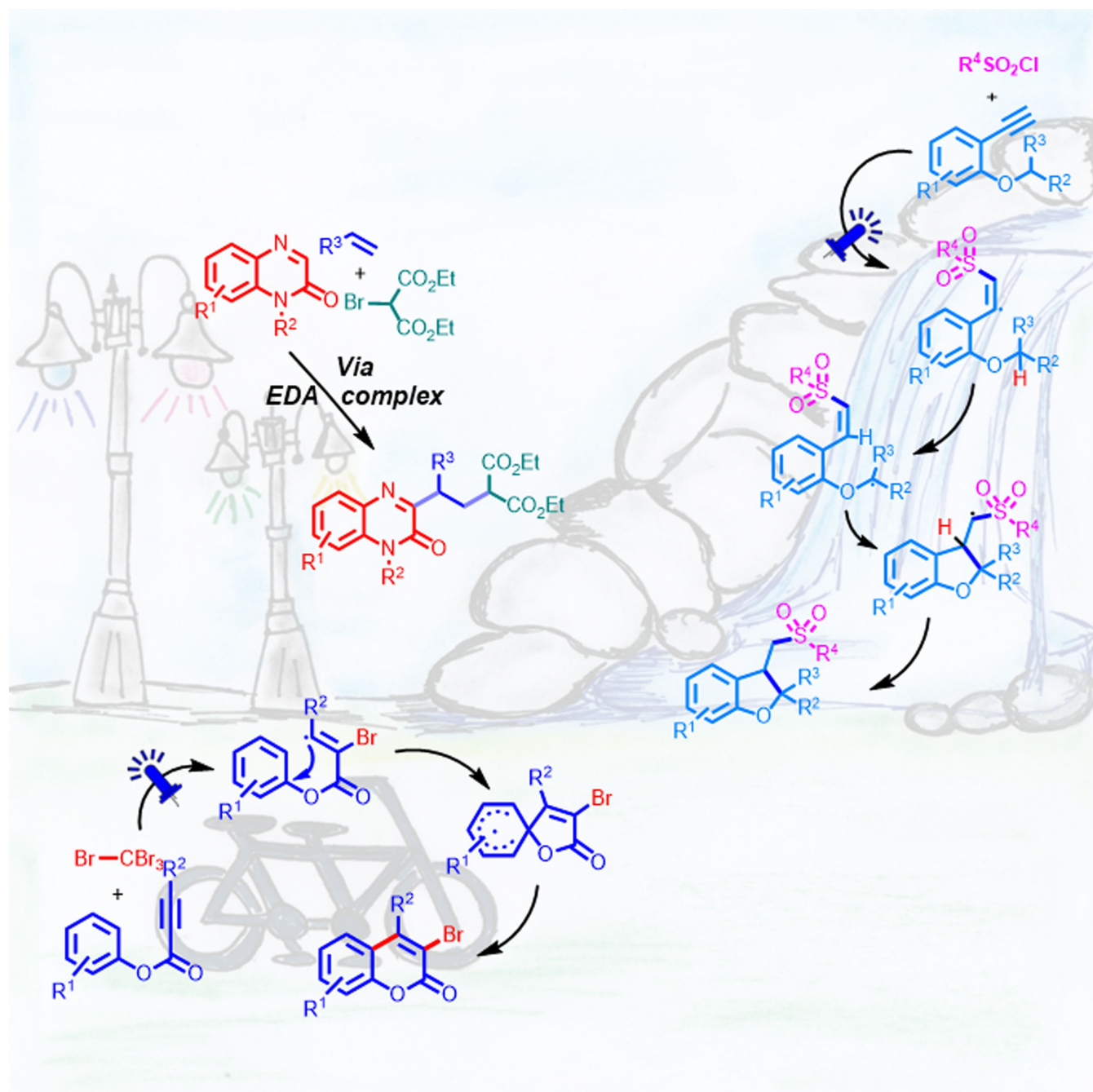


# Light-Induced Domino and Multicomponent Reactions: How to Reach Molecular Complexity without a Catalyst

Polyssena Renzi,<sup>\*,[a]</sup> Jacopo Scarfiello,<sup>[a]</sup> Alberto Lanfranco,<sup>[a]</sup> and Annamaria Deagostino<sup>[a]</sup>



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 thank 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 have 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.<sup>[1]</sup>

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.<sup>[2]</sup> 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.<sup>[3]</sup> 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.<sup>[4]</sup> 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.<sup>[5]</sup>

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.<sup>[6]</sup> 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

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detailed definition of domino/tandem reactions in organic synthesis see the paper from Tietze.<sup>[7,8]</sup>

## 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.<sup>[9]</sup> 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.<sup>[10]</sup> 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-enynes **1** in the presence of bromomalonates **2** under irradiation at 405 nm (Scheme 1).<sup>[11]</sup> 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.<sup>[12]</sup> 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 R<sup>1</sup>, 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 R<sup>2</sup> group was explored only for carbonylated benzofurans. The employed malonates **2** were, generally, methyl or ethyl esters bearing as R<sup>3</sup> 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-enyne **1** is able to absorb the light going to a singlet state (1\* S<sub>1</sub>) which upon intersystem crossing (ISC) proceeds to its triplet excited state (1\* T<sub>1</sub>). Having a relatively long lifetime,



Polyssena Renzi completed her PhD in 2014 at the University of Rome La Sapienza (Italy) working on the development of novel strategies for asymmetric synthesis and their optimization via Design of Experiment. In 2015, she joined the group of Prof. R. M. Gschwind (Regensburg University, Germany) as a postdoctoral fellow, where she dealt with mechanistic investigations of organocatalyzed reactions by means of NMR techniques. Since February 2020, she has been tenure track researcher at the University of Turin where she works in the field of photocatalysis, in the synthesis of molecules for BNCT applications and metal complexes for oxygen-reduction reactions.



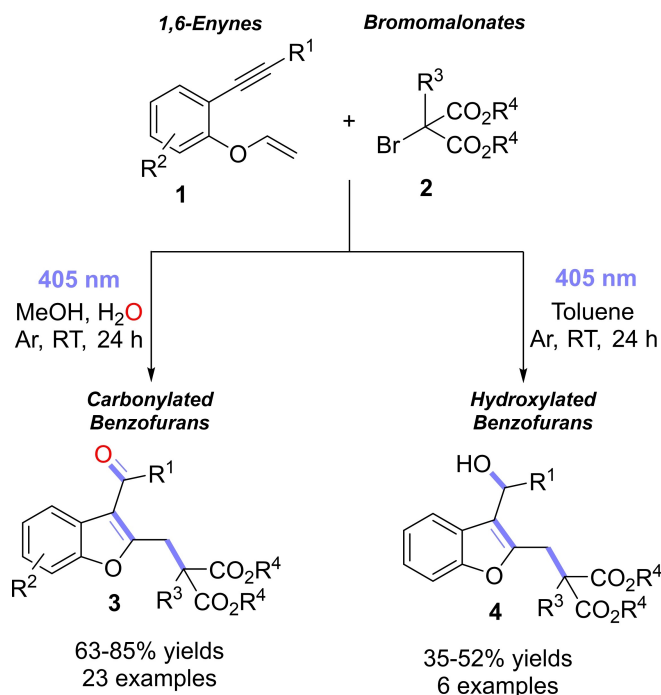
Alberto Lanfranco obtained his Master's degree in chemistry at the University of Turin in 2019 presenting a thesis on the synthesis of a biotin-functionalized carborane for BNCT/MRI applications. In 2020, he got a Ph.D. position in Annamaria Deagostino's group with a doctoral fellowship (AIRC IG). His Ph.D. project deals with the synthesis of sulfamido-functionalized carboranes for inhibition of carbonic anhydrase IX and BNCT applications.



Jacopo Scarfiello received his Master's degree in industrial chemistry from the University of Turin in 2019. His thesis consisted of synthesizing chalcones through micellar catalysis employing green surfactants in the aqueous phase. In 2022, he got a Ph.D. position in Deagostino/Renzi's research group with a doctoral fellowship (PNRR) from Perugia University in collaboration with Hydrochem srl. His Ph.D. project deals with UV-visible light-promoted chlorination reactions using photoredox catalysis.



Annamaria Deagostino is associate professor of organic chemistry at the University of Turin. She graduated in chemistry at the University of Turin and after a fellowship at the University of Padova, supervisor Prof. Fulvio Di Furia, in 1998 she received her Ph.D. in chemistry at the University of Turin, supervisor Prof. Paolo Venturello, and in the same year she obtained a postdoctoral fellowship at the University of Caen, under the supervision of Prof. Marie-Claire Lasne. In 1999, she became assistant professor of organic chemistry at the University of Torino. The main interests of her research group are in the field of synthetic organic chemistry, mainly focused on organopalladium chemistry, visible light photo-catalysis and the synthesis of BNCT (Boron Neutron Capture Therapy) theranostic agents.



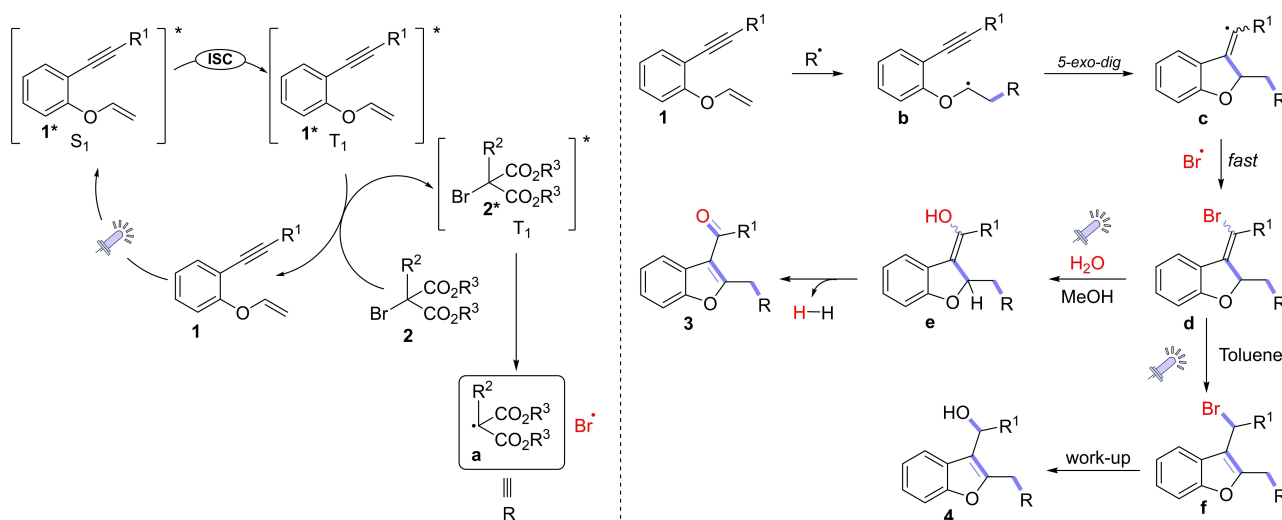
Scheme 1. Divergent synthesis of carbonylated **3** and hydroxylated **4** benzofurans.

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-enyne **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  $\text{Br}\cdot$  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  $\text{S}_{\text{N}}\text{Ar}$  process, followed by aromatization and the loss of  $\text{H}_2$

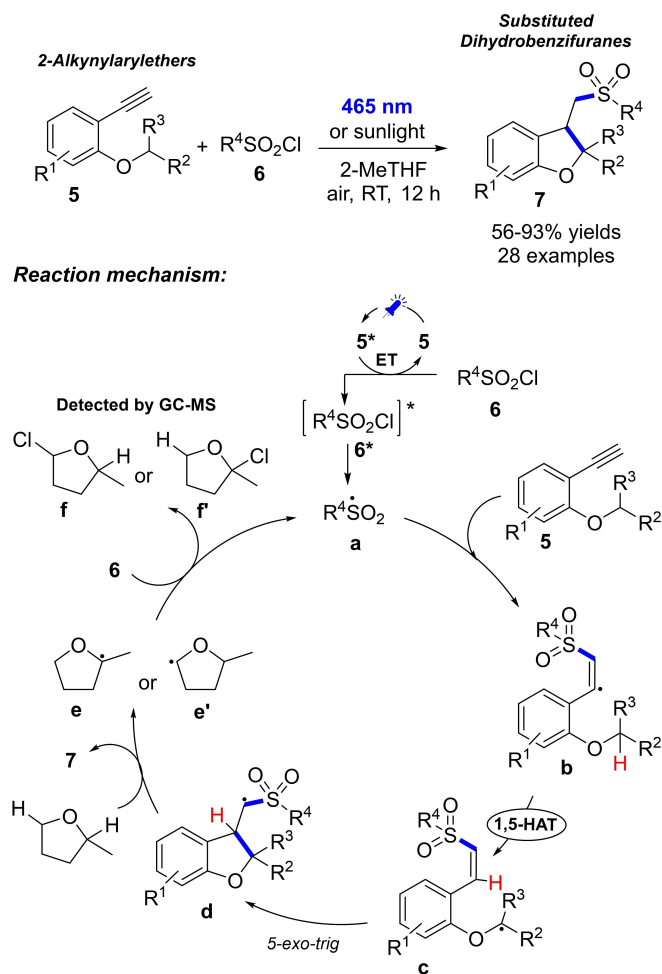
(proved by deuteration experiment). Alternatively, in toluene, intermediate **d** can directly give aromatization to **f**. During the work-up the labile bromine atom is substituted with an OH group to give the compound **4** (Scheme 2).

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).<sup>[13]</sup> 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-sulfonyl chlorides were suitable. No reaction was observed substituting the oxygen with a nitrogen atom in compound **5**.

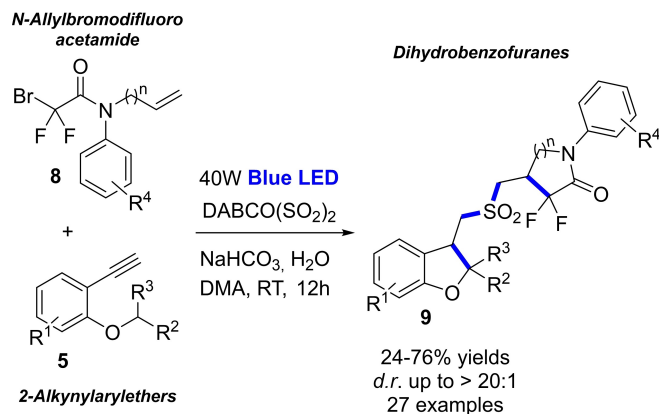
On-off experiments confirmed the light to be essential for reactivity, even though the solvent can support the reaction for a certain time by radical relay. This point was further confirmed by GC-MS analysis which allowed to determine the formation of 2-chloro-2-methyltetrahydrofuran **f'** and 2-chloro-5-methyltetrahydrofuran **f**, proving the existence of  $\alpha$ -oxo radicals **e/e'** able to abstract the chlorine atom from the sulfonyl 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



Scheme 2. Proposed mechanism for the divergent synthesis of carbonylated **3** and hydroxylated **4** benzofurans.



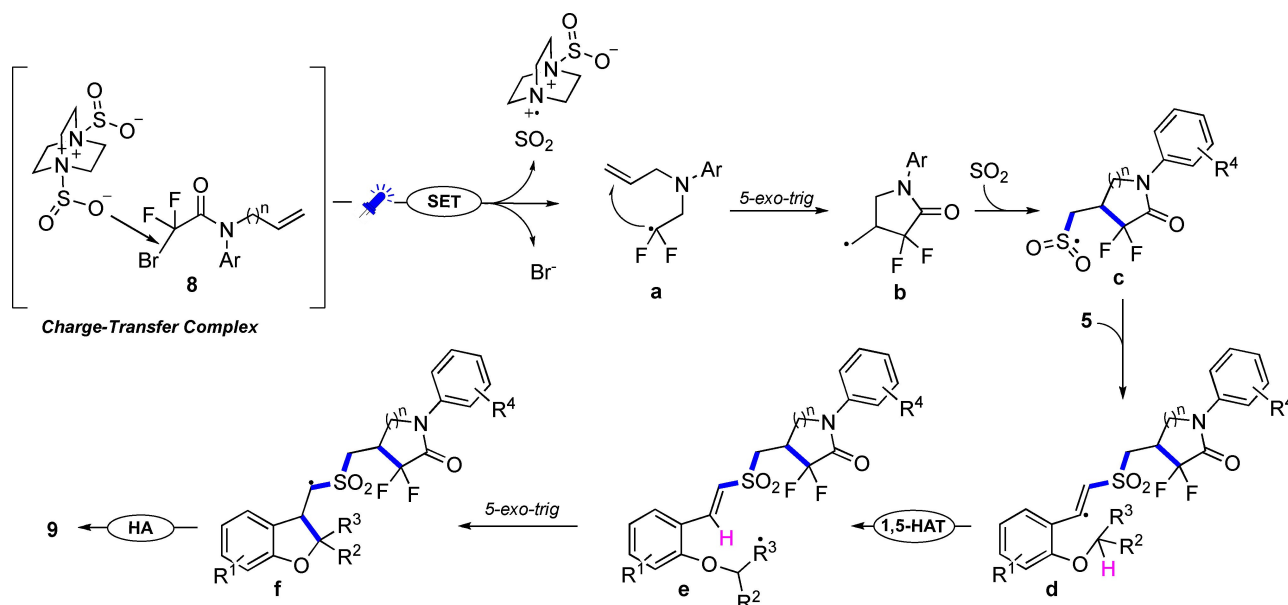
**Scheme 3.** Visible light-mediated tandem radical addition/1,5-hydrogen atom transfer/cyclization of 2-alkynylarylethers **5** with sulfonyl chlorides **6**.



**Scheme 4.** Blue light-mediated synthesis of difluoroamidodifluoro dihydrobenzofuranes **9**.

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  $\alpha$ -oxo radicals **e/e'**.

2-Alkynylarylethers **5** were exploited by Shen et al. as well to develop a new protocol for obtaining difluoroamidodifluoro dihydrobenzofuranes **9** (Scheme 4).<sup>[14]</sup> 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<sub>2</sub>)<sub>2</sub> was employed as sulfur dioxide surrogate, while *N*-allylbromodifluoro acetamides **8** were used as synthons for the second ring bearing a nitrogen atom and a CF<sub>2</sub> group. Sodium hydrogencarbonate was employed as the base and DMA/H<sub>2</sub>O as the solvents. Considering the scope, the electronic properties of substituents on the benzene ring of *N*-allylbromodifluoro acetamide derivatives **8** seemed not to influence the



**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  $R^2/R^3$  groups, present on 2-alkynylarylethers **5**, causing a decrease in yields while increasing their steric hindrance.

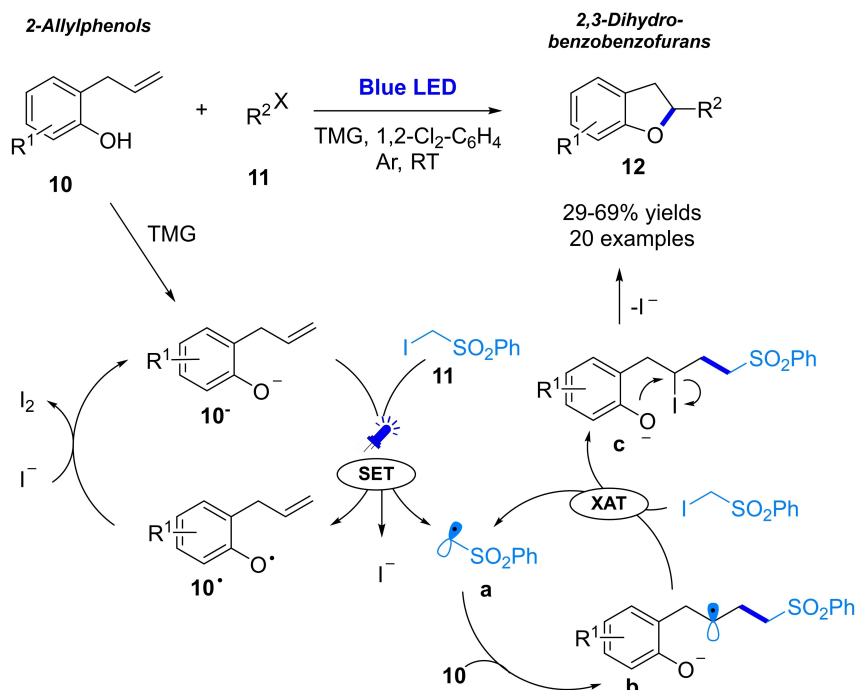
The reaction mechanism was elucidated by control experiments and UV-Vis spectroscopy (Scheme 5). The formation of a CT-complex between the acetamide **8** and  $\text{DABCO}(\text{SO}_2)_2$  was confirmed by a change on the absorbance of **8** upon the addition of the  $\text{SO}_2$  surrogate. Once 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  $\text{SO}_2$ . A 5-exo-trig cyclization allows the first ring closure giving the radical intermediate **b** which, reacting with  $\text{SO}_2$ , 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).<sup>[15]</sup> 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

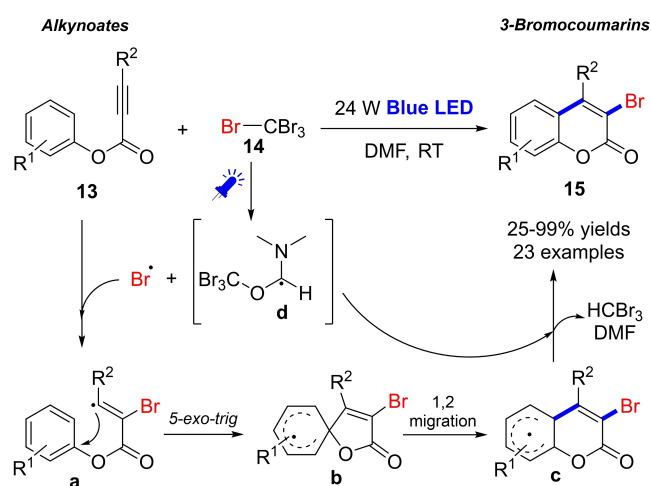
Among oxygenated heterocycles, coumarin and chromone structures are present in a variety of biological active compounds or natural products.<sup>[16]</sup> In the last years, because of the mild reaction conditions, visible light-induced cyclization has been largely exploited.<sup>[17]</sup> Interestingly, 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  $\text{CBr}_4$  **14** as bench stable and easy to handle brominating reagent in DMF under blue LED illumination.<sup>[18]</sup> Interestingly, the solvent has a central role in mediating this tandem radical brominative addition/cyclization generating, upon interaction with  $\text{CBr}_4$  under irradiation, a



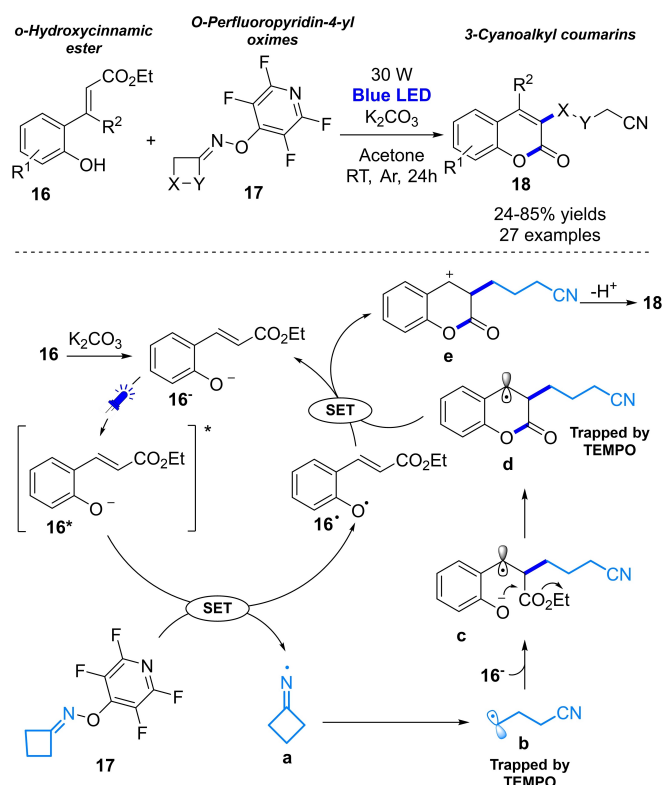
**Scheme 6.** Synthesis of 2,3-dihydrobenzofurans **12** from 1-allylphenols **10** under blue light irradiation.

bromine radical and the radical intermediate **d** (Scheme 7). The formation of  $\text{Br}\cdot$  after addition to the  $\alpha$ -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  $\text{R}^2$  group while keeping  $\text{R}^1$  as a hydrogen atom. As the  $\text{R}^1$  group



**Scheme 7.** Tandem radical brominative addition/cyclization of alkynoates for the synthesis of 3-bromocoumarins **15**.



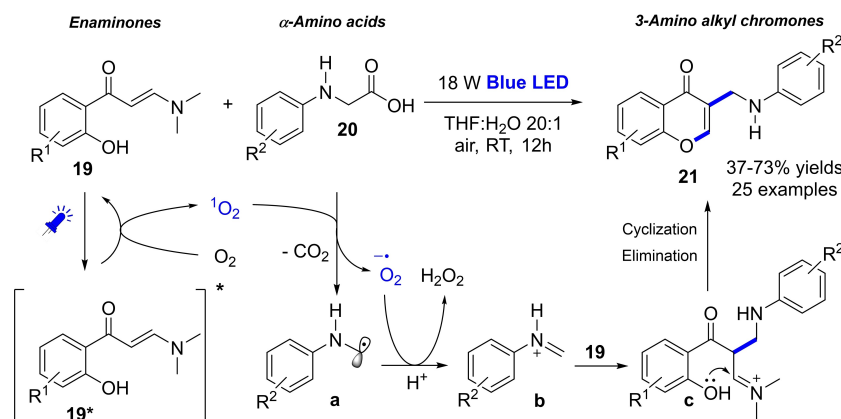
**Scheme 8.** Synthesis of 3-cyanoalkyl coumarins **18** from *o*-hydroxycinnamic esters **16**: reaction conditions and proposed mechanism.

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  $\text{R}^1$  was a  $\text{NO}_2$  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).<sup>[19]</sup> In this case, *o*-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.  $\text{K}_2\text{CO}_3$ , argon atmosphere and blue light were essential to have reactivity. The base, in fact, is necessary to deprotonate the *o*-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 *o*-hydroxycinnamic esters **16**, strong EWG such as  $\text{NO}_2$  were not suitable while halogens, alkyl and alkyloxy groups gave from good to high yields. A poor scope was demonstrated for the  $\text{R}^2$  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).<sup>[20]</sup> This reaction was mediated by blue light, under air in a mixture of THF/ $\text{H}_2\text{O}$ . The electronic properties of the  $\text{R}^1$  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  $\text{NO}_2$  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  $\text{O}_2$  to form singlet oxygen  $^1\text{O}_2$ . Once  $^1\text{O}_2$  is formed, it can interact with the *N*-arylglycine **20** causing its decarboxylation and the generation of the superoxide radical. The  $\alpha$ -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



**Scheme 9.** Catalytic- and additive-free decarboxylative coupling cyclization of enaminone **19** with *N*-arylglycine **20** mediated by light.

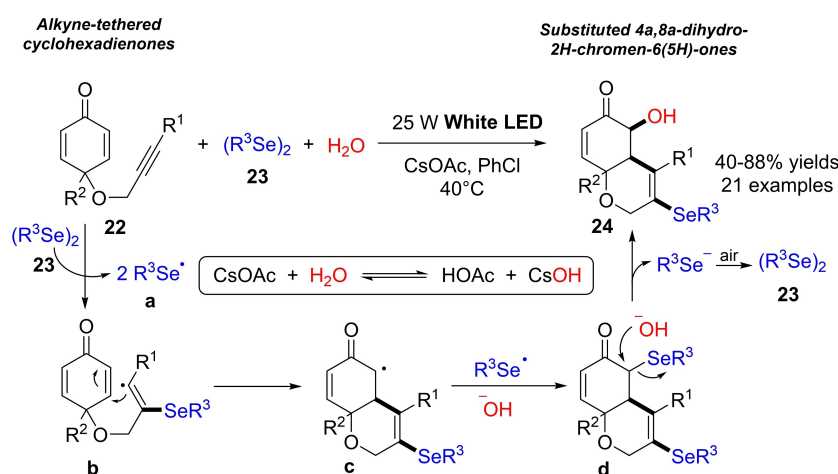
cyclization/elimination to form the desired 3-amino alkyl chromones **21**.

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.<sup>[21]</sup> 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<sup>1</sup> group, while R<sup>2</sup> 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 H<sub>2</sub><sup>18</sup>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 **a** 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.<sup>[22]</sup> 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



**Scheme 10.** Synthesis of **24** through metal-free visible light-induced cyclization/substitution cascade reaction.

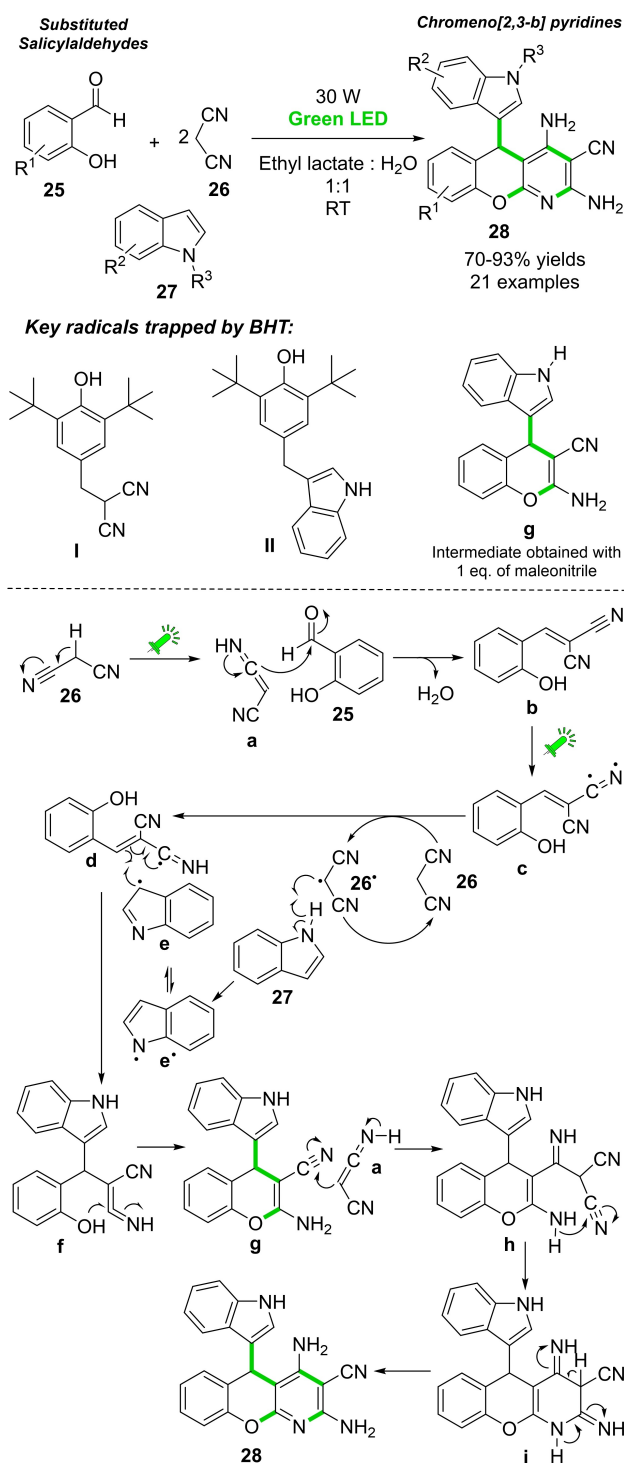


with a good tolerance towards substituents both on **25** and **27**. The reaction is initiated by light inducing malononitrile **26** tautomerization thus triggering a Knoevenagel condensation with **25**. After the elimination of water intermediate **b** is formed. Its subsequent irradiation with light 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 pyryl 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-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile derivatives **31** (Scheme 12).<sup>[23]</sup> 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 condense 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**.

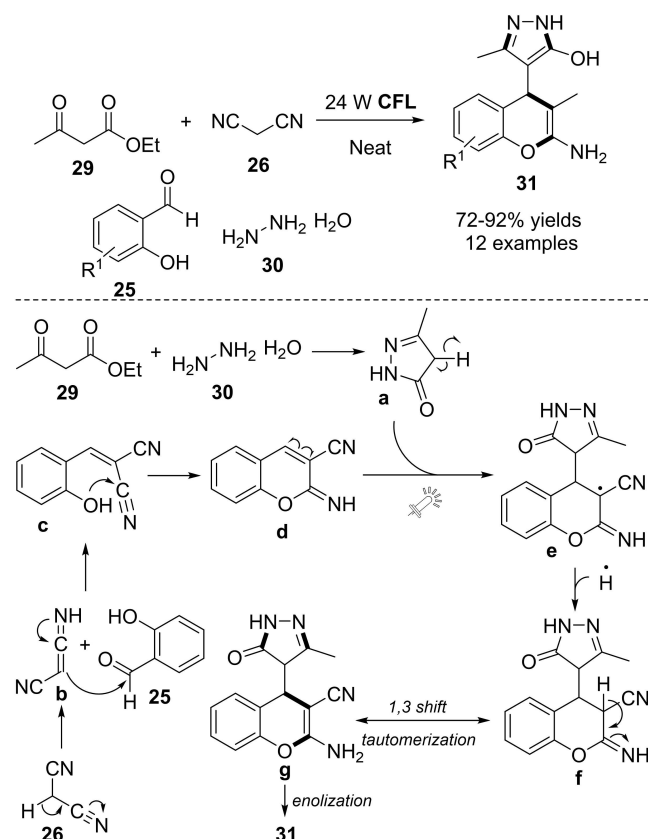
$\alpha$ -Cyanoketones **32** and malononitrile **26** can be reacted under illumination with a white LED in EtOH/H<sub>2</sub>O with isatins **33** or aldehydes **35** to give spirooxindoles **34** and 2-amino-4*H*-pyran-3,5-dicarbonitriles **36** respectively (Scheme 13).<sup>[24]</sup> In both cases, Zhang et al. exploited a one-pot, three component strategy based on a previously described Knoevenagel condensation and activation mode of **26** under irradiation.<sup>[22]</sup> 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  $\alpha$ -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



**Scheme 11.** Visible light-initiated catalyst-free one-pot, multicomponent synthesis of 5-substituted indole chromeno[2,3 b]pyridines **28**.

impact of light wavelength on the reaction stereoselectivity (Scheme 14).<sup>[25]</sup> 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,

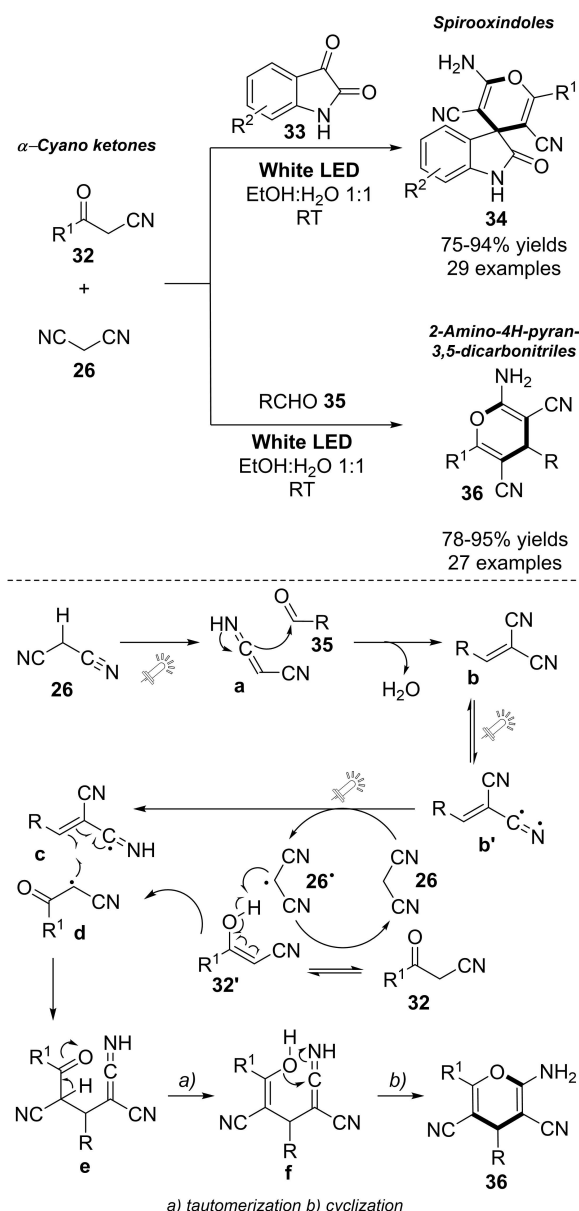


**Scheme 12.** Four-component, one-pot synthesis of 4-substituted-2-amino-4H-chromones **31**.

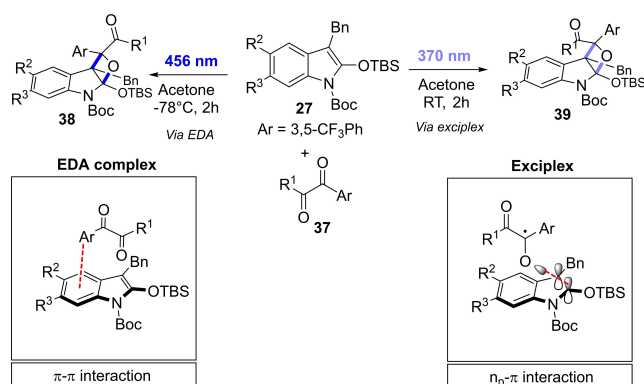
exciplex formation, conventional triplet pathways). Moreover, a light or steric factors diastereo-differentiation can be realized. Thus, illuminating at 405 nm, a direct excitation of the EDA CT-band is possible and the 8-exo product **38** is preferentially formed. While at 370 nm the reaction proceeds *via* exciplex formation with a preference for the 8-endo product **39**. 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 **37** in diluted conditions reacts *via* the exciplex; while EDA formation is preferred with electron-rich indoles **27** 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)<sup>[26]</sup> and as bioactive core in drugs and pharmaceuticals.<sup>[27]</sup> 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.



**Scheme 13.** Light-initiated three-component synthesis of 2-amino-4H-pyran-3,5-dicarbonitrile derivatives **34/36** in a pot.



**Scheme 14.** Impact of light on the stereoselectivity of the Paternò-Büchi reaction between indoles **27** and ketones **37**.

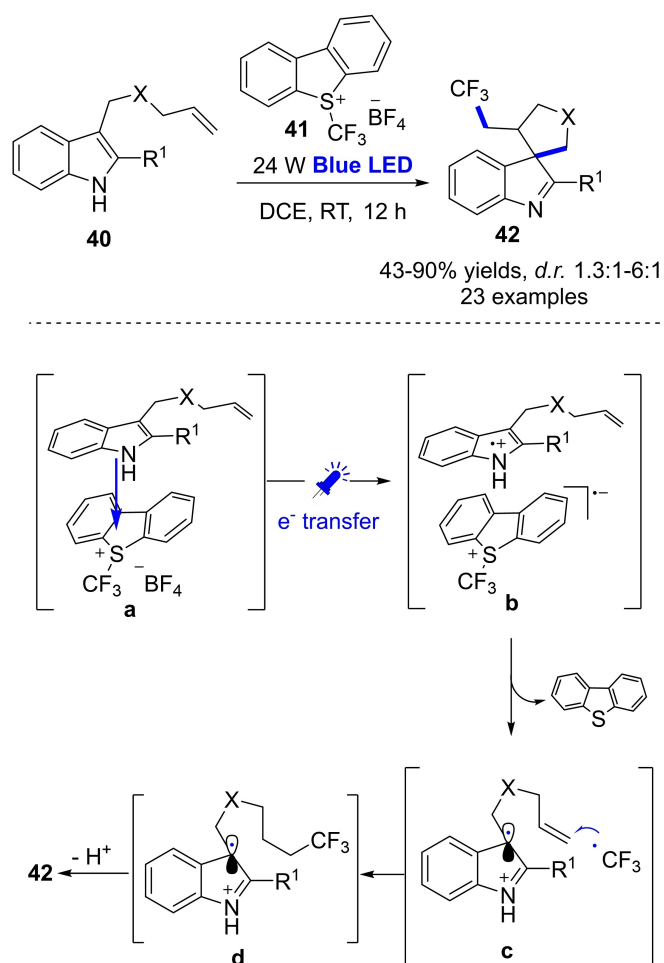
cyclic amines, an immediate observation is their stability in physiological conditions and their ability of accepting or donating protons at those pH values. Thus, it is not surprising that more than 85% of all biologically active compounds comprises a heterocycle and among them 75% of FDA approved small molecules drugs possess at least one *N*-heterocycle in their structures.<sup>[28]</sup> 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.<sup>[29]</sup> 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 **40** in the presence of Umemoto's reagent **41** to afford trifluoromethyl-substituted spiro-indolenines **42** by the use of visible light.<sup>[30]</sup> More than 20 spiroindolenines **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 **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 **40** and Umemoto's reagent **41**: the transient complex **a** is formed, and upon visible light irradiation undergoes a SET from the donor to the acceptor (**b**). At this point,  $\bullet\text{CF}_3$  radical, produced through S-CF<sub>3</sub> bond cleavage, adds to the terminal alkene affording intermediate **d**. Finally, the desired product **42** is obtained, after deprotonation, by radical-radical recombination (Scheme 15).

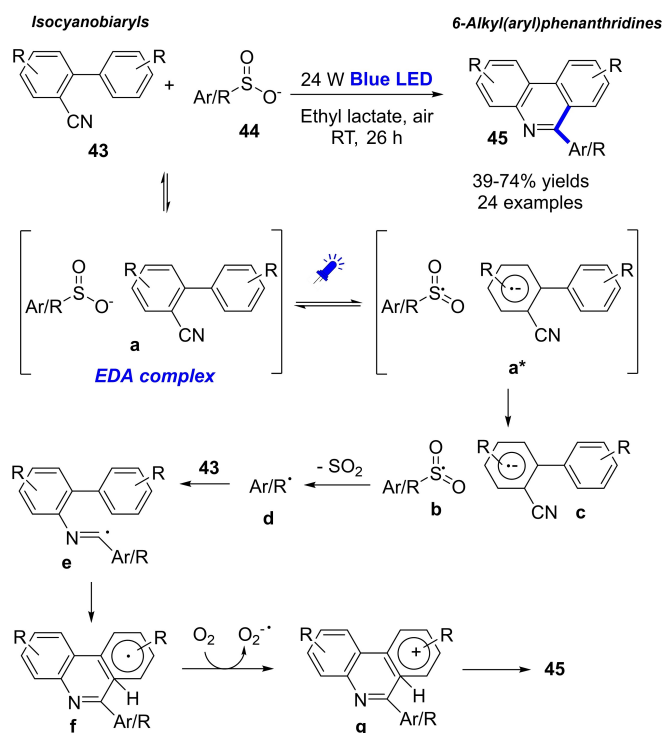
Exploiting the formation of an EDA complex between alkyl(aryl)sulfinates **44** and isocyanobiaryls **43**, Natarajan et al. reported a methodology for the preparation of 6-alkyl(aryl)phenanthridines **45** in ethyl lactate under aerobic conditions (Scheme 16).<sup>[31]</sup> 24 products were synthesized 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 **a** is reversibly formed between the



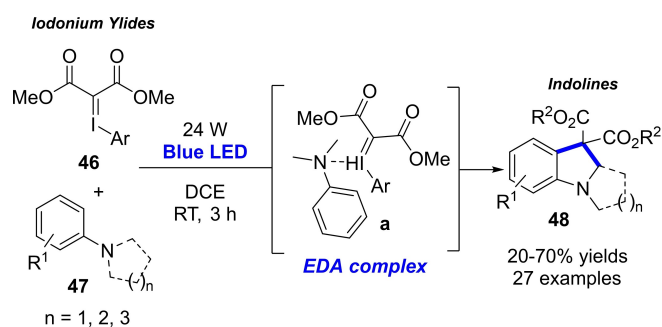
Scheme 15. Additive-free cascade trifluoromethylation and dearomatization of indoles **40** through an EDA complex.

sulfinates **44** and the isocyanates **43**. The complex **a** upon visible light irradiation, is excited and the dipolar species **a\*** is produced by a SET process. Thereafter, **a\*** is broken up into **b** and **c**. The loss of SO<sub>2</sub> immediately occurs to produce intermediate **d** from radical **b**. Then, the addition of the alkyl/aryl radical **d** to the ground state of the isocyanobiaryl **43** affords the imidoyl radical **e**, which undergoes an intramolecular cyclization reaction to give the new intermediate **f**. In the last steps, its oxidation by molecular oxygen affords the cationic intermediate **g** evolving to the final product **45**.

An EDA complex was also involved in the synthesis of indolines **48** via the cyclization of tertiary aryl amines **47** with iodonium ylides **46** under visible light irradiation at room temperature (Scheme 17).<sup>[32]</sup> The same heterocycles were previously prepared, via the use of iodonium ylides, under heating.<sup>[33]</sup> The reported methodology was applied both to cyclic and acyclic *ortho*-, *meta*-, and *para*-substituted anilines **47** bearing EWG or EDG affording 27 indolines **48** in 20–70% yields. An example applied to *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 *N,N*-dimethylaniline, affording the corresponding indoline **48** in 61% yield.



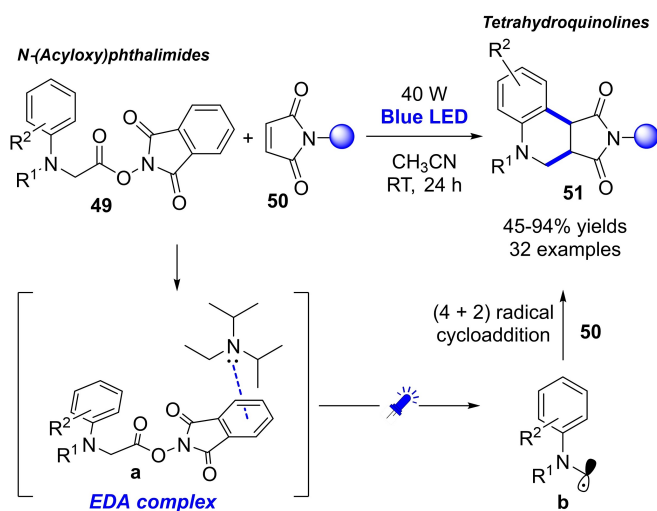
**Scheme 16.** Proposed mechanism for the synthesis of 6-alkyl(aryl)phenanthridines **45** under visible light irradiation.



**Scheme 17.** Synthesis of indolines **48** via cyclization of tertiary amines and iodonium ylides **46**.

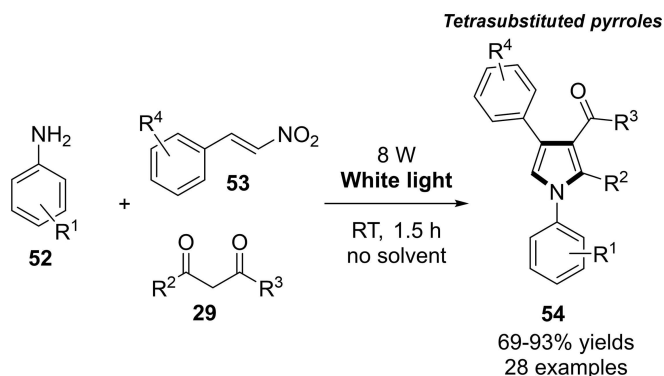
Mechanistic investigations confirmed the involvement of radicals and the EDA complex **a** formed between the tertiary aryl amine and the iodonium salt **46**.

A visible light-mediated radical (4 + 2) annulation between alkyl *N*-(acyloxy)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).<sup>[34]</sup> 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*-(acyloxy)phthalimides **50**, affording tetrahydroquinolines **51** in discrete to excellent yields (43–80%).

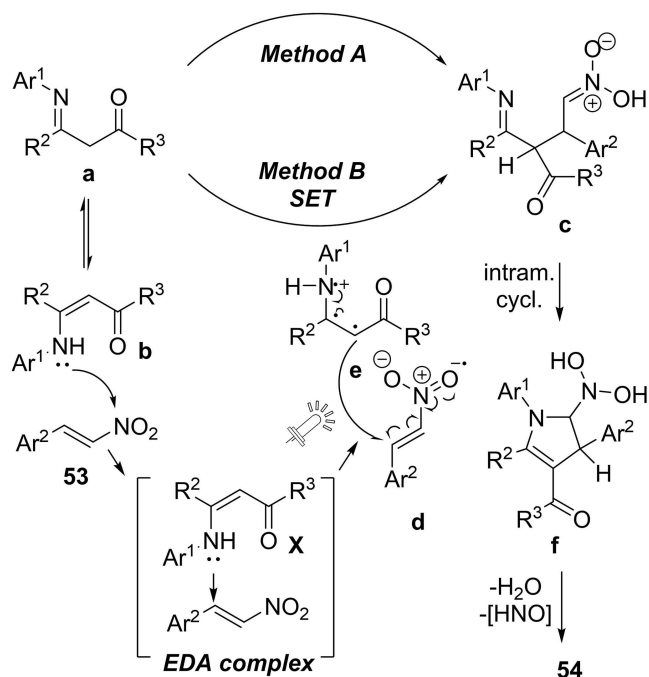


**Scheme 18.** Fused tetrahydroquinolines from alkyl *N*-(acyloxy)phthalimides **49** and *N*-substituted maleimides **50**.

Tetrasubstituted pyrroles **54** were prepared by a catalyst- and solvent- free, three-component approach at room temperature and under white light (Scheme 19).<sup>[35]</sup> The reaction proceeds *via* enamine formation between a primary amine **52** and a 1,3-dicarbonyl compound **29** followed by the Michael addition with  $\beta$ -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  $\mu$ M. 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



**Scheme 19.** Three-component reaction to afford pyrroles **54** under white light irradiation.



**Scheme 20.** Mechanism proposal for the three-component reaction to prepare tetrasubstituted pyrroles **54**.

with ethyl acetoacetate **29** to generate imine **a**, which affords enamine **b**, by undergoing keto-enol tautomerism. The following step is a Michael addition with  $\beta$ -nitro styrene **53** to generate the Michael adduct **c** either by method A or B. The adduct **c** involves a SET mechanism *via* the radical anion **d** and radical cation **e** through a coloured EDA complex. Michael adducts further undergoes intramolecular cyclization to generate intermediate **f**, which leads to the desired tetrasubstituted pyrrole **54** on aromatization with the elimination of water and HNO (Scheme 20).

### 3.2. Pyrrolidinones and Oxindoles

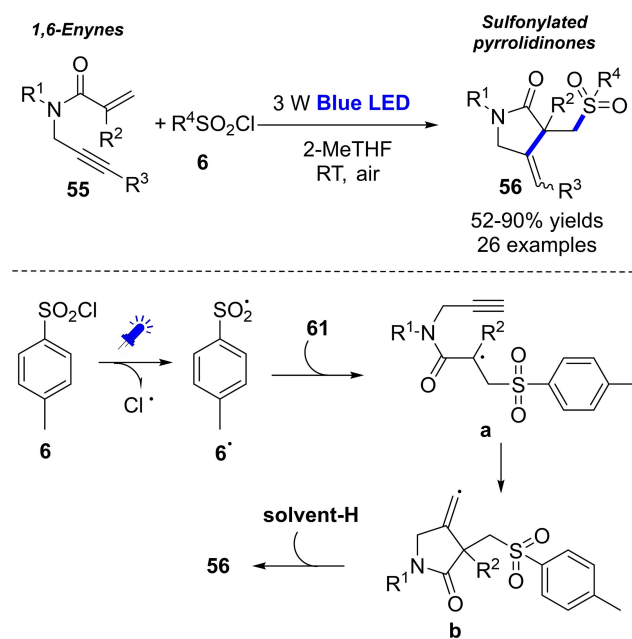
Oxindoles are privileged scaffolds usually found in several drugs and natural products which are used as therapeutic for tuberculosis, antitumoral, antiviral, antimalarial, antidepressant agents, and progesterone receptor agonists.<sup>[36]</sup> The development of synthetic strategies, mediated by visible light, has been extensively studied by various research groups.<sup>[37]</sup>

A visible light-initiated regioselective sulfonylation/cyclization of 1,6-enynes **55** with sulfonyl chlorides **6** to afford sulfonylated lactams **56** was proposed by X.-X. Meng.<sup>[38]</sup> 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 **6** and 1,6-enynes **55** 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 **55**. Very good results were obtained, for example, with *para*-methoxy and

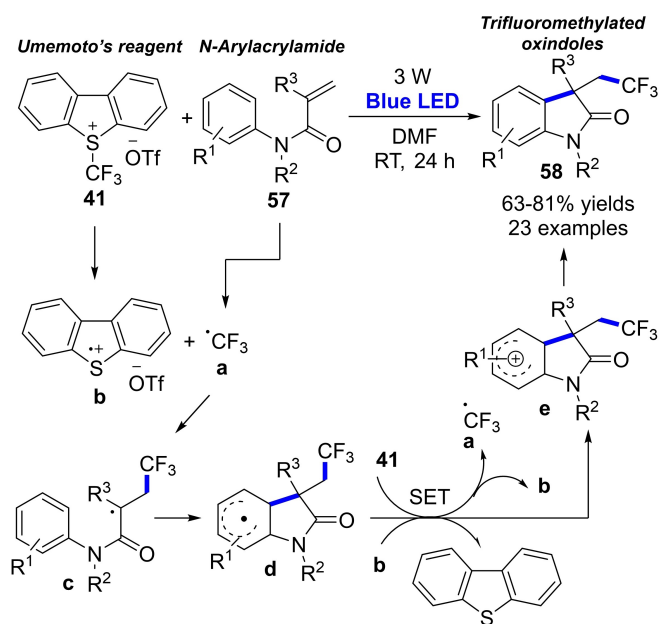
*para*-trifluoromethyl-*N*-aryl derivatives **55** affording the corresponding lactams **56** in excellent yields (Scheme 21). A gram scale reaction was reported with very good efficiency both under sunlight and 3 W blue LED. Mechanistic studies proposed a cascade reaction promoted by the sulfonyl radical **6•** generated under visible light-irradiation.

Umemoto's reagent **41** was used as the fluorinating reagent, also, in the visible light trifluoromethyl-arylation of *N*-arylmethacrylamides **57** without the need for any transition metal, photocatalyst and additive at room temperature, in DMF under inert atmosphere.<sup>[39]</sup> 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 **58** 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 **41** after irradiation with visible light, then the so-formed  $F_3C\bullet$  radical **a** interacts with the *N*-arylacrylamide **57** through addition onto the double bond generating the radical intermediate **c**, which affords radical **d** after intramolecular cyclization. Oxidation of radical **d** by either Umemoto's reagent **41** or intermediate **b** produces the corresponding cyclic carbocation **e** which deprotonation releases product **58** (Scheme 22).

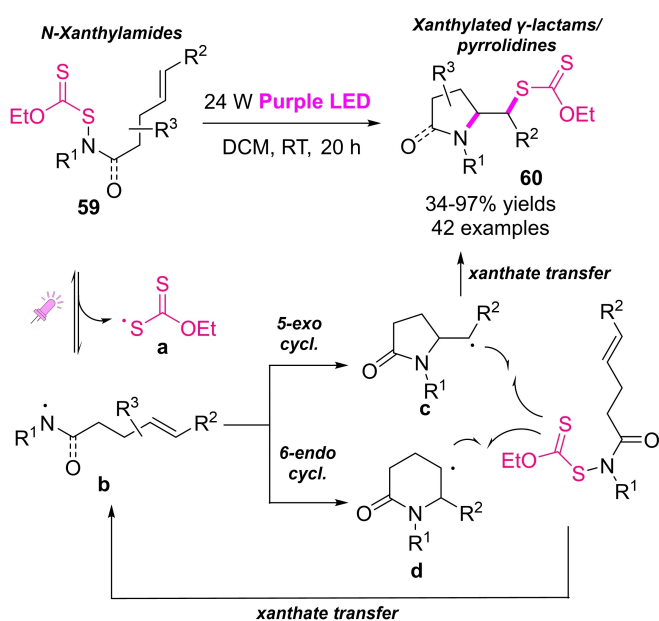
$\gamma$ -Lactams,  $\delta$ -lactams in addition to pyrrolidines, indolones, quinolinones, and fused polycyclic were obtained by *N*-xanthylamides **59** bearing an un-activated olefins by the simple action of a purple LED in  $CH_2Cl_2$  under photocatalyst-/additive-free conditions (Scheme 23).<sup>[40]</sup> 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



**Scheme 21.** Regioselective sulfonylation/cyclization of 1,6-enynes **55** with **6** to afford sulfonylated lactams **56**.



**Scheme 22.** Trifluoromethyl-arylation of *N*-arylmethacrylamides **57** with Umemoto's reagent **41**.



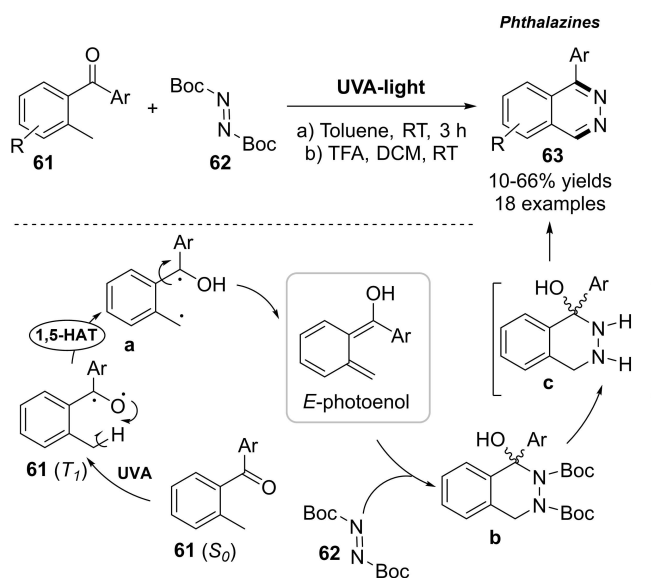
**Scheme 23.** Synthesis of xanthylated pyrrolidines and piperidines **60** via cascade xanthate transfer-cyclization.

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 **60** 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 **59** 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 *o*-methyl benzophenones **61** as reagents in the presence of di-*tert*-butyl azodicarboxylate **62** has been recently reported.<sup>[41]</sup> Phthalazines constitute the subunits of a wide variety of natural products with remarkable biological activities.<sup>[42]</sup> Moreover, they are used as ligands for transition metal complexes.<sup>[43]</sup> The strategy, described by the group of Tsogoeva was based on the combination of light-mediated enolization of commercially available *o*-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 photoenolization, *o*-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

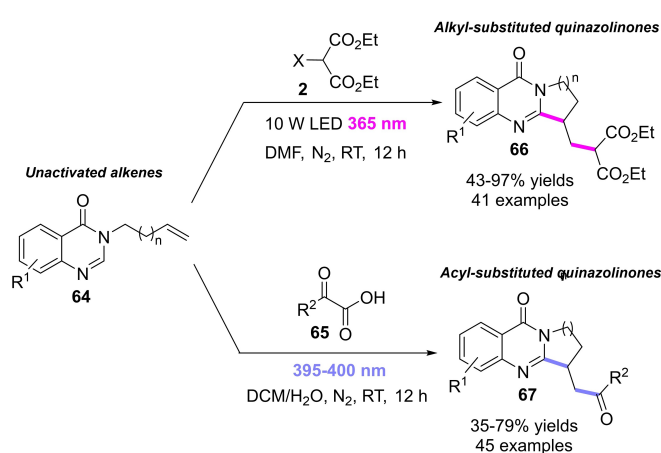


**Scheme 24.** Mechanistic proposal for the metal-free four-step one-pot synthesis of functionalized phthalazines **63**.

tetrahydrophthalazin-1-ol **c**, which converts to the desired phthalazine **63**, upon the loss of water and aromatization.

An early example of photoenolization under 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 carbocyclic compounds.<sup>[44]</sup>

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.<sup>[45]</sup> Among the different approaches which can be pursued for their synthesis,<sup>[46]</sup> 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).<sup>[47]</sup> 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.<sup>[47a]</sup> For acylated quinazolinones **67** the solvent choice played a vital role and the highest yields were obtained in DCM/H<sub>2</sub>O at 395–400 nm excluding the air from the reaction mixture.<sup>[47b]</sup> 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 alkenes **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<sup>1</sup> group was in position 8 of the aromatic ring. Alkyl bromides showed the lowest reactivity, while the

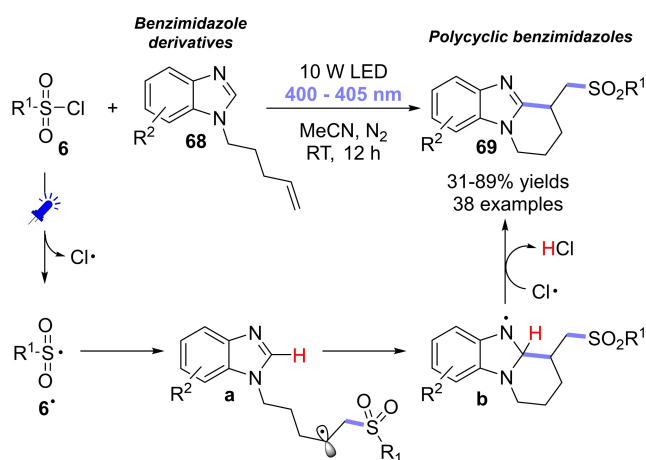


**Scheme 25.** Photoinduced dehalogenative alkylation/cyclization (top) and homolytic decarboxylative acylation/cyclization of un-activated alkenes **64**.

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<sup>2</sup> 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.<sup>[47b]</sup>

The same research group also reported the synthesis of polycyclic benzimidazoles **69** using a similar approach (Scheme 26).<sup>[48]</sup> 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,<sup>[47]</sup> 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 photochemical cascade process has been recently proposed to access several complex polyheterocyclic molecular architectures **72**.<sup>[49]</sup> 20 examples were reported (42–81% yield) with significant growth of molecular complexity over three-steps. An unprecedented [2 + 2] reactivity of ESIPT (Excited State Intramolecular Proton Transfer) by *in situ* generated azaxylylenes was the key of the process. The reaction started with a transition metal-free

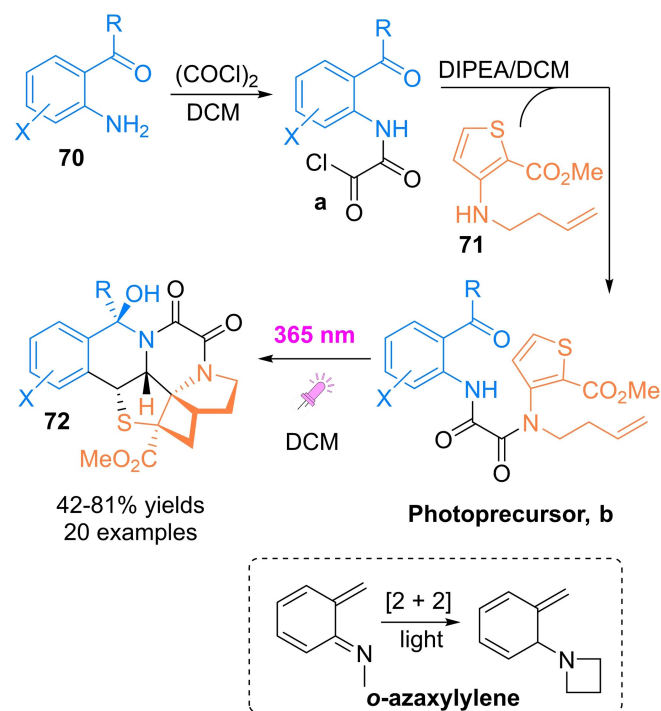


**Scheme 26.** Light-induced radical cascade sulfonylation/cyclization of derivatives **69** with sulfonyl chlorides.

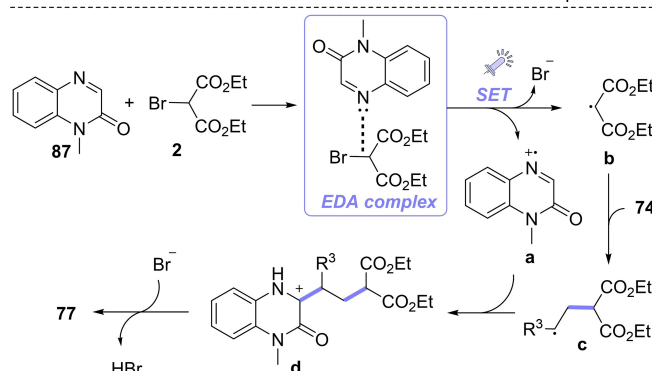
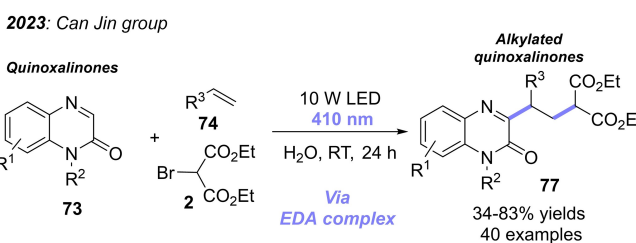
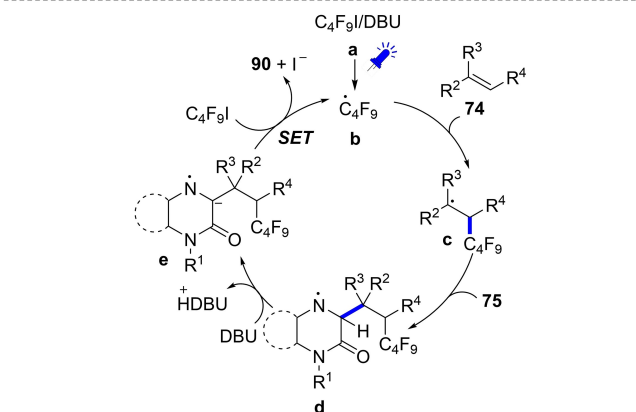
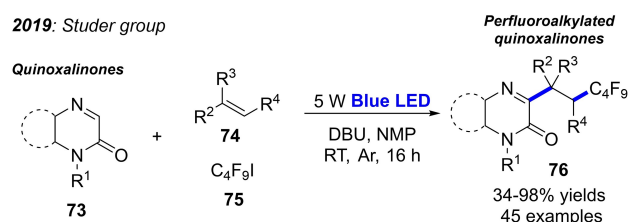
intramolecular  $C_{sp^2}$ – $C_{sp^3}$  cross coupling of aromatic amides **70** to produce the photo-precursor **b** which is subjected to irradiation with a purple light (Scheme 27). Then the reaction can proceed through the excited state of the photo-precursor **b** engaging a [2 + 2] cycloaddition between the homoallyl and the aminothiophene moieties leading to a tricyclic dihydrothiophene cycloadduct. A second excitation *via* ESIPIT 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 quinoxalines **73** in water (Scheme 28 bottom).<sup>[50]</sup> Previously, visible light photoredox catalysis was exploited for the functionalization of quinoxalin-2(1*H*)-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).<sup>[51]</sup> In this case, perfluoroalkylated quinoxalines **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=N bond of **73** to deliver the amidyl 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



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



Scheme 28. Multicomponent approaches for the synthesis of substituted quinoxalines **76/77**.

quinoxalin-2(1*H*)-one **73** and diethyl  $\alpha$ -bromomalonate **2**. After a SET, quinoxalines 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 quinoxalines 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, alkenyl and alkynyl groups (51–77% yield). As far as the alkene is concerned, both

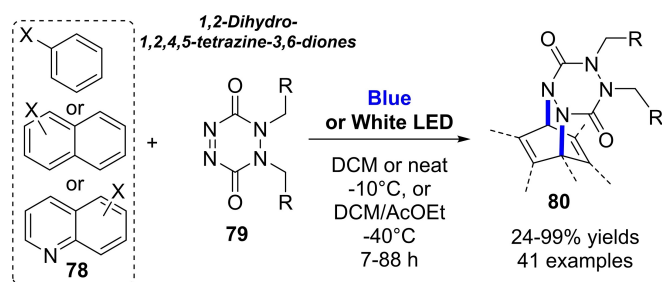


styrene and aliphatic alkenes were tested (49–79%), with the highest yields obtained with 4-fluoro-styrene and 1-allylnaphthalene (82 and 83% yield, respectively).

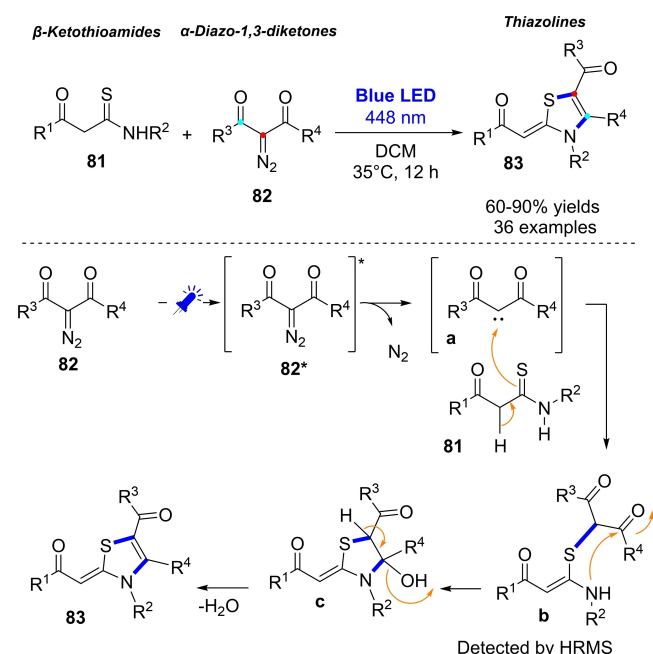
Ikeda et al. recently reported the visible-light promoted [4 + 2] cycloaddition between 1,2-dihydro-1,2,4,5-tetrazine-3,6-diones **79** (TETRADs) and aromatics, under white light-irradiation in DCM at  $-10^{\circ}\text{C}$ , allowing the isolation of the corresponding cycloadducts **80** (Scheme 29).<sup>[52]</sup> Aromatic compounds substituted with EWG and EDG, naphthalenes, or *N*-heteroaromatic compounds were exploited to afford a total of 41 products, with yields ranging from 24 to 99%. Best results were obtained with naphthyl derivatives; when the 2-substituted naphthalene was employed as the starting material, a product derived from two cycloadditions on both rings was observed.

#### 4. Sulfur Containing Heterocycles

Together with oxygen and nitrogen heterocycles, also sulfur-containing compounds include a wide range of pharmaceuticals and bioactive molecules.<sup>[53]</sup> Classical approaches for their syn-



**Scheme 29.** Dearomative [4 + 2] cycloaddition between 1,2-dihydro-1,2,4,5-tetrazine-3,6-diones **79** (TETRADs) and aromatics **78**.



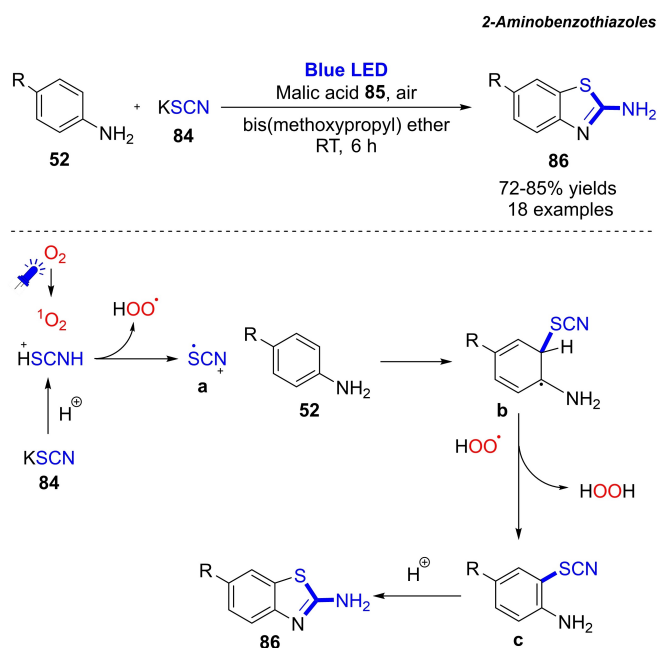
**Scheme 30.** Visible light-induced synthesis of substituted thiazolines **83**.

thesis generally involve multi-step operations and the employment of catalysts or additives.<sup>[54]</sup> Since visible light has been shown to be an effective activator for several organic molecules, 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  $\beta$ -ketothioamides **81** and  $\alpha$ -diazo-1,3-diketones **82**, operating under visible light at moderate temperature in open air (Scheme 30).<sup>[55]</sup>

It is already known that carbenes **a** can be produced through photolysis of  $\alpha$ -diazo-1,3-diketones **82**.<sup>[56]</sup> In the presence of  $\beta$ -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  $\beta$ -ketothioamides **81** and  $\alpha$ -diazo-1,3-diketones **82** were performed. Regarding substituents on the keto group of  $\beta$ -ketothioamides **81**, both aromatic, bearing EDG and EWG, heteroaromatic, extended aromatic, or aliphatic substituents were investigated.  $\text{R}^2$  on the nitrogen atom can be an alkyl or an aromatic side chain. Also symmetrical and asymmetrical  $\alpha$ -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  $\alpha$ -hydrogen atoms of the  $\beta$ -ketothioamides turned out to be crucial. As illustrated in Scheme 30, the blue light triggers the photolysis of  $\alpha$ -diazo-1,3-diketones **82** thus generating singlet carbene intermediate **a** through denitration. The more nucleophilic sulfur center of the  $\beta$ -ketothioamides **81** can react with **a** due to the loss of its acidic  $\alpha$ -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-aminobenzothiazole **86**. This scaffold has been proven to be a valuable structural motif for pharmaceuticals, especially antifungal agents.<sup>[57]</sup> 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.<sup>[58]</sup> Alternatively, a copper catalyst together with oxygen as an oxidant can be utilized.<sup>[59]</sup> In this field, He et al., in 2020, developed a protocol to synthesize 2-aminobenzothiazoles **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).<sup>[60]</sup> 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

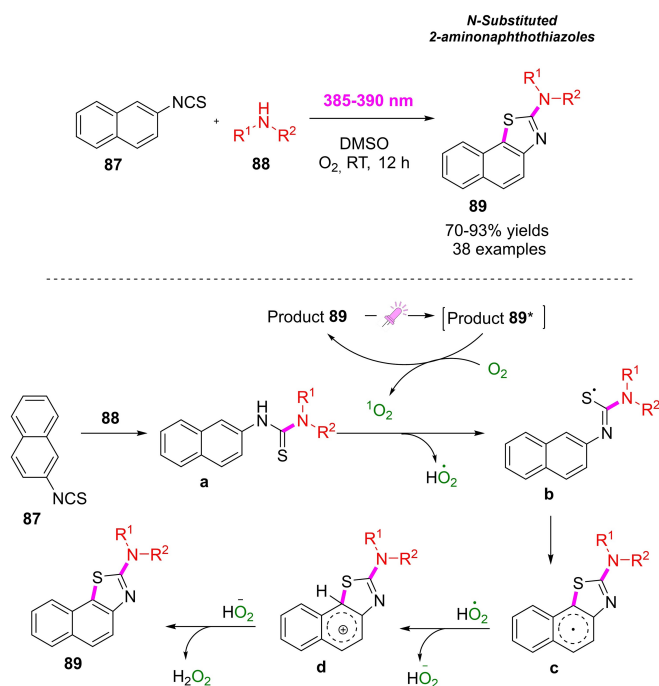


**Scheme 31.** Preparation of 2-aminobenzothiazoles **86** through visible light-induced cascade reaction.

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  $^1\text{O}_2$  under irradiation. In the meantime, malic acid **85** reacts with potassium thiocyanate **84**, producing thiocyanic acid *in situ*. Consequently, singlet oxygen subtracts 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  $\text{H}_2\text{O}_2$  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**.

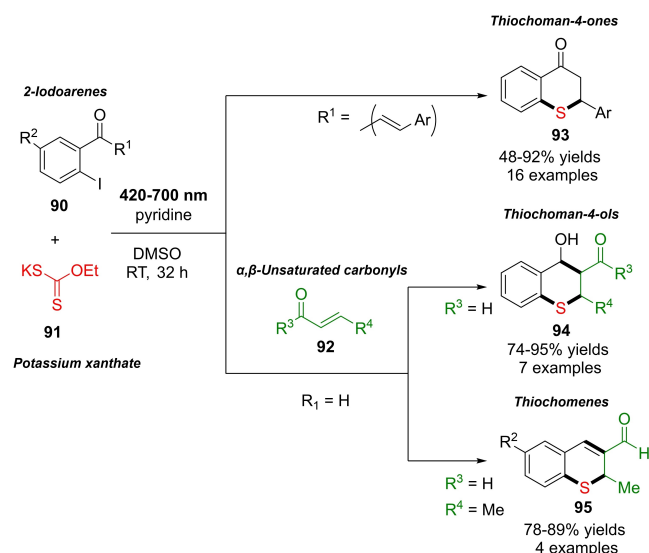
Other thiazoles investigated by He and his team, consisted of *N*-substituted 2-aminonaphtho[1,2-*d*]thiazoles **89**, a family of drugs for the treatment of ataxia, epilepsy and hypertension.<sup>[61]</sup> They were prepared through a visible light-assisted, additive- and photocatalyst-free cascade reaction, starting from 2-isothiocyanatonaphthalenes **87** and primary or secondary amines **88**, under oxygen atmosphere (Scheme 32).<sup>[62]</sup> It was deduced that the isothiocyanate **87** completely converted after 6 hours, by monitoring the reaction as a function of time, *via*  $^1\text{H-NMR}$ . The reaction proceeds with the immediate formation of a certain amount of **89** together with thiourea **a** obtained by the nucleophilic addition of the amine's nitrogen to the



**Scheme 32.** Visible light-assisted cascade reaction to produce *N*-substituted 2-aminonaphtho[1,2-*d*]thiazoles **89**.

isothiocyanate's carbon. Oxygen, as well as light, have a crucial role in the reaction for which a free radical pathway was hypothesized according to Scheme 32. Thiourea **a** can react with the active singlet state oxygen to generate  $\text{HO}_2^{\bullet}$  and the sulfur radical **b** which undergoes intramolecular radical addition to form **c**. The latter is subsequently oxidized to the aromatic cation **d**. Finally, the target product **89** is formed through hydrogen extraction having hydrogen peroxide as the sole byproduct, detected using a KI-starch paper test.

Thiochromanes represent a significant class of sulfur-containing heterocycles with a valuable role as anticancer and potential new antifungal pharmaceuticals.<sup>[63]</sup> These species were traditionally synthesized starting from 2-acyliodobenzenes and xanthates, using a copper catalyst in DMSO.<sup>[64]</sup> Later, a visible light-promoted C–S cross-coupling reaction was achieved starting from iodobenzenes and thiols without employing any photocatalyst.<sup>[65]</sup> Recently, Sekar et al. developed a visible light-mediated photocatalyst-free protocol to accomplish the cascade synthesis of thiochroman-4-ones **93**, thiochroman-4-ols **94** and thiochromenes **95** using pyridine as base, in DMSO at room temperature. 2-Acyliodobenzenes **90** and potassium xanthate **91** were necessary to obtain thiochroman-4-ones **93**, while the addition of  $\alpha,\beta$ -unsaturated carbonyl compounds **92** was required to generate thiochroman-4-ols **94** and thiochromanes **95** following a three-component cross-coupling reaction (Scheme 33).<sup>[66]</sup> Initially, the scope for the synthesis of thiochroman-4-one **93** was investigated. Several 2-iodochalcones **90** bearing different aryl substituents were screened. 2-Aryl-substituted thiochroman-4-ones bearing neutral or electron rich, electron-poor, heterocyclic and polycyclic substituents were generated with good yields (48–92%). The same method-

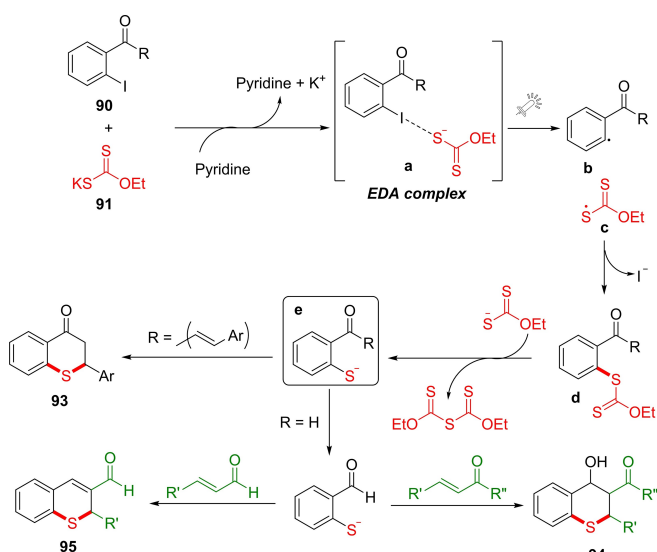


**Scheme 33.** Cascade visible light reactions diagram for the synthesis of compounds **93–95**.

ology was applied for the synthesis of thiochroman-4-ols **94** starting from 2-iodobenzaldehyde and  $\alpha,\beta$ -unsaturated ketones with different  $R^3$  and  $R^4$  groups (74–95% yields). When 2-iodobenzaldehyde was reacted with an  $\alpha,\beta$ -unsaturated aldehyde the main product turned out to be the corresponding thiochromene **95** as a result of further dehydration of thiochromanol **94**.

To investigate the mechanism, several control reactions were performed proving the role of the xanthate ester **91**, light and pyridine. Moreover, experimental and computational studies confirmed the formation of the EDA complex **a** between the iodocarbonyl reactant **90** and the xanthate **91** (Scheme 34).

The interaction with the visible radiation of the EDA complex generates the aryl radical **b**, the thiyl radical **c** and

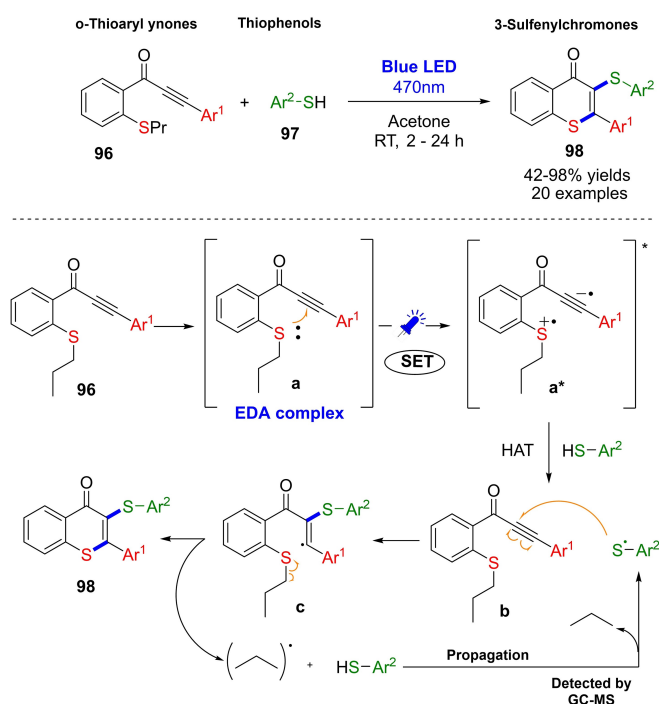


**Scheme 34.** Plausible reaction mechanism for **93–94** formation.

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  $\alpha,\beta$ -unsaturated aldehydes as Michael acceptor allows the generation of thiochromenes **95** as a result of the dehydration of the thiochromanol itself.<sup>[67]</sup>

As far as the synthesis of 3-sulfenylthiochromones is concerned, Song and co-workers developed a protocol from *o*-thioaryl ynone **96** and thiophenols **97**, employing *tert*-butylhydroperoxide (TBHP) as additive, at 80 °C, in MeCN under nitrogen atmosphere.<sup>[67]</sup> Based on these results, Panteado et al. built up a protocol to synthesize 3-sulfenylthiochromones **98** starting from the same reactants **96** in an additive-free conditions exploiting a blue LED radiation (470 nm), at room temperature, in acetone in open air (Scheme 35).<sup>[68]</sup>

Regarding *o*-thioaryl ynone **96**, different  $Ar^1$  were explored varying among EDG and EWG. Moreover, a large variety of aromatic thiols **97** was screened by changing the  $Ar^2$  substituent thus obtaining yields between 42% and 98%. Surprisingly, no reaction was observed with an alkyl thiols and poor yields were obtained utilizing a *n*-pentyl substituted ynone (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 ynone to establish EDA complexes,<sup>[69]</sup> 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 **97** is crucial for the cyclization reaction, undergoing hydrogen abstraction thus generating the sulfur-



**Scheme 35.** Visible light-assisted synthesis of 3-sulfenylchromones **98** and proposed mechanism.

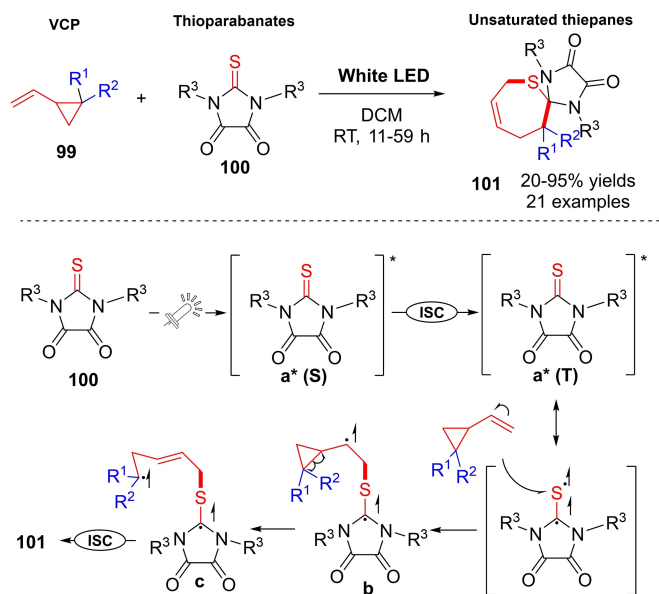
centered radical which, attacking the alkyne moiety, starts a radical cascade cyclization leading product **98** (Scheme 35).

Sulfur-containing seven-membered heterocycles, such as unsaturated thiepanes, are known as bioactive molecules for the treatment of HIV.<sup>[70]</sup> On the other hand, vinylcyclopropanes (VCPs) **99** are useful reagents to perform cycloadditions generating five- or seven-membered rings.<sup>[71]</sup> Since, thiocarbonyl compounds, e.g. thioparabanate **100**, exhibits appealing photochemical behavior under visible light-irradiation,<sup>[72]</sup> 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).<sup>[73]</sup>

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 diisopropyl as R<sup>3</sup>, 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.<sup>[74,75]</sup>



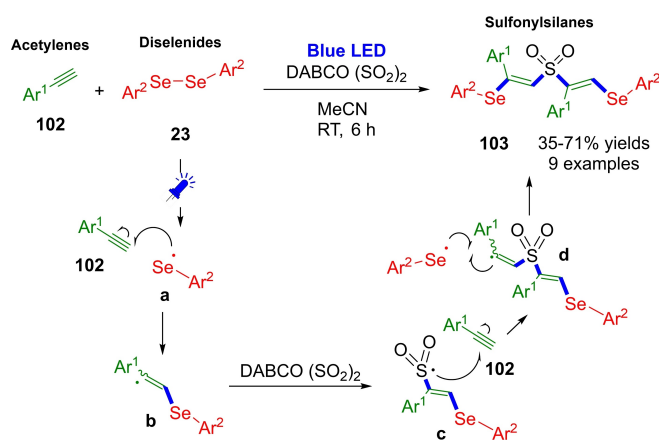
Scheme 36. Visible light-induced [5 + 2] cycloaddition of VCPs **99** and thioparabanates **100**.

Selenium atoms are generally introduced employing diselenides **23** as the selenium source in combination with transition-metal catalysts.<sup>[76-79]</sup> Interestingly, diselenides **23** have been proven to generate radical species through the homolytic cleavage of the Se–Se bond under visible light-irradiation.<sup>[80]</sup> In 2019, Xu and co-workers developed a methodology to synthesize sulfonylsilanes **103** by reacting aryl acetylenes **102**, diarylselenides **23** and DABCO(SO<sub>2</sub>)<sub>2</sub>, under blue light, in MeCN at room temperature (Scheme 37).<sup>[81]</sup>

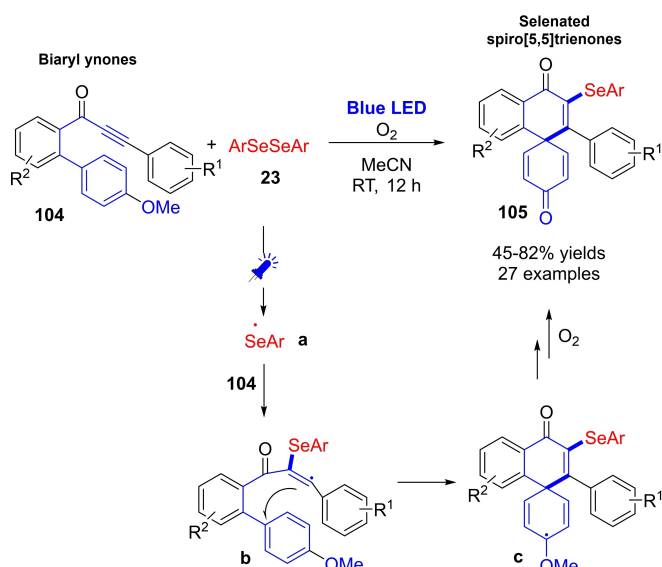
Modest to good yields (35–71 %) were obtained with different EDG and EWG on Ar<sup>1</sup>. As far as a mechanistic hypothesis is concerned, the diselenide **23** undergoes homolytic cleavage in the presence of light. The so-generated selenium radical **a** attacks the triple bond of arylacetylenes **102**, 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 arylacetylene **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).<sup>[82]</sup>

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**.



Scheme 37. Multicomponent light-promoted radical reaction for sulfonylsilanes **103** synthesis.



Scheme 38. Visible light-promoted radical selenylative spirocyclization of biaryl ynones 105.

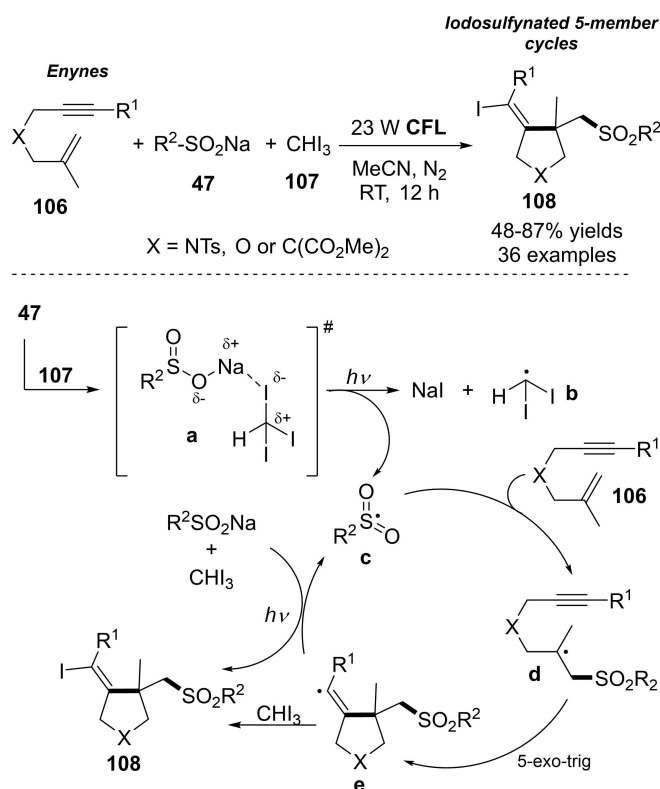
## 6. Miscellaneous

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.

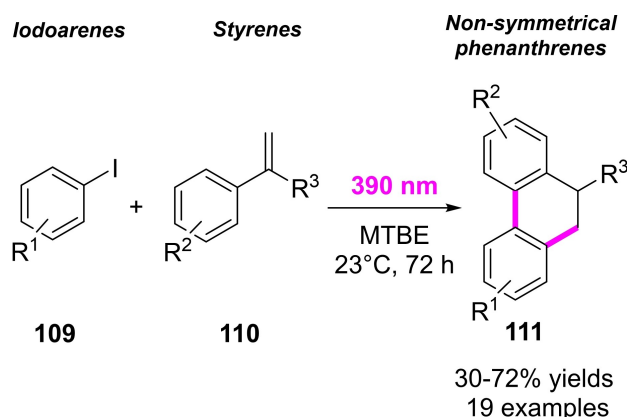
### 6.1. Cyclic derivatives

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).<sup>[83]</sup> 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  $R^1$  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.<sup>[84]</sup> 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



Scheme 39. Three-component iodosulfonylative cyclization.

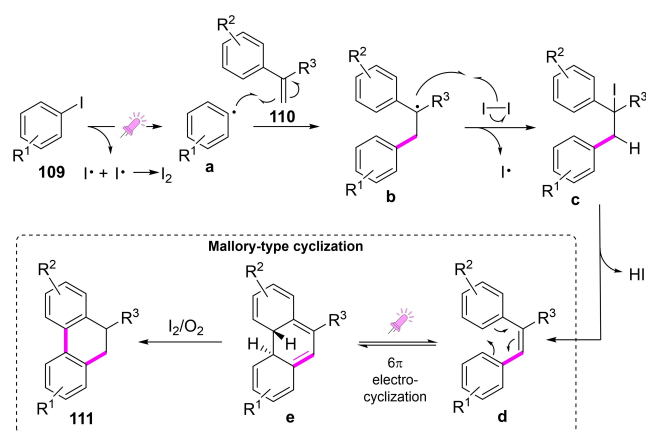


Scheme 40. Domino synthesis of phenanthrenes **111** from iodoarenes **109** and substituted styrenes **110**.

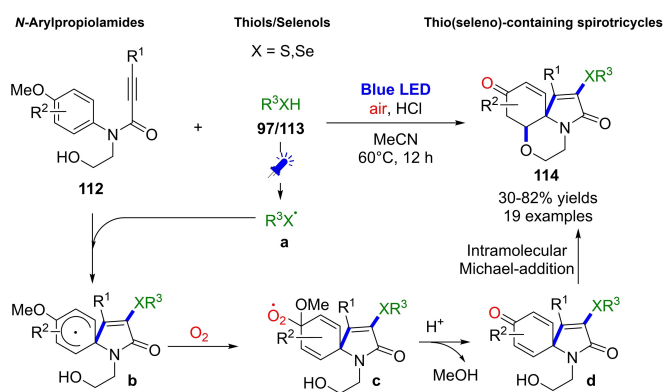
arylation/cyclization cascade mediated by a 390 nm light. Functionalized phenanthrenes **111** were obtained in moderate to good yields up to 5 mmol scale. An aryl analogue of the allosteric modulator NMDA was also obtained in 93% yield. Both EWG and EDG on the aryl iodide **109** were investigated, 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  $R^2$  groups, while  $R^3$  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  $I^\bullet$  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  $I^\bullet$  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  $I^\bullet$  or  $I_2$ . The elimination of HI produces the stilbene **d** which undergoes a photo-promoted Mallory-type cyclization to generate dihydrophenanthrene **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.<sup>[85]</sup> Since transition-metal catalysis is generally required to generate these scaffolds,<sup>[86,87]</sup> 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**,



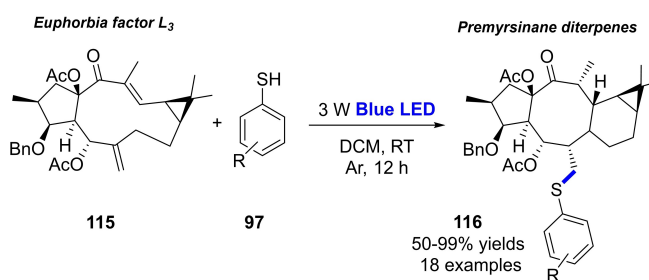
Scheme 41. Rationalization of light-mediated phenanthrenes **111** mechanism.



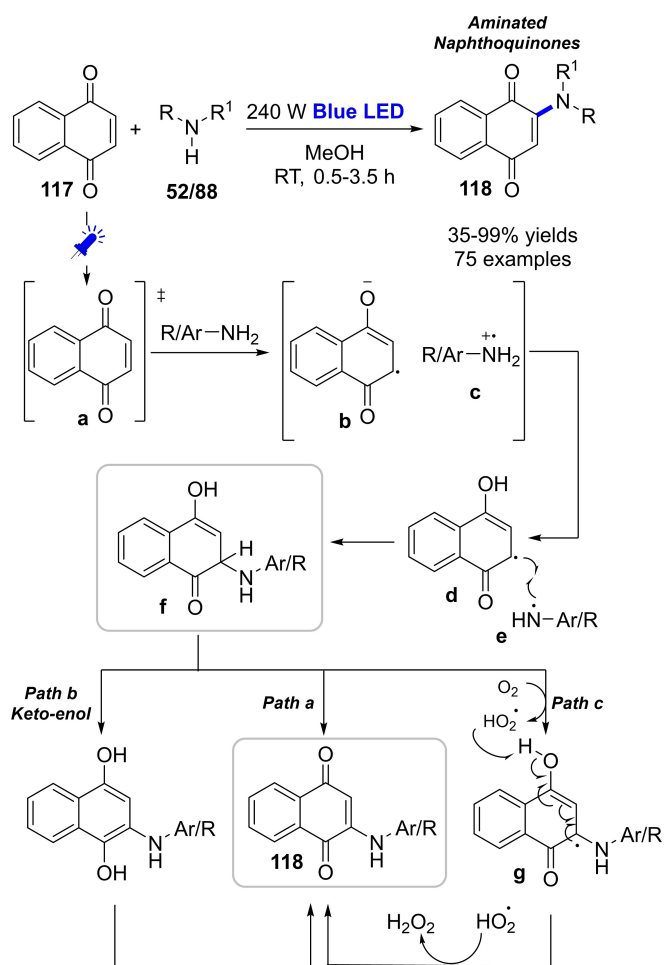
Scheme 42. Visible light-promoted catalyst-free synthesis of spirotricycles **114**.

starting from *N*-arylpropiolamides **112** and thio(seleno)phenols **97/113**, employing blue light, HCl, in MeCN at 60 °C in air (Scheme 42).<sup>[88]</sup>

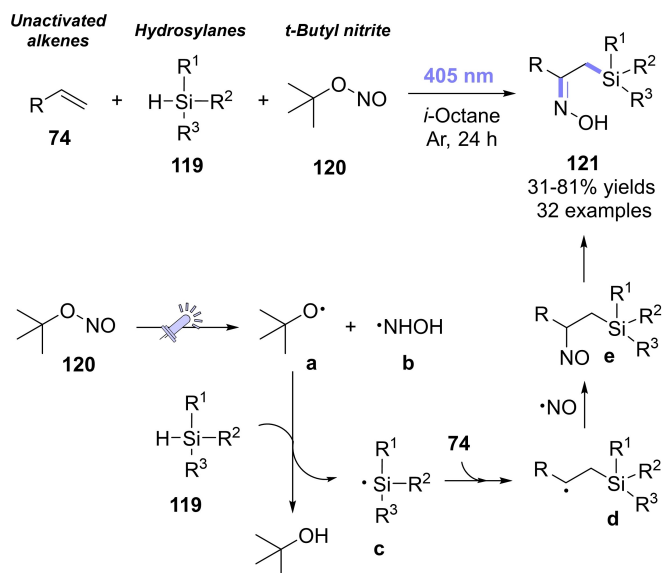
In the scope, different  $R^1$  substituents on **112** were investigated with alkyl, aryl, heteroaryl and polyaromatic groups giving the corresponding products from low to high yields. The introduction of halogen atoms on the  $R^2$  groups had no influence on the reaction. Several thiols bearing aryl substituents (67–76% yields) and heteroaryl side chains (37–38% yields) were employed. In the mechanism proposal, light induces the



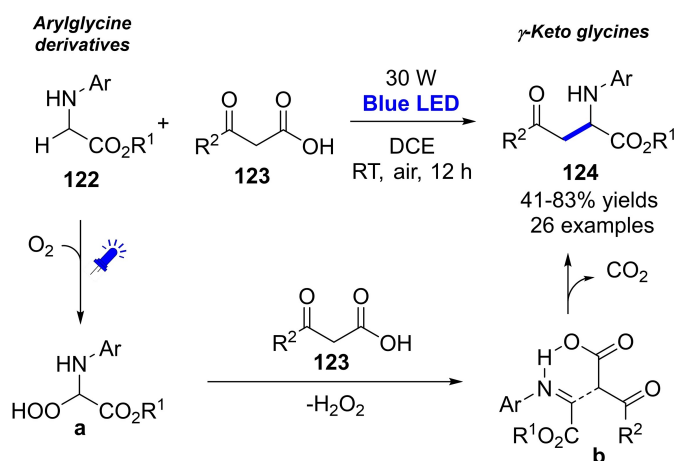
Scheme 43. Tandem thiol-ene click reaction/transannulation cyclization of *Euphorbia factor L3* promoted by blue light.



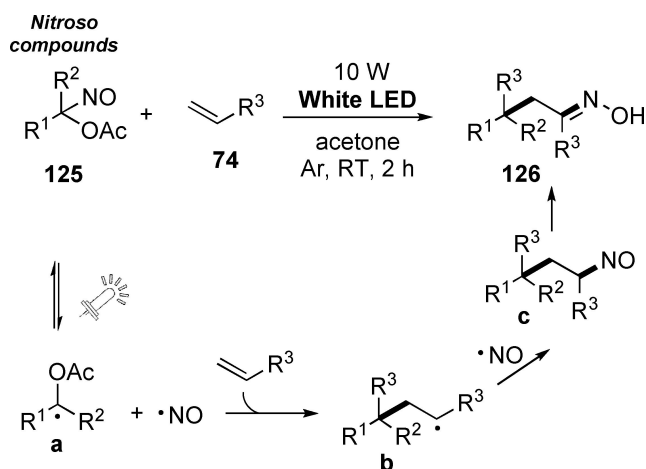
Scheme 44. Mechanism proposal for the blue light-driven amination of  $C(sp^2)$ -H bond of naphthoquinones **118** and quinones.



**Scheme 45.** Radical silyl-oximation of electron-poor alkenes **74** with silanes **119** and TBN **120**.



**Scheme 46.** Blue light cross-dehydrogenative/decarboxylative coupling cascades to  $\gamma$ -ketoglycines **124**.



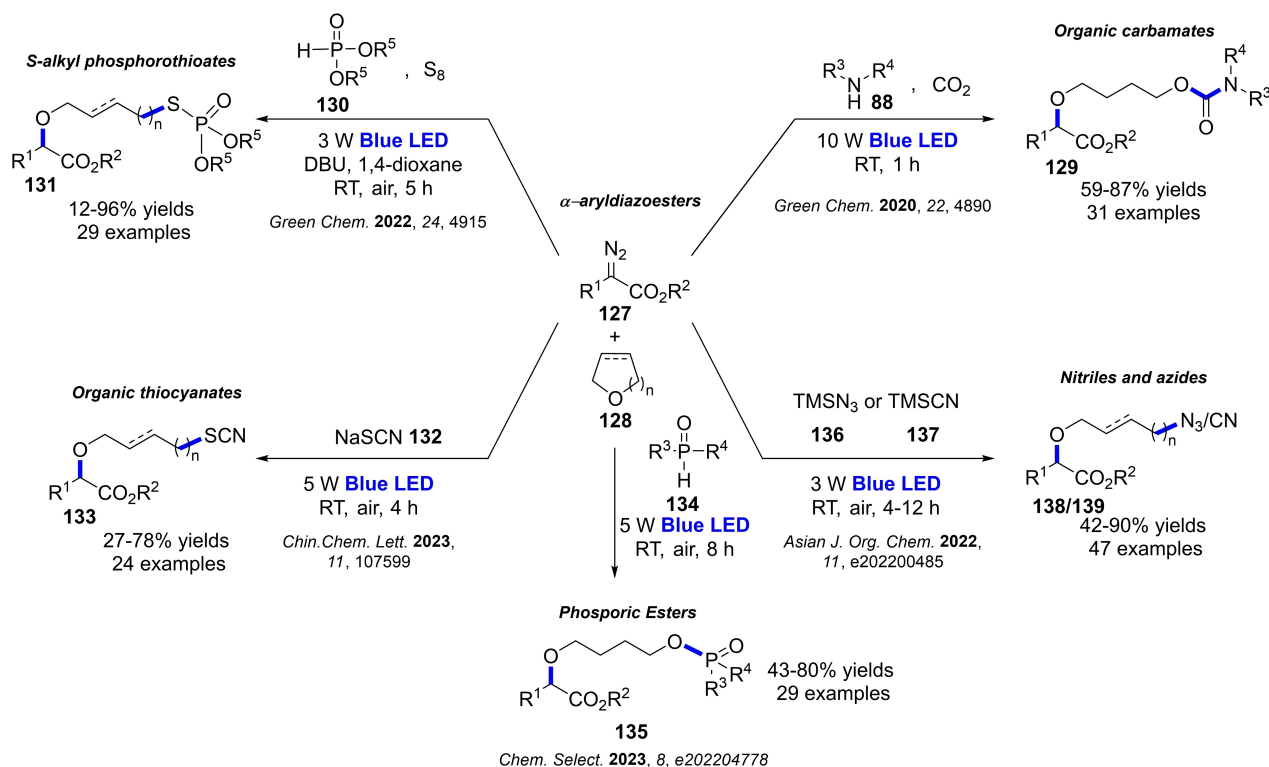
**Scheme 47.** White light-promoted radical addition reaction of nitroso compounds **125** to alkenes **74**.

homolysis of S–H or Se–H bond generating the sulfur/selenium radicals **a**.  $\alpha$ -Addition on the triple bond of *N*-arylpropiolamide **112** followed by *ipso*-cyclization forms radical **b** which is able to capture O<sub>2</sub> from the air releasing **c**. The loss of methanol followed by an intramolecular Michael addition generates the tricyclic product **114**.

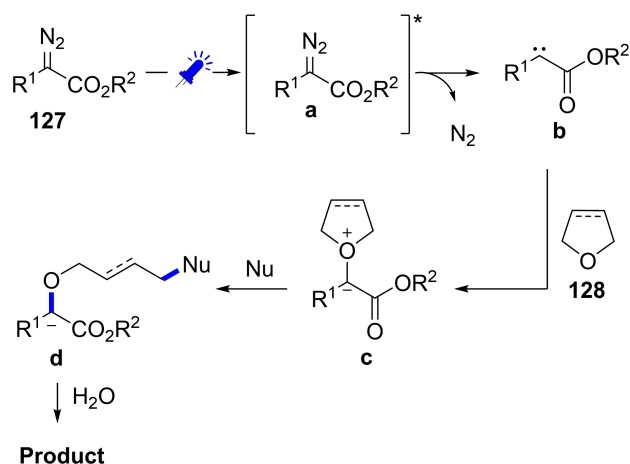
## 6.2. Later chain functionalization

The introduction of sulfur atoms is regarded as a valuable feature, in particular in those compounds exhibiting anti-HIV activity (e.g. nelfinavir,<sup>[89]</sup> 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)-thymine,<sup>[90]</sup> and a sulfanyltriazole analogue<sup>[91]</sup>). For this reason, in 2023, the group of Gao developed a tandem approach for the functionalization of *Euphorbia* diterpenes **115** with a sulfur-containing moiety through a thiol-ene click reaction followed by a transannulation cyclization mediated by blue light in the absence of any catalyst or additive (Scheme 43).<sup>[92]</sup> The obtained premysinane diterpenes **116** were subsequently converted to myrsinane-type diterpenes by an elegant and selective cyclopropane ring-opening mediated by 4-bromothiophenol as the catalyst under purple light-irradiation. *Euphorbia* factor L<sub>3</sub>, a naturally occurring lathyrane-type diterpene, bearing a terminal alkene was chosen as starting material. Compound **115** underwent the *anti*-Markovnikov addition of a series of substituted aromatic thiols **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 diastereoisomers in a *d.r.* always higher than 5:1. A wide variety of aryl mercaptans **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<sub>2</sub>)–H bond of naphthoquinones and quinones **117** with aliphatic and aromatic amines **52/88** for the preparation of 2-amino-naphthoquinones and 2-amino-quinones **118** has been reported by Jha et al. in 2023.<sup>[93]</sup> 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 **52**, bearing both EDG and EWG were successfully coupled with compounds **117** (16 examples, 79–96% yield). Primary and secondary aliphatic amines **88** afforded 2-amino-naphthoquinones in 35–99% yields. Moreover 5 examples of large-scale synthesis, one of them affording 3 grams of product **118**, were reported. The radical pathway was confirmed by both computational and experimental investigations. The reaction probably proceeds starting from the reduction of naphthoquinone **117** to form a highly oxidizing naphthoquinonyl biradical **a** upon irradiation. Consequently, electron transfer from the amine to **a** leads to a naphthoquinonyl radical anion **b** and aminyl radical cation **c**. A proton transfer and delocalization leading to a



**Scheme 48.**  $\alpha$ -Aryldiazoesters as valuable starting-materials for the synthesis of carbamates **129**, phosphorothioates **131**, thiocyanates **133**, nitriles **138**, azides **139** and phosphoric esters **135** under blue light irradiation.



**Scheme 49.** General mechanism for the functionalization of  $\alpha$ -aryldiazoesters **127** with cyclic ethers and a nucleophile.

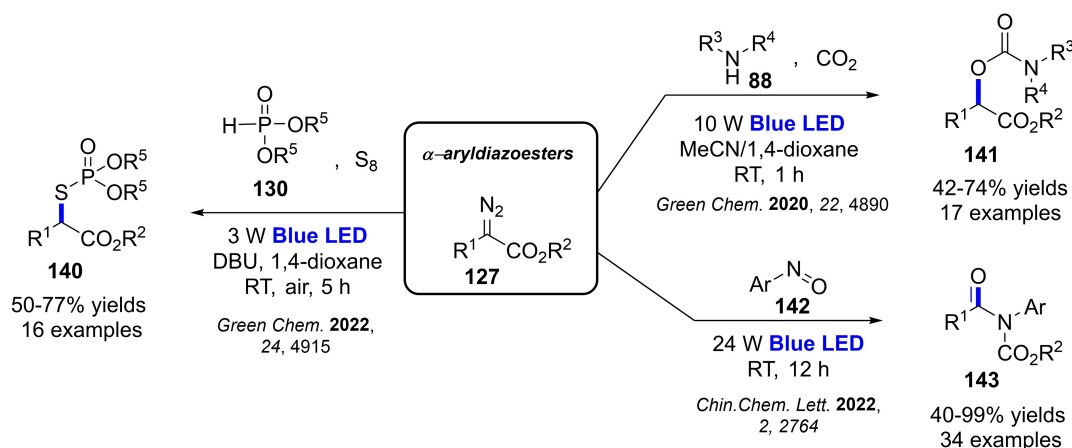
carbon-centered naphthoquinonyl radical **d** followed. The cross-coupling of the naphthoquinonyl carbon-centered **d** and aminyl nitrogen radical **c** forms a C–N bond, with subsequent elimination of hydrogen gas affording the desired product **118**. Three different pathways to reach product **118** 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 **121** can be realized following the methodology of Studer et al. (Scheme 45).<sup>[94]</sup> This radical cascade, exploiting hydrosilanes **119** and *t*-butyl nitrite **120** (TBN) in *i*-octane, allowed the functionalization of electron-poor alkenes by photo-induced cleavage of TBN **120** and the concomitant formation of *t*-butoxyl **a**, silyl **c** and persistent NO radicals at 405 nm. To increase the yields, the authors pointed out that TBN **120** should be slowly added over a period of 6 hours. To explore the generality of the reaction, different substituted silanes **119** 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  $\alpha$ -functionalization of arylglycine **122** with  $\beta$ -keto acids **123** under blue light was developed by Jiang et al. in 2022.<sup>[95]</sup>  $\gamma$ -Keto glycines **124** were obtained by a cascade process including a dehydrogenative/decarboxylative coupling reaction at room temperature (Scheme 46). Satisfying results were obtained with different  $\beta$ -keto acids **123** bearing an aromatic ring as  $R^2$  group (60–81% yield). When  $R^2$  was an





Scheme 50. Alternative reactivity of  $\alpha$ -aryldiazoesters **127** under blue light.

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  $R^1$  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  $H_2O_2$  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).<sup>[96]</sup> 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  $R^2$  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–NO homolysis thus a persistent NO• radical is formed along with an  $\alpha$ -oxy-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.<sup>[97]</sup> The radical defunctionalization of electron-poor alkenes to afford oximes was realized under irradiation with a 415 nm LED in dry DMSO.

$\alpha$ -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  $\alpha$ -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**,<sup>[98]</sup> phosphorothioates **131**,<sup>[99]</sup> thiocyanates **133**,<sup>[100]</sup> nitriles **138** and azides **139**<sup>[101]</sup> under blue light irradiation. Adjusting the reaction conditions according to the coupling partners, the  $\alpha$ -aryldiazoesters **127** and THF were reacted with carbon dioxide and an amine **88**,<sup>[98]</sup> elemental sulfur and H-phosphonates **120**,<sup>[99]</sup> and TMSCN **137**/TMSN<sub>3</sub> **136**,<sup>[101]</sup> respectively. Only in 2023, the reaction was extended to NaSCN **132**<sup>[100]</sup> and to organic phosphinic acids **134**, the latter methodology was employed to produce phosphoric esters **135**.<sup>[102]</sup>

A general reaction mechanism for all the previous methodologies is described in Scheme 49. The excited state of the  $\alpha$ -aryldiazoesters **a**, formed upon absorption of blue light, can release  $N_2$  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  $\alpha$ -aryldiazoesters **127** were reacted with elemental sulfur and H-phosphonates **130**,<sup>[99]</sup> carbon dioxide and an amine **88**<sup>[98]</sup> 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.

**Keywords:** photoinduced · domino reactions · catalyst-free · heterocycles · multicomponent reactions

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