bond on the alkyne-tethered cyclohexadienone forming radical b. This compound is able to trigger an intramolecular radical addition closing the second ring thus forming c. The latter can be easily trapped by a second PhSe* radical, forming the isolated intermediate d. In the presence of the base, a nucleophilic substitution by water can happen giving the final product 24.

Increasing molecular complexity, a practical methodology to access 5-substituted indole chromeno[2,3-b]pyridines 28 was reported by Zhang et al. in 2019.\(^\text{[22]}\) Salicylaldehydes 25 were reacted with substituted indoles 27 and 2 equivalents of malononitrile 26 under irradiation with a green LED. A mixture of biomass-derived ethyl lactate and water was employed as the solvent. Five new bonds were formed in a one-pot fashion...
with a good tolerance towards substituents both on 25 and 27. The reaction is initiated by light inducing malononitrile 26 tautomerization thus triggering a Knoevenagel condensation with 25. After the elimination of water intermediate b is formed. Its subsequent irradiation with light results in the conversion to its excited state c which is able to extract a hydrogen atom from malononitrile 26, which in a cascade fashion abstracts a hydrogen atom from indole 27. Experiments with BHT as radical trapping reagent and analysis of the crude mixture by HPLC-MS revealed the formation of two key radicals I and II (Scheme 11). Another intermediate along the pathway to product 28 was identified running the reaction in the presence of 1 equivalent of malononitrile 26. Once intermediate g is formed, it can react with the second equivalent of 26 by attacking the CN group of the pyranyl ring. Cyclization allowed the formation of the second ring thus providing the final 5-substituted indole chromeno[2,3-b]pyridine 28.

Substituted salicylaldehydes 25 were also exploited as substrates by Jaiswal et al. to obtain 2-amino-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromene-3-carbonitrile derivatives 31 (Scheme 12). Compared to Zhang et al. protocol, the second equivalent of malononitrile 26 was substituted with hydrazine hydrate 30 and the indole with ethyl acetoacetate 29. The four component, one-pot reaction was run neat under irradiation with a CFL lamp. The scope was limited to 12 products with good yields and no need for column chromatography to isolate the pure product. Based on a literature survey, the authors proposed a mechanism similar to what proposed by Zhang et al. in Scheme 11 for the Knoevenagel condensation of salicylaldehydes 25 and malononitrile 26. At the same time, hydrazine hydrate 30 and ethyl acetoacetate 29 can condensate to deliver intermediate a. In the presence of light a reacts with d resulting in the radical species e. Final, tautomerization followed by enolization gives the product 31.

α-Cyanoketones 32 and malononitrile 26 can be reacted under illumination with a white LED in EtOH/H2O with isatins 33 or aldehydes 35 to give spirooxindoles 34 and 2-amino-4H-pyranyl-3,5-dicarbonitriles 36 respectively (Scheme 13). In both cases, Zhang et al. exploited a one-pot, three component strategy based on a previously described Knoevenagel condensation and activation mode of 26 under irradiation. Intermediate b can absorb the light going to the excited state which is a good hydrogen abstractor able to trigger a cascade of hydrogen abstraction and proton transfers. The subsequent combination of radicals c and d delivers intermediate e, which after tautomerization and cyclization, lead to the final product 31. For spirooxindoles 34, EWG or EDG substituted isatins 33 were converted to the product independently from their electronic properties, with a slight decrease on yield when the substituent was in the meta position. Halogens were well tolerated offering a possibility for further functionalization. As the synthesis of 36 is concerned, the steric hindrance on the aldehyde caused a small erosion in the yield, while the substituents on α-cyanoketone 32 had no effect.

In the late 2022, the group of Dell’Amico published an interesting study on the mechanism of the Paternò-Büchi reaction between indoles 27 and ketones 37 unveiling the impact of light wavelength on the reaction stereoselectivity (Scheme 14). In general the oxetane stereochemistry on the product is determined by the spatial arrangement of the reagents, this having a direct effect on the geometry of the CT state. The wavelength selection is, therefore, very relevant to the stereochemical outcome. The authors found out that the reaction can proceed following different pathways (EDA,
exciplex formation, conventional triplet pathways). Moreover, a light or steric factors diastereo-differentiation can be realized. Thus, illuminating at 405 nm, a direct excitation of the EDA CT-band is possible and the 8-exo product is preferentially formed. While at 370 nm the reaction proceeds via exciplex formation with a preference for the 8-endo product. Moreover, at 405 nm diastereo-differentiation based on the steric factors can be realized according to the ketone structure, the temperature and the reaction dilution. More electron-deficient ketones in diluted conditions reacts via the exciplex; while EDA formation is preferred with electron-rich indoles and electron-poor benzophenone in concentrated solutions.

3. Nitrogen Heterocycles

Cyclic molecules containing a heteroatom are among the most important structures in organic chemistry. When such heteroatom is a nitrogen, the heterocycle also acquires a crucial significance in medicinal chemistry. Indeed, N-based heterocycles characterize life science, being found both in natural products (alkaloids, vitamins, hormones, and antibiotics), and as bioactive core in drugs and pharmaceuticals. The reason for such vast diffusion might be imputed to the particular features conferred to the molecules by the presence of the nitrogen atom. Considering the simplest heterocycles, e.g.
cyclic amines, an immediate observation is their stability in physiological conditions and their ability of accepting or donating protons at those pH values. Thus, it is not surprising that more than 85% of all biologically active compounds comprises a heterocycle and among them 75% of FDA approved small molecules drugs possess at least one N-heterocycle in their structures.\footnote{28} This represents a crucial point even for modern organic synthesis. Firstly, we should remark the urgency to develop more synthetic methods tolerating polar groups and, among them, amines and N-heterocycles, especially. Secondly, new reactions are needed, particularly non-traditional disconnections allowing for heterocyclic ring synthesis. Photochemical methodologies meet these purposes.

3.1. Additive-free methodologies involving EDA complexes

An elegant strategy allowing for additive- and catalyst-free photochemical reactions, surely, relies on the formation of EDA complex.\footnote{29} Originated from non-covalent interactions between an electron-poor and an electron-rich compound, the EDA complex allows the participation of colourless organic compounds in visible light-mediated reactions. Upon EDA complex formation, the absorbance of visible light becomes possible thanks to a new CT band characteristic of the complex itself. A single-electron transfer, triggered between the species in the complex, is able to promote the formation of a couple of radicals, which can evolve towards the product in mild conditions.

This strategy was exploited by You and co-workers in the intramolecular dearomatization of indole derivatives \textit{40} in the presence of Umemoto’s reagent \textit{41} to afford trifluoromethyl-substituted spiro-indolenines \textit{42} by the use of visible light.\footnote{30} More than 20 spiroindolenines \textit{42}, containing a quaternary stereogenic center, were obtained in good yields (up to 90%) simply mixing the starting-materials in 1,2-dichloroethane (DCE) at room temperature under blue light irradiation. The authors observed that indoles \textit{40}, bearing strong EWG, required longer reaction time, whereas the diastereomeric ratio was strongly dependent on the substrate structure. The reaction was successfully scaled-up to gram scale. Authors suggested a mechanism which involves an EDA complex between indole derivatives \textit{40} and Umemoto’s reagent \textit{41}: the transient complex \textit{a} is formed, and upon visible light irradiation undergoes a SET from the donor to the acceptor (\textit{b}). At this point, CF\textsubscript{3} radical, produced through S-CF\textsubscript{3} bond cleavage, adds to the terminal alkene affording intermediate \textit{d}. Finally, the desired product \textit{42} is obtained, after deprotonation, by radical–radical recombination (Scheme 15).

Exploiting the formation of an EDA complex between alkyl(aryl)sulfinates \textit{44} and isocyanobiaryls \textit{43}, Natarajan et al. reported a methodology for the preparation of 6-alkyl(aryl)phenanthridines \textit{45} in ethyl lactate under aerobic conditions (Scheme 16).\footnote{31} 24 products were synthesized with yields between 39 and 74%. The reaction was also scaled-up to 7 mmol with a yield of 72%. According to the mechanism proposed, the EDA complex \textit{a} is reversibly formed between the sulfinates \textit{44} and the isocyanates \textit{43}. The complex \textit{a} upon visible light irradiation, is excited and the dipolar species \textit{a}*$ is produced by a SET process. Thereafter, \textit{a}* is broken up into \textit{b} and \textit{c}. The loss of SO\textsubscript{2} immediately occurs to produce intermediate \textit{d} from radical \textit{b}. Then, the addition of the alkyl/aryl radical \textit{d} to the ground state of the isocyanobiaryl \textit{43} affords the imidoyl radical \textit{e}, which undergoes an intramolecular cyclization reaction to give the new intermediate \textit{f}. In the last steps, its oxidation by molecular oxygen affords the cationic intermediate \textit{g} evolving to the final product \textit{45}.

An EDA complex was also involved in the synthesis of indolines \textit{48} via the cyclization of tertiary aryl amines \textit{47} with iodonium ylides \textit{46} under visible light irradiation at room temperature (Scheme 17).\footnote{32} The same heterocycles were previously prepared, \textit{via} the use of iodonium ylides, under heating.\footnote{33} The reported methodology was applied both to cyclic and acyclic ortho-, meta-, and para-substituted anilines \textit{47} bearing EWG or EDG affording \textit{27} indolines \textit{48} in 20–70% yields. An example applied to \textit{L}(-)-borneol methyl ester was also reported. Reactions were carried out on 0.1 mmol of aniline, and scaled-up to 1.5 mmol, in the case of \textit{N,N}-dimethylalanine, affording the corresponding indoline \textit{48} in 61% yield.
Mechanistic investigations confirmed the involvement of radicals and the EDA complex a formed between the tertiary aryl amine and the iodonium salt 46.

A visible light-mediated radical (4 + 2) annihilation between alkyl N-(acyloyloxy)phthalimides (NHPIs) 49 and N-substituted maleimides 50 in the presence of DIPEA was the key to obtain fused tetrahydroquinolines 51 under metal- and catalyst-free conditions (Scheme 18). Mechanistic investigations supported the involvement of an EDA complex between alkyl NHPI esters 49 and DIPEA which can be excited by blue light. It should be underlined that NHPI esters 49 are bench stable and can be easily obtained by the reaction of the corresponding carboxylic acids and N-hydroxyphthalimides. The scope was studied both on electronically diverse N-aryl maleimides and N-(acyloyloxy)phthalimides 50, affording tetrahydroquinolines 51 in discrete to excellent yields (43–80%).

Tetrasubstituted pyrroles 54 were prepared by a catalyst- and solvent-free, three-component approach at room temperature and under white light (Scheme 19). The reaction proceeds via enamine formation between a primary amine 52 and a 1,3-dicarbonyl compound 29 followed by the Michael addition with β-nitro styrene 53 and subsequent intramolecular cyclization and aromatization to yield 1,2,3,4-tetrasubstituted pyrroles 54. The reaction was applied to different anilines, nitro compounds and 1,3-dicarbonyl compounds affording 28 substituted pyrroles 54 in 69–93% yield. Two different protocols were used with similar outcomes, one carried out at room temperature for 5 h without light, the other exploiting white light as reaction promoter thus allowing the reaction time reduction to 1.5 h. In vitro cytotoxicity tests against Hepatocellular carcinoma cells (HepG2) using MTT (3-(4, 5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay were performed, proving the anticancer activity of substituted pyrroles 54 with IC<sub>50</sub> value of 17.82 μM. Two different mechanisms were proposed, either an ionic (A) or a SET pathway (B) in the presence of light (Scheme 20). Initially, the amine reacts
generate the Michael adduct. The following step is a Michael addition with β-nitro styrene to generate the Michael adduct. The adduct involves a SET mechanism via the radical anion and radical cation through a coloured EDA complex. Michael adduct further undergoes intramolecular cyclization to generate the imine, which leads to the desired tetrasubstituted pyrrole on aromatization with the elimination of water and HNO (Scheme 20).

### 3.2. Pyrrolidinones and Oxoindoles

Oxoindoles are privileged scaffolds usually found in several drugs and natural products which are used as therapeutic for tuberculosis, antitumoral, antiviral, antimarial, antidepressant agents, and progesterone receptor agonists. The development of synthetic strategies, mediated by visible light, has been extensively studied by various research groups.

A visible light-initiated regioselective sulfonylation/cyclization of 1,6-enynes with sulfonyl chlorides to afford sulfonylated lactams was proposed by X.-X. Meng. This protocol is carried out in open air, at room temperature, using 2-MeTHF as the solvent, without the use of strong oxidants, photocatalysts and other additives. The scope was studied both on sulfonyl chlorides and 1,6-enynes affording 26 products in good to excellent yields. As far as sulfonyl chlorides, both aryl and alkyl derivatives successfully reacted with slight differences in yields, the same was observed for enynes. Very good results were obtained, for example, with para-methoxy and para-trifluoromethyl-N-aryl derivatives affording the corresponding lactams in excellent yields (Scheme 21). A gram scale reaction was reported with very good efficiency both under sunlight and 3 W blue LED. Mechanistic studies proposed a cascade reaction promoted by the sulfonyl radical generated under visible light-irradiation.

Umemoto’s reagent was used as the fluorinating reagent, also, in the visible light trifluoromethyl-arylation of N-arylmethacylamides without the need for any transition metal, photocatalyst and additive at room temperature, in DMF under inert atmosphere. A broad functional group tolerance was showed with good yields both with sterically hindered substituents and in the presence of carbonyl groups and its analogous, e.g. cyano, acetyl and ester groups. An overall of 23 trifluoromethylated oxindoles were produced with yields ranging from 63 to 81%. Preliminary mechanistic experiments indicated that the reaction process involves a homolytic cleavage of Umemoto’s reagent after irradiation with visible light, then the so-formed F₂C• radical interacts with the N-arylacylamide through addition onto the double bond generating the radical intermediate, which affords radical after intramolecular cyclization. Oxidation of radical by either Umemoto’s reagent or intermediate produces the corresponding cyclic carbocation which deprotonation releases product (Scheme 22).

γ-Lactams, δ-lactams in addition to pyrrolidones, indolones, quinolinones, and fused polycyclic were obtained by N-xanthylamides bearing an un-activated olefins by the simple action of a purple LED in CH₂Cl₂ under photocatalyst- and additive-free conditions. The key of the process was a cascade xanthate transfer-cyclization. Forty-two examples were reported with yields up to 97%, and good functional group tolerance. The reaction was successfully accomplished by the...
action of sunlight, and scaled-up to 1.5 mmol. Interestingly, the protocol was applied to substrates bearing an endocyclic double bond to obtain complex fused polycyclic \( \gamma \)-lactams in good yields and diastereoselectivities. Several experiments were carried out in order to elucidate the mechanism, which it seems to involve a chain propagation. Upon the absorption of visible light, substrates are converted into a xanthate radical \( a \) and amidyl radical \( b \) via N–S bond homolysis. Then, the amidyl radical \( b \) undergoes a 5-exo or a 6-endo addition to the internal olefin. The resulting cyclized radical \( c \) or \( d \) finally adds to the thiocarbonyl of the starting xanthates 59, thus producing the xanthate-substituted N-heterocycles 60 regenerating the amidyl species \( b \) to propagate the chain.

3.3. Miscellaneous synthesis of N-containing heterocycles

A metal-free four-step one-pot synthesis of functionalized phthalazines 63 using \( \alpha \)-methyl benzophenones 61 as reagents in the presence of di-tert-butyl azodicarboxylate 62 has been recently reported. Phthalazines constitute the subunits of a wide variety of natural products with remarkable biological activities. Moreover, they are used as ligands for transition metal complexes. The strategy, described by the group of Tsogoeva was based on the combination of light-mediated enolization of commercially available \( \alpha \)-methyl benzophenones 61, a Diels-Alder reaction domino process with a subsequent one-pot deprotection/ aromatization. No catalysts or additives were needed. The reaction exploited UVA-visible light, in toluene at room temperature and 18 products were obtained in discrete yields (10-66%). The so-obtained phthalazines 63 were tested in vitro showing antiviral efficacy against HCMV and SARS-CoV-2. According to the proposed mechanism for photo-enolization, \( \alpha \)-methyl benzophenone 61 is excited to \( S_1 \) state affording the relatively long-lived triplet state \( (T_1) \) by ISC (Scheme 24). This latter is subjected to an intramolecular 1,5-HAT to produce the 1,4-biradical of the ketyl group \( a \) in the relaxed geometry. Initially, both the (\( Z \))- and the (\( E \))-photoenols are formed in about equal amount. However, the (\( Z \))-photoenol rapidly reverts to the starting ketone through efficient 1,5-HAT, differently from the (\( E \))-photoenol which being a long-lived intermediate can undergo re-ketonization to the starting-material only through a relatively slow solvent-mediated proton transfer. Once formed, the (\( E \))-photoenol is trapped by 62 to produce tetrahydrophthalazin-1-ol \( b \). Deprotection delivers free
tetrahydrophthalazin-1-ol c, which converts to the desired phthalazine 63, upon the loss of water and aromatization.

An early example of photocatalysis utilizing black LEDs coupled with a Diels–Alder strategy in the presence of substituted maleimides was exploited in 2016 by Dell’Amico et al. to access benzannulated carboxylic compounds.\[44\]

Other important \(N\)-containing heterocycles exhibiting diverse biological activities are quinazolinone and benzimidazole derivatives, as a matter of fact their moieties are found in many drugs, pharmaceuticals and agrochemicals.\[45\] Among the different approaches which can be pursued for their synthesis,\[46\] photocatalyst-free protocols based on a cascade cyclization have been extensively studied in the last years by the group of Can Jin. Polycyclic quinazolinones and benzimidazoles were easily synthesized by regioselective radical cascades avoiding the low yields and multi-step sequences characterizing traditional approaches. Fused alkyl- or acyl-substituted quinazolinones 66/67 were obtained with good to high yields starting from a common substrate, e.g. substituted quinazolin-4(3\(H\))-ones 64, functionalized with a butenyl or pentenyl side chain, employing malonates 2 or \(\alpha\)-keto acids 65 as coupling partners under visible light-irradiation (Scheme 25).\[47\] In the case of alkyl-substituted quinazolinones 66 the reaction was performed in DMF as the solvent, irradiating for 12 hours with a 365 nm LED.\[47a\] For acylated quinazolinones 67 the solvent choice played a vital role and the highest yields were obtained in DCM/H\(_2\)O at 395–400 nm excluding the air from the reaction mixture.\[47b\] In both cases, the tandem radical cyclization was initiated by the generation of the alkyl or acyl radical by ET from the excited state of the un-activated alkene 64 followed by C–X homolysis or decarboxylation. Once the radical was formed, its addition to the double bond generated a carbon-centered radical thus inducing the intramolecular cyclization. The consecutive 1,2-hydrogen shift or hydrogen atom abstraction gave the corresponding products, respectively 66 and 67. Both protocols demonstrated a good substrate scope for substituted quinazolin-4(3\(H\))-ones 66. The lowest yields were obtained when the \(R^1\) group was in position 8 of the aromatic ring. Alkyl bromides showed the lowest reactivity, while the corresponding chlorides were well tolerated. As far as the \(\alpha\)-keto acids 65 are concerned, both aliphatic and aromatic derivatives could be employed, notably aliphatic \(R^1\) groups performed better than aromatic substituents. Regarding acyl-substituted quinazolinones 67, Jin et al. reported a scale up to 5 mmol under flow conditions and sunlight-irradiation. Notably, yields of gram-scale reactions could be increased from 48% in batch to 67% in flow conditions.\[47b\]

The same research group also reported the synthesis of polycyclic benzimidazoles 69 using a similar approach (Scheme 26).\[48\] This environmentally friendly protocol exploited sulfonyl chlorides 6 as the sulfonyl radical precursors in MeCN as the solvent, at room temperature under irradiation at 400–405 nm. Under the optimized conditions, the group of Jin explored the versatility of the newly developed protocol showing high compatibility with benzimidazoles 68 containing substituents on different positions of the benzene ring. Also di-substituted rings were well tolerated. The highest reaction efficiency was obtained with aryl and heteroaryl sulfonyl chlorides, EWG gave good yields while with aliphatic sulfonyl chlorides a general decrease on yield was observed (30–47%). In this case, the reaction mechanism did not proceed via electron transfer or EDA formation, indeed the illumination of S–Cl bond at 400–405 nm caused the generation of the key sulfonyl radical. Thus, as described before by the same authors,\[47\] the so-formed radical can attack the double bond inducing the tandem cyclization (Scheme 26). The cascade process is closed by a direct hydrogen abstraction by the chlorine radical to form HCl. DFT calculations demonstrated this hydrogen abstraction to be barrier free. A gram-scale reaction was also performed.

An interesting strategy, which exploits a photoredox cascade process has been recently proposed to access several complex polyheterocyclic molecular architectures 72.\[49\] 20 examples were reported (42–81% yield) with significant growth of molecular complexity over three-steps. An unprecedented [2 + 2] reactivity of ES IPT (Excited State Intramolecular Proton Transfer) by \(\text{in situ}\) generated azaxylylenes was the key of the process. The reaction started with a transition metal-free...
intramolecular Csp$_2$–Csp$_3$ cross coupling of aromatic amides 70 to produce the photo-precursor b which is subjected to irradiation with a purple light (Scheme 27). Then the reaction can proceed through the excited state of the photo-precursor b engaging a [2 + 2] cycloaddition between the homoallyl and the aminothiophene moieties leading to a tricyclic dihydrothiophene cycloadduct. A second excitation via ESiPT involves the azaxylylene generated in situ, which could act as an internal triplet sensitizer. It is still not clear whether the process is concerted.

In 2023, the group of Can Jin also reported a multi-component cascade mediated by visible light for the alkylation of quinoxalinones 73 in water (Scheme 28 bottom).$^{[50]}$ Previously, visible light photoredox catalysis was exploited for the functionalization of quinoxalin-2(1H)-one derivatives, but always in the presence of a catalyst or an additive, except for the example reported by Studer et al. (Scheme 28 top).$^{[51]}$ In this case, perfluoroalkylated quinoxalinones 76 were obtained in mild conditions by a three-component radical cascade under blue light-irradiation and in the presence of DBU as a base able to deprotonate the key acidic aminyl radical intermediate. The reaction was assumed to be initiated by the light-induced C–I homolysis of the complex a formed between the halide and the base, followed by the radical b addition to the alkene 74. Radical intermediate c is nucleophilic enough to attack the C=NN bond of 73 to deliver the amyl radical d, which deprotonation by DBU produced the strong reducing radical anion e. The final product 76 is obtained by a SET between e and the halide 75.

The employment of an additive or a photocatalyst was completely avoided by Can Jin group, since their protocol proceeded via the formation of an EDA complex between the quinoxalin-2(1H)-one 73 and diethyl α-bromomalonate 2. After a SET, quinoxaline amino radical cation a is formed generating also a diethyl malonate radical b which can immediately attack the double bond of alkene 74 to afford radical intermediate c. Its coupling with a, followed by a deprotonation, releases the product 77. In general, a lower reactivity with incomplete consumption of the substrates was obtained with quinoxalinones substituted at the 6- and 7-positions with EWG (35–45 % yield). Aliphatic substituents on the nitrogen (R$_2$ group) were well tolerated (82–98 % yield). A slight decrease on the yield was observed with alkyl chains substituted with esters, benzoyl, phenyl, alkanyl and alkynyl groups (51–77 % yield). As far as the alkene is concerned, both

Scheme 27. Photochemical cascade process strategy to obtain molecular complexity via o-azaxylylene.

Scheme 28. Multicomponent approaches for the synthesis of substituted quinoxalinones 76/77.
4. Sulfur Containing Heterocycles

Together with oxygen and nitrogen heterocycles, also sulfur-containing compounds include a wide range of pharmaceuticals and bioactive molecules. Classical approaches for their synthesis generally involve multi-step operations and the employment of catalysts or additives. Since visible light has been shown to be an effective activator for several molecular, discovering new simple protocols to synthesize sulfur-containing heterocycles through cascade reactions, avoiding catalysts and additives, is becoming an intriguing research topic.

In 2020, Singh et al. reported an innovative domino protocol to synthesize highly functionalized thiazolines 83 starting from β-ketothioamides 81 and α-diazo-1,3-diketones 82, operating under visible light at moderate temperature in open air. It is already known that carbene can be produced through photolysis of α-diazo-1,3-diketones 82. In the presence of β-ketothioamides 81, they can perform a cycloaddition reaction toward the formation of thiazolines 83 in benign and simple conditions, with 100% atom economy and high yield. Experiments conducted in the dark or with either a green or white light did not furnish the desired product, implying blue light to be indispensable for the success of the reaction. In addition, yields followed an inversely proportional trend with the temperature. After the optimization, reactions with several β-ketothioamides 81 and α-diazo-1,3-diketones 82 were performed. Regarding substituents on the keto group of β-ketothioamides 81, both aromatic, bearing EDG and EWG, heteroaromatic, extended aromatic, or aliphatic substituents were investigated. R1 on the nitrogen atom can be an alkyl or an aromatic side chain. Also, symmetrical and asymmetrical α-diazo-1,3-diketones 82 were employed. A large-scale experiment (5 mmol) was carried out to verify the practicability and the synthetic utility of the optimized procedure. Several control experiments were carried out to better understand the mechanism and the acidity of the α-hydrogen atoms of the β-ketothioamides turned out to be crucial. As illustrated in Scheme 30, the blue light triggers the photolysis of α-diazo-1,3-diketones 82 thus generating singlet carbene intermediate a through denitrification. The more nucleophilic sulfur center of the β-ketothioamides 81 can react with a due to the loss of its acidic α-hydrogen atom to generate the open-chain intermediate b. Finally, an intramolecular N-cyclization occurs to achieve the thiazolines 83.

Another remarkable sulfur-containing heterocycle is 2-aminothiazole 86. This scaffold has been proven to be a valuable structural motif for pharmaceuticals, especially antifungal agents. A method to synthesize 86 consists in reacting anilines with thiocyanates 84. However, traditional methods generally require toxic oxidants, and hydrochloric/acetic acids as solvents. Alternatively, a copper catalyst together with oxygen as an oxidant can be utilized. In this field, He et al., in 2020, developed a protocol to synthesize 2-aminothiazoles 86 through visible light-initiated, malic acid-promoted cascade cyclization from aromatic amines 52 and potassium thiocyanate 84 employing air as an oxidant in an eco-friendly solvent as bis(methoxypropyl) ether (Scheme 31). Several anilines bearing different EDG and EWG in para position were adopted as substrates to investigate the scope. This procedure showed a valuable group tolerance since high yields were
obtained (72–85%), even employing aromatic polycyclic and aromatic hetero-polycyclic anilines.

Both light and Brønsted acid are necessary for the success of the reaction. A free-radical pathway was suggested by the authors, being the reaction completely suppressed by radical scavengers. Moreover, singlet oxygen was identified as a reactive intermediate by experiments with the singlet oxygen scavenger 1,4-diazabicyclo[2,2,2]octane (DABCO). As shown in Scheme 31, the oxygen molecules in the air are promoted to ¹⁰₂ under irradiation. In the meantime, malic acid 85 reacts with potassium thiocyanate 84, producing thiocyanic acid in situ. Consequently, singlet oxygen extracts an electron from thiocyanic acid generating a thiocyanate radical a and a hydroperoxyl radical. The thiocyanate radical a easily reacted with the aniline 52 to produce b. Then the radical hydroperoxyl, extracting a hydrogen atom, generates intermediate c and H₂O₂ through dehydro-aromatization. Finally, the amino group was nucleophilic enough to attack the carbon atom of the thiocyanate group to produce the target 2-aminobenzothiazoles 86.

Other thiazoles investigated by He and his team, consisted of N-substituted 2-aminonaphtho[1,2-d]thiazoles 89, a family of drugs for the treatment of ataxia, epilepsy and hypertension. They were prepared through a visible light-assisted, additive-mediated photocatalyst-free cascade reaction, starting from iodobenzenes and thiols without employing any photocatalyst. Recently, Sekar et al. developed a visible light-mediated photocatalyst-free protocol to accomplish the cascade synthesis of thiocroman-4-ones 93, thiocroman-4-ols 94 and thiocromenes 95 using pyridine as the base, in DMSO at room temperature. 2-Acylidobenzenes 90 and potassium xanthate 91 were necessary to obtain thiocroman-4-ones 93, while the addition of α,β-unsaturated carbonyl compounds 92 was required to generate thiocroman-4-ols 94 and thiocromanes 95 following a three-component cross-coupling reaction (Scheme 33). Initially, the scope for the synthesis of thiocroman-4-one 93 was investigated. Several 2-iodochalcones 96 bearing different aryl substituents were screened. 2-Aryl-substituted thiocroman-4-ones bearing neutral or electron rich, electron-poor, heterocyclic and polycyclic substituents were generated with good yields (48-92%).

**Scheme 31. Preparation of 2-aminobenzothiazoles 86 through visible light-induced cascade reaction.**

**Scheme 32. Visible light-assisted cascade reaction to produce N-substituted 2-aminonaphtho[1,2-d]thiazoles 89.**
ology was applied for the synthesis of thiochroman-4-ols starting from 2-iodobenzaldehyde and α,β-unsaturated ketones with different R3 and R4 groups (74-95% yields). When 2-iodobenzaldehyde was reacted with an α,β-unsaturated aldehyde the main product turned out to be the corresponding thiochromene as a result of further dehydration of thiochromanol.

To investigate the mechanism, several control reactions were performed proving the role of the xanthate ester, light and pyridine. Moreover, experimental and computational studies confirmed the formation of the EDA complex a between the iodocarbonyl reactant and the xanthate (Scheme 34).

The interaction with the visible radiation of the EDA complex generates the aryl radical b, the thiyl radical c and iodide anion. Consequently, the xanthate ester d is obtained through the radical coupling of b and c. This step is followed by the formation of the corresponding thiolate e. If the starting molecule is a 2-iodochalcone the reaction proceeds through an intramolecular Michael addition giving the respective thiochromanone 93. The use of α,β-unsaturated aldehydes as Michael acceptors allows the generation of thiocromones 95 as a result of the dehydration of the thiochromanol itself.

As far as the synthesis of 3-sulfenylthiochromones is concerned, Song and co-workers developed a protocol from o-thioaryl yrones and thiophenols, employing tert-butylhydroperoxide (TBHP) as additive, at 80 °C, in MeCN under nitrogen atmosphere. Based on these results, Panteado et al. built up a protocol to synthesize 3-sulfenylthiochromones starting from the same reactants in an additive-free conditions exploiting a blue LED radiation (470 nm), at room temperature, in acetone in open air (Scheme 35).

Regarding o-thioaryl yrones, different Ar1 were explored varying among EDG and EWG. Moreover, a large variety of aromatic thiols was screened by changing the Ar2 substituent thus obtaining yields between 42% and 98%. Surprisingly, no reaction was observed with an alkyl thiol and poor yields were obtained utilizing a n-pentyl substituted thiol (28%). The process can be promoted by sunlight but in lower yields. On the basis of Taylor and Unsworth observations on the ability of indole-tethered yrones to establish EDA complexes, the authors reported the formation of complex a which upon irradiation triggers a SET process affording a* bearing a radical cation on the sulfur atom and a radical anion on the alkyne. The presence of thiophenols is crucial for the cyclization reaction, undergoing hydrogen abstraction thus generating the sulfur.

Scheme 33. Cascade visible light reactions diagram for the synthesis of compounds 93–95.

Scheme 34. Plausible reaction mechanism for 93–94 formation.

Scheme 35. Visible light-assisted synthesis of 3-sulfenylchromones and proposed mechanism.
centered radical which, attacking the alkyne moiety, starts a radical cascade cyclization leading product 98 (Scheme 35).

Sulfur-containing seven-membered heterocycles, such as unsaturated thiepanes, are known as bioactive molecules for the treatment of HIV. On the other hand, vinyldicyclopropanes (VCPs) 99 are useful reagents to perform cycloadditions generating five- or seven-membered rings. Since, thiocarbonyl compounds, e.g. thioparabanate 100, exhibits appealing photochemical behavior under visible light-irradiation, Zheng and co-workers developed a methodology to synthesize unsaturated thiepanes 101 starting from VCPs 99 and thioparabanates 100 by a visible light-induced catalyst- and additive-free [5 + 2] cycloaddition at room temperature, in DCM, under nitrogen atmosphere (Scheme 36).[73]

Initially, the scope was investigated operating with symmetrical VCPs 99, bearing either geminal diesters or geminal nitrile groups. No product was obtained employing geminal diphenylsulfonyl substituents. Furthermore, spirovinylcyclopropyl oxindoles/lactones were chosen as asymmetrical VCPs. Only two thioparabanates 100 were investigated bearing dimethyl and disopropyl as R, respectively. Scale-up to 7 mmol was also reported with a slight decrease of the yield. UV-vis spectroscopy proved thioparabanates 100 to be able to absorb light up to 500 nm. In the excited singlet state, 100+ (S1) undergoes ISC to its triplet state followed by addition to the double bond of 99. Radical b is subjected to rearrangement giving the 1,7-biradical intermediate c. The occurrence of a radical recombination by ISC produces the desired product 101.

5. Selenium-containing derivatives

Other interesting compounds are organoselenium derivatives with potential antitumoral and antimicrobial activities. Selenium atoms are generally introduced employing diselenides as the selenium source in combination with transition-metal catalysts.[69–71] Interestingly, diselenides 23 have been proven to generate radical species through the homolytic cleavage of the Se–Se bond under visible light-irradiation.[80] In 2019, Xu and co-workers developed a methodology to synthesize sulfonylthiepanolanes 103 by reacting aryl acetylenes 102, diarylselenides 23 and DABCO(SO$_2$)$_2$, under blue light, in MeCN at room temperature (Scheme 37).[81]

Modest to good yields (35–71 %) were obtained with different EDG and EWG on Ar. As far as a mechanistic hypothesis is concerned, the diselenide 23 undergoes homolytic cleavage in the presence of light. The so-generated selenium radical a attacks the triple bond of ary lacetylenes 102, affording the vinyl radical b, which is easily captured by sulfur dioxide forming the sulfonyl radical intermediate c. The product 103 is formed by a consecutive addition of another ary lacetylene 102 followed by a second selenium radical a.

The reaction of alkynyl moieties with selenium-centered radicals from diselenides 23 under visible light-irradiation was further exploited by Zhou et al. In this case, selenylated spiro[5,5]trienones 105 were synthesized through a radical visible light-induced cascade from biaryl ynones 104 and diarylselenides 23, in presence of oxygen at room temperature, using MeCN as the solvent (Scheme 38).[82]

Several functional groups were well tolerated both on diselenides 23 and the ynones 104 obtaining selenylated products 105 from good to excellent yields (45–82 %). As previously described, blue light irradiation causes the homolytic cleavage of the Se–Se bond affording the arylselenium radical a. This active species, giving addition to the α-carbon of the biaryl ynone 104, generates radical b. This latter undergoes cyclization with the formation of a radical in the carbon adjacent to the methoxy group. Oxidation and demethylation affords selenylated spiro[5,5]trienones 105.
6. Miscellaneous

In this section, all the methodologies leading to products that cannot be classified in the previous sections are summarized and divided into cyclic and acyclic derivatives.

6.1. Cyclic derivatives

In 2022, a new methodology to obtain iodo-sulfonylated five-membered heterocycles was developed by Zhu employing enynes 106 as starting materials in a three-component visible light-mediated iodosulfonylative cyclization (Scheme 39). Iodoform 107 and sodium sulfinates 47 were employed as the other two components delivering vinyl iodides 108 in the (Z)-configuration because of the steric effect of the R' substituent. The latter group on the enyne can be either an unsubstituted or substituted aromatic ring. A broad range of sodium sulfinates 47 were used, both aromatic and aliphatic. The reaction could be extended to 6-membered heterocycles but in some cases HI elimination was observed. Regarding the reaction mechanism, the formation of the sulfonyl radical c is mediated by iodoform 107 under visible light-irradiation after the formation of intermediate a. Once the sulfonyl radical is formed, it attacked the double bond of enyne 106, triggering a 5-exo radical cyclization to give intermediate d. The product is obtained by visible light-induced iodine atom transfer of vinyl radical e, iodoform and sodium sulfinate 47.

As shown in Scheme 40, a photo-induced synthesis of non-symmetrical phenanthrenes 111 was reported in 2023. Overcoming the need for preformed stilbenes precursors, hazardous reagents and harsh conditions leading to low functional group tolerance and by-products formation, Parasram et al. simply engaged iodo-arenes 109 and substituted styrenes in an arylation/cyclization cascade mediated by a 390 nm light. Functionalized phenanthrenes 111 were obtained in moderate to good yields up to 5 mmol scale. An aryl analogue of the allosteric modulator NMDA was also obtained in 93% yield. Both EWG and EDG on the aryl iodide 109 were investigated, which included sensitive functional groups such as alcohols, cyano and halogens. When aryl iodide substituted in the meta position were used, a 2:1 mixture of regioisomers of the corresponding phenanthrene 111 was obtained. The styrene 110 scope was limited to a halogen or a methyl as R' groups, while R' was generally a hydrogen or a boronic acid pinacol ester.
In the mechanism proposal, the formation of an EDA was excluded since only the aryl iodide $^{109}$ is able to absorb the light. Following the irradiation of iodoarenes $^{109}$ by UV-Vis spectroscopy, the authors noticed the formation of a band centered at 461 nm which was assigned to $I_2$. This suggested a photoinduced C–I bond homolysis, leading to $I^*$ whose recombination allowed for the formation of $I_2$. Its formation was additionally proved by the inhibition of the reaction by a catalytic amount of starch. As shown in Scheme 41, the reaction mechanism was rationalized as follows: after C–I homolysis, the formation of $I^*$ is accompanied by the generation of an aryl radical a. Its addition to the styrene $^{110}$ gives a benzyl radical intermediate b which releases c after iodination by $I^*$ or $I_2$. The elimination of HI produces the stilbene d which undergoes a photo-promoted Mallory-type cyclization to generate dihydro-phenanthrene e. A final oxidation by air and $I_2$ yields the desired phenanthrene $^{111}$.

Fused spiro tricyclic compounds represent an important alkaloid structure for several bioactive molecules.$^{[85]}$ Since transition-metal catalysis is generally required to generate these scaffolds,$^{[86,87]}$ a catalyst-free visible light cascade reaction may be noteworthy. In this regard, Lin and co-workers built up a method to synthesize thio(seleno)-containing spirotricycles $^{114}$, starting from  N-arylpropionalamides $^{112}$ and thio(seleno)phenols $^{97/113}$, employing blue light, HCl, in MeCN at 60 °C in air (Scheme 42).$^{[246]}$

In the scope, different $R^1$ substituents on $^{112}$ were investigated with alkyl, aryl, heteroaryl and polyaromatic groups giving the corresponding products from low to high yields. The introduction of halogen atoms on the $R^2$ groups had no influence on the reaction. Several thiols bearing aryl substituents (67–76 % yields) and heteroaryl side chains (37–38 % yields) were employed. In the mechanism proposal, light induces the
homolysis of $\text{S--H or Se--H}$ bond generating the sulfur/selenium radicals $\text{a}$. $\alpha$-Addition on the triple bond of $\text{N-arylpropiolamide 112}$ followed by ipso-cyclization forms radical $\text{b}$ which is able to capture $\text{O}_2$ from the air releasing $\text{c}$. The loss of methanol followed by an intramolecular Michael addition generates the tricyclic product $\text{114}$.

6.2. Later chain functionalization

The introduction of sulfur atoms is regarded as a valuable feature, in particular in those compounds exhibiting anti-HIV activity (e.g. nelfinavir,$\text{[89]}$ $1\text{-}[2\text{-hydroxyethoxy}-\text{methyl}]\text{-6-}\text{(phenylthio)}\text{-thymine},\text{[90]}$ and a sulfanyltriazole analogue $\text{[91]}$). For this reason, in 2023, the group of Gao developed a tandem approach for the functionalization of $\text{Euphorbia}$ diterpenes $\text{115}$ with a sulfur-containing type diterpenes by an elegant and selective cyclopropane ring-opening mediated by blue light in the absence of any catalyst or additive (Scheme 43).$\text{[92]}$ The obtained premyrsinane diterepenes $\text{116}$ were subsequently converted to myrsinane-type diterpenes by an anti-Markovnikov addition of a series of substituted aromatic thiols $\text{97}$ in DCM at room temperature under blue light-irradiation. $\text{Euphorbia}$ factor $\text{L_3}$, a naturally occurring lathyrane-type diterpene, bearing a terminal alkene was chosen as starting material. Compound $\text{115}$ underwent the anti-Markovnikov addition of a series of substituted aromatic thiols $\text{97}$ in DCM at room temperature under blue light-irradiation. The thiol addition triggered an intramolecular cyclization closing a new cycle with the formation of a pair of diasteroisomers in a d.r. always higher than 5 : 1. A wide variety of aryl mercaptans $\text{97}$ were tested (substituted with EWG and EDG, 4-mercaptophenol and 4-aminobenzenethiol, heteroaryl thiols). In general, a reduction on the reactivity was observed with ortho substituted compounds, although high yield could be obtained increasing the reaction time to 48–72 hours. The protocol was extended to phenyl selenol, but only one example was reported. As shown in Scheme 44, a blue light-driven amination of C(sp$^2$)-H bond of naphthoquinones and quinones $\text{117}$ with aliphatic and aromatic amines $\text{52/88}$ for the preparation of 2-amino-naphthoquinones and 2-amino-quinones $\text{118}$ has been reported by Jha et al. in 2023.$\text{[93]}$ The coupling was extensively studied and 75 aminated products were successfully obtained simply irradiating the reagents with a blue LED in MeOH, at room temperature for 3.5 h. Several aromatic amines $\text{52}$, bearing both EDG and EWG were successfully coupled with compounds $\text{117}$ (16 examples, 79–96 % yield). Primary and secondary aliphatic amines $\text{88}$ afforded 2-amino-naphthoquinones in 35–99 % yields. Moreover 5 examples of large-scale synthesis, one of them affording 3 grams of product $\text{118}$, were reported. The radical pathway was confirmed by both computational and experimental investigations. The reaction probably proceeds starting from the reduction of naphthoquinone $\text{117}$ to form a highly oxidizing naphthoquinonyl biradical $\text{a}$ upon irradiation. Consequently, electron transfer from the amine to $\text{a}$ leads to a naphthoquinonyl radical anion $\text{b}$ and aminyl radical cation $\text{c}$. A proton transfer and delocalization leading to a
carbon-centered naphthoquinonyl radical and aminyl nitrogen radical forms a C-N bond, with subsequent elimination of hydrogen gas affording the desired product 118. Three different pathways to reach product 118 from the key intermediate f were hypothesized.

6.3. Acyclic derivatives

As reported in the following examples, visible light-mediated reactions are exploited not only for the synthesis of cyclic compounds and heterocycles but also for multi-functionalization of acyclic compounds. For example, the 1,2-difunctionalization of alkenes to afford silylated oximes can be realized following the methodology of Studer et al. (Scheme 45). This radical cascade, exploiting hydrosylanes and t-butyl nitrite (TBN) in i-octane, allowed the functionalization of electron-poor alkenes by photo-induced cleavage of TBN and the concomitant formation of t-butoxyl, silyl and persistent NO radicals at 405 nm. To increase the yields, the authors pointed out that TBN should be slowly added over a period of 6 hours. To explore the generality of the reaction, different substituted silanes were tested. In general, a decrease of the yield was observed increasing the number of phenyl rings, while the substitution of a phenyl with a benzyl ring had no effect on the reaction efficiency. A wide range of electron-poor alkenes were suitable. Moreover, the reaction was scaled up to 3 mmol without affecting the yield.

The catalyst-free α-functionalization of α-aryldiazoesters with cyclic ethers and a nucleophile.

Scheme 48. α-Aryldiazoesters as valuable starting-materials for the synthesis of carbamates, phosphorothiates, thiocyanates, nitriles, azides and phosphoric esters under blue light irradiation.

Scheme 49. General mechanism for the functionalization of α-aryldiazoesters with cyclic ethers and a nucleophile.
aliphatic group (Me or Et), the yield substantially decreased (49 and 41%, respectively). As far as the arylglycine esters 122 scope is concerned, only substrates bearing an aromatic group on the nitrogen atom were tested, while R' should be a benzene ring bearing different substituents. In the presence of halogens, a lower reactivity was observed because of the poor solubility and increased instability of the starting-material itself.

A key role in the reaction mechanism was played, not only by the light, but also by the oxygen producing the hydroperoxide intermediate a. The loss of H₂O₂ and formation of the transition state b by hydrogen bonding with 123, releases the final product 124 upon decarboxylation.

Exploiting a white LED as light source, the group of Studer developed an intermolecular cascade leading to functionalized oximes 126 from acyloxy nitroso compounds 125 and electron-deficient alkenes 74 (Scheme 47).Á Aryl vinyl and alkyl vinyl ketones gave from moderate to good yields. The highest yield was obtained with trifluoroethyl acrylate. Free primary alcohols interfered with the process, while acrylamides, vinyl sulfones and acrylonitrile were suitable (38–83 % yield). The reactivity of styrenes was related to the electronic properties of the substituent on the aromatic ring. Also vinylpyridines and acroleins were eligible acceptors. Various acyloxy nitroso compounds 125 were tested in this process and the authors proved that the acetyl protecting group could be easily varied. Interestingly, the nitroso compound could bear from four- to twelve-membered ring as R² group. To not prepare sensitive nitroso compounds, the protocol was extended to a one-pot two-steps process employing oximes as starting materials. Moreover, the process is controlled by a Persistent Radical Effect (PRE). In fact, after light absorption, the nitroso compound 125 gives easily C=N-O homolysis thus a persistent NO• radical is formed along with an α-oxo-C radical a. The latter attacks the alkene and the so-formed radical adduct is trapped by the NO• radical. The tautomerization of the nitrosoalkene affords the final oxime 126.

Exploiting alkylboronic pinacol esters as precursors for C-centered radicals, the reactivity of persistent NO• radical, derived from N-nitrosoamines, was further extended by Studer in 2023.Á The radical defunctionalization of electron-poor alkenes to afford oximes was realized under irradiation with a 415 nm LED in dry DMSO.

α-Aryldiazoesters 127 are versatile compounds which can be easily activated under blue light irradiation to release a reactive carbene intermediate via photolysis. Since 2020, different research groups have developed efficient and environmentally friendly methodologies to couple α-aryldiazoesters 127 with different partners in multicomponent reactions (Scheme 48). When THF or cyclic ethers 128 were employed as the solvent, the latter actively participated in the reaction becoming one of the coupling partners. In this context, the groups of Jiang, Qi, Wei, Yue, Zhong, He and Xu extensively worked in this field, managing to develop different catalyst- and additive-free methodologies for the synthesis of carbamates 129,Á phosphorothiates 131,Á thiocyanates 133,Á nitriles 138 and azides 139Á under blue light irradiation. Adjusting the reaction conditions according to the coupling partners, the α-aryldiazoesters 127 and THF were reacted with carbon dioxide and an amine 88Á elemental sulfur and H-phosphonates 120,Á and TMSCN 137/TMSN 136,Á respectively. Only in 2023, the reaction was extended to NaSCN 132Á and to organic phosphinic acids 134, the latter methodology was employed to produce phosphoric esters 135Á.

A general reaction mechanism for all the previous methodologies is described in Scheme 49. The excited state of the α-aryldiazoesters a, formed upon absorption of blue light, can release N₂, forming the carbene intermediate b. In the presence of THF or a cyclic ether, intermediate b is trapped to generate an oxonium ylide c. The latter is trapped by the appropriate nucleophile affording the desired product after protonation.

A novel pathway was opened leading to S-alkyl phosphorothioates 140, carbamates 141 and amides 143 when α-aryldiazoesters 127 were coupled with elemental sulfur and H-phosphonates 130,Á carbon dioxide and an amine 88Á or a nitrosoarene 142 in a solvent different from THF (Scheme 50).
7. Summary and Outlook

This review reports the state of the art of light-promoted reactions, published in last five years, in which no photocatalyst is required. At the same time, complex molecules are produced by simple and straightforward protocols exploiting domino/tandem, cascade or multicomponent reactions. In addition, strategies which employ the “in situ” formation of colored intermediates, such as EDA complexes, have been also described. The attention towards novel approaches mediated by light which conjugate efficiency with mild reaction conditions will, surely, increase in the next years. Light-initiated synthesis carried out at room temperature in easy to handle solvents producing complex structures in high yields and the gram-scale represents one of the most important challenges for chemists in the future.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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[8] According to Tietze definition a domino reaction is a “transformation of two or more bond- forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former bond forming reactions”. Always according to Tietze, the term domino is more general and should be preferred to the term tandem which should only be applied to reactions in which two bonds are sequentially formed.