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Visible photons as ideal reagents for the activation of coloured organic compounds

Lorenzo Di Terlizzi, Luca Nicchio, Stefano Protti * and Maurizio Fagnoni *

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In recent decades, the traceless nature of visible photons has been exploited for the development of efficient synthetic strategies for the photoconversion of colourless compounds, namely, photocatalysis, chromophore activation, and the formation of an electron donor/acceptor (EDA) complex. However, the use of photoreactive coloured organic compounds is the optimal strategy to boost visible photons as ideal reagents in synthetic protocols. In view of such premises, the present review aims to provide its readership with a collection of recent photochemical strategies facilitated *via* direct light absorption by coloured molecules. The protocols have been classified and presented according to the nature of the intermediate/excited state achieved during the transformation.

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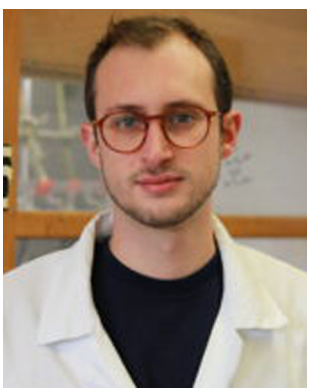
1. Introduction

If only Giacomo Ciamician, while exposing an ethanolic solution of benzophenone to the *Italian sun*, had imagined what would happen a century later... *come on*, he predicted exactly that photochemistry would acquire a predominant role in organic synthesis![1–7] The capabilities of photons as reactants,[8–13] capable of promoting the chemical conversion of a substrate without leaving traces in the reaction vessel, have been fully exploited in the last two decades through the overwhelming achievements of visible-light photocatalysis (in most cases, of photoredox catalysis) in synthesis.[14–19] Such success has enabled the design of a plethora of versatile synthetic strategies, which have found wide application ranging from the synthesis of polyfunctionalized materials to the late-stage functionalization of bioactive molecules.[20] Along with chemical reactions, new photochemical devices and reactors have been proposed, thanks to the widespread availability of unexpensive visible-light sources, including compact fluorescent lamps and LEDs, apart from natural sunlight.[21,22]

PhotoGreen Lab, Department of Chemistry, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy. E-mail: stefano.protti@unipv.it, fagnoni@unipv.it

Lorenzo Di Terlizzi

Lorenzo Di Terlizzi obtained his master's degree in organic chemistry in 2020 with a thesis on the development of aggressive diradicals starting from chloroaryl substituted carboxylic acids in the PhotoGreen lab under the supervision of Prof. Fagnoni and Prof. Protti. After that, he started his PhD in the same group, focusing on the use of arylazo sulfones to generate reactive intermediates under visible-light irradiations. He is currently a post-doc in the PhotoGreen Lab dealing with visible-light induced polymerizations, visible-light photoacid generators and photochemical synthesis.



Luca Nicchio

Luca Nicchio received his master's degree in chemistry from the University of Pavia (Italy) in 2022, under the supervision of Prof. Maurizio Fagnoni (Photogreen Lab). Luca is currently a second year PhD student in a joint PhD program between Université Paris-Saclay and University of Pavia (Université Paris-Saclay International Joint PhD Program ("Cotutelle") 2022), under the supervision of Profs. Luc Neuville and Prof. Stefano Protti. His research subject focuses on the development of new and green synthetic approaches through visible-light generation of radical intermediates from arylazo sulfones and arylazo sulfonates.

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In these strategies, the photocatalyst plays the role of absorbing photons and promoting, through its excited state, a chemical modification of (the) substrate(s) *via* different pathways that include electrons, atoms (*e.g.*, hydrogen[23] and halogens[24]) or energy transfer[25] (a representative example in Scheme 1a).

Obviously, a photocatalyst is not even needed if a photoreactive molecule, prone to undergo chemical conversion through direct visible-light absorption, is available; however, several organic compounds are colorless and absorb exclusively in the UV region. To overcome this limitation, alternative strategies have been designed to generate a coloured species *in situ* (or at least to enable the use of a longer wavelength to promote the process).

The first approach involves chromophore activation mainly through a complexing agent (*e.g.*, Lewis and Brønsted acids).[26] In this case, the chromophore (*e.g.*, an enone **A**) may enhance its ε value by complexing with a Rh complex, thus facilitating the [2+2] cycloaddition onto a C=C bond (Scheme 1b). Alternatively, the protonation of colourless dithiane **B** generates a coloured thionium ion **C**, which is prone to forming a cyclobutane ring upon irradiation (Scheme 1c).[27] Honestly, the latter two routes have not found a widespread application and have been applied only to selected cases.

The formation of an electron donor acceptor (EDA) complex *via* electronic interaction of two (or more) colourless reaction partners (Scheme 1d) is a quite common strategy.[28–33] The thus formed complex has a distinct absorption profile (a bathochromic shift occurred) different from that of the starting materials. The main drawback of this approach is the requirement for markedly different electronic characteristics of the reaction partners, necessitating the use of both a good electron-rich (*e.g.*, the indole **D**) and an electron-poor (a benzyl bromide **E**) derivative to promote the EDA formation. An intriguing alternative is the generation of the coloured species **H** through the *in situ* chemical reaction of the starting (colourless) substrate **F** (having a leaving group LG) with an organic catalyst (in most cases, a nucleophile **G**, Scheme 1e).[34] However, this approach is still in its infancy and only a few examples have been reported. These "colouring" strategies have been successfully applied either to a small range of substrates that bears a complexing site or to reactants having electronic properties conducive to the formation of an EDA complex. Another emerging approach involves the incorporation of a dyedauxiliary group in a colourless compound to impart both color and photoreactivity. An exemplary case is that of arylazo sulfones **J** (Scheme 1f), obtained in two steps from anilines **I** and prone to generating several radical intermediates upon photolysis.[35,36] Saying so, the ideal case is the photochemical conversion of a (purposely designed) coloured compound into a valuable product without any additives, as it is the case for α-diazoesters **K**, which are widely used as precursors of carbenes **L** (Scheme 1g).[37]

Nonetheless, the fact that a given organic compound is coloured does not guarantee that it is photochemically active upon visible-light absorption. As an example, C-nitroso compounds (*e.g.*, nitrosoaromatics) are green/blue coloured species but photochemically inactive due to their easy conversion to *Z*- and *E*-azodioxy dimers.[38] In rare instances, such as in the case of 2-methyl-2-nitrosopropane (λ_{max} at 680 nm due to an nπ* transition), photodissociation occurs.[39]

At the same time, the photoreactivity of a coloured substance may lead to interesting applications, as in the case of diazoarenes, discovered in 1883, probably the most well-known (and investigated) class of coloured compounds. The significant absorption in the visible region (430–450 nm, ε = 500–1500 M^{-1} cm^{-1}) is largely due to the partially forbidden nπ* electronic transition which leads to *E*/*Z* isomerization,[40] the phenomenon mostly applied in fields different from organic synthesis such as the development of photoswitches.[41]

Stefano Protti

Stefano Protti completed his PhD in Pavia (2007). Later he moved to the LASIR Laboratory (Lille, France) at the iBitTec-S laboratory (CEA Saclay, France) carrying out studies on photocatalyzed oxidation reactions for energy storage, he moved again to the University of Pavia, where has been serving as an Associate Professor since 2018. He currently serves as an editor for the SPR in Photochemistry (Royal Society of Chemistry), member of the International Advisory Board of EuJOC and an associate editor of the Photochemical and Photobiological Sciences. His work is mainly focused on the development of visible light mediated synthetic strategies.

Maurizio Fagnoni

Maurizio Fagnoni is currently a Full Professor in Organic Chemistry at the University of Pavia (PhotoGreen Lab, Italy). His research interests are mainly focused on the photoinduced or photocatalytic generation of reactive intermediates such as (bi)radicals, (phenyl) cations and radical ions and their application in eco-sustainable synthesis or in photolithography as well as biological application. He is currently a member of the committees of the Interdivisional group of Green Chemistry and Photochemistry of the Italian Society of Chemistry. In 2022, he received the Theresian Medal from the University of Pavia.

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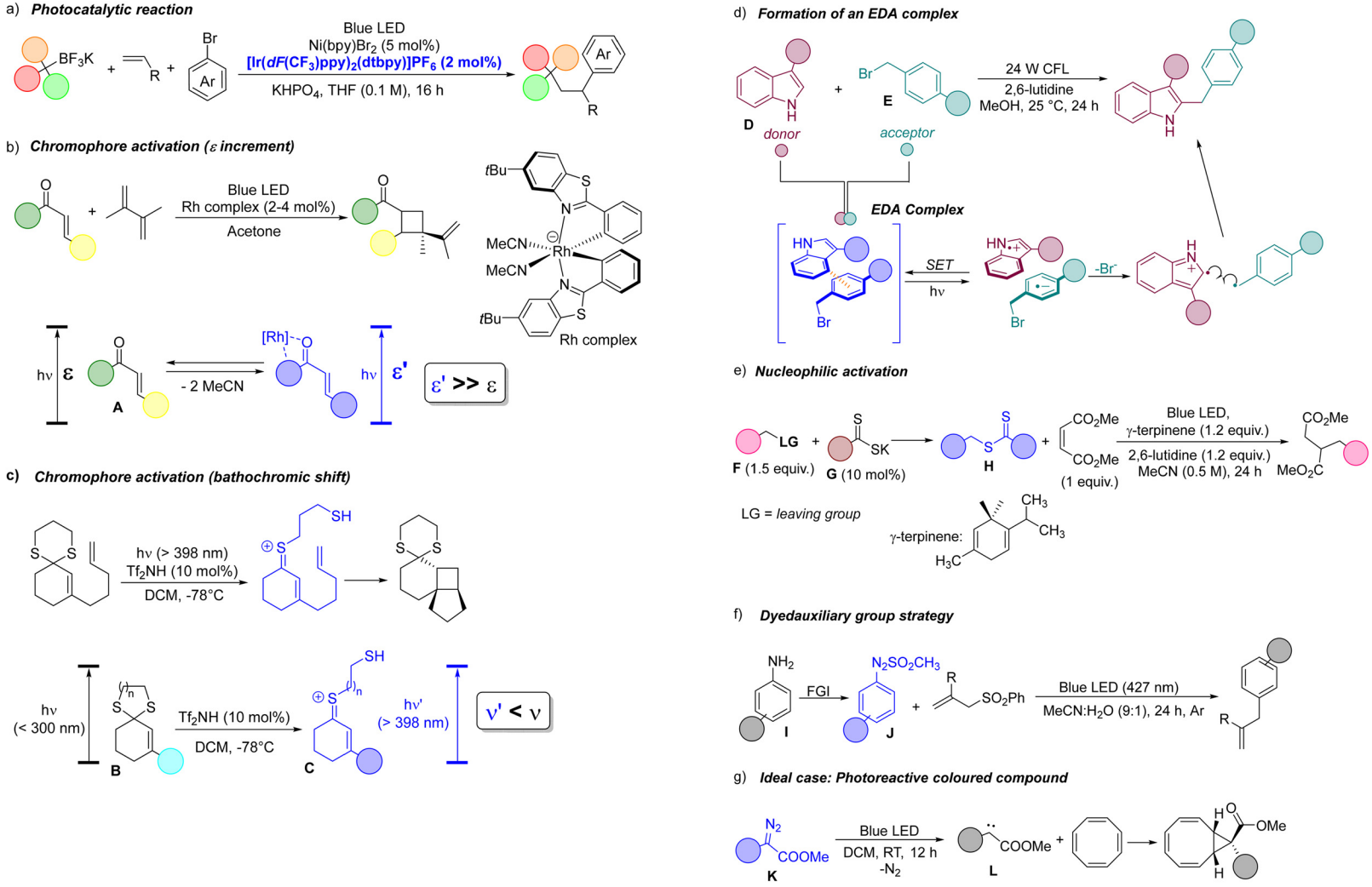

Scheme 1 (a) A photocatalytic reaction (the coloured PC promotes the transformation upon light absorption). Colouring strategies to allow visible photons to induce a chemical reaction in a colourless compound through (b) and (c) chromophore activation by a Brønsted/Lewis acid, (d) and (e) the *in situ* formation of either an EDA complex or a coloured reactive species through nucleophilic activation and (f) the incorporation of a dyedauxiliary group in the colourless compound. The ideal case is (g) the direct photolysis of a coloured compound. Blue color represents the species that absorb visible photons.

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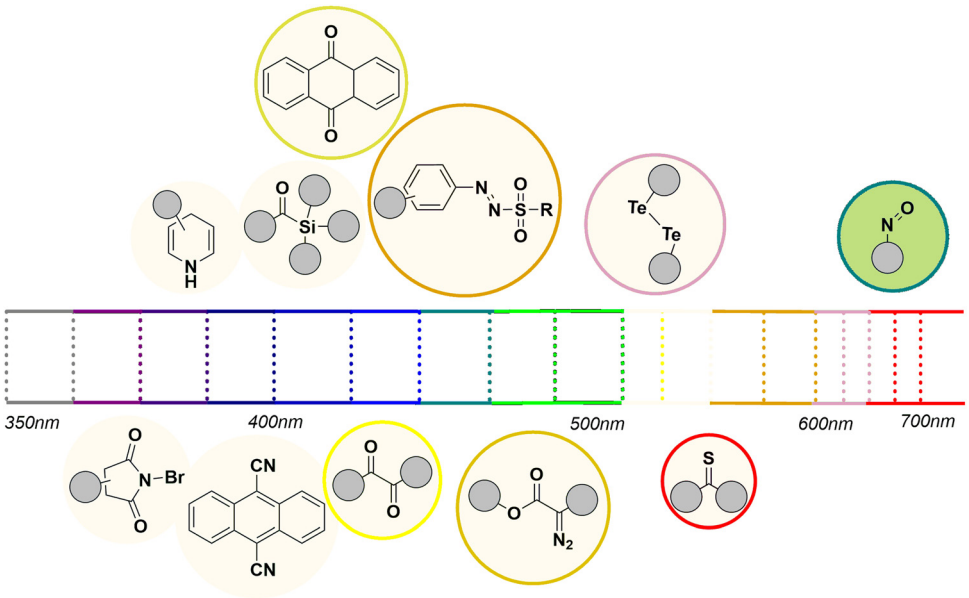

Fig. 1 Light absorption range in the visible region of selected coloured photoreactive organic compounds.

A selection of compounds having photoreactive chromophores whose absorption lies in the visible region is briefly described below and sketched in Fig. 1.

Carbonyls. It is well known that simple ketones do not absorb in the visible region, with the remarkable exception of some aromatic derivatives such as thioxanthone,[42] 9-fluorenone[42] and 5,7,12,14-pentacenetetrone,[43] which may find application as photoorganocatalysts.[18] In contrast, α-diketones are slightly coloured and undergo the typical reactions of the carbonyl group (*via* the nπ* excited state) upon visible-light irradiation[44–46] including [2+2]-heterocycloadditions.[47] Quinones exhibit an absorption band in the 400–450 nm range,[48] and have been employed in valuable reactions including cycloadditions,[49] single electron transfer (SET) processes or photooxidations. Anthraquinones and naphthoquinones are well-investigated chromophores, capable of absorbing blue light and acting as triplet sensitizers (*via* the ππ* state) as well as photoredox and HAT photocatalysts.[50,51]

Thioketones mainly absorb in the 500–600 nm region, thanks to a dipole-forbidden n → π* transition, but they are rather rarely used in photochemistry compared to the corresponding ketones.[52] The main application of these compounds is the synthesis of thietanes *via* a thia-Paternò-Büchi but mostly under UV radiation.[47,53]

The photochemistry of ***cyanoarenes*** (and in particular the significant reduction potential in the singlet excited state (*e.g.*, >3.00 V *vs.* SCE for 1,2,4,5-tetracyanobenzene)[54] was fundamental in the development of electron transfer processes.[54] Some compounds belonging to this class (such as 9,10-dicyanoanthracene, DCA and 1,2,3,5-tetrakis(carbazole-9-yl)-4,6-dicyanobenzene, 4CzIPN) have found application in photoredox catalysis.[55] Among aromatic derivatives, polycyclic aromatic hydrocarbons having at least four fused aromatic rings are coloured and known to undergo [4+4] photocyclodimerization.[56–58]

Two main classes are known to deliver carbenes upon photolysis, namely, acylsilanes and diazoderivatives. ***Acylsilanes*** exhibit an absorption band in the 350–420 nm region, making such compounds ideal precursors of α-siloxy carbenes upon visible-light irradiation *via* 1,2-photo Brook rearrangement.[59,60] Similarly, ***diazocompounds*** including α-diazoesters and α-diazoketones are characterized by an absorption band in the 400–500 nm region, imparted by the N═N moiety.[61,62]

A few other classes of compounds are known to release radicals by photohomolysis.[63] The long wavelength absorption band of 1,4-***dihydropyridines*** (such as the calcium-channel blocking drug Nifedipine[64,65]) located around 360 nm (ε = 7000 M^{-1} cm^{-1}) extends beyond 400 nm and is attributed to a ππ* internal charge transfer transition. Recently, such compounds have been employed as electron and proton donors[66] as well as alkyl radical precursors[67] in photoredox catalyzed processes but the direct photocleavage of a C–C bond is an option.

Arylazo sulfones (Scheme 1f)[35,36] and ***arylazo sulfonates***[68] show an absorption band in the 400–450 nm range, arising from a nπ* transition. Irradiating these sulfones with blue light induces the homolytic cleavage of the N–S bond, resulting in the subsequent formation of aryldiazenyl, sulfonyl and aryl radicals,[35] making these compounds ideal candidates for the uncatalyzed formation of C–C bonds.[69]

N-Iodo and N-bromo amides and imides have been reported to absorb light above 400 nm and undergo *N*-halogen bond cleavage, releasing a halogen atom.[70,71] Among hypervalent iodine(III) reagents, ***benziodoxoles*** are the only ones reported as photoreactive under visible-light irradiation and employed

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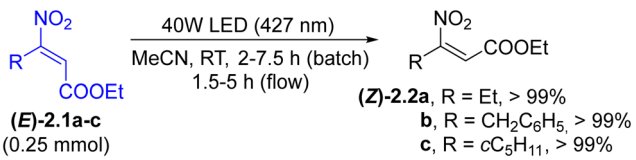
in alkynylation processes.[72] Finally, both ***diselenides and ditellurides*** have a significant absorption tail in the visible region (400–550 nm), which has been assigned to the nσ* transition band,[73–75] which is responsible for inducing Se–Se and Te–Te bond cleavage. In some instances, visible-light is an important tool for the uncaging of functional groups.[76]

As hinted above, all these classes were found to undergo chemical transformations when irradiated with visible-light (*via* the formation of either a reactive intermediate or a concerted reaction). We then recognized that in the last few years, the interest in the use of coloured organic compounds (whether commercially available or purposely prepared) in synthesis dramatically increased through the adoption of visible-light uncatalyzed procedures.[77] We thus prepared the present review with the aim to provide the reader with a realistic portrait of the capabilities of the photochemical approach and to encourage interest in a new era of photocatalyst-free processes. The procedures described have been classified based on the reaction mechanism and mostly are referred to the 2015–2023 period along with previous seminal examples.

2. Intermediate free reactions

The intermediate free reactions involve a C═X (X═C, O) or a N═N bond and mainly belong to two categories, namely, *E*/*Z* isomerization and cycloaddition.

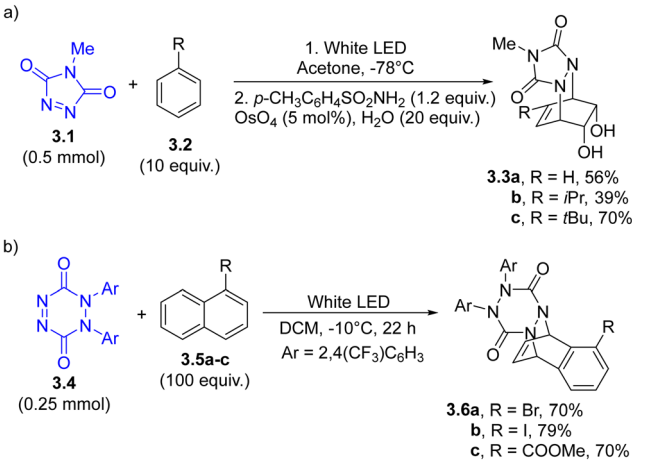
E/*Z isomerization*. Photochemical and photocatalyzed *E*/*Z* isomerization of double bonds[40,78] is considered as the preferred approach for changing the stereochemical configuration under mild conditions. Usually, the approach is used to obtain the less stable *Z* isomer. In this context, (heteroaryl)azo derivatives can undergo *E*/*Z* isomerization when irradiated with an appropriate visible wavelength. However, despite its application in several fields, azo group isomerization has limited synthetic importance.[40] On the other hand, only few classes of olefins exhibit a significant absorption in the visible region. These mainly include nitro alkenes and stilbenes. Thus, poorly available and rather unstable (*Z*)-β-nitroacrylates (**(*Z*)-2.2a–c**) have been prepared in quantitative yields from the corresponding *E*-isomers (**(*E*)-2.1a–c**) upon blue light irradiation (Scheme 2). The transformation was performed under both batch and flow conditions. The process allowed the use of *Z*-derivatives in cycloaddition reactions in a stereocontrolled manner.[79] Similarly, the *E* to *Z* isomerization of styrylpyridin-2(1*H*)-ones has been described to occur under blue light (420 nm) irradiation under an argon atmosphere.[80] The



(*E*)-2.1a-c (0.25 mmol)

(*Z*)-2.2a, R = Et, > 99%
b, R = $CH_2C_6H_5$, > 99%
c, R = cC_5H_{11}, > 99%

Scheme 2 Visible-light promoted selective *E*/*Z* conversion of β-nitroacrylates.



Scheme 3 Photoinduced dearomatization of (a) benzenes and (b) naphthalenes.

conversion of *E*-stilbenes to *Z*-stilbenes took place efficiently in a MeCN–NaOH 10 : 1 mixture again upon blue light irradiation.[81]

The *E* to *Z* isomerization of amino cinnamates at 405 nm in the presence of a chiral phosphoric acid catalyst was used to induce the formation of atropisomeric *N*-aryl quinolones with low rotational barriers, yielding up to 94% and up to > 99% ee, thus opening an interesting route to axially chiral materials.[82]

Cycloaddition. As in the case of *E*/*Z* isomerization, cycloadditions represent a research field where photochemistry always plays a key role as a powerful alternative to thermal and catalyzed approaches.[83] As an example, the N═N double bond may act as an arenophile in [4+2] photocycloadditions, enabling the chemical dearomatization of arenes and naphthalenes.[84] Thus, *N*-methyl-1,2,4-triazole-3,5-dione **3.1** (Scheme 3a) was employed in the photoinduced dearomative dihydroxylation and diaminodihydroxylation of simple arenes to produce substituted cyclohexenes **3.3a–c**. The protocol was applied in the synthesis of, among the others, carbasugar MK7607.[85]

1,2-Dihydro-1,2,4,5-tetrazine-3,6-diones (**3.4**, an example in Scheme 3b) have been recently investigated as dearomative agents for naphthalenes (**3.5a–c**), arenes and nitrogen-based heterocycles. The so obtained cycloadducts **3.6a–c** were efficiently functionalized by utilizing different approaches, including palladium- or copper catalyzed allylic substitution processes and non-catalytic hydroboration reaction.[86]

The photoinduced arene–alkyne [3+2] cycloaddition of 1-alkynylnaphthalen-2-ols (**4.1a–c**, Scheme 4) under photocatalyst-free conditions followed by air mediated oxidation of the obtained hexacycles **4.2a–c** was exploited for the efficient and stereoselective preparation of complex three-dimensional hexacyclic architectures **4.3a–c** in good yields and complete stereoselectivities.[87]

The light-driven [2+2] cycloaddition of olefins has been often exploited as an atom efficient tool to achieve cyclobutane scaffolds. The preparation of *syn*-cyclobutanes (**5.2a–c**, Scheme 5) was recently achieved by irradiating a solid-state

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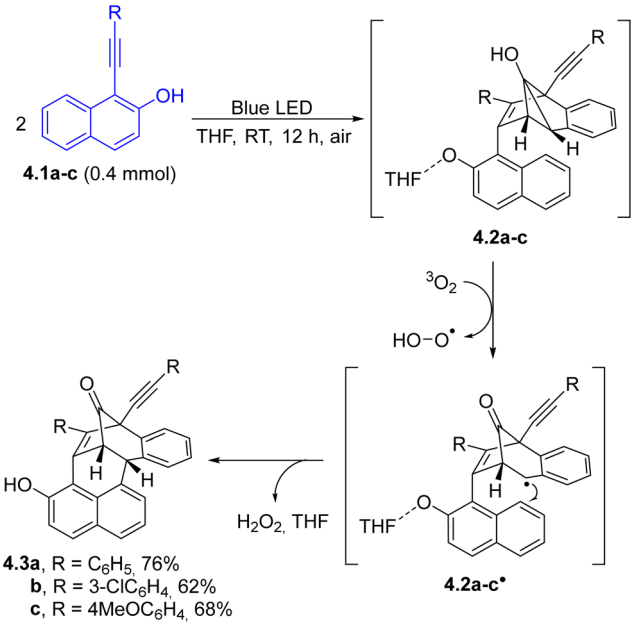
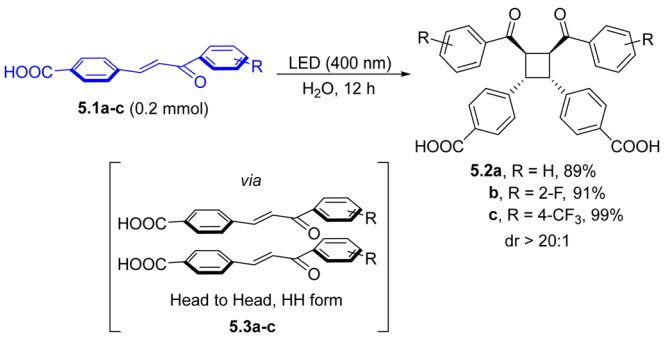


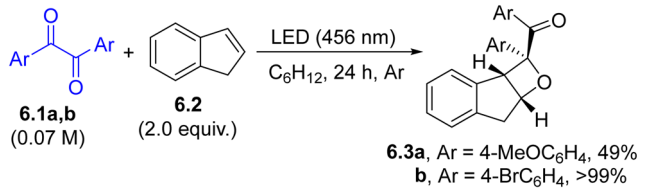
Scheme 4 Photoinduced [3+2] cycloaddition of 1-alkynylnaphthalen-2-ols.



Scheme 5 Purple light mediated synthesis of cyclobutanes **5.2a–c**.

suspension of **5.1a–c** in water, efficiently furnishing the desired products with excellent diastereoselectivity.[88] The supramolecular complexes **5.3a–c** played a key role in driving the regioselectivity of the [2+2] addition. Interestingly, the head-to-head species **5.3a–c** can be smoothly converted to the corresponding head to tail form through melt crystallization, allowing for a divergent and versatile strategy.

The achievements in visible-light photocatalysis in the last few decades have also brought traditional photochemical processes into focus, including Paternò–Büchi cycloadditions.[89–92] However, the visible-light mediated, photocatalyst-free synthesis of oxetanes has only been sparsely reported in the literature. Benzyls (**6.1a** and **b**, Scheme 6), which exhibit a weak absorption in the visible region (400–450 nm), were successfully employed in both regio- and stereoselective [2+2] cycloaddition with simple olefins (*e.g.*, **6.2**) to produce the desired oxetanes **6.3a** and **b**, along with a minor amount of 1,4-dioxanes derived from a [4+2] cycloaddition. The reaction was optimized under



Scheme 6 Visible-light promoted preparation of oxetanes.

continuous flow conditions and the products were obtained with similar satisfactory selectivity and yield.[93] Analogously, visible-light mediated Paternò–Büchi reactions on simple olefins have been performed by using anthraquinones[94] or α-ketoesters[95] as carbonyl donors.

2-(4-Hydroxyphenyl)-substituted aldehydes and ketones (**7.4a–c**) bearing a diaryl-substituted quaternary stereocenter have been prepared *via* a visible-light-assisted and zinc triflate-catalyzed multicomponent reaction of benzoquinone (**7.1**), alkynes **7.2a–c**, and a nitrogen or sulfur containing nucleophilic partner such as an indole **7.3** or a thiol.[96] In the suggested mechanism illustrated in Scheme 7, **7.2a–c** underwent a Paterno–Buchi [2+2] cycloaddition with the photoexcited ^{1}**7.1**, forming 1,4-singlet biradicals ^{1}**7.5a–c** (paths a and b) which in turn are converted to spiro-oxetene derivatives **7.6a–c** *via* intramolecular coupling (path c). These rather unstable species are smoothly converted to *p*-quinone methides **7.7a–c** *via* retroelectrocyclization (path d). Coordination of **7.7a–c** with $Zn(OTf)_2$ enables the nucleophilic addition of **7.3** (path e) to afford, after protonation of intermediates **7.8a–c** the desired adducts **7.4a–c** with the concomitant release of the Lewis acid catalyst (path f).[96] An asymmetric version of this protocol has been recently developed using chiral phosphoric acid catalysis.[97] An analogous approach involves CuCl as the Lewis acid and alcohols as nucleophiles and it was applied in the synthesis of alkoxysubstitued aldehydes, a set of compounds exhibiting interesting antifungal activity.[98] Dihydroquinoxalines were instead formed by irradiating a mixture of *p*-quinones, alkynes and *ortho*-phenylenediamines under basic conditions (NaOAc, 20 mol%).[48]

In Scheme 8, a rare example of 6π-photocyclization promoted by visible-light under photocatalyst-free conditions is described. Thus, *ortho*-biaryl-appended β-ketoesters **8.1a–d** (in equilibrium with the enol tautomers **8.3a–d**) underwent an efficient 6-*endo*-trig cyclization/1,5-H shift to yield 9,10-dihydrophenanthren-9-ols **8.2a–d**. The authors postulated a conrotatory ring closure followed by a suprafacial 1,5-hydrogen shift to explain the reactivity.[99]

Photochemistry was also used for the skeleton rearrangement of azaarenes. Thus, under purple LED irradiation, quinoline *N*-oxides **9.1a–c** promoted the formation of 3,1-benzoxazepines **9.3a–c**, which upon acid treatment gave *N*-acylindoles **9.2a–c** in variable yields (Scheme 9). The process can be described as a C2-selective, net carbon deletion of azaarenes and the mildness of this approach facilitated the late-stage elaboration of compounds of pharmaceutical interest.[100]

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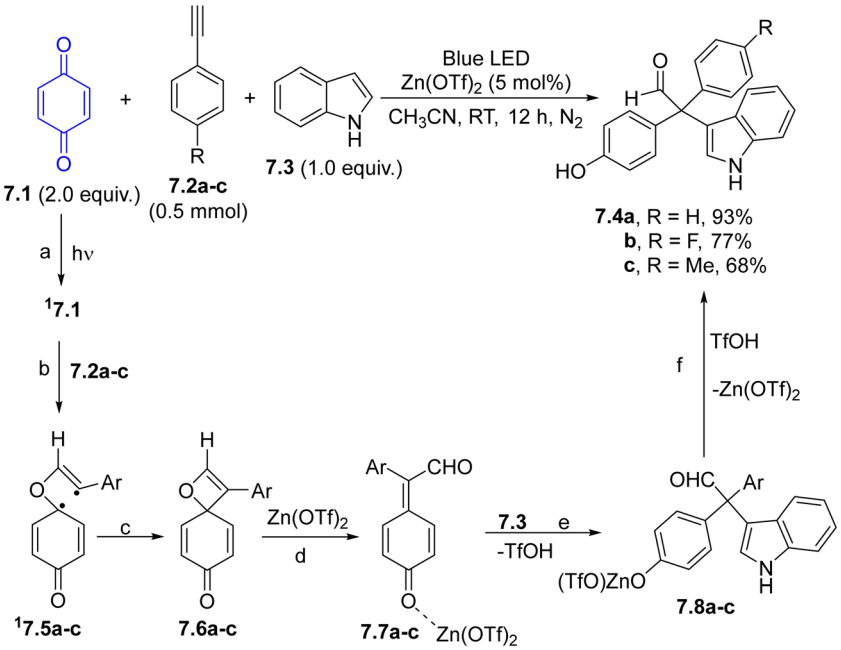
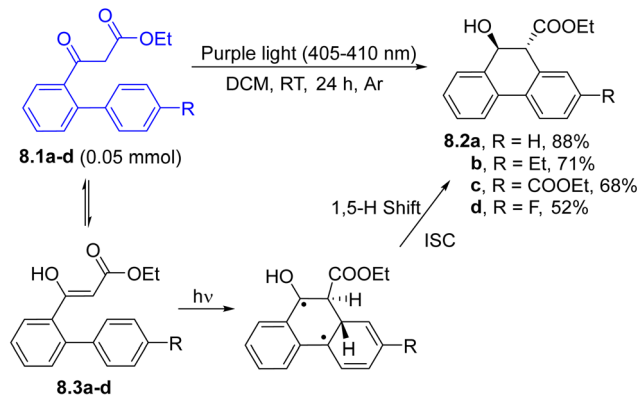
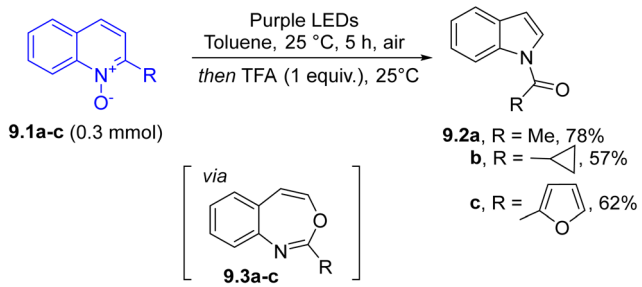


Scheme 7 Three-component reaction for the preparation of 2-(4-hydroxyphenyl)-substituted aldehydes and ketones.



Scheme 8 Visible-light-induced 6π-photocyclization.



Scheme 9 Photoinduced ring contraction of quinoline-*N*-oxides for the synthesis of *N*-acylindoles.

Noteworthily, when 3,1-benzoxazepines underwent an oxidative cleavage (*via* ozonolysis at −78 °C) followed by heating at 90 °C, a direct conversion of quinolines into quinazolines took place. This transformation has important implications in drug discovery since it replaces an aromatic carbon atom with a nitrogen atom through a C-to-N transmutation.[101]

3. Reactions *via* carbon-based radicals

3.1. C(sp^3)-based radicals

3.1.1. α-Non-stabilized alkyl radicals. Alkyl radicals may be obtained starting from coloured Barton and Hantzsch esters, as well as from a particular class of borates and they find applications in the formation of C–C or C–heteroatom bonds.[67]

N-(Acyloxy)-2-thiopyridones are a class of coloured compounds also known as Barton esters, which represent a promising alternative in the generation of radicals under tin-free conditions.[102] The use of such derivatives pertains to the dyedauxiliary strategy (Scheme 1f) since a (photo)labile N–O bond is installed upon esterification of the corresponding carboxylic acid with *N*-hydroxythiopyridone.

In particular, the photoinduced cleavage of the N–O bond followed by CO_2 loss resulted in the formation of an alkyl radical. This behavior has found several synthetic applications, including the Minisci reaction[103] reported in Scheme 10. In this case, adamantyl radical (in turn generated *via* visible-light mediated decarboxylative decomposition of ester **10.1**) was trapped by lepidinium camphorsulphonate **10.2** (a heteroaromatic protonated base) and led to 2-substituted lepidine **10.3** in almost quantitative yield.[104]

Various aliphatic nitriles have been smoothly prepared from the corresponding Barton esters. As an example, oleic acid derivative **11.1** was successfully used to obtain the corresponding nitrile **11.3** in a high yield in the presence of

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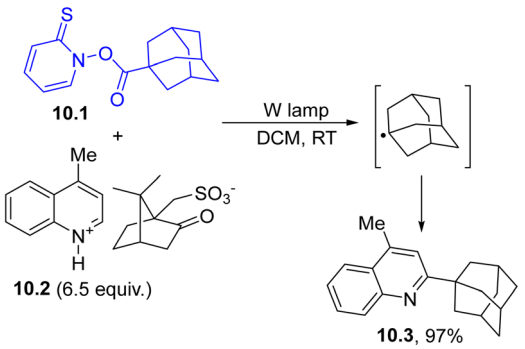
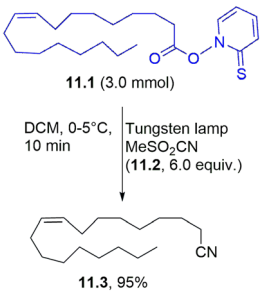
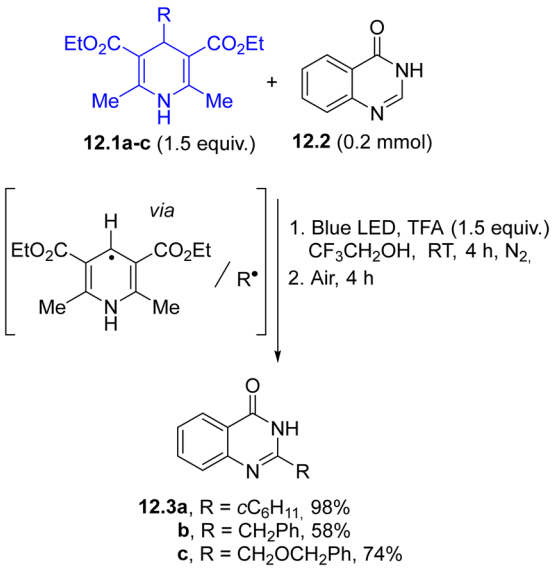


Scheme 10 Visible-light generation of alkyl radicals for the functionalization of lepidine.



Scheme 11 Visible-light promoted synthesis of nitriles.



Scheme 12 Hantzsch esters as a source of alkyl radicals.

methanesulfonyl cyanide **11.2** (Scheme 11).[105] The same approach was used to achieve thiocyanates by the photolysis of Barton esters in the presence of methanesulfonyl (or *p*-toluensulfonyl) isothiocyanate.[106]

In the last decade, Hantzsch esters (HEs) have been recognized as stable and easily available reservoirs of carbon-based radicals under photochemical conditions.[66] The construction of a dihydropyridine scaffold makes HEs coloured and photoreactive (Scheme 1f). Alkyl-1,4-dihydropyridines **12.1a–c** have been employed in the regioselective late-stage alkylation of nitrogen-based heterocycles (including quinazolin-4(3*H*)-one **12.2**, Scheme 12) under blue light irradiation.[107] The radical pair is formed by direct C–R cleavage in compounds **12.1a–c**. The photochemistry of such compounds has been elegantly combined with Ni-based catalysis, to develop a protocol for promoting a C(sp^2)–C(sp^3) cross-coupling between aryl bromides and benzyl radicals generated from HEs.[108] In this case, the excitation of HEs promoted an electron transfer with a Ni(I) species and the resulting radical cation released the desired radical through fragmentation. More recently, such derivatives were also employed as neutral precursors of alkyl radicals for the preparation of trifluoromethylated amino acids under continuous microflow conditions, by using *in situ* generated α-CF_3 ketimine esters as the radical acceptor.[109]

Boracene-based borates (absorption wavelength with a tail up to 430 nm) have been recently reported as a source of tertiary, secondary, and primary alkyl radicals.[110] Such derivatives (in analogy with HEs) may release the radical *via* direct excitation or by acting as a strong SET reductant where the radical is released from the oxidized form of the boracene. The boracene dyedauxiliary group here has been introduced by reaction with a Grignard or an organolithium reagent. Recently, 2,2′-(pyridine-2,6-diyl)diphenol-based borates **13.1a–c** have been employed for the development of several synthetic protocols including decyanoalkylation of pyridines, acylation and Giese-type hydroalkylation of electron-poor alkenes (**13.2**, Scheme 13a).[111] An NHC carbene catalyzed three-component process involving boronate **13.4**, an alkene (mainly styrenes, **13.5**) and acyl imidazoles **13.6** has been proposed as a method for the alkylacylation of olefins to form highly functionalized ketones **13.8** (Scheme 13b).[112] The reaction was promoted by the initial formation of an acyl azolium intermediate through the reaction of the NHC carbene (generated *in situ* by deprotonation of triazolium **13.7**) and **13.6,** which engaged in a SET reaction with excited **13.4**.

Ethynylbenziodoxolones (EBXs) are traditionally employed as alkyne donors in photoredox catalyzed alkynylation reactions. However, the use of aryl substituted EBXs **14.1** as visible-light alkynylating agents in the presence of monoalkyl oxalate salts **14.2a** and **b** (Scheme 14) has been recently described.[113] The excited EBX may oxidize **14.2a** and **b**, allowing the release of the desired alkyl radical, which is capable of reacting with **14.1**, resulting in the formation of a C(sp^3)–C(sp) bond to give **14.3a** and **b**. The versatility of the method is evident from the alternative use of carboxylic acid, alkyl trifluoroborates and even *N*-substituted aldimines as radical precursors in place of the oxalate salt.[113] It should be noticed, however, that when the reaction took place under 4-CzIPN photocatalyzed conditions, a lower excess of **14.1** was required resulting in a better overall yield.

Photogenerated alkyl radicals have been also employed in the formation of C–heteroatom bonds. A protocol for the photochemical remote borylation of unactivated C(sp^3)–H

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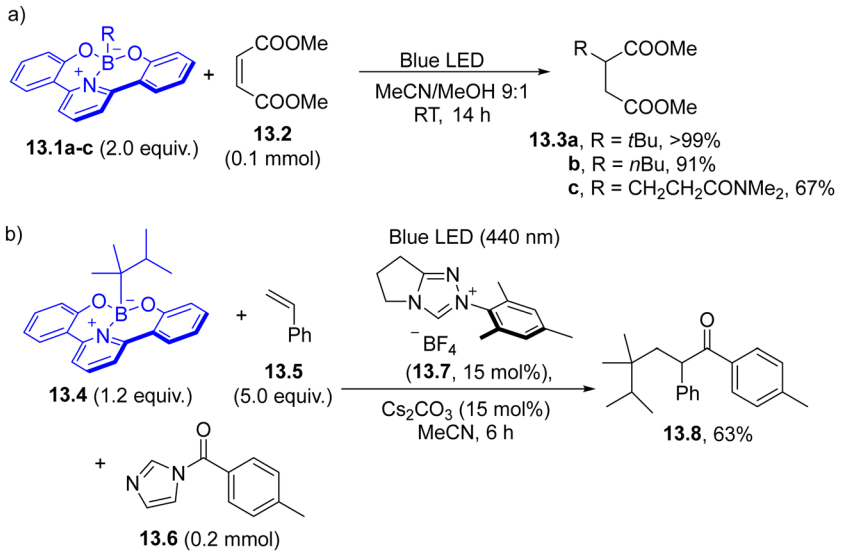
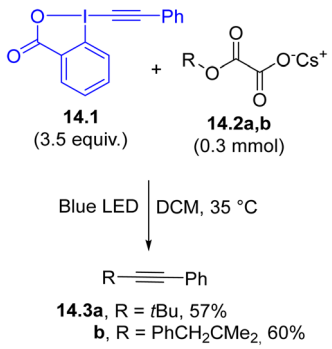


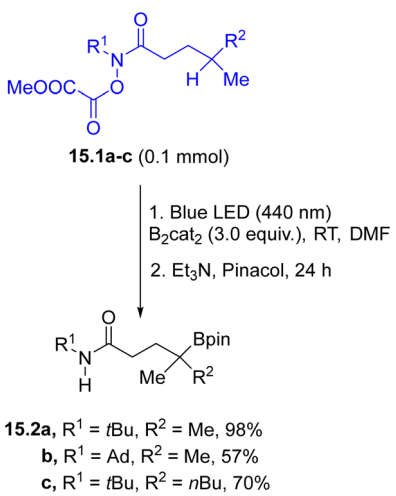
Scheme 13 Use of boracene-based borates as a source of alkyl radicals for (a) Giese reaction and (b) for the preparation of unsymmetrical ketones.



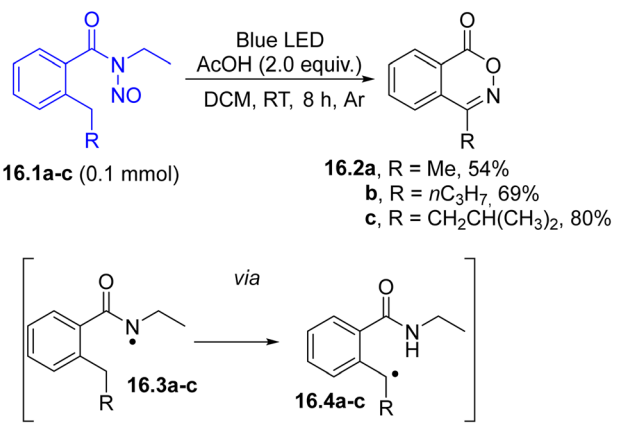
Scheme 14 Blue light induced synthesis of internal alkynes.

bonds tethered to an *O*-oxalate hydroxamic ester (**15.1a–c**, Scheme 15) was applied in the preparation of linear and cyclic tertiary and secondary borylation products **15.2a–c**.[114] The reaction started from the homolysis of the N–O bond followed by a 1,5-HAT step where the resulting carbon radical was trapped by bis(catecholato)diboron. The method was also applied for the C–H borylation of biologically relevant compounds.

The irradiation of a Barton ester in the presence of thionitrites led to a decarboxylative nitrosation resulting in the formation of *trans*-nitroso dimers,[115] whereas alkyl azides have been obtained in the presence of ethanesulfonyl azide.[116] Another route for forming a carbon-nitrogen bond involved a Barton nitrite ester-type cyclization. Thus, photoactive *N*-ethyl-*N*-nitrosobenzamides **16.1a–c** (Scheme 16) underwent a cyclization to afford substituted benzo[*d*][1,2]oxazin-1-ones **16.2a–c**. The key-intermediates are alkyl radicals **16.4a–c**, generated *via* remote C–H atom bond abstraction occurring in *N*-centered radical **16.3a–c**. Radicals **16.4a–c** intercepted the previously released persistent nitric oxide radical (NO), forming the



Scheme 15 Visible-light driven remote C–H borylation protocol.



Scheme 16 Preparation of benzo[*d*][1,2]oxazin-1-ones upon visible-light photohomolysis of the N–N bond in *N*-ethyl-*N*-nitrosobenzamides **16.1a–c**.

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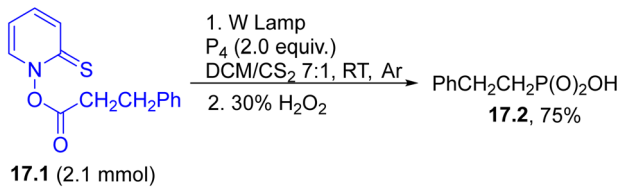


Scheme 17 Synthesis of a phosphonic acid.

corresponding oximes, which upon cyclization formed **16.2a–c**.[117]

C–P bonds can instead be achieved by trapping a photogenerated alkyl radical (in turn obtained *via* photolysis of derivative **17.1**) using white phosphorous (P_4) followed by treatment with 30% H_2O_2 to afford the corresponding aliphatic phosphonic acid (**17.2**, Scheme 17).[118]

Synthetic interest in photolabile esters also arises from the conversion of carboxylic acids into alcohols, which can be achieved by using modified Barton esters, namely, *N*-hydroxy-4-methyl-2-thiazolinethiones (*e.g.* **18.1**, Scheme 18). In this case, the alkyl radical generated from **18.1** reacted with oxygen and a thiol giving an hydroperoxide that was, in turn, reduced by PPh_3 to afford alcohol **18.2** in a good yield.[119]

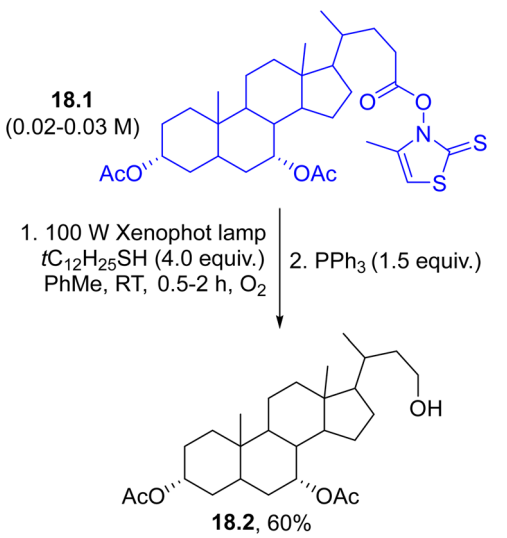
Also, C–S bonds can be easily formed using Barton esters. Thiosulfonates (RSO_2SPy; Py = pyridine) can be formed in up to 90% yield by trapping of the photogenerated alkyl radical with liquid SO_2 (used as cosolvent with DCM).[120] The products are, however, easily converted into sulfones and sulfonamides. A Barton ester may likewise be prepared from a modified glycine appended to a Wang type resin. The ensued irradiation enabled the synthesis of peptides containing modified amino acids.[121]

3.1.2. α-Stabilized alkyl radicals. This section will focus on the generation and application of carbon radicals having a heteroatom-based substituent at the α-position. As expected, the nature (either electron-withdrawing or electron-donating) of the substituent can dramatically influence the reactivity of the generated intermediates.

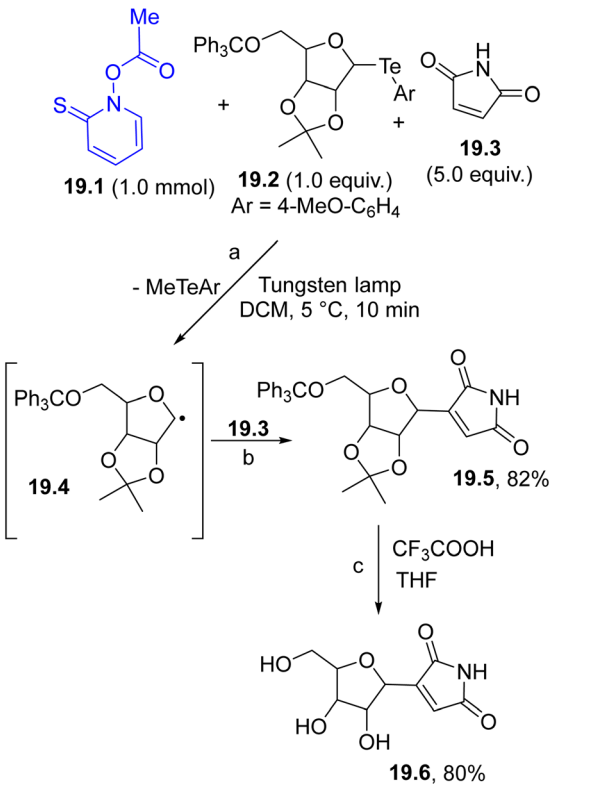
The carbon-based radical generated by the photochemical decomposition of a Barton ester (again following the strategy described in Scheme 1f) can be used in the generation of a further reactive radical *via* group transfer reaction. The strategy was applied in the synthesis of nucleoside antibiotic showdomycin (**19.6**, Scheme 19). In this case, the photocleavage of the Barton ester **19.1** released a methyl radical that in turn reacted with organotellurium **19.2** (path a) to form the α-oxy radical intermediate **19.4**. Trapping of **19.4** by **19.3** followed by oxidation afforded maleimide **19.5** (path b). Treatment of the latter imide under acidic conditions resulted in the formation of the desired **19.6** (path c).[122]

The photohomolysis of the O–NO bond in acyloxy nitroso compounds (nitrite esters) has recently been described to promote the generation of α-(acyloxy)alkyl radicals along with nitric oxide. Both generated radicals were used in the 1,2-functionalization of electron-poor olefins to form α-oximinoketones.[123]

α-Oxy radicals are the intermediates for the reductive alkylation of 1,2-diketones using visible-light and organic halides (mainly iodides, Scheme 20). The SET reaction between the excited phenanthrene-9,10-dione **20.1** and triethylamine led to the concomitant formation of the α-oxy radical **20.4** and an α-aminoalkyl radical, that promoted the C–X bond cleavage in halides **20.2a–e** *via* a halogen atom transfer process (XAT). The



Scheme 18 Decarboxylative hydroxylation *via* modified Barton esters.



Scheme 19 Preparation of showdomycin **19.6** *via* the photogenerated α-oxy radical **19.4**.

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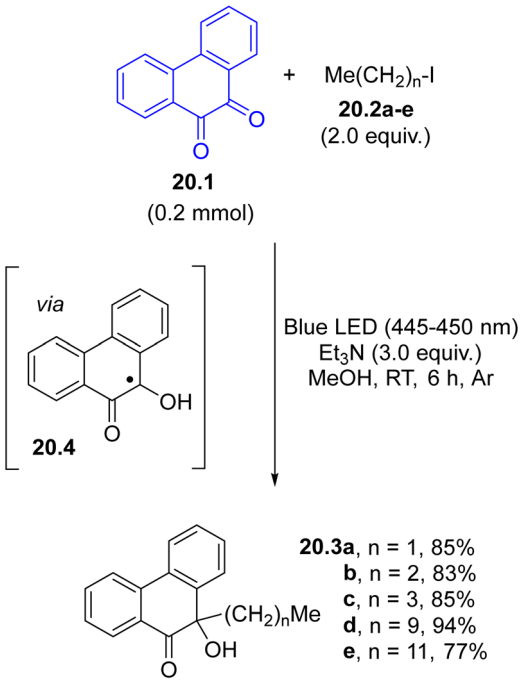
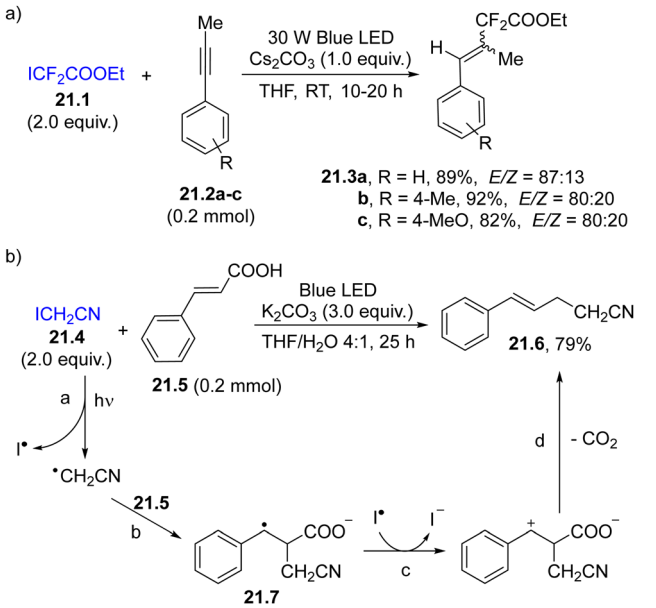


Scheme 20 Photoinduced coupling between a 1,2-diketone and alkyl iodides.



Scheme 21 Photohomolysis of a C–I bond for the carbon-based radical addition onto (a) phenyl acetylenes and (b) cinnamic acid.

coupling with the resulting alkyl radicals and **20.4** led to the formation of the desired α-hydroxyl ketones **20.3a–e** in a very good yield. The reaction worked to some extent even when aryl halides were used.[46]

Some substituted alkyl halides may show a weak absorption in the visible region and thanks to the photolability of the C–X bond (mainly C–I), they are an interesting source of carbon-based radicals capable of attacking double or triple C–C bonds.

As an example, ethyl difluoroiodoacetate **21.1** (Scheme 21a) exhibits weak absorption in the blue region (400–500 nm), enough to promote the homolysis of the C–I bond, resulting in the release a difluoroalkyl radical/iodine radical pair that has been exploited in the 1,2-functionalization of alkynes **21.2a–c** to form styrenes **21.3a–c**.[124] When bromodifluoroacetamides were irradiated in the presence of (iodoethynyl)arenes, alkynyldifluoroacetamides were obtained in good yields *via* a formal C(sp)–C(sp^3) bond cross-coupling.[125] Similarly, photolysis of ICH_2CN (**21.4**, an example in Scheme 21b) resulted in the formation of an α-cyanomethyl radical (path a) readily trapped by cinnamic acid (**21.5**, path b). The resulting benzyl radical **21.7** underwent oxidation (path c) and decarboxylation (path d), forming nitrile **21.6** in *ca.* 80% yield.[126]

A wide range of electrophilic carbon-based intermediates including, among the others, α-cyanomethyl, acetonyl radical and dichloromethyl radicals have been generated *via* hydrogen atom transfer between an aryl radical (in turn generated *via* visible-light irradiation of an arylazo sulfone) and acetonitrile, acetone and dichloromethane, respectively.[127] The resulting radicals have been applied in the synthesis of indolinones from the corresponding *N*-aryl acrylamides.[127]

The blue light photolysis of α-halo boronic esters (*e.g.*, α-iodo BPin) and the subsequent formation of α-boryl radicals was recently employed for the preparation of allyl boronic esters *via* reaction with substituted styrenes.[128]

3-Substituted chroman-4-ones **22.5a–c** have been accessed *via* a carbon–carbon bond-forming cyclization cascade promoted by a C(sp^3)–Br homolytic cleavage occurring under visible-light irradiation (Scheme 22). In the proposed mechanism, the first formed radicals **22.2a–c** (path a) were involved in a cascade radical cyclization, to form alkoxy radicals **22.3a–c** (path b) and α-hydroxy radicals **22.4a–c** from them after a 1,2-hydrogen shift (path c). The oxidation of **22.4a–c** by bromo atoms afforded, upon deprotonation (path d), the desired products **22.5a–c** with high regio- and diastereoselectivity (dr always $>20:1$).[129]

The synthesis of *gem*-dihaloenones from tetrahalomethanes (*e.g.*, tetrabromomethane **23.1**, Scheme 23) and arylacetylenes **23.2a–c** has been described to occur in organic/aqueous solvent upon blue light irradiation.[130] As depicted in Scheme 23, the photoinduced homolysis of the C–Br bond in **23.1** promoted the formation of a $Br^{\bullet}/CBr_3^{\bullet}$ radical pair (path a). The carbon radical was trapped by **23.2a–c**, producing vinyl radicals **23.4a–c** (path b), which then coupled with $Br^{\bullet}$ to form the Kharasch adduct **23.5a–c** (path c). Allylic substitution between **23.5a–c** and water gave the final enones **23.3a–c** after HBr release (paths d and e). A similar approach was also proposed by using aqueous DMSO or neat alcohols as reaction media.[131] The generation of a trihalomethyl radical was also exploited in the iron(0) catalysed benzannulation of allylarenes to form 1-halonaphthalenes.[132]

Umemoto's reagent **24.1** (Scheme 24) has traditionally been employed in photoredox catalysed trifluoromethylation. Recently, the possibility of generating a trifluoromethyl radical

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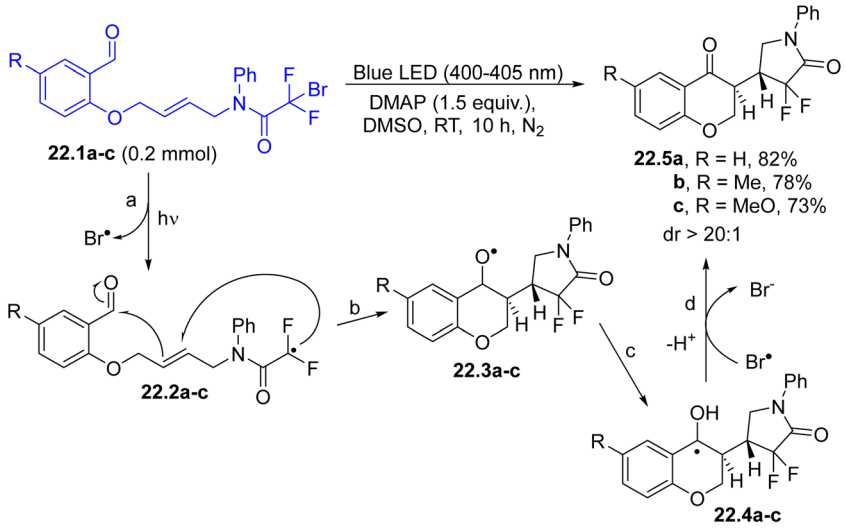
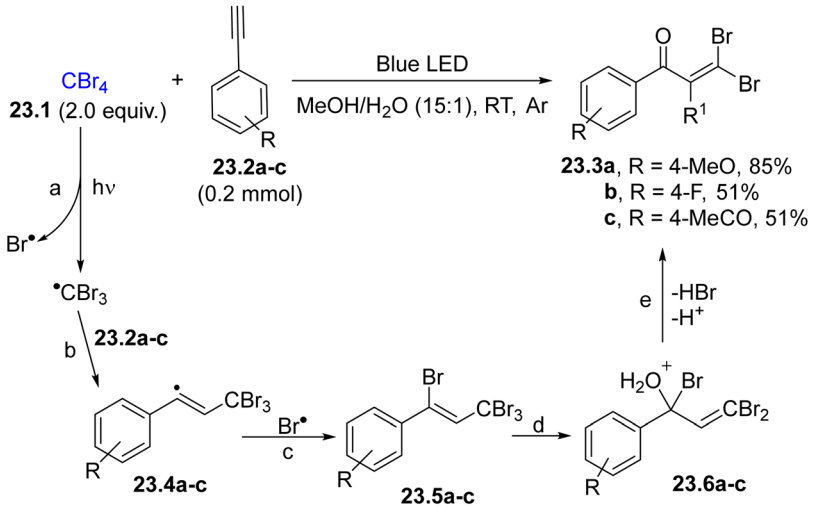
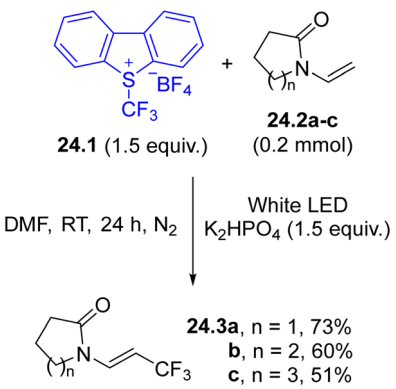


Scheme 22 3-Substituted chroman-4-ones *via* photoinduced cascade radical cyclization.



Scheme 23 Synthesis of *gem*-dihaloenones.



Scheme 24 Umemoto's reagent for the light-driven uncatalyzed trifluoromethylations.

via direct irradiation of **24.1** has been identified and exploited for the preparation of β-trifluoromethyl enamides **24.3a–c**[133] and in the trifluoromethylation-arylation of *N*-acrylamides to produce oxindoles.[134]

3.2. C(sp^2)-based radicals

3.2.1. Acyl radicals. As stated in the previous section, Hantzsch esters can act as radical reservoir upon visible-light irradiation. Recently, 4-acyl-Hantzsch ester (**25.1**, Scheme 25) has been employed in the hydroacylation of several Michael acceptors including enones, *para*-quinone methides and **25.2a–d**.[135] The same photoactivatable substrates have been also employed in the acylation of nitrogen-based heterocycles, thioflavones[136] and benzothiazoles.[137]

The preparation of acyl trifluoromethylthio and trifluoromethylseleno esters has been made possible by irradiating

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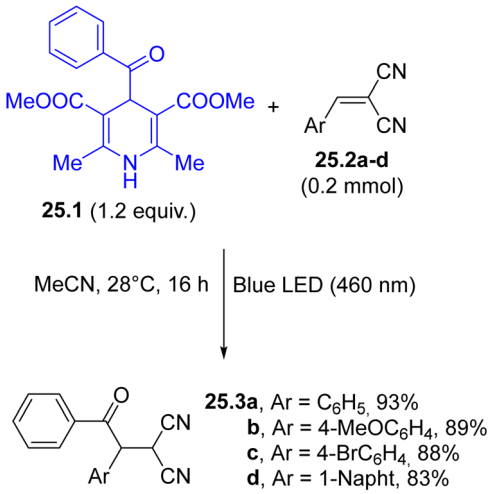


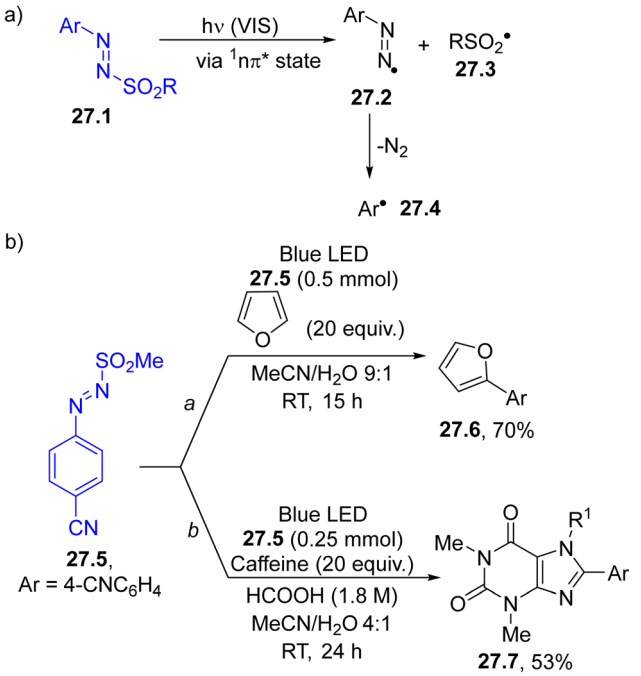
Scheme 25 Hantzsch esters for visible-light driven acylation reactions.

4-acyl substituted Hantzsch esters with visible-light in the presence of *S*-(trifluoromethyl) 4-methylbenzenesulfonothioate and Se-(trifluoromethyl) 4-methylbenzenesulfonoselenoate as the radical traps.[138]

The hydroacylation of azoarenes **26.1a–e** (some examples in Scheme 26) has been achieved by using α-ketoacids as acyl radical precursors. In the suggested mechanism, photoexcited **26.1*a–e** underwent reductive quenching by **26.2**, leading to the formation of, after proton and CO_2 loss, the corresponding acyl radical **26.4**. The latter intermediate coupled with radical anions **26.5a–e**, resulting in the formation of acyl hydrazines **26.3a–e** through the protonation of the anions **26.6a–e**.[139]

Acyl radicals arising from α-ketoacids have also been employed for the synthesis of multi-functionalized cyclopentane scaffolds *via* tandem radical addition on terminal alkynes, translocation and cyclization in water.[140]

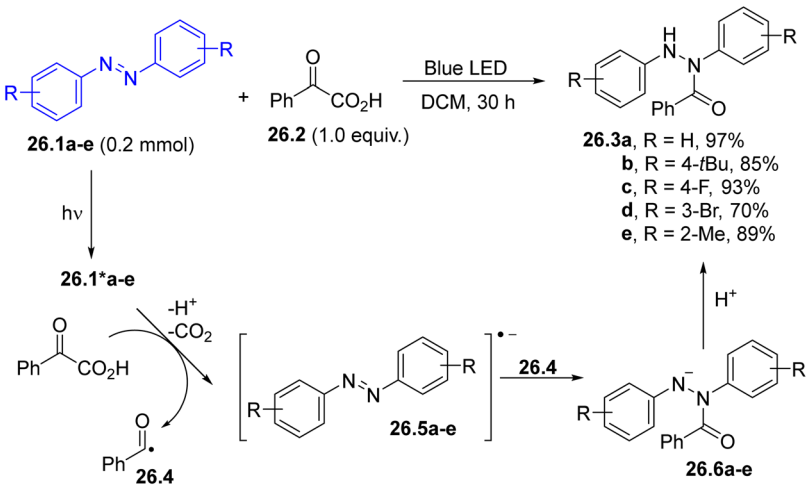
3.2.2. Aryl radicals. Arylazo sulfones (**27.1**, Scheme 27a) are crystalline, coloured (yellow to red) derivatives that bear a



Scheme 27 (a) Photocleavage of the N–S bond in arylazo sulfones. (b) Arylation of heterocycles *via* photogenerated aryl radicals.

dyedauxiliary N=N–SO_2R moiety, capable of imparting both colour and photoreactivity to the starting compound (Scheme 1f).[35,36,141] Accordingly, upon visible-light irradiation, a N–S bond homolytic cleavage occurred from the $^1n\pi^*$ singlet excited state of **27.1**, producing a diazenyl radical **27.2** and the sulfonyl radical **27.3**. Aryl radical **27.4** is then released upon nitrogen loss from **27.2**, and such an intermediate has been applied in the development of a plethora of protocols for the formation of both C–C and C–heteroatom bonds.

As summarized in Scheme 27b, aryl radicals generated from arylazo sulfones **27.5** may be trapped by heterocycles including furans (path a), thiophenes[142] or xanthines (path b)[143] yielding



Scheme 26 Photoinduced hydroacylation of azoarenes.

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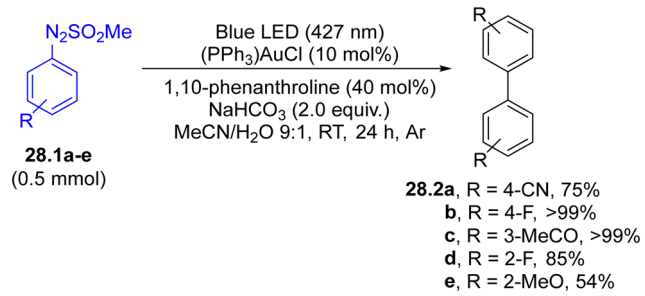


Scheme 28 Blue LED driven preparation of biaryls.

the corresponding (hetero)biarenes **27.6** and **27.7** in high regioselectivity. The latter compounds have been likewise isolated in comparable yields upon natural sunlight exposition in a sun-flow reactor, enabling a significant reduction in the residence time (down to 4 h).[144] The visible-light mediated arylation of quinoxalin-2(1*H*)-ones was described by using both arylazo sulfones[145] and aryl acyl peroxides as sources of aryl radicals.[146]

Arylation of aryl boronic acids using arylazo sulfones to yield biaryls took place in modest yield under gold(I) catalysis in the presence of a base, where the *ipso*-substitution observed was directed by the presence of the $B(OH)_2$ moiety.[147] However, in the absence of an aryl boronic acid, the irradiation induced the selective formation of the corresponding (hetero)biaryls **28.2a–e** (Scheme 28) in up to quantitative yield, with impressive functional group tolerance. The protocol was likewise successfully applied in the synthesis of binaphthyls and 2,2′-bipyridines.[148]

The generation of aryl radicals from arylazo sulfones has been investigated in the presence of different π-bond systems. As a result, valuable compounds, including α-aryl carbonyls **29.3a–d** (Scheme 29, path a, by reaction with enol silyl ethers **29.2**)[149] and allyl arenes **29.5a–d** (in the presence of allyl sulfones **29.4**, Scheme 29, path b)[150] have been smoothly prepared. The trapping of a photogenerated aryl radical by an isonitrile in aqueous solvent was also found to be useful in promoting the synthesis of aroyl amides.[151]

Arylazo sulfones have been largely applied in the formation of aryl-heteroatom bonds, giving access, among the others, to aryl boronates and aryl trifluoroborate salts,[152] aryl stannanes **30.3a–c** (in the presence of an hexaalkylstannane **30.2**, Scheme 30, path a),[153] aryl phosphonates,[154] unsymmetrical aryl selenides **30.5a–c** and tellurides (Scheme 30, path b[155]) and aryl trifluoromethylthioethers **30.7a–c** (Scheme 30, path c).[156]

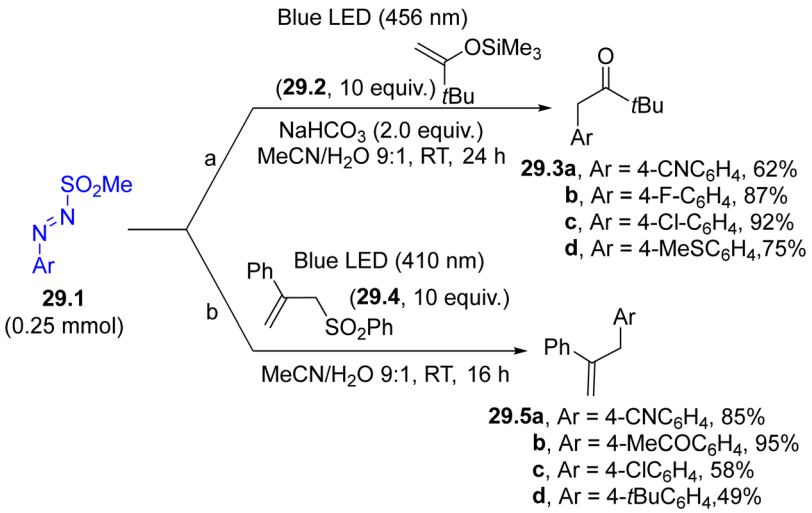
Finally, visible-light irradiation of arylazo sulfones in deuterated media (isopropanol-d^8/H_2O 9 : 1) resulted in a deuterodeamination process, yielding the corresponding monodeuterated arene.[157]

Aryl radicals may be generated by a visible-light driven atom transfer. This is a rare case where a coloured organic compound absorbed the light, but it was not incorporated in the end product. In fact, the photocleavage of the labile S–S bond (BDE *ca.* 50 $kcal^{-1}$ mol^{-1})[158] in disulfide **31.2** generated a thiyl radical, which promoted the desilylation of arylsilanes **31.1**. This resulted in the formation of aryl radicals **31.4** and desilylated derivatives **31.3** from it through a HAT step (Scheme 31).[159]

4. Reactions *via* heteroatom-based radicals

4.1. Boron-based

A rare case involving the use of boryl radicals is exemplified in Scheme 32 in the context of the pyridylation of several carbon/heteroatom-hydrogen bonds. In fact, the visible-light homolysis of the N–O bond in *N*-methoxypyridinium salts **32.1a–c** generated a methoxy radical, which then abstracted a hydrogen atom from an amine-borane (*e.g.* **32.2**) to release a boron-based radical **32.3**. Addition of **32.3** to **32.1a–c** led to the assembly of various pyridines (**32.4a–c**) with the concomitant release of a methoxy radical, which further propagated the reaction.[160]



Scheme 29 Aryl radicals for the synthesis of α-aryl carbonyls and allyl arenes.

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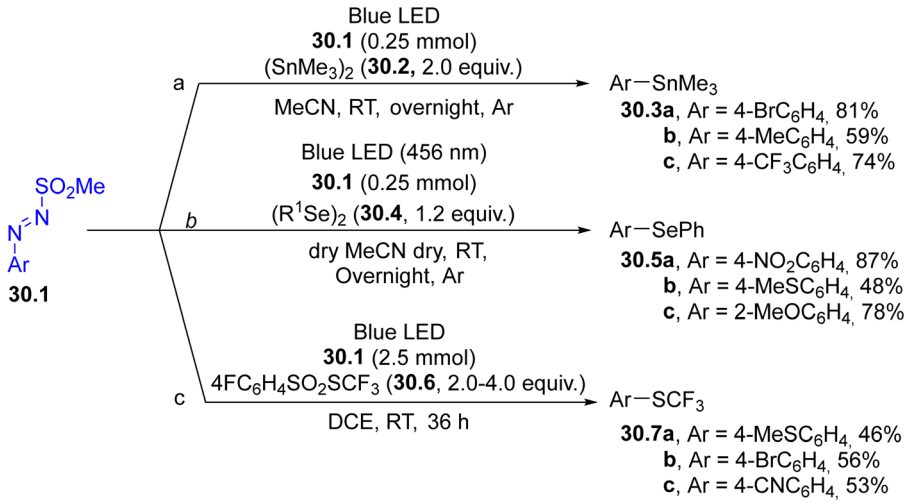
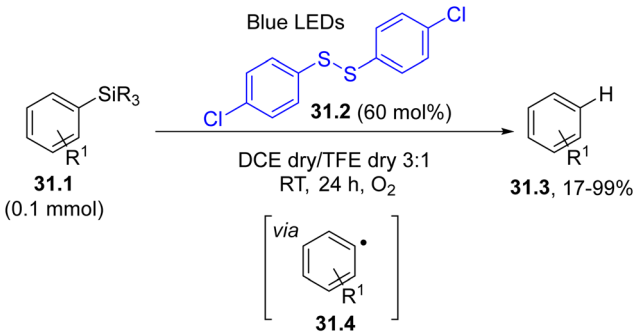
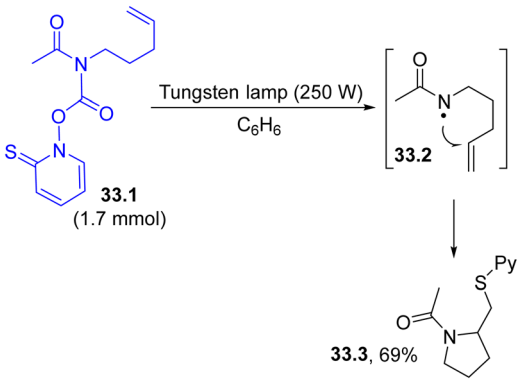


Scheme 30 Formation of an Ar–heteroatom bond *via* photogenerated aryl radicals.



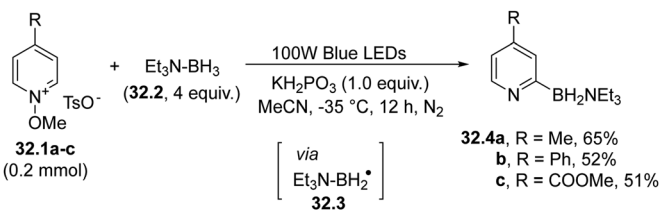
Scheme 31 Aerobic visible-light induced desilylation of arylsilanes.



Scheme 33 Preparation of *N*-acyl pyrrolidines *via* photogenerated amidyl radicals.

4.2. Nitrogen-based

Nitrogen centered radicals are, in most cases, formed *via* the visible-light induced homolysis of a N-heteroatom bond present in purposely designed derivatives. An exception is the dated example presented in Scheme 33, where the C–N bond in *N*-acyl PTOC (*N*-hydroxy-pyridine-2-thione) carbamate **33.1** was found to be sufficiently labile for cleavage upon tungsten lamp irradiation, resulting in the release of amidyl radical **33.2.** Radical cyclization (in a 5-*exo* mode) onto the tethered double bond followed by the incorporation of the –SPy group led to the synthesis of *N*-acyl pyrrolidine **33.3** in *ca.* 70% yield.[161]



Scheme 32 Visible-light formation of an Ar–B bond *via* photolysis of *N*-methoxypyridinium salts.

Nitrogen-centered radicals may also be formed starting from a carbamate (a protected primary aliphatic amine having leaving groups bearing labile N–O bonds) under photoenzymatic conditions. Thus, the radicals generated under blue LED irradiation were engaged in an enantioselective intermolecular radical hydroamination of styrenes, driven by an enereductase.[162]

The amidyl radical was likewise generated from a stable and isolable *N*-dithiocarbamate **34.3** (in turn obtained from a carboxylic acid (**34.1**) and a thiocarmabamylsulfenamide (**34.2**)) through an amido coupling reaction (Scheme 34). The photolysis of **34.3** led to the formation of two radical species: the amidyl **34.4** and the sulfur-centered radical **34.5.** Intramolecular HAT promoted by the nitrogen radical enabled the site specific derivatization of a remote C–H bond. The resulting carbon radical was then able to couple with **34.5** to complete a selective and efficient dithiocarbamylation (product **34.6**).[163]

The generation of a nitrogen-based radical can also be achieved by cleaving a *N*-halogen bond such as in the case of *N*-bromosaccharin **35.1** (Scheme 35). Ambient light exposure

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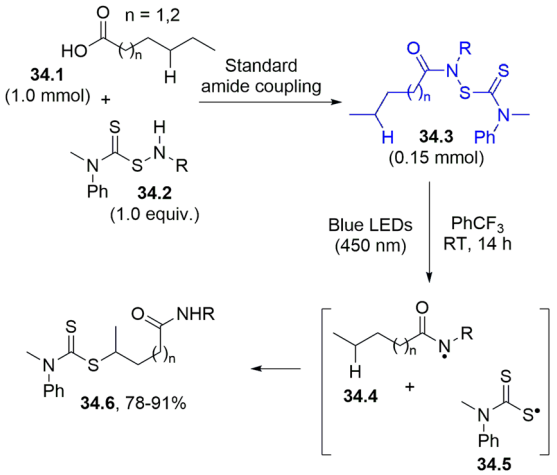
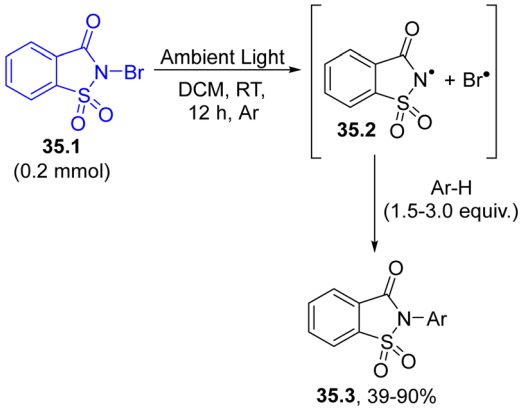


Scheme 34 Synthesis of alkyl dithiocarbamates.

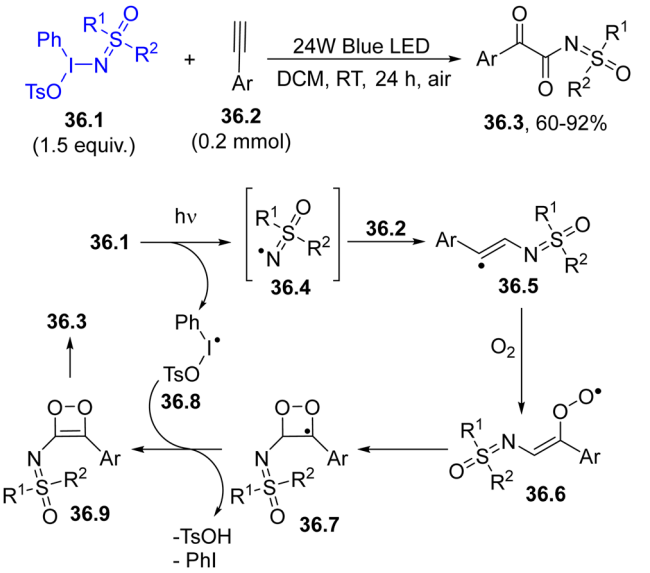


Scheme 35 Visible-light driven imidation of arenes employing *N*-bromosaccharin.

caused the homolytic cleavage of the N–Br bond in **35.1**. Then, the saccharin nitrogen radical **35.2** promoted the imidation of different (hetero)arenes Ar–H in a good regio- and chemoselective fashion.[164]

Hypervalent iodine derivatives have been successfully employed for the α-ketoacylation of sulfoximines by using aryl alkynes. The excitation of the hypervalent iodine compound **36.1** was carried out using blue light and a sulfoximidoyl radical **36.4** was then formed. The trapping of **36.4** by aryl alkyne **36.2** released a reactive vinyl radical **36.5**, which was subsequently trapped by dioxygen, forming peroxyl radical **36.6**. This intermediate evolved into the unstable 1,2-dioxete **36.9**, which ultimately rearranged to yield the desired *N*-α-ketoacylated-sulfoximine **36.3** (Scheme 36).[165]

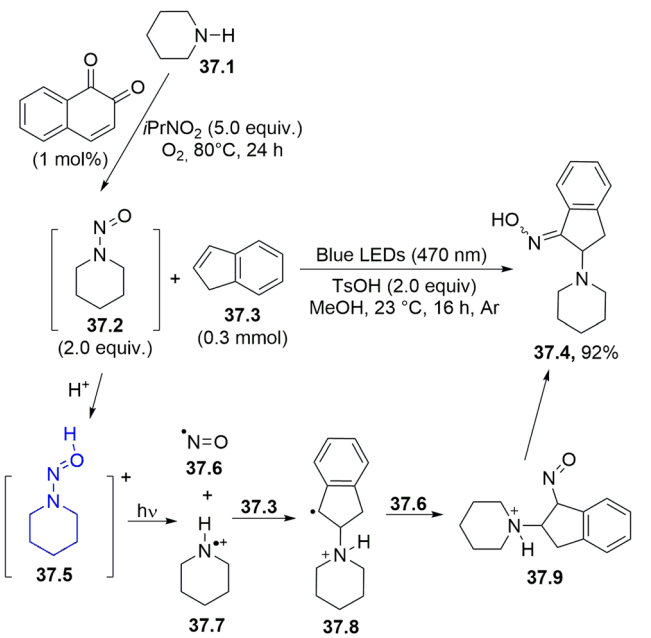
The *in situ*-performed oxidation of alkylamines (*e.g.* **37.1**) under aerobic conditions was adopted to obtain *N*-nitrosoalkylamines **37.2**, a photoreactive class of molecule, which, after irradiation in acidic media with blue or purple light gave two reactive species from the corresponding *N*-nitrosammonium ion **37.5**, namely, an aminium radical cation **37.7** and nitric



Scheme 36 Visible-light driven α-ketoacylation of sulfoximines.

oxide **37.6**. The former species attacked a C=C bond in alkenes (*e.g.*, **37.3**) generating a carbon radical **37.8** which recombined with nitric oxide, yielding **37.9** that readily tautomerized to oxime **37.4**. (Scheme 37).[166] The reaction was also effective when a mixture of **37.2** and **37.3** was photolyzed under blue LED irradiation, although the authors preferred to carry out most of the reactions by using purple LED (395–405 nm).

A different method to form a C–N bond is by employing the dyedauxiliary strategy (Scheme 1f), making use of aryldiazenyl radicals **38.4** photogenerated from arylazo sulfones **38.1**. Exposing arylazo sulfone to blue light in the presence of



Scheme 37 Visible-light induced one-pot tandem 1,2-diamination of alkenes.

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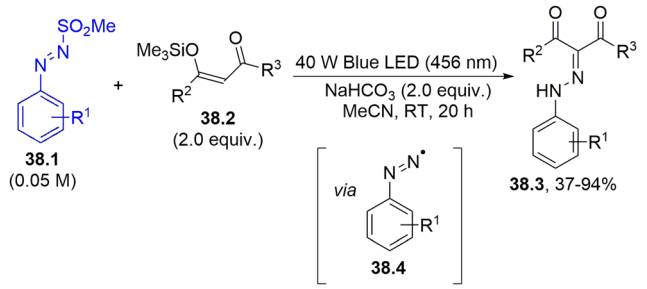


Scheme 38 Synthesis of aryldiazenyl-1,3-diketones *via* photogenerated aryldiazenyl radicals.

enol silyl ethers of 1,3-diketones **38.2** led to the diazenylation of the double bond, forming aryldiazenyl-1,3-diketones **38.3** (Scheme 38).[167]

The photohomolysis of a N–O bond was indeed used to form iminyl radicals **39.2,** thanks to the incorporation of a nitroaromatic as dyedauxiliary group. For example, the near-visible-light irradiation of *o*-nitrobenzyl oxime ethers **39.1** in a mixture of DMSO and a sodium phosphate buffered aqueous solution smoothly released iminyl radicals **39.2**. The mechanism involved an initial intramolecular hydrogen atom transfer at the benzylic position by the nitro group, which promoted the cleavage of the N–O bond present in the oxime moiety. The cyclization of the thus formed radical onto the adjacent aromatic ring gave access to differently substituted phenanthridines **39.3** (Scheme 39).[168] Noteworthily, this process may proceed even in a cellular environment where a bioactive derivative may be released.

4.3. Oxygen and sulfur-based

Chalcogen-based radicals were widely used in synthesis. These radicals may be formed from various precursors exploiting the lability of a Ch–X bond (often a Ch–Ch bond).

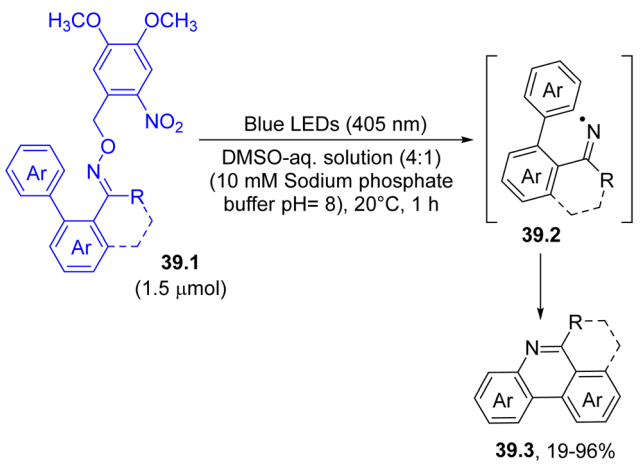
The generation of oxygen-based radicals is well known. However, the direct visible-light generation is not trivial and in selected cases, photohomolysis of the N–O bond can be a solution even though the resulting radicals (mostly carbonyloxy) are prone to fragmentation, giving access to other reactive radical species.[169] On the other hand, sulfur-based radicals are readily accessed by the photocleavage of (aryl) disulfides. In fact, the lability of the S–S bond (the BDE_{S-S} for PhSSPh is *ca.* 50 $kcal^{-1}$ mol^{-1})[158] coupled with the absorption in the visible region (at least for aromatic disulfides) made these compounds the elective substrates for the preparation of thiyl radicals. As a matter of fact, radical routes to C–S bonds are rather common.[170,171]

This approach was adopted for the photoinduced intramolecular annulation of 2-alkynylbiphenyls **40.2** with various disulfides **40.1.** Thus, blue light irradiation of **40.1** in acetonitrile for 8 h released two thiyl radicals, which upon addition to the triple bond of **40.2** led to the formation of 9-sulfenylphenanthrenes **40.4** upon vinyl radical (**40.3**) cyclization. (Scheme 40).[172]

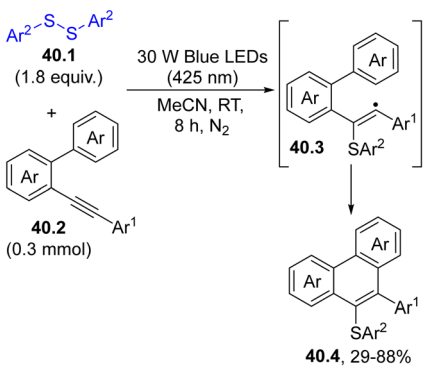
The photocleavage of a PhS–SPh bond was used for a multicomponent radical cross-coupling reaction initiated with the sulfur radical addition onto [1.1.1]propellane that, in the presence of N-heterocycles, formed potentially bioactive 1-arylthiol-3-heteroaryl bicyclo[1.1.1]pentanes.[173]

The direct cleavage of an S–H bond to generate a thiyl radical in the presence of an alkene (or an alkyne) is quite common under UV irradiation to perform the so-called thiol–ene (or a thiol–yne) reaction.[174–176] In rare instances, the reaction may be promoted by visible-light as depicted in Scheme 41. Thus, the naturally abundant Euphorbia factor L3 (**41.2**) was functionalized by attack of a visible-light-generated arylthiyl radical (from differently substituted thiophenols **41.1**) on the exocyclic double bond. The resulting radical **41.3** underwent cyclization onto the endocyclic double bond, forming a seven-membered ring and a five-membered ring in one step. The new compounds obtained (**41.4**) belong to a new group of biorelevant sulfur-containing premyrsinane-type diterpenes (Scheme 41).[177]

A thiol–ene reaction was applied to 1,3-butadiene (an important feedstock). The thiyl radical generated from a diaryldisulfide added to the diene and the resulting allyl radical was trapped by a Ti(III)-based catalyst, and the formed adduct in



Scheme 39 Synthesis of phenanthridine from the photolysis of *o*-nitrobenzyl oxime ethers.



Scheme 40 Photochemical access to 9-sulfenylphenanthrenes.

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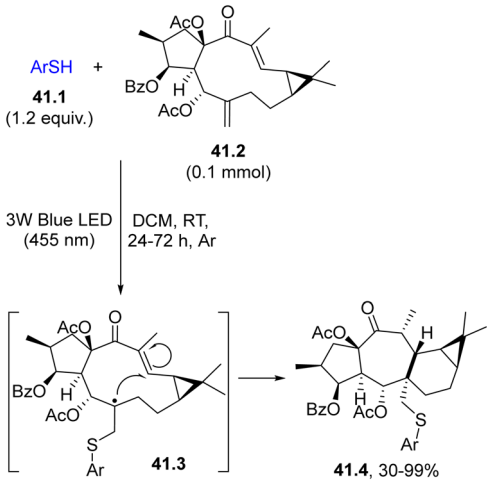


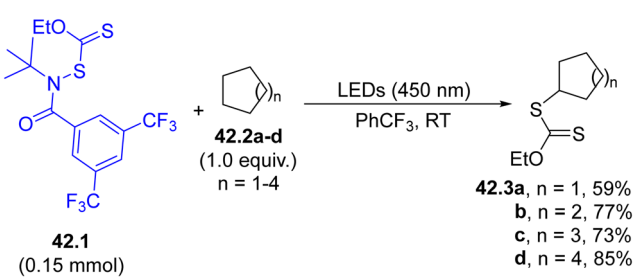
Scheme 41 Thiol–ene reaction for the preparation of sulfur-containing premyrsinane-type diterpenes.

turn reacted with an aldehyde to give several allylic 1,3-thioalcohols with exceptional regio- and diastereoselectivity.[178]

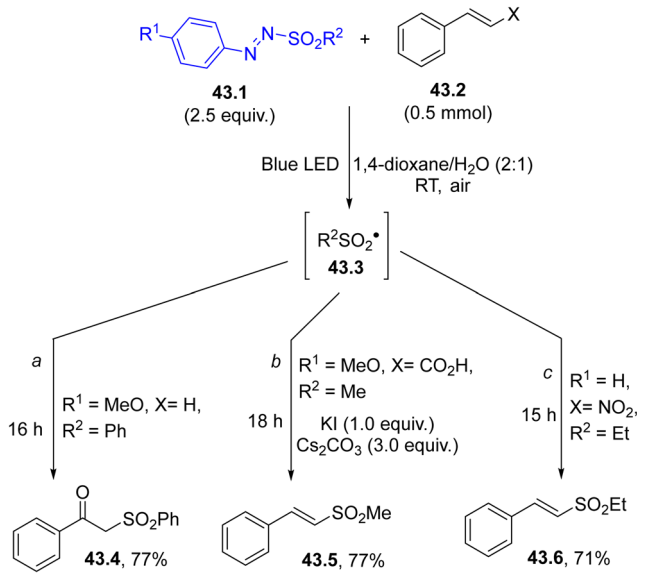
The generation of a sulfur centered radical can be efficiently achieved by employing coloured *N*-xanthylamides. As an example, the visible-light exposure of **42.1** caused the N–S cleavage and the resulting amidyl radical was capable of abstracting a hydrogen atom from a cycloalkane **42.2a–d**. The resulting cycloalkyl radical may now couple with the previously formed sulfur radical, enabling a valuable C–H xanthylation process to yield *O*-ethyl carbonodithioates **42.3a–d** (Scheme 42).[179]

The versatility of aryl azosulfones (see Schemes 27–30) in sulfonylation processes is witnessed by their use even as sulfonyl radical generators. Scheme 43 presents some examples.

The sulfonyl radical **43.3** liberated from **43.1** added onto unsubstituted styrenes and the resulting benzyl radical reacted with molecular oxygen, releasing β-oxo sulfone **43.4** (Scheme 43, path a).[180] The same oxysulfonylation products were also formed by the reaction of photogenerated **43.3** with phenyl alkynes under aerated conditions.[181] On the other hand, the fate of the reaction was different when the sulfonyl radical attacked cinnamic acid (Scheme 43, path b). The benzyl radical intermediate was oxidized to a cation and captured by an iodide anion. The concomitant loss of the iodide anion and carbon dioxide assured the regeneration of the double bond and an (*E*)-vinyl sulfone **43.5** was isolated in a good yield.[182] The competitive addition of the aryl radical onto the double bond was prevented by its conversion to phenol, thanks to



Scheme 42 C–H xanthylation of cycloalkyls.

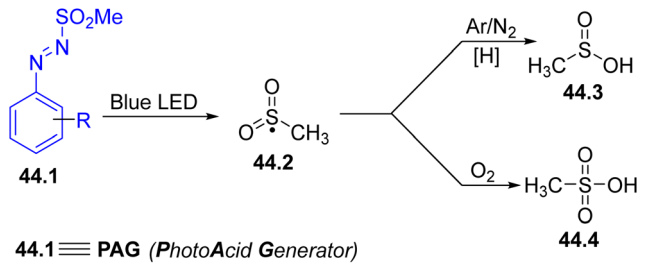


Scheme 43 Visible-light-promoted functionalization of differently substituted styrenes through arylazo sulfones.

the presence of water and air in the reaction mixture. A related reaction involved the addition of **43.3** onto β-nitrostyrenes where again an (*E*)-vinylsufone **43.6** was formed by the elimination of the NO_2 group (Scheme 43, path c).[183] More recently, a procedure for the 1,2-difunctionalization of styrenes *via* arylazo sulfones and the subsequent synthesis of α-sulfonyl arylhydrazones in a 100% atom economy fashion has been proposed. Also, in this case, the initial step is the regioselective addition of the photogenerated sulfonyl radical onto the double bond of styrenes.[184]

The sulfonyl radical produced from arylazo sulfones (Scheme 1f) was also employed for the functionalization of 1,6-enynes (*e.g.*, *N*-phenyl-*N*-(prop-2-yn-1-yl)methacrylamides), delivering a range of sulfonylated γ-butyrolactams.[185] Interestingly, if the sulfonyl radical **44.2** is not trapped in the reaction it is converted into an acid depending on the reaction conditions, namely, methanesulfinic acid **44.3** (a weak acid) under an inert atmosphere or methansulfonic acid **44.4** (a strong acid) in oxygenated media (Scheme 44). Accordingly, sulfones **44.1** may behave as PhotoAcid Generators (PAGs).[186]

This behaviour prompted the application of these new PAGs to catalyze different chemical transformations in an eco-sustainable way with the advantage of the slow release of the



Scheme 44 Visible-light promoted generation of acidic species by irradiation of arylazo sulfones.

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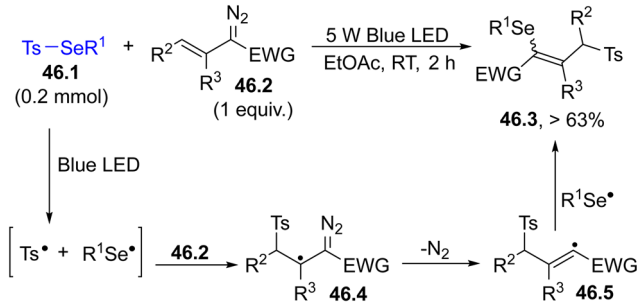
acid in solution during the irradiation event (Scheme 45). In doing so, the protection of alcohols as THP acetals has been successfully carried out employing arylazo sulfone **45.2** as a PAG (Scheme 45a).[186] In particular, alcohol **45.1** was converted into the corresponding acetal **45.3** (an orthogonally protected diol) in quantitative yield with no competitive deprotection of the silyl ether.[186]

Moreover, the acidity resulting from the photolysis of **45.4**, was able to catalyze the protection of aldehydes (or ketones) as dioxolanes (**45.5**) or *N*-methyl oxazolidines (**45.6**) in up to 99% yield in a benign DMC solvent (Scheme 45b).[187] In the latter case, due to its structure, the PAG served as a traceless promoter since the byproducts nitrogen, benzene and the sulfonic acid may be easily eliminated from the final mixture, enabling the isolation of the protected aldehydes through a simple filtration on silica gel. Finally, arylazo sulfones proved to be efficient PAGs also in the visible-light mediated Friedel–Crafts reaction of aldehydes on differently substituted indoles for the smooth preparation of diarylmethanes **45.8** (Scheme 45c).[188]

The photocleavage of a Se–S bond in selenosulfonates **46.1** enabled the functionalization of different vinyldiazo compounds **46.2**. The tosyl radical formed in the irradiation added to the double bond of **46.2** causing a nitrogen loss from intermediate **46.4**. Recombination with the PhSe• radical completed the radical 1,3-selenosulfonylation (Scheme 46).[189] The advantage of the method is the high atom economy and the use of an inexpensive light source (Blue LED) and of a green solvent.

The same TsSePh derivative was likewise used for the preparation of valuable 8-membered sulfonyl-benzo[*b*]-azocines *via* a radical 8-endo sulfonylcyclization.[190] The tosyl radical may derive from the photohomolysis of the S–I bond in Ts–I under blue LED irradiation, inducing a radical cyclization in 1,6-diynes.[191]



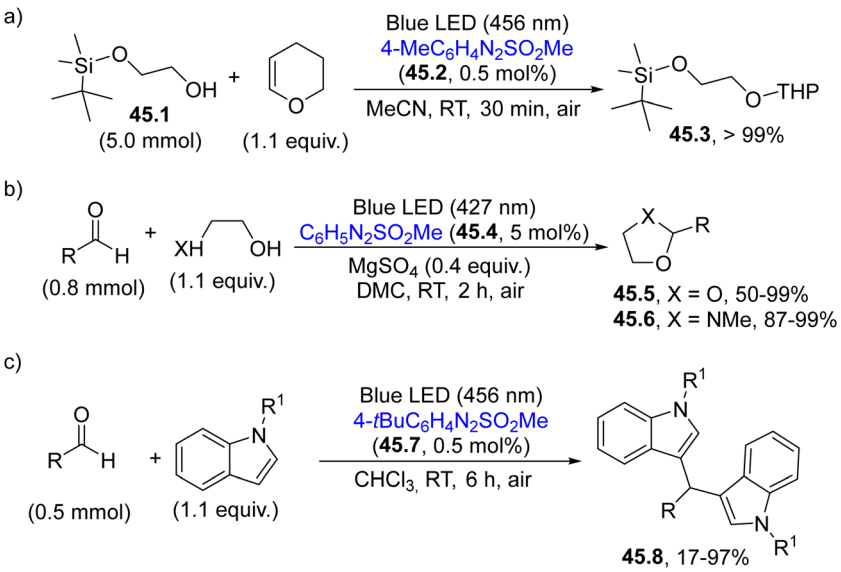
Scheme 46 Visible-light radical 1,3-selenosulfonylation of vinyldiazo derivatives.

The sulfonyl radical may be generated by carbon radical addition onto a SO_2 surrogate (DABSO = DABCO·$(SO_2)_2$). A devised strategy, involved the photolysis of $PhI(OCOCH_2F)_2$ to liberate the CH_2F radical, which was promptly trapped by DABSO to generate a monofluoromethylsulfonyl radical, which was used for the preparation of oxindoles from *N*-arylacrylamides in up to 97% yields.[192]

The synthesis of 1,2,4-dithiazoles **47.2** was carried out starting from thioamides **47.1** by simply employing visible-light sources and oxygen as the oxidant (Scheme 47). The mechanism hypothesized indicated a PET reaction between **47.1** and oxygen to deliver the thioamidyl radical **47.3** that was captured by another molecule of **47.1**, generating the heterocycle *via* an intermolecular nucleophilic addition and desulfurization.[193]

4.4. Selenium-based

The adoption of mild routes to the formation of Se–X bonds is desirable in the frame of green and mild approaches. The use



Scheme 45 Application of arylazo sulfones as visible-light absorbing PAGs for the (a) protection of alcohols (b) protection of carbonyls and (c) preparation of diarylmethanes.

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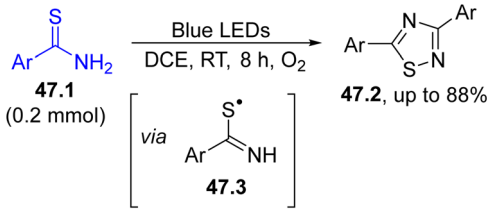


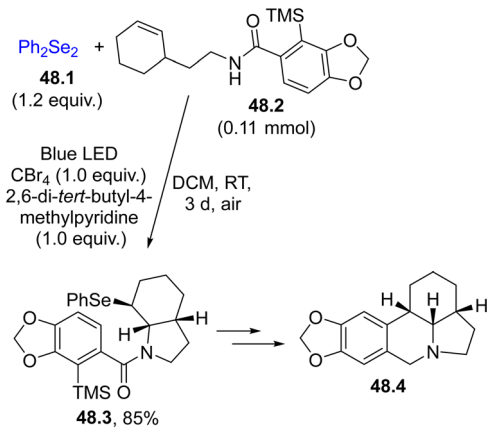
Scheme 47 Aerobic visible-light induced synthesis of 1,2,4-thiadiazoles from thioamides.

of a photochemical reaction to promote a selenylation event is an appealing choice. Usually, the selenylating agent is a diselenide RSeSeR (mostly R is an aryl group)[75] that showed an absorption tail in the visible region ($\lambda < 500$ nm), attributed to the n → σ* transition, coupled with the labile nature of the Se–Se bond (the BDE_{Se-Se} for PhSeSePh is *ca.* 41 kcal^{-1} mol^{-1}).[158] Thus, the species derived from the cleavage of the Se–Se bonds may be used for the functionalization of alkenes, alkynes and (hetero)aromatics.

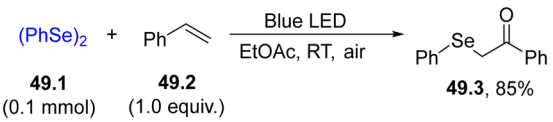
As an example, Scheme 48 shows an example of the selenofunctionalization of alkenes. The reaction of PhSe• (released from the photolysis of diselenide **48.1**) with CBr_4 to yield PhSeBr was invoked as the key intermediate. Derivative **48.3** was obtained in an 85% yield, which upon elaboration gave the amaryllidaceae alkaloid (±)-γ-lycorane **48.4**.[194]

The peculiar photochemistry of diselenide **49.1** has been exploited to achieve the oxoselenylation of vinylarene **49.2** (Scheme 49). The so-formed α-aryl selenomethyl ketone **49.3** resulted from the attack of the selenium-based radical onto **49.2** followed by reaction with oxygen. Although the reaction gave good yields under blue LED irradiation, a CFL lamp was mainly adopted.[195]

A related reaction was carried out in the presence of a sulfonimide (*e.g.*, saccharin **50.2**) where a visible-light-induced three component reaction took place resulting in an intermolecular aminoselenation of alkenes. The mechanism is depicted in Scheme 50. Thus, the selenyl radical **50.4** generated by the blue LED irradiation of diselenide **50.1** added to styrene **50.3**, forming



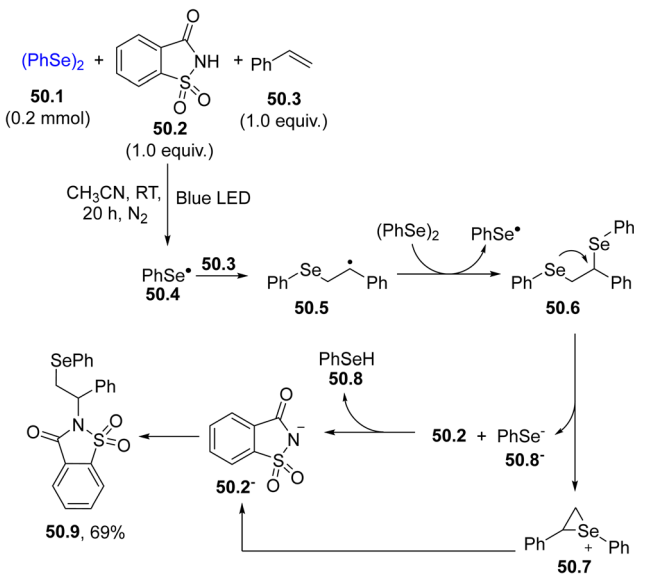
Scheme 48 Selenofunctionalization of a C=C bond as the key step in the preparation of the alkaloid (±)-γ-lycorane **48.4**.



Scheme 49 Photochemical route to α-aryl selenomethyl ketones.

the β-seleno alkyl radical **50.5,** which further reacted with **50.1** affording an unstable 1,2-bis(diselenide) **50.6.** An intramolecular nucleophilic attack of selenium at the benzylic position took place generating an aryl-stabilized seleniranium ion **50.7** and the phenylselenyl anion **50.8**$^-$, which deprotonated saccharin **50.2**, releasing neutral phenylselenol **50.8** and the saccharin anion **50.2**$^-$. Saccharin derivative **50.9** was then obtained by coupling between **50.2**$^-$ and **50.7**. A broad variety of aminoselenation products was accessible in good yields with excellent functional group compatibility again by adopting a CFL lamp as the light source.[196]

Selenium-based radicals were likewise engaged in the selenylation/cyclization of enaminones **51.1** for the practical synthesis of 3-selanyl-4*H*-chromen-4-ones **51.2**/**51.4**. Two main approaches have been followed (Scheme 51). The first one was performed under (photo)catalyst free conditions and no additional oxidants were needed to obtain the final product **51.2**. The selenium source was derived again from diaryl selenides (path a).[197] In this case the PhSe• formed was oxidized by air to the corresponding PhSe$^+$, which promoted a ring closure upon addition onto the C=C bond in **51.1** (Scheme 51, path a).[197] The second approach is a green and practical protocol, using trifluoromethyl tolueneselenosulfonate **51.3** and enaminones **51.1** to synthesize a wide range of chromones **51.4** under photocatalyst and oxidant free conditions (Scheme 51, path b). The first step was the photogeneration of CF_3Se• which smoothly reacted with the double bond of **51.1** and the thus obtained radical was oxidized to the



Scheme 50 Intermolecular aminoselenation of alkenes.

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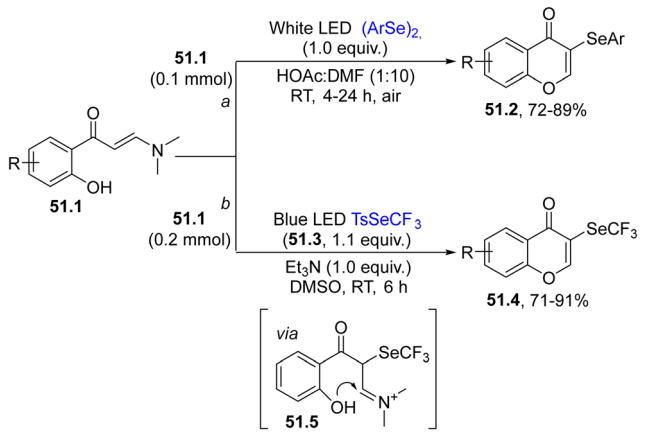


Scheme 51 Visible-light synthesis of chromones employing selenium-based radicals.

corresponding cation by oxygen to generate iminium **51.5.** The intramolecular attack of the OH group followed by *N*,*N*-dimethyl group loss, yielded chromones **51.4** in up to 91% yield, where various functional groups were tolerant to the photoirradiation conditions.[198]

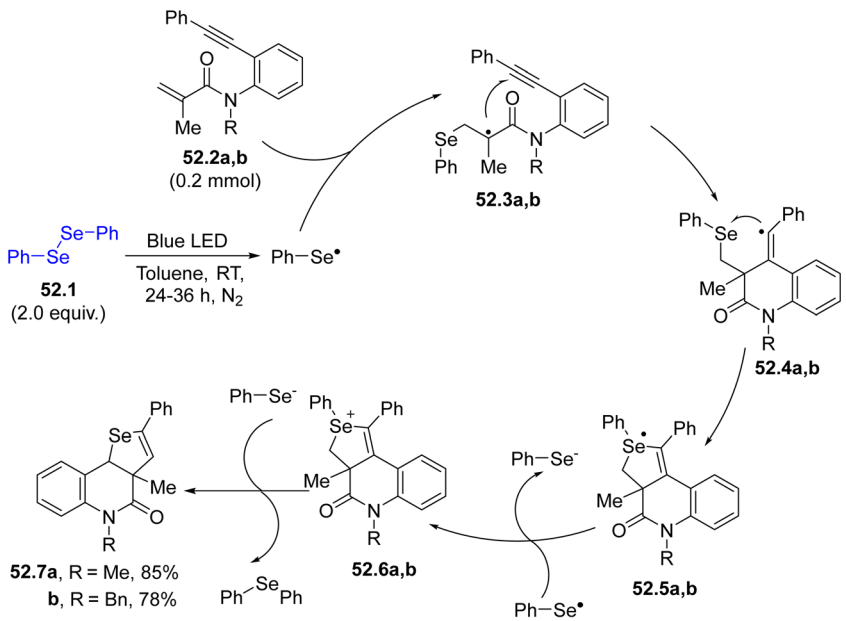
An alternative methodology for the construction of heterocycles is presented in Scheme 52 where two C–Se bonds and one C–C bond are constructed simultaneously. Following this approach, a dichalcogenide **52.1** serves as the source of a selenium centered radical. Upon irradiation, the radical formed by the homolytic cleavage of the chalcogen–chalcogen bond, underwent a radical domino reaction leading to a [2+2+1] heteroannulation of 1,7-enynes **52.2a, b.** The chalcogen-based radical reacted readily with the electron-poor olefin, forming the radical intermediates **52.3a, b**, which cyclized onto the triple bond affording vinyl radicals **52.4a, b.** The latter closed the cycle by attacking the chalcogen moiety and, after few more steps, selenopheno[3,4-*c*]quinolin-4(5*H*)-ones **52.7a, b** (or even thieno[3,4-*c*]quinolin-4(5*H*)-ones) were formed.[199] Moreover, the selenium radical addition onto the C–C triple bond in methyl(2-(phenylethynyl)phenyl)sulfanes was developed as a novel route for synthesizing 3-arylselanyl benzothiophenes.[200]

Seleno-benzo[*b*]azepines were readily formed upon photohomolysis of Ts-SePh in the presence of *N*-allyl-4-methyl-*N*-(2-(1-phenylvinyl)phenyl)benzenesulfonamide. Despite the first step being the generation of the PhSe• radical, the authors postulated the addition onto the C=C double bond of $PhSe^+$ derived from the oxidation of the latter radical by dioxygen.[201]

Another important process involving selenium radicals is their addition onto C–C triple bonds for the formation of substituted double bonds. Scheme 53 shows that phenyl acetylenes are ideal reaction partners. Thus, the regioselective addition of the phenylselenyl radical (from **53.1**) onto the C–C triple bond of **53.2** generated an alkenyl radical that attacked the cyclohexadienone scaffold intramolecularly. The capture of another phenylselenyl radical by the resulting α-keto radical led to the formation of heterocycle **53.3.** The action of basic water on **53.3** resulted in a nucleophilic displacement, forming chrom-6(5*H*)-enone **53.4,** a potent cytotoxic agent against HepG-2 cell lines.[202]

The construction of multiple C–Se and C–S bonds was achieved in the three component reaction between a diselenide, phenyl acetylene, and DABCO·$(SO_2)_2$, resulting in the formation of β-sulfonylvinylselanes (mostly in the *E* configuration).[203]

Electron-poor alkynes are likewise good radical traps for the selenyl radicals. As an example, ynones **54.2a, b** were used in the preparation of 3-selenospiroindolenines (**54.4a, b**, having a promising anticancer activity, Scheme 54). The attack of PhSe• onto the triple bond followed by the cyclization on the indole



Scheme 52 Visible-light mediated photocatalytic synthesis of selenopheno[3,4-*c*]quinolin-4(5*H*)-ones.

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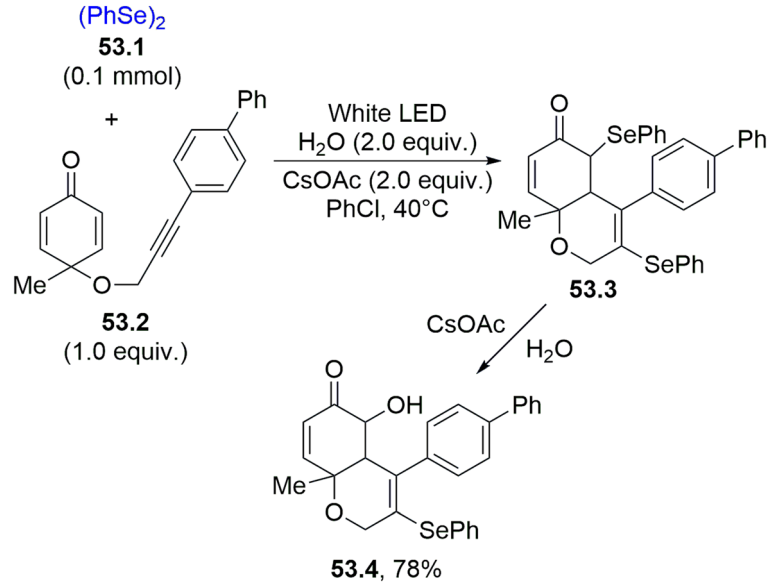
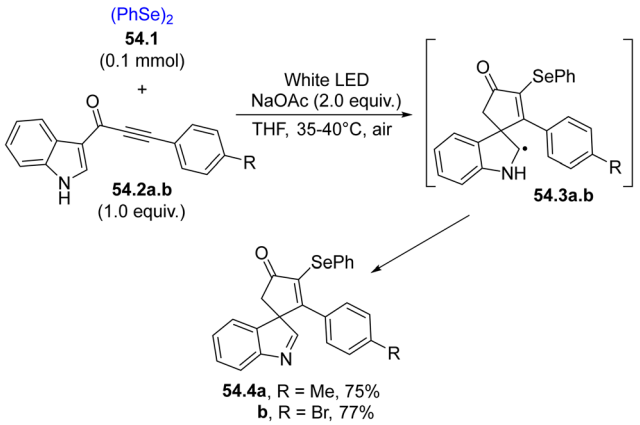


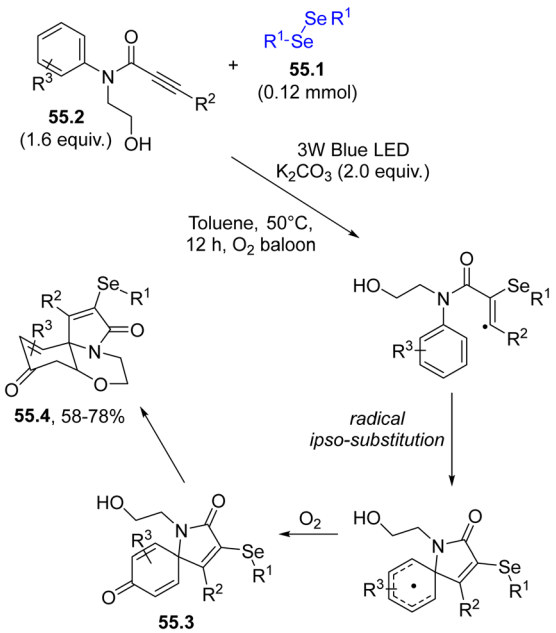
Scheme 53 Phenylselenyl radical addition onto C–C triple bond for the synthesis of chromen-6(5*H*)-ones.

ring released the adduct radicals **54.3a, b**, which upon oxidation and deprotonation of the hydrogen atom of the NH group yielded the spirocompounds **54.4a, b** in moderate to good yields.[204]

Similarly, spiro-cyclohexadienones were obtained by a dearomative selenylative carbo-spirocyclisation promoted by the phenylselenyl radical addition onto aromatic homologated-ynones.[205] Again, a dearomative cascade cyclization of biaryl ynones with diselenides yielded a series of selenated spiro[5.5]trienones in moderate to good yields.[206] If the same approach was applied to *N*-aryl-*N*-(2-hydroxyethyl)propiolamides **55.2** as reaction partners (under oxygenated conditions), a dearomative oxo-spirocyclization took place affording a series of selenium-containing benzo[*b*]pyrrolo[2,1-*c*][1,4]oxazine-3,9-diones **55.4.** In the mechanism, the selenium radical triggered an *ipso*-cyclization which was followed by an oxo-Michael addition onto the cyclohexadienone **55.3** (Scheme 55).[207]



Scheme 54 Preparation of 3-selenospiroindolenines.



Scheme 55 Visible-light dearomative oxo-spirocyclization of *N*-aryl-*N*-(2-hydroxyethyl)propiolamides.

In some instances, aryl alkynoates were used in spirocyclization reactions, such as in the domino reaction leading to 1,1-diselenidealkenes **56.7** (Scheme 56). The usual addition of the selenyl radical onto **56.2** promoted a domino reaction and after a 1,4-migration (on intermediate **56.4**), decarboxylation and selenyl radical recombination, **56.7** was isolated as a result of a double selenium radical addition on aryl alkynoate **56.2.**[208]

The usefulness of selenium-based radicals can be also appreciated in the functionalization of electron-rich

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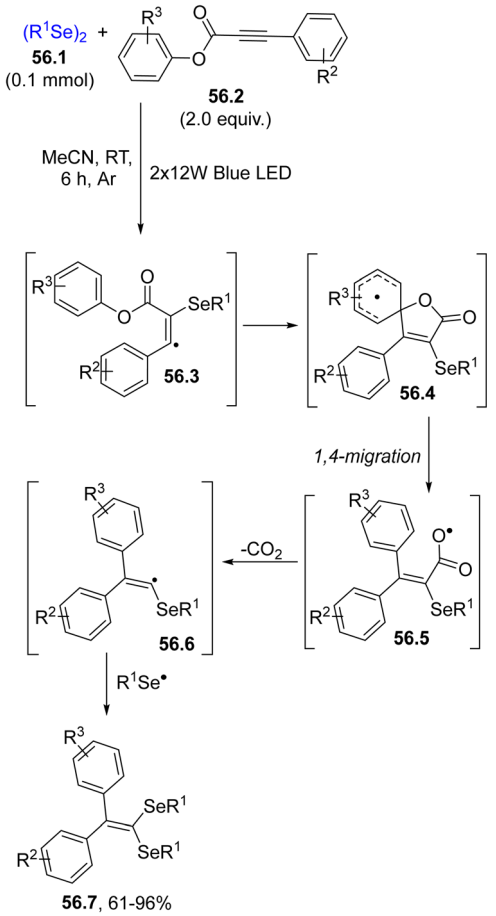
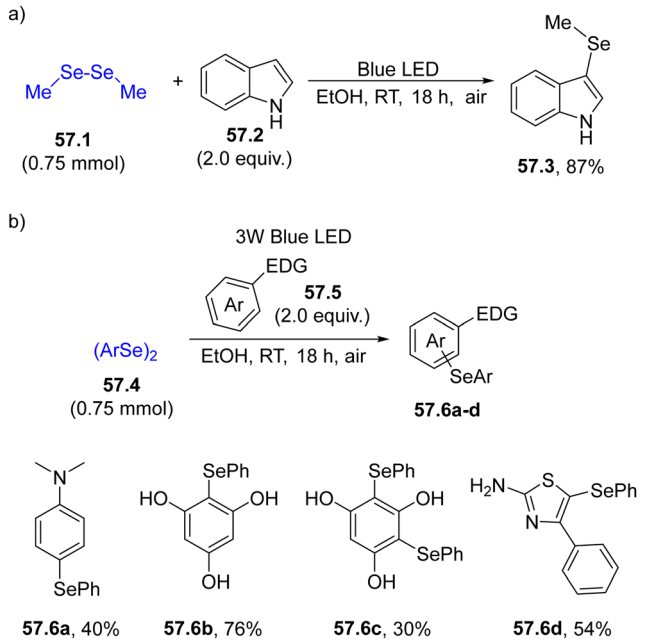


Scheme 56 Visible-light synthesis of 1,1-diselenidealkenes.



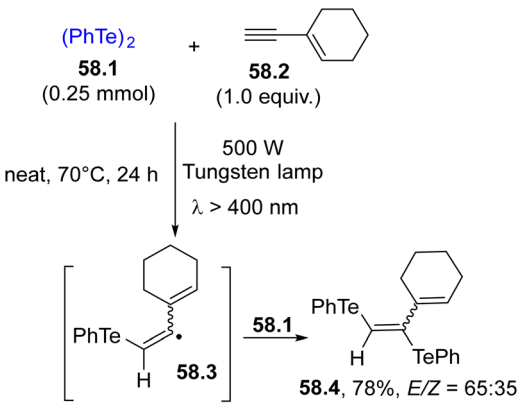
Scheme 57 Photoinduced forging of an Ar–Se bond for the preparation of (a) 3-selenylindoles and (b) for the derivatization of electron-rich benzenes.

(hetero)aromatics (*e.g.*, indoles) under mild conditions. Thus, dialkyldiselenide **57.1** was easily broken under blue light irradiation, generating 3-selenylindoles **57.3** in a good yield upon reaction with unsubstituted indole **57.2** (Scheme 57a). The protocol was also effective in the derivatization of anilines, phenols or other heterocycles while maintaining EtOH as the benign solvent (Scheme 57b).[209]

4.5. Tellurium-based

In the frame of chalcogen-based radicals, the use of tellurium derivatives is sparsely reported. In analogy with selenium radicals, diaryl ditellurides are the elective radical sources due to their absorption up to 550 nm. Terminal alkynes may be easily functionalized to give bis(phenyltelluro)alkenes by the formation of two C–Te bonds.[210] Irradiation of **58.1** induced the ditelluration of alkyne **58.2**, resulting in the formation of trifunctionalized alkene **58.4** in a good yield but with poor *E* selectivity (Scheme 58).[74] The initial homolysis of the Te–Te bond liberated a PhTe• radical which upon addition onto **58.2** generated vinyl radicals **58.3** and **58.4** from it through reaction with another molecule of **58.1**.

In some cases, ditellurides were used in combination with other $(ArCh)_2$ (with Ch = chalcogen) derivatives. In fact, the photolysis of **59.1** in the presence of isonitrile **59.3** resulted in



Scheme 58 Visible-light induced ditelluration of an alkyne.

an unproductive reaction. However, when **59.2** was added to the reaction mixture, a thiotelluration reaction took place where product **59.4** was easily isolated in a good yield (Scheme 59).[211] Lower yields were however detected when the aryl isocyanide did not bear strong electron-withdrawing groups.

4.6. Halogen atoms

Halogen atoms may serve as useful intermediates for eco-sustainable halogenation reactions but they are rarely used. The generation of these radicals has been proposed for the preparation of α-halomethyl ketones starting from terminal alkynes **60.2** (Scheme 60). Irradiation of *N*-bromo- or *N*-iodosuccinimides **60.1a, b** with 450 nm light liberated the corresponding halogen radical that readily added to **60.2** and

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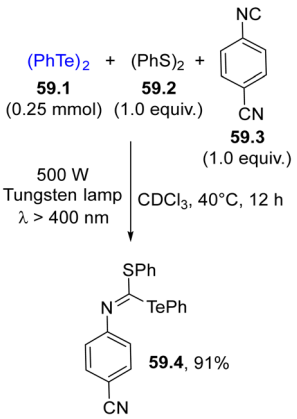
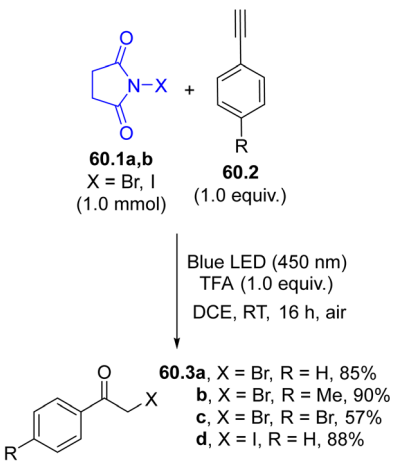


Scheme 59 Thiotelluration of aryl isocyanides.

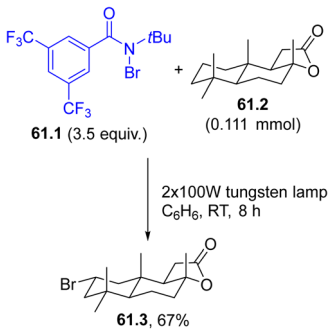
the resulting vinyl radical was oxidized by oxygen, yielding ketones **60.3a–d**.[71]

A bromo atom may be incorporated into complex structures, namely, the terpenoid natural product (+)-sclareolide (**61.2**), by the photolysis of a *N*-bromoamide (**61.1**, Scheme 61). The visible-light induced (using a 100 W tungsten lamp) cleavage of the N–Br bond in **61.1** resulted in the liberation of a reactive amidyl radical that abstracted a hydrogen atom from **61.2** in a selective fashion (out of 26 aliphatic C–H bonds). The combination of the resulting carbon radical with the bromine atom afforded the C2-equatorial bromination product **61.3** as a single regio- and stereoisomer in a satisfying yield.[70]

An intriguing reaction is the concise and efficient ring-opening difluorination strategy developed for the synthesis of highly functionalized hydroxy-containing α,α-difluoro-β-keto-amides **62.3a–c** through derivatization of 4-aminocoumarins **62.2a–c** in dimethyl carbonate (DMC) as a green solvent (Scheme 62). The target was smoothly achieved under visible-light irradiation in air at room temperature without the addition of any other external photocatalysts. With this protocol, compounds **62.3a–c** were successfully synthesized under mild conditions in up to 91% yield.[212]



Scheme 60 Functionalization of terminal alkynes using NBS or NIS as the source of halogen atoms.



Scheme 61 Photoinduced bromination of (+)-sclareolide.

The first photochemical event was the release of a fluorine atom through the photocleavage of the N–F bond in NFSI **62.1**, which smoothly added to **62.2a–c**. The *N*-centered radical **62.4** underwent a HAT reaction with **62.5**, yielding **62.7**. A further radical addition/HAT sequence led to the formation of imine intermediate **62.9**. Finally, the water hydrolysis of **62.9** produced the primary amine **62.11** that promoted the aminolysis of the lactone moiety on the resulting ketone **62.10**, thus leading to the desired α,α-difluoro-β-ketoamides.[212]

5. Reactions *via* nitrenes

Photogenerated nitrenes are less used intermediates with respect to carbenes (see Section 6) although they can lead to valuable intramolecular insertion reactions onto C(sp^2)–H or N–H bonds. The photolysis of an azido group is often used for the generation of nitrenes. As an example, nitrene **63.3** (formed from vinyl azide **63.1** by photoinduced nitrogen loss) underwent an intramolecular attack to yield 2*H*-azirine **63.4** (Scheme 63). Then, the attack of a cyanamide anion (obtained by deprotonation of **63.2**) opened the three-membered ring, releasing 2-aminoimidazole **63.6** (useful for the preparation of anti-infective and anti-cancer derivatives) in a good yield.[213] Curiously, the same reaction took place by adopting microwave irradiation in place of light.

A similar intermediate, 2*H*-azirine, was reported in the synthesis of (*E*)-stilbenes through the irradiation of 3-(2-aminoaryl)-2-azido-1-arylprop-2-en-1-ones, followed by an 1,2-acyl migration[214] and in the synthesis of pyrroles from α-keto vinyl azides.[215]

Nitrenes may be easily formed starting even from aryl azides. Thus, the visible(solar) light-driven photocyclization of functionalized aryl azides **64.1a–c** yielded 2*H*-indazole-3-carboxamides **64.3a–c** (Scheme 64). A N–N bond coupling was achieved starting from **64.1a–c** upon a photodenitrogenation step followed by nitrene, **64.2a–c**, insertion and by the aromatization of the resulting intermediate.[216]

The generation of nitrenes from aryl azides, a well-known phenomenon, has been recently rediscovered. An aryl nitrene, photogenerated by Blue LED exposure of azide **65.1**, formed a strained 2*H*-azirine through nitrogen insertion onto the C1–C2 arene π-bond (Scheme 65). The resulting strained three-

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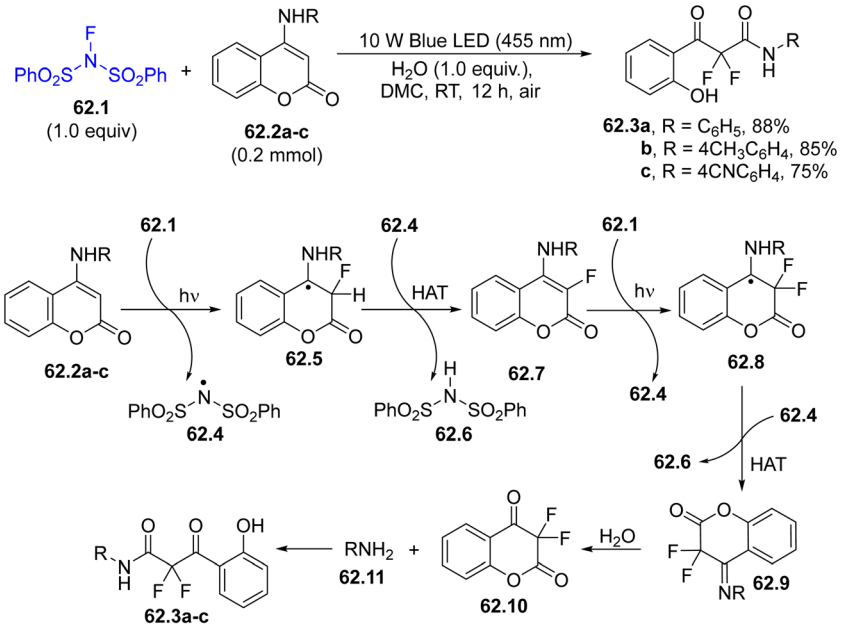
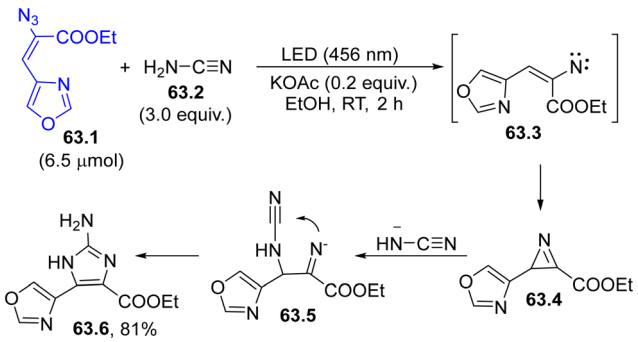
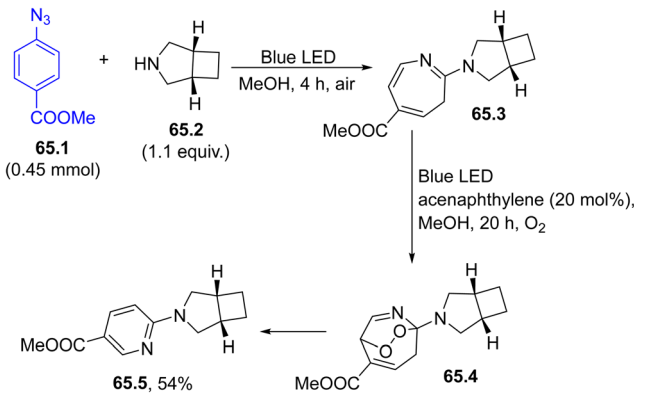


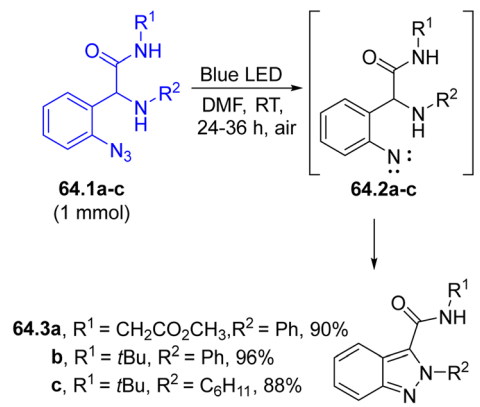
Scheme 62 Photochemical synthesis of α,α-difluoro-β-ketoamides.



Scheme 63 Photogenerated nitrenes for the synthesis of 2-amino-imidazoles.



Scheme 65 Conversion of aryl azides into 2-aminopyridines.



Scheme 64 Photochemical synthesis of 2*H*-indazole-3-carboxamides *via* nitrene generation.

membered ring underwent a thermal 6π electrocyclic opening, forming a seven-membered electrophilic ketenimine that was intercepted by amine **65.2** to yield azepine **65.3**. The latter compound could be isolated or treated with photogenerated singlet oxygen (by acenaphthylene sensitization) to produce endoperoxide **65.4** that evolved into 2-aminopyridine **65.5**.[217] If the reaction is carried out by using ethylaminoehanol as the secondary amine, the resulting azepine can be treated with *N*-bromocaprolactam to produce a pyridyl derivative through an *ipso*-selective nitrene internalization.[218]

A similar process involved irradiation of aryl azides in the presence of alcohols followed by treatment with trifluoroacetic anhydride (TFAA), resulting in the formation of *ortho*-aminophenols *via* a dearomative-rearomative sequence.[219]

Azides, however, are known hazardous compounds. Accordingly, coloured aryl sulfilimines (**66.1**, Scheme 66) were devised as safer alternatives for aryl nitrene generation. Thus, visible-

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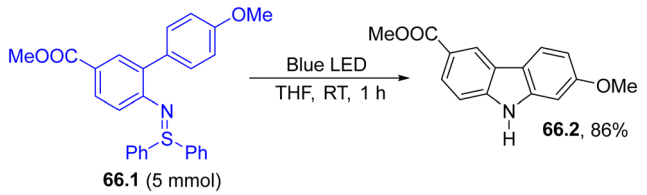


Scheme 66 Aryl sulfilimines as precursors for the preparation of Clausine C (**66.2**).

light exposure of **66.1** promoted the intramolecular C–H insertion of an aryl ring of the resulting nitrene, producing Clausine C (**66.2** a natural compound) in a very good yield on a 5 mmol scale.[220]

Aminoiodinanes **67.1a–c** are a class of compounds capable of generating nitrenes after visible-light exposure. Utilizing these compounds, a two-step protocol allowing the C–H amination of cyclic ethers followed by the reduction of the resulting products **67.3a–c** has been developed for the preparation of amino alcohols **67.4a–c** (Scheme 67). The initial C–H functionalization was accelerated by visible-light, improving the reactivity compared to the thermal process performed in the dark. The key step was the formation of the nitrene intermediates **67.2a–c**, which can interconvert between the singlet and the triplet state. Both states reacted selectively towards the methylene group of THF present at the α position with respect to the oxygen atom (C–H insertion for the singlet and hydrogen atom transfer for the triplet), both leading to **67.3a–c**.[221]

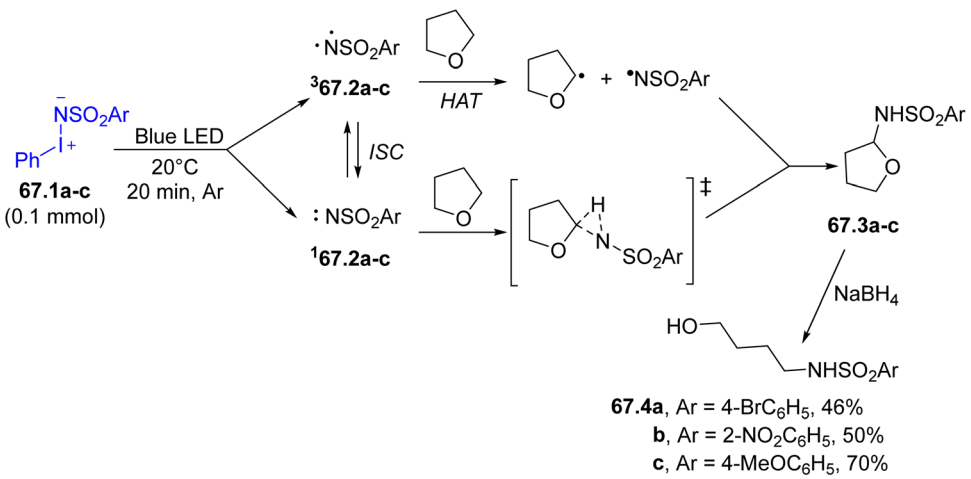
Triplet nitrenes formed from compounds **67.1** may be used for the formation of C–N bonds in the C–H functionalization of allylic methylene groups (*e.g.*, in α-methyl styrene). Interestingly, the reactivity shifted when a photocatalyst (*e.g.*, a Ru(III) complex) was present since a nitrene radical anion was formed, leading to the aziridination of the olefin.[222] In the same way, the reaction of aminoiodinanes **68.1** with sulfides **68.2** or allyl sulfides **68.3** can yield two different reaction outcomes although, in both cases, the first step was the singlet nitrene addition onto the sulfur atom (Scheme 68). In the case of sulfides **68.2**, sulfilimines **68.4a–c**, were readily formed, but the allyl-substituted sulfilimine generated from **68.3** underwent a [2,3]-sigmatropic rearrangement to furnish allylic sulfenamides **68.5a–d** as final products.[223]

Recently, there has been an increased interest in the photochemistry of nitroarenes.[224] As a matter of fact, aryl nitrenes were also obtained through the visible-light photolysis of nitroaromatics (*e.g.*, **69.1**, Scheme 69). Thus, the excited **69.1** underwent deoxygenation with $P(OiPr)_3$ to form nitrene **69.4** and the corresponding aminoazepine from it. Treatment with TFAA facilitated the conversion of the seven-membered ring to *ortho*-phenylenediamine **69.3** in a modest yield.[225] Otherwise, photolysis of the initially formed 3*H*-azepin-2-amine may induce an excited-state-4π electrocyclization, which upon hydrogenolysis generated bicyclic amine derivatives with full diastereocontrol.[226]

6. Reactions *via* carbenes

Among the possible intermediates that can be formed, carbenes are probably the most easily generated species under visible-light irradiation, thus expanding their role in syntheses based on carbene transfer reactions.[227–230] These carbenes may exist as singlets or triplets and the relative stability strongly depends on the structure of the precursors. The presence of a lone pair adjacent to the vacant 2p-orbital at the carbenic site stabilizes singlets rather than triplets. As a matter of fact, the different multiplicity of carbenes may affect their reactivity and chemoselectivity.[231,232]

As emphasized in the Introduction section (Scheme 1g), diazo derivatives (especially α-diazo ketones (esters) **70.1**, Scheme 70) are the preferred species for carbene photogeneration.[62,233–237] Visible-light irradiation of compounds **70.1** ($R^1 \neq OR$) generates an α-keto carbene that rapidly rearranges to a ketene **70.2**, *via* a Wolff rearrangement (Scheme 70, path a). However, the photolysis of α-diazo esters led a diverted chemistry since carbene **70.3** is exclusively



Scheme 67 Photoinduced C–H amination of THF.

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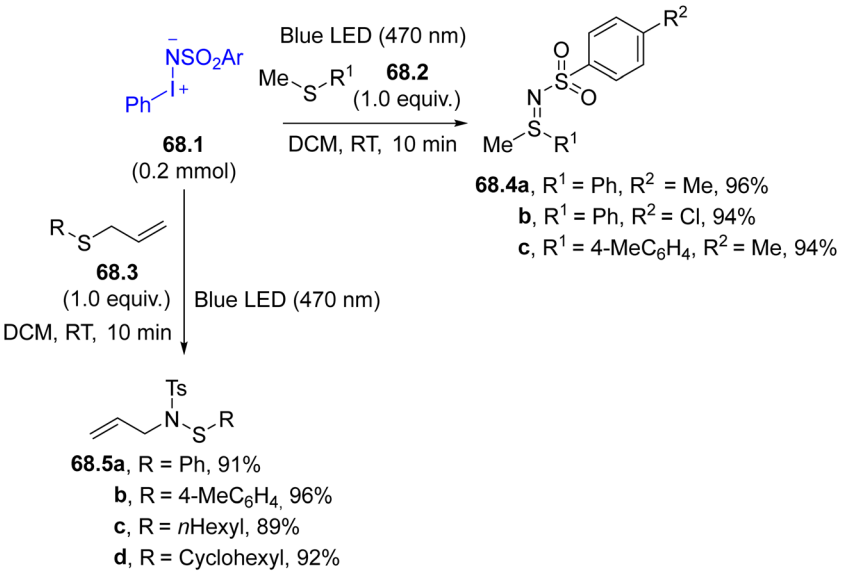
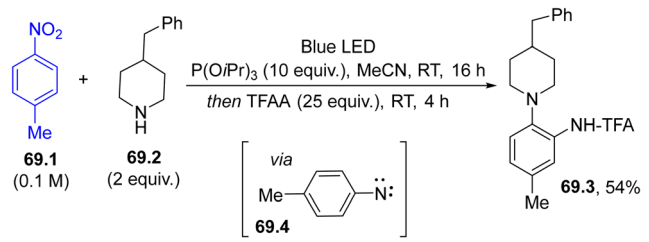


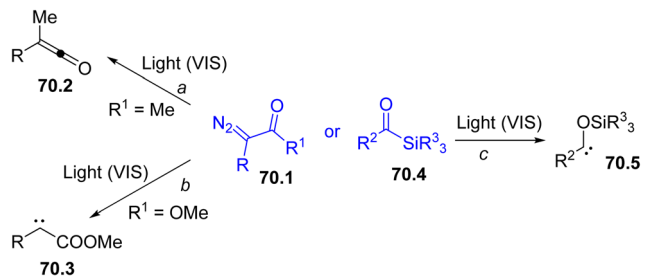
Scheme 68 Synthesis of sulfilimines and allylic sulfenamides.



Scheme 69 Preparation of *ortho*-phenylenediamines *via* dearomative rearomative coupling of nitrobenzenes and amines.

formed (path b). Another class of coloured carbene precursors is acylsilanes (**70.4**).[238] These compounds readily undergo a photoinduced 1,2-rearrangement (the so-called Brook rearrangement, path c) to siloxy carbenes **70.5**.[59,230]

The synthetic applications of these carbenes range from X–H and C–H insertion, cycloaddition onto unsaturated bonds, addition onto a heteroatom nucleophile to generate ylide intermediates, often inducing Doyle–Kirmse rearrangement like reactions.



Scheme 70 Main approaches for the photochemical generation of carbenes.

6.1. Formation of a three-membered ring

A three-membered ring may be easily formed by the addition of a carbene onto an electron-rich double or a triple C–C bond (Scheme 1g). A typical example is described in Scheme 71a where a cyclic triene **71.3** was exclusively formed upon a regio- and stereoselective carbene addition onto a polyunsaturated carbocycle (cyclooctatetraene **71.2**). The usefulness of compound **71.3** was demonstrated by its facile derivatization *via* a 6π-electrocyclization/Diels–Alder reaction cascade.[37] Allyl alcohols have been likewise cyclopropanated starting from aryldiazoacetates to yield valuable cyclopropane-fused bicyclic lactones. In this case, the OH group was involved in the transesterification event with no competitive O–H insertion in the reaction with the carbene.[239]

When siloxy carbenes add to a C=C bond, a cyclopropanol derivative is formed. As an example, in Scheme 71b, trifluoroacetylsilane **71.4** was converted into the corresponding carbene (of triplet multiplicity as proved by calculations) that smoothly added to both aromatic and aliphatic alkenes (*e.g.*, styrenes **71.5a–d**), resulting in a *cis*-selective [2+1] cyclization reaction yielding silyl ethers **71.6a–d**, that can be converted to cyclopropanols through simple treatment with TBAF.[240]

The reaction can be applied to aromatic acylsilanes having a tethered olefin moiety on the aromatic ring. Upon visible-light absorption an intramolecular [2+1]-cycloaddition took place releasing bicyclo[3.1.0]hexanes and bicyclo[4.1.0]heptanes in a good yield. Owing to the nucleophilicity of the photogenerated carbene, the addition onto electron-poor olefins such as acrylates was also effective.[241]

Rarely, carbene may be formed by the photolysis of a C,Se-selenonium ylide (**71.7**, Scheme 71c). The resulting disubstituted carbene led to cyclopropanes **71.9a–c** by reaction with electron-rich (**71.8a, b**) and electron-poor (**71.8c**) olefins.[242]

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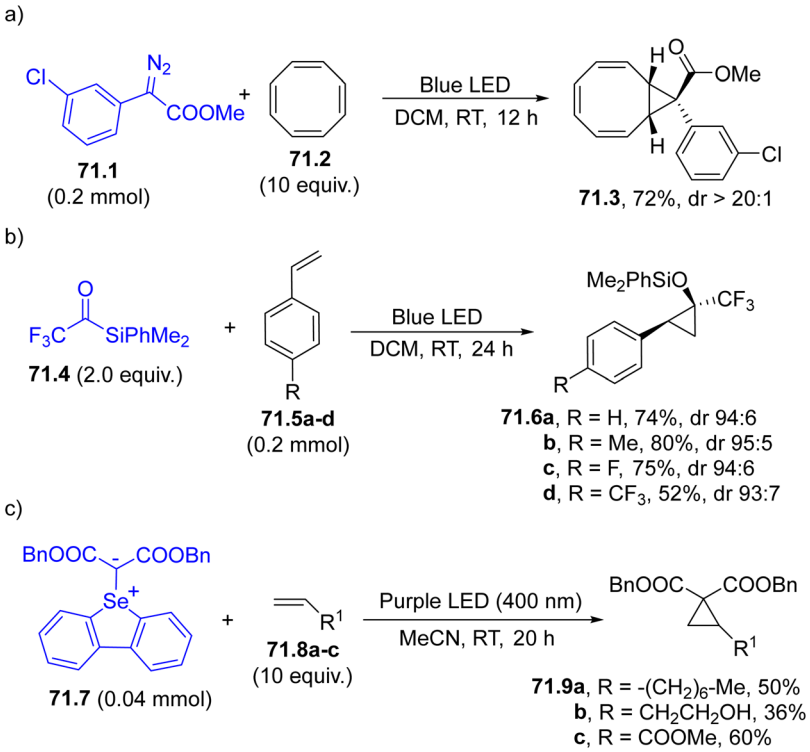
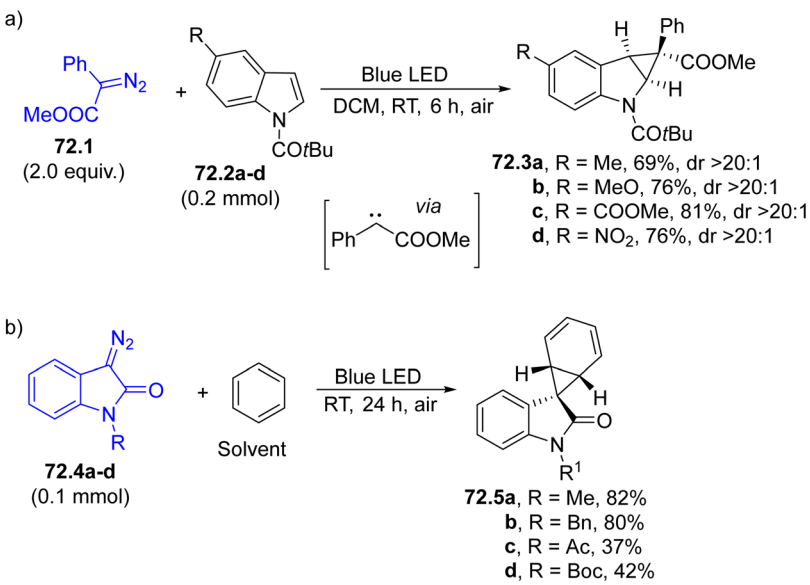


Scheme 71 Synthesis of cyclopropanes *via* addition of a photogenerated carbene onto (a) a tetraene (b) styrenes and (c) alkenes.

The reactivity of the carbenes is so high that even a C=C bond included in a (hetero)aromatic ring may be used for the construction of a three-membered ring. Indole is the elective heteroaromatic ring that enables the synthesis of cyclopropane-fused indolines. Thus, the straightforward addition of a carbene onto indoles **72.2a–d** led to derivatives **72.3a–d** with satisfactory yields and diastereoselectivity (Scheme 72a).[243] An intramolecular version of this reaction was applied to a diazoacetate prepared from a tryptamine leading to azepino[4,5-*b*]indoles.[244]

Even benzene (used as the reaction solvent) can serve as a reaction partner to form the corresponding norcaradiene derivatives through cyclopropanation.[245] A useful application of this strategy is shown in Scheme 72b. 3-Diazooxindoles **72.4a–d** smoothly reacted with benzene under blue LED irradiation to form spiro[norcaradiene-7,3′-indolin]-2′-ones **72.5a–d** in



Scheme 72 Photogenerated carbenes for the (a) cyclopropanation of indoles and (b) synthesis of spiro[norcaradiene-7,3′-indolin]-2′-ones.

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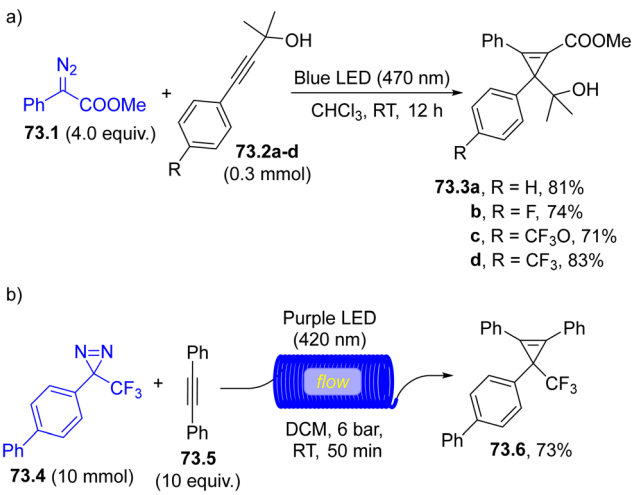
variable yields. The resulting cyclohexadienes were easily converted by means of rearrangement and epoxidation reactions.[246]

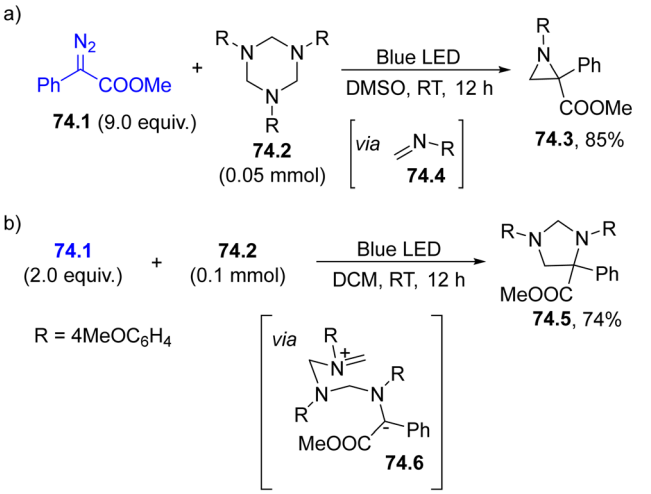
The trapping of a carbene with a triple C–C bond yields a cyclopropene. Thus, photolysis of a diazoderivative in the presence of phenyl acetylene easily formed the corresponding phenyl cyclopropenes.[247] The carbene addition was efficient even when decorated alkynes such as propargylic alcohols were used (**73.2a–d**, Scheme 73a). The metal-free conditions adopted here showed an orthogonal behavior with respect to related metal-catalyzed carbene transfer reactions where the OH group was the reactive site. However, the outcome of the photochemical reaction depended on the substitution of the carbinol carbon since an O–H insertion product was formed when primary alcohols were tested.[248]

Diazo compounds are not the exclusive precursors of carbenes. In fact, diazirine **73.4** easily liberated a carbene upon purple LED irradiation to yield 3-trifluoromethyl-3-aryl-cyclopropene **73.6** with yields up to 97% when trapped by diphenylacetylene **73.5** (Scheme 73b). Such a cyclopropenation occurred more efficiently under continuous flow conditions and adduct **73.6** was formed in 73% yield when the reaction was run at a 10 mmol scale for a residence time of 50 min. Diazirines was more effective than the corresponding diazo compounds as demonstrated by the control experiment although a diazo compound was formed to some extent from the diazirine during the reaction.[249]

In one instance, a three-membered ring heterocycle was obtained starting from an α-diazo ester (Scheme 74a). The reaction is a formal [2+1] cycloaddition between the carbene photogenerated from **74.1** and a formaldimine (**74.4**) resulting from the decomposition of hexahydro-1,3,5-triazine **74.2** in DMSO. Noteworthily, a solvent-controlled divergent cycloaddition took place when the reaction was performed in DCM, leading instead to the formation of imidazolidine **74.5** *via* the intermediate **74.6** (Scheme 74b).[250]



Scheme 73 Preparation of cyclopropenes *via* photogenerated carbenes from (a) diazoalkanes and (b) diazirines.



Scheme 74 Solvent dependent preparation of (a) three-membered and (b) five-membered heterocycles.

6.2. C–C bond formation

An intriguing approach in C–C bond formation *via* carbenes is the insertion into a C(sp^n)–H bond as shown in Scheme 75. The generation of a carbene in cycloalkanes as reaction media led to C(sp^3)–H insertion although with modest yield.[251] Nevertheless, photolysis of phenyl NHPI diazoacetates in a DCM/cycloalkane 1 : 1 mixture yielded the corresponding C–H insertion products in a very good yield.[252] However, the intramolecular insertion led to better results as in the irradiation of **75.1** where the photogenerated carbene **75.2** cleanly gave lactone **75.3** in more than 90% yield (Scheme 75a).

A related strategy was applied for the synthesis of valuable spiro-β-lactones and -lactams.[253] The insertion into aromatic or alkynyl C–H bonds required metal catalysis. To promote C–H insertion into a naphthtyl amine, a quinoline unit must be incorporated, playing the role of a directing group (see compound **75.5** in Scheme 75b). The presence of two nitrogen atoms in **75.5** allowed for the formation of a Pd(II) complex that underwent a carbene addition and the desired naphthyl acetate **75.6** was formed through reductive elimination from the resulting Pd(IV) complex. The reaction did not require any reaction media since diazoacetate **75.4** functioned as the solvent.[254] The C–H insertion into a C(sp)–H bond required the use of a copper catalyst and a modified bisoxazoline *Sa*Box ligand (*e.g.* **75.9**, Scheme 75c). The process was based on the trapping of the α-siloxy carbene onto the *Sa*Box/Cu(I) catalyst, resulting in the release an α-siloxy Fischer metal carbene that ultimately led to alkynyl alcohol **75.10** in a high yield showing a good broad substrate scope and a remarkable heterocycle tolerance.[255]

In rare instances, a photogenerated carbene may be engaged in a formal C–C bond insertion. Again, a diazoderivative (**76.1**, Scheme 76) was the ideal substrate for the carbene liberation. In this case, the addition of the carbene on the enolic form of 1,3-diketone **76.2**, generated the cyclopropanol derivative **76.4**, which upon C–C cleavage enabled the isolation of 1,4-diketone **76.3**.[256]

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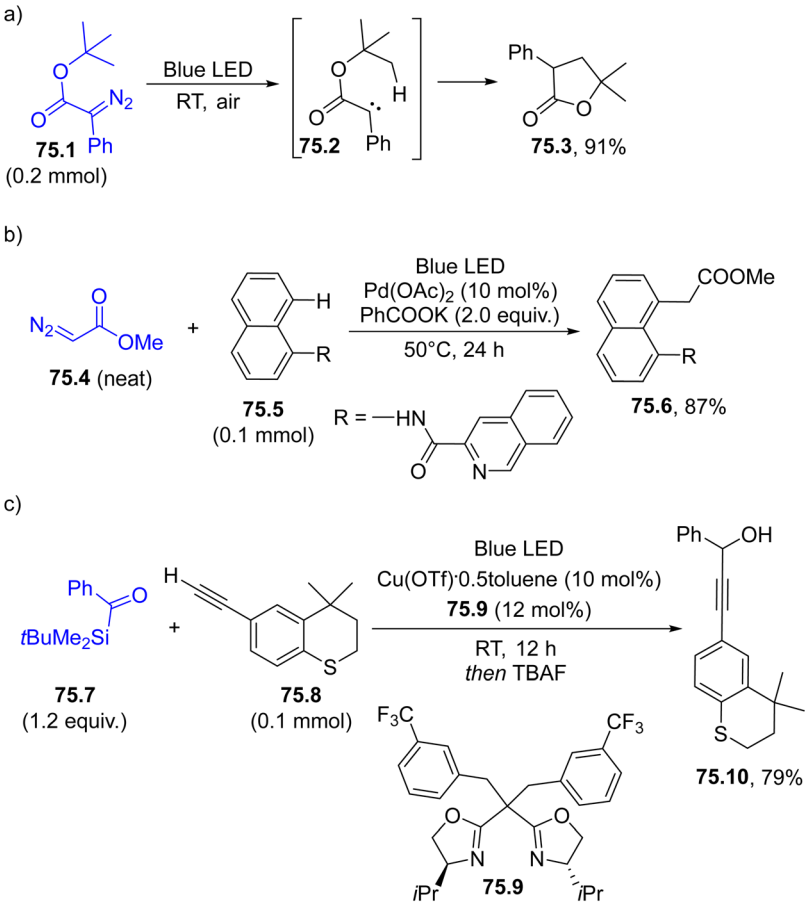
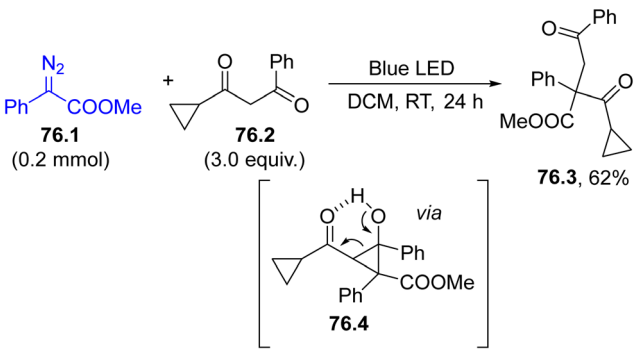


Scheme 75 Carbene insertion onto (a) a C(sp^3)–H, (b) a C(sp^2)–H, and (c) a C(sp)–H bond.



Scheme 76 Synthesis of a 1,4-diketone *via* C–C bond insertion.

A related free carbene transfer reaction of α-diazoesters with γ-diketones was developed by using a chiral bifunctional guanidine-amide organocatalyst to prepare δ-diketones having a quaternary carbon chiral center.[257] The same kind of compounds were prepared through a formal carbene insertion reaction of 1,3-diketones with diazoesters. The enantioselectivity of the thus formed quaternary center was assured by the presence of a chiral phosphoric acid catalyst.[258]

In other instances, the cyclopropane obtained *via* [2+1] cycloaddition was not stable, thus leading to intriguing chemistry. As an example, carbene addition onto enaminones led to unstable cyclopropyl amine that upon nitrogen atom-driven ring opening followed by elimination of a secondary amine formed an α-substituted γ-ketoester.[259] Carbene addition onto electron-poor dienes such as dicyano-2-methylenebut-3-enoates induced a cyclopropanation–vinyl cyclopropane rearrangement sequence, yielding decorated cyclopentenes *via* a formal [4+1] cycloaddition.[260]

Another interesting application of photogenerated carbenes is the preparation of olefins. A possible strategy is illustrated in Scheme 77a. A carbene formed from aryl diazoacetate **77.1** was trapped by the sulfur ylide **77.2**. The negatively polarized carbon atom initiated a nucleophilic attack on the electrophilic carbene site, yielding intermediate **77.4** and trisubstituted olefin **77.3** from it *via* dimethyl sulfide elimination. The approach was used for the formal synthesis of an ET_A receptor radioligand.[261]

Diphenylmethanethiones can also be used as reaction partners. In fact, addition of the carbene (from a diazoindolone) on the sulfur atom of the thione resulted in the formation of a sulphonium ylide that ultimately led to substituted 3-arylidene oxindoles *via* an electro-cyclization reaction followed by elemental sulfur elimination from the resulting episulfide.[262]

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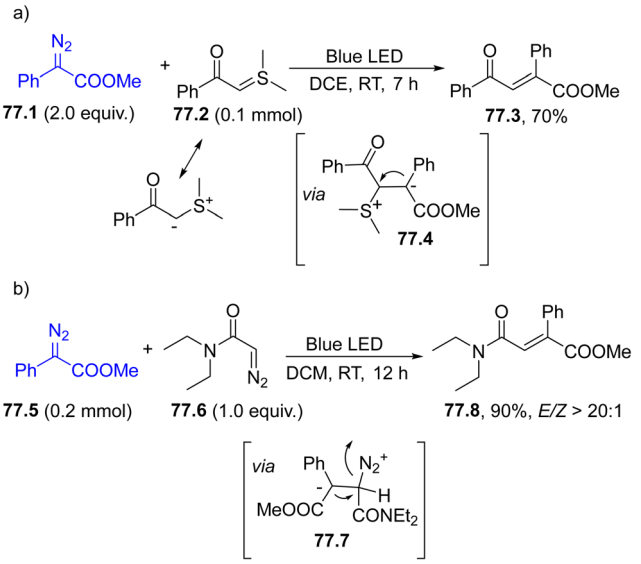
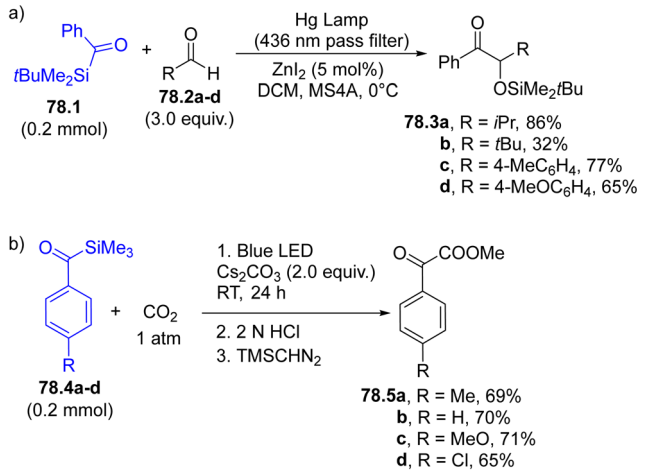


Scheme 77 Preparation of alkenes *via* visible-light reaction of carbenes with (a) a sulfur ylide and (b) a α-diazoamide.



Scheme 78 Synthesis of (a) α-siloxyketones and (b) α-ketoesters *via* photogenerated siloxy carbenes.

All-carbon tetra-substituted olefins were instead formed in moderate to good yields through the visible-light induced coupling between a diazo compound and an iodonium ylide.[263] Moreover, densely substituted itaconimides were easily prepared under solvent-free conditions through a multicomponent reaction by adopting (substituted) pyridines, aryl diazoesters and *N*-alkylmaleimides as the reaction partners.[264]

The selective use of the wavelength enabled the coupling of two diazoesters (**77.5** and **77.6**), where a single carbene was formed (from **77.5**), and the subsequent addition onto **77.6** led to intermediate **77.7**, which upon dinitrogen extrusion formed the trisubstituted alkene **77.8** (mostly in the *E* configuration, Scheme 77b).[265]

As mentioned previously, acylsilanes are converted into siloxy carbenes upon photolysis. However, in rare cases, the carbonyl group of the starting acyl derivative may be restored at the end of the reaction. In fact, the siloxy carbenes generated from acyl silane **78.1** was engaged in the nucleophilic addition onto aldehydes **78.2a–d** (activated by the Lewis acid ZnI_2). A zwitterionic intermediate was formed, which upon 1,4-silyl migration, yielded α-siloxyketones **78.3a–d** in variable yields in what was considered a sort of formal cross benzoin-type condensation (Scheme 78a).[266] The reaction achieved some success even in the absence of any Lewis acids.[267] The electrophilicity of fluorinated ketones was also sufficient, enabling them to function as nucleophilic carbene trapping reagents, resulting in the formation of trifluoromethylated benzoin-type adducts in almost quantitative yields.[268] The addition of siloxy carbenes onto a C=O group may take place intramolecularly. Accordingly, benzoyl silane was coupled with an *N*-phenyl maleimide *via* Rh catalysis and the resulting adduct led to the formation of interesting tricyclic γ-lactams upon visible-light irradiation.[269]

An intriguing application of siloxy carbenes involves their trapping with carbon dioxide. Thus, irradiation of silanes **78.4a–d** under 1 atm CO_2 released the corresponding α-ketocarboxylates that can be easily converted onto the corresponding methyl esters **78.5a–d** through the *in situ* addition of $TMSCHN_2$ (Scheme 78b). Mechanistic investigations highlighted the involvement of the singlet state of the siloxy carbene as the intermediate.[270]

Siloxy carbenes may release a ketone as the final product even when reacting with double or triple C–C bonds. In the first case, acylsilanes were used for a light promoted copper-catalyzed enantioselective allylic acylation. Thus, the carbene was intercepted first by a chiral Cu(I) complex, which upon addition of an allylic phosphate formed an acylcopper(I)–alkene complex, which upon excitation liberated an allyl ketone in up to >99% ee.[271]

Finally, the silylacylations of an alkyne may take place in an inter- or intra-molecular manner to give functionalized enonyl silanes (in the former case)[272] or silylated chromones (in the latter)[273] in a satisfactory yield *via* a cyclopropene intermediate. The intermolecular version of the reaction demonstrated synthetic significance only when using alkynes having electron-withdrawing substituents.

The carbene generated from cyclic diazo imides exhibited solvent-dependent reactivity when thiols were present in the reaction mixture. In fact, in DCM, the carbene was formed in the triplet state and was involved in a C–H functionalization/thiolation process, yielding indane-fused pyrrolidines *via* an intramolecular cyclization. On the other hand, in MeCN as the reaction medium, a clean reaction took place and hydrazones were formed where the thiols acted as the reductant.[274]

In rare instances, the addition of a carbene onto a heteroatom led to a C–C bond formation. Thus, the photogenerated α-carboxymethyl carbenes **79.4a–c** added to the boron atom of an arylboronic acid **79.2** (paths, a and b). The ylides **79.5a–c** formed underwent a 1,2-sigmatropic shift (path c) and the hydrolysis of the obtained boronates **79.6a–c** (path d) yielded α-substituted esters **79.3a–c** in a discrete yield (Scheme 79). This approach was applied for the synthesis of different

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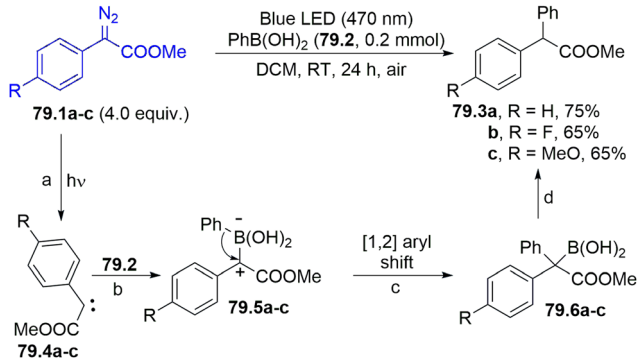
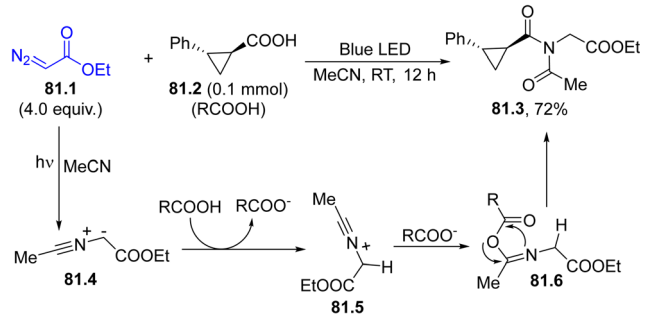


Scheme 79 Preparation of α-substituted esters **79.3a–c**.



Scheme 81 Visible-light synthesis of a diacylglycine ester.

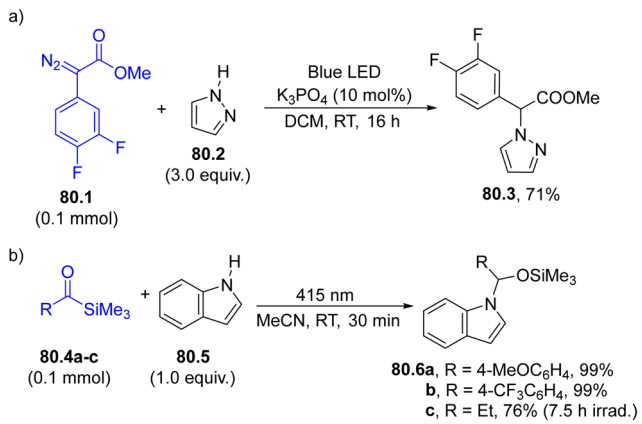
pharmaceutics, including, among the others, muscarinic antagonists Benactyzine and Aprophen.[275]

6.3. C–N bond formation

The main method for the formation of a C–N bond *via* photogenerated carbenes (whether from diazocompounds or acylsilanes) involves N–H insertion into N-heterocycles always under metal-free conditions. Scheme 80a illustrates the case of a pyrazole. The carbene derived from **80.1** underwent a nucleophilic attack by the azarene **80.2** and the N–H inserted derivative **80.3** was obtained in a good yield.[276] When the same protocol was applied to 1,2,3-triazoles, the reaction proceeded successfully even in the absence of the base.[276]

However, the most investigated N-heterocycle is indole. The N–H insertion may take place with the most used photogenerated carbenes. As an example, Scheme 80b shows the insertion of siloxycarbenes (from silanes **80.4a–c**) into indole **80.5**, yielding stable silylated *N,O*-acetals **80.6a–c** in almost quantitative yield in a very short time (30 min for benzoyl silanes).[277] The same approach was used for the functionalization of the indole core in tryptophan-containing oligopeptides.[278]

The carbene generated from azidophenyl diazoacetate was reacted with indole to form a key compound for the preparation of the natural product (−)-psychotrimine. In this work, it was



Scheme 80 Photoinduced release of carbenes for the N–H insertion into (a) pyrazole and (b) indole.

found that the efficiency of the synthesis of the *N*-alkylated products depended on the nature of the indoles (high for 3-substituted indoles having electron-withdrawing groups and low for those having electron-donating groups).[61] As a matter of fact, carbenes readily inserted into the N–H bond of carbazole,[279] dibenzoazepines,[279] and even purine derivatives, causing a site-selective N^1-alkylation for the construction of acyclic nucleoside analogues.[280]

Another approach for the C–N bond formation involves the addition of the carbene onto a nitrile (used as the reaction medium). The carbene, in turn generated from visible-light photolysis of diazoacetate **81.1**, was trapped by MeCN to generate the corresponding nitrile ylide **81.4**, which upon proton transfer with a carboxylic acid (**81.2**) yielded a nitrilium ion **81.5**, which was prone to undergo a nucleophilic attack by the carboxylate anion. The resulting intermediate **81.6** was then converted into diacylglycine ester **81.3** *via* a Mumm rearrangement (Scheme 81).[281,282]

In a related process, the nitrile ylide formed by the addition of a carbene onto MeCN promoted the synthesis of polysubstituted oxazoles in 95% yield, thanks to the presence of a catalytic amount of $(^iPr)_3SiCl$ as the Lewis acid catalyst.[283]

A formal enantioselective N–H insertion can be achieved when the carbene is generated in the presence of an excess of DMSO (32 equiv.), a chiral phosphoric acid and an aniline. The carbene was initially trapped by DMSO, forming a C–S bond in an achiral sulfoxonium ylide. Protonation of the ylide by the chiral acid led to a diastereomeric mixture of sulfoxonium ions, which underwent a preferential attack of the amine to form the desired enantioenriched α-aminoester *via* dynamic kinetic resolution.[284]

A formal C–N insertion may take place when the carbene adds to the nitrogen atom. The carbene generated from **82.1** was intercepted by allyl amine **82.2**, yielding the α,α-disubstituted amino ester **82.3** in a good yield (Scheme 82). The desired compound resulted from a [2,3]-sigmatropic shift occurring on the first-formed ammonium ylide **82.4** intermediate.[285]

The photodecomposition of aryl diazoacetates was adopted for the smooth preparation of nitrones. The carbene (obtained from **83.1** under Blue LED irradiation) here coupled with a nitrosoarene (**83.2**), leading to nitrone **83.3** again without the need for any additives and catalysts (Scheme 83). The protocol

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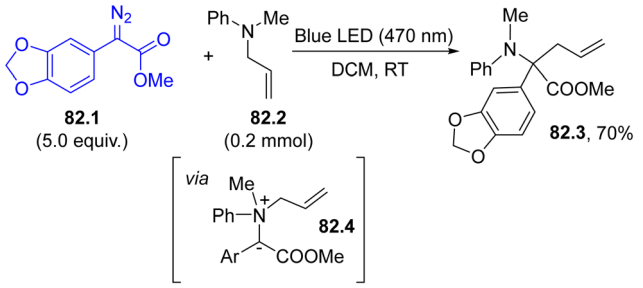
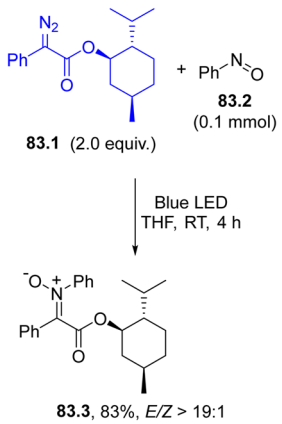


Scheme 82 [2,3]-Sigmatropic shift induced by the addition of a photogenerated carbene onto allyl amines.



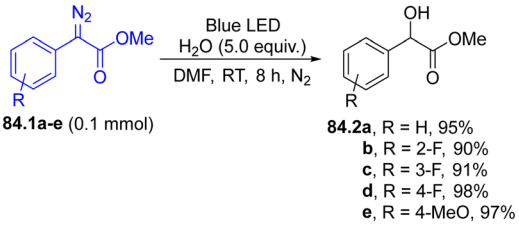
Scheme 83 Photoinduced coupling between a diazocompound and a nitrosoarene.

developed showed a good broad substrate scope and functional group tolerance for both reacting partners.[286]

In rare instances, the formation of a C–N bond was promoted by a sulfur ylide formed upon addition of the carbene onto a disulfide. This step initiated a Cu-catalyzed asymmetric [4+1] cycloaddition with ethynyl benzoxazinones, resulting in the production of several chiral indolines bearing C2-quaternary stereocenters.[287]

6.4. C–O bond formation

The construction of a C–O bond may be achieved through the insertion of carbenes onto the O–H bond in water or other OH containing derivatives or by reaction with cyclic ethers (*e.g.*, THF). α-Hydroxy and α-alkoxy esters or ketones are the core backbones of a wide range of biologically active compounds including, among the others, cefamandole and paclitaxel. In this frame, a metal-free strategy based on the O–H bond insertion by a photogenerated carbene (in turn obtained from diazoesters **84.1a–e**) was described (Scheme 84). The protocol was optimized under both batch and continuous flow conditions. In particular, by using a mesoflow photoreactor, the product **84.2a** was isolated on a multigram scale in 91% yield with a residence time of 4 h.[288] Cyclic diazoamides have been also employed as photoactivatable substrates in the preparation of α-hydroxy and α-alkoxy amides by using (fluorinated)

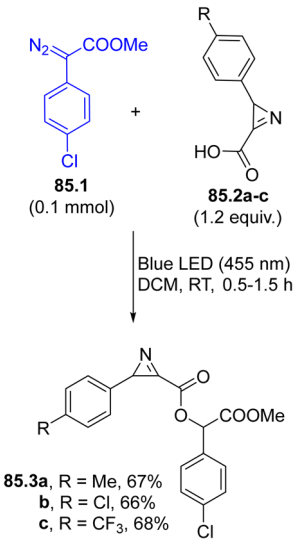


Scheme 84 Preparation of α-hydroxy esters *via* photogenerated carbenes.

alcohols and phenols as oxygenated partners.[289] Analogously, *O*-, *S*- and *N*-alkylated phenylacetate esters have been prepared in good to satisfactory yields by using 2-pyridones (phenols), 2-mercaptopyridine and anilines, respectively, as the coupling agents.[290]

Two orthogonal approaches for the conversion of azirine-2-carboxylic acids **85.2a–c** (Scheme 85) by using diazoesters have been recently reported. Indeed, blue light activation of diazoester **85.1** led to the O–H bond insertion of the generated carbene on **85.2a–c**, producing derivatives **85.3a–c**. Notably, in the presence of an Au(I) catalyst, the nitrogen atom in the azirine ring was the exclusive reacting site and a 1,3-oxazin-6-one ring was formed.[291]

A divergent strategy for the coupling of the oxime **86.1** and an aryldiazo acetate **86.2** was developed by simply tuning the nature of the reaction media (Scheme 86). Indeed, in neat DCM, direct O–H insertion occurred, releasing the corresponding oxime ether **86.3**. In contrast, when tetrahydrofuran or other oxygen-based heterocycles were used, incorporation of the ring opened form of the solvent into the final product **86.4** took place.[292] The mechanism involved the initial formation of the ylide **86.5**, followed by the nucleophilic induced ring opening of the five-membered ring and addition onto **86.1**. The capability of carbenes to activate cyclic ethers was thoroughly investigated through a dual experimental and computational approach,



Scheme 85 *O*-Functionalization of azirine-2-carboxylic acids.

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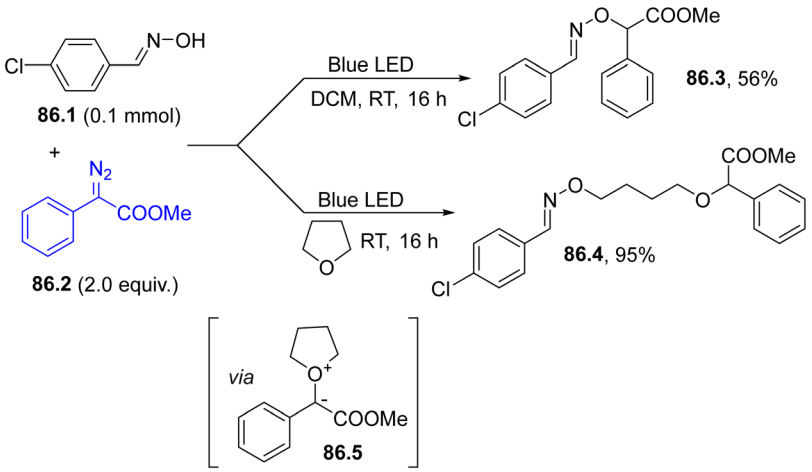


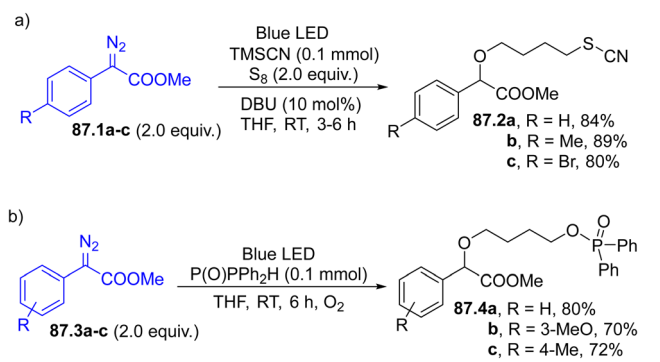
Scheme 86 Solvent dependent reactivity of carbenes with oxime **86.1**.

which confirmed the formation of the oxonium ylide **86.5** as the key step.[293,294]

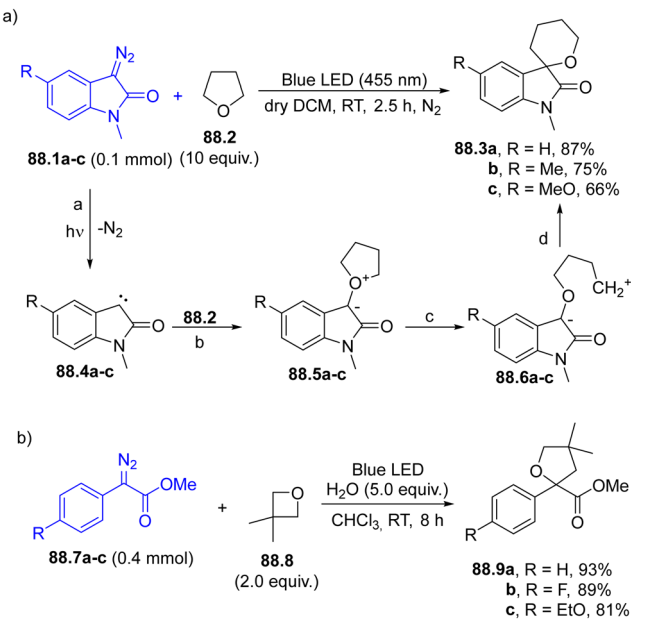
In this context, THF was intensively exploited for the development of a wide range of multicomponent processes, for the synthesis, among the others, of thiocyanates **87.2a–c** (in the presence of elemental sulfur and trimethylsilyl cyanide, Scheme 87a),[295] *S*-alkyl dithiocarbamates,[296] organophosphorus derivatives **87.4a–c** (under aerated conditions in the presence of phosphine oxides as the coupling partner, Scheme 87b),[297] polysubstituted nitrogen-based heterocycles[298,299] and 1,3-diketones.[298]

The formation of an ylide intermediate between a cyclic ether and a carbene was the key step of a ring expansion/contraction process. A versatile synthesis of oxacyclic spirooxindoles (**88.3a–c**, Scheme 88a) was described to occur from unstrained *O*-containing heterocycles (*e.g.* (substituted) tetrahydrofurans **88.2**) with 3-diazoindolin-2-ones **88.1a–c**. Mechanistic investigation highlighted that the initial formation of carbenes **88.4a–c** (path a) and their ensuing addition to ether **88.2** resulted in the formation of ylides **88.5a–c** (path b), which in turn underwent ring opening to form zwitterions **88.6a–c** (path c), which upon ring closure (path d) afforded the desired spirocompounds.[300] A ring expansion was also invoked for the preparation of substituted tetrahydrofurans **88.9a–c** (Scheme 88b) or tetrahydrothiophenes starting from the corresponding oxetanes **88.8** or thietanes.[301] The protocol was also performed on a gram scale on 3,4-dihydrofurans under continuous flow conditions. In this case, a ring contraction occurred leading to a vinyl oxetane.[302] Recently, a carbene was reported to undergo addition to the oxygen atom of ethynylbenziodoxolones. As a result, a visible-light-promoted oxy-alkynylation took place, delivering propargylic esters *via* an oxonium ylide intermediate.[303]

An interesting case is the visible-light driven preparation of trisubstituted hydroxylamines (**89.4a–d**) *via* multicomponent coupling of an aryldiazo acetate (**89.1**) a 2-nitrosopyridine (**89.2**) and β-keto esters **89.3a–d** (Scheme 89a). The reaction started with a thermal nitroso aldol reaction between **89.2** and



Scheme 87 THF as the reaction partner in the carbene promoted C–O bond formation for the preparation of (a) thiocyanates and (b) organophosphorus derivatives.



Scheme 88 Synthesis of (a) oxacyclic spirooxindoles and (b) tetrahydrofurans *via* ring enlargement.

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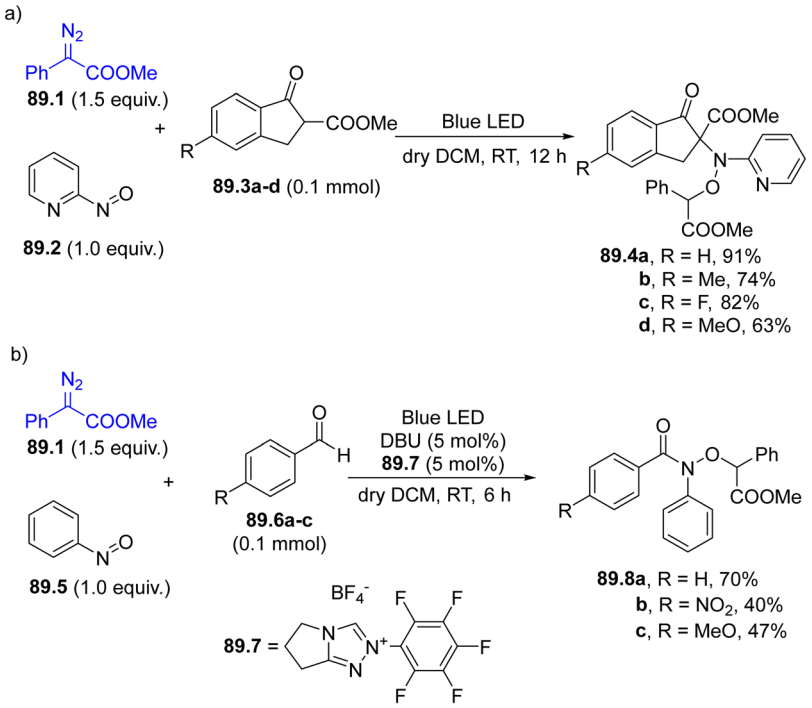
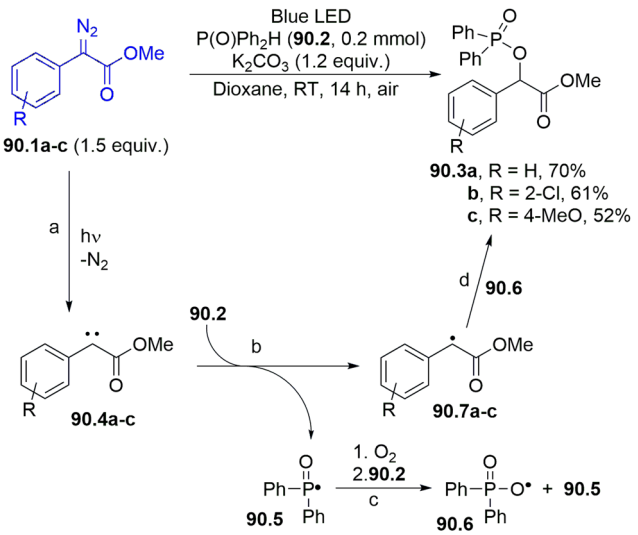


Scheme 89 Synthesis of substituted hydroxamic acid esters starting from (a) β-ketoesters (b) and benzaldehydes.

89.3a–d. The insertion of the carbene onto the O–H bond of the thus formed aldol adduct yielded the desired hydroxylamines **89.4a–d**. When switching to THF as the solvent, a four-component reaction occurred in up to quantitative yield.[304] A related photochemical three multicomponent carbene transfer reaction is described in Scheme 89b. Here, DBU promoted the deprotonation of the triazolium salt **89.7**, releasing a N-heterocyclic carbene (NHC) catalyst, which engaged in a reaction with aldehydes **89.6a–c** to form protected hydroxamic acids *via* a Breslow intermediate. Trapping of these acids with the carbene yielded differently substituted hydroxamic acid esters **89.8a–c** in discrete yields. This approach has been successfully exploited in the preparation of modified natural and bioactive products including vitamin E, borneol and anesthetic propofol.[305] The carbene formed from aryl diazoacetates was, however, able to attack the oxygen bond in aldehydes. The resulting carbonyl ylides engaged in a [3+2] cycloaddition with substituted maleimides, forming 4,6-dioxo-hexahydro-1*H*-furo[3,4-*c*] pyrrole in excellent yields.[306]

The photogeneration of carbenes from aryldiazo acetate esters **90.1a–c** in the presence of H-phosphine oxide **90.2** resulted in an oxyphosphorylation process that occurred under aerated conditions on a gram scale and in good to satisfactory yields (Scheme 90).[307] The mechanism here involved the hydrogen abstraction operated by the carbenes **90.4a–c** (paths a,b) from **90.2** and the resulting phosphinoyl radical **90.5** was trapped by dioxygen to form, after the decomposition of the resulting peroxy radical, phosphine-oxy radical **90.6** (path c) which then coupled with intermediates **90.7a–c** (path d), furnishing the desired product.



Scheme 90 Visible-light mediated oxyphosphorylation of α-diazo esters.

In one instance, the addition of the carbene onto a nitrosoarene led to the synthesis of α-ketoesters *via* initial addition onto the N atom of the NO group.[308]

6.5. C–S bond formation

Similar to C–O bond formation, the formation of a C–S bond occurred *via* a S–H insertion or a reaction deriving from a sulfur ylide obtained by carbene addition onto a sulfur atom. The S–H bond insertion reaction of photogenerated carbenes was exploited in the α-functionalization of esters by aromatic and

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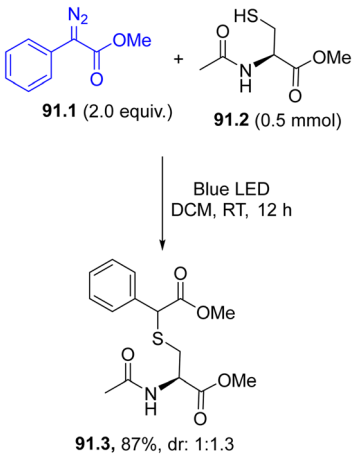


Scheme 91 Visible-light construction of a C–S bond *via* a carbene S–H insertion.

aliphatic thiols,[309] including substituted cysteines[310] (**91.2**, an example in Scheme 91).

By adopting an approach analogous to those described in Section 6.4, *S*-alkyl phosphorothioates (**92.2a–c**, Scheme 92a) were obtained *via* a three-component coupling of α-diazoesters **92.1a–c**, elemental sulfur and H-phosphonates in the presence of DBU as the additive.[311] Similarly, a multicomponent reaction involving aryldiazoesters **92.3a–c**, carbon disulfide and secondary amines was exploited for the preparation of alkyl dithiocarbamates **92.4a–c** (Scheme 92b).[312]

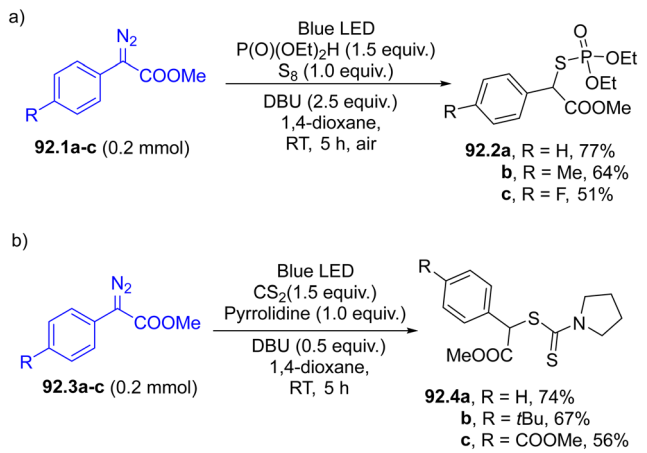
A C–S bond may result from an initial addition of the carbene on the sulfur atom in sulfides, yielding an *S*-ylide, which in turn may react with a reaction partner or undergo rearrangement. An exemplary case belonging to the first class was the synthesis of a set of chiral indolines bearing C2-quaternary stereocenters with good enantio- and diastereoselectivity. These compounds were formed *via* copper-catalyzed asymmetric [4+1] cycloadditions of ethynylbenzoxazinones with sulfur ylides; the sulfur ylides, in turn, were obtained *via* coupling between a photogenerated carbene and a sulfide.[303]

However, the rearrangement of the ylide is the most common case. As an example, upon irradiation of diazoesters **93.1a–c** with visible-light and subsequent generation of singlet carbenes **93.3a–c** (Scheme 93, path a) in the presence of allylsulfide **93.2**, the formation of 3,3-difluoroallylated sulfonium ylides **93.4a–c** (path b) was observed. The latter ylides then underwent a [2,3] sigmatropic shift (a Doyle-Kirmse reaction), forming *gem*-difluoroallyl esters **93.5a–c** (path c).[313] The same approach was recently applied for the synthesis of 4-allyl-4-(arylthio)-1,4-dihydroisoquinolin-3-ones.[314] Notably, when **93.2** was replaced with propargylic sulfides, functionalized allenes were formed.[315] In the case of *N*-sulfenyl phthalimide as the sulfonylated partner, a [1,2] sigmatropic rearrangement took place instead, simultaneously formimg a C–N and a C–S bond.[316]

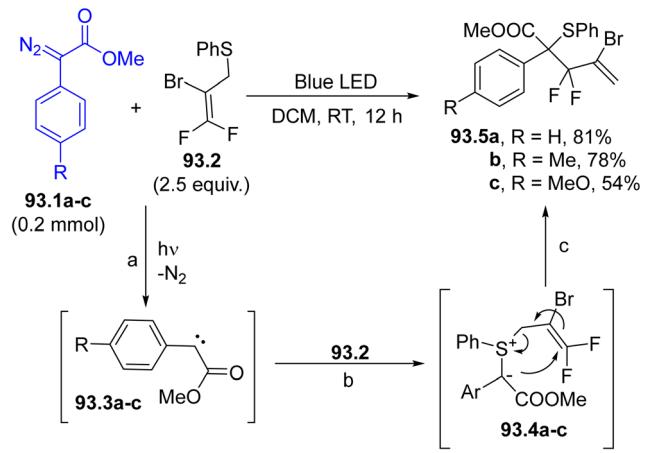
Photogenerated carbenes are also reactive towards C=S bonds. In fact, upon irradiation of an α-diazo 1,3-diketone (**94.1**, Scheme 94) with visible-light in the presence of β-ketothioamides **94.2a–c** yielded thiazoline derivatives **94.3a–c** *via* the intermediacy of the *N*,*S*-acetals **94.4a–c**. The protocol was also performed on a gram scale.[317]

The visible-light-driven [1+5] annulation of phosphoryl diazomethylarenes (**95.1a–d**, Scheme 95) and pyridinium 1,4-thiolate **95.2** has been employed for the preparation, in good yields and excellent diasteroselectivity, of a wide range of trifunctionalized dialkyl 1-phosphoryl-1,9*a*-dihydropyrido[2,1-*c*][1,4]thiazine-3,4-dicarboxylates **95.3a–d**.[318] The heterocyclic product was obtained through the addition of the carbene onto the thiolate anion, resulting in zwitterions **95.4a–d** where the pyridinium nucleus underwent nucleophilic attack on the C=N bond.

A particular case is the efficient visible-light mediated approach for the trifluoromethylsulfonylation of diazo compounds (**96.1a–e**, Scheme 96). Here the photogenerated carbene reacted with an intermediate formed between $Mn(acac)_3$ (herein employed as the catalyst) and the rather unstable



Scheme 92 Synthesis of (a) *S*-alkyl phosphorothioates and (b) alkyl dithiocarbamates.



Scheme 93 *gem*-Difluoroallyl esters from a photoinduced Doyle–Kirmse reaction.

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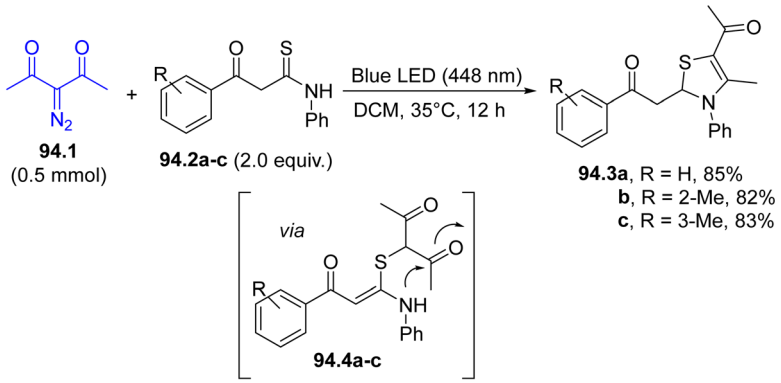


Scheme 94 Visible-light promoted preparation of thiazolines.

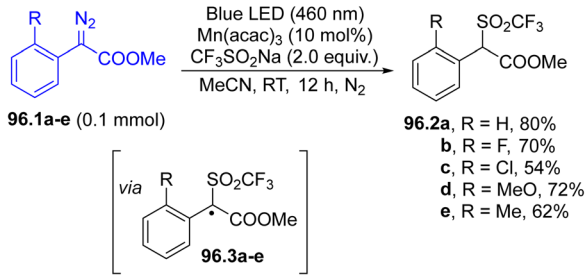
trifluoromethylsulfonyl radical formed through the Mn catalyzed oxidation of CF_3SO_2Na to yield **96.3a–e**. Reduction to an anion followed by protonation enabled the attainment of the desired sulfonated products **96.2a–e,** even on a gram scale.[319]

6.6. Other C–X bond formation

In rare instances, the carbene formed from the photolysis of a coloured compound led to the formation of other C–X bonds. Very few examples described the trapping of a carbene intermediate by a boron containing derivative. Singlet siloxycarbenes arising from the irradiation of acylsilanes afforded α-alkoxyorganoboronate esters *via* insertion reactions within the B–H bond in HBpin derivatives.[232] A B–H insertion took place likewise in the synthesis of **97.3**, starting from aryldiazoacetate **97.1**, and NHC-borane **97.2** (Scheme 97). However, when using N-heterocyclic carbene (NHC)-borane complexes, a site-selective cyclopropanation of the double bond of the heterocyclic ring occurred.[320]

A rare case of the formation of a C–Si bond was observed through the insertion of carbenes into Si–H bonds in trialkylsilanes, resulting in the preparation of α-trialkylsilyl esters **98.2a–c** (Scheme 98).[321]

More recently, acylsilanes (*e.g.*, **99.1**, Scheme 99) were employed in the preparation of α-hydroxyphosphorus oxides

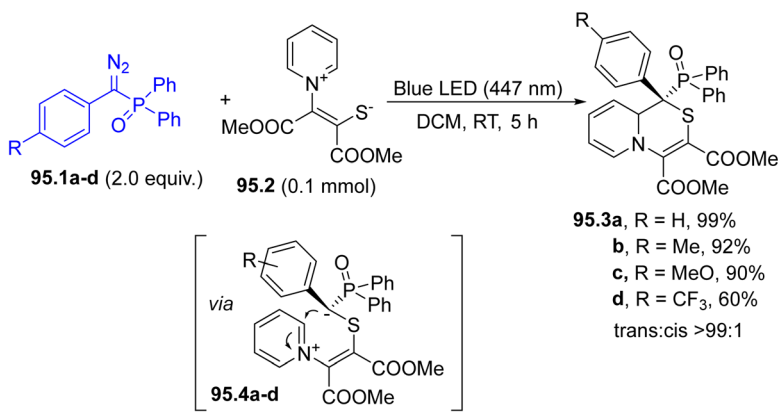


Scheme 96 Visible-light mediated trifluoromethylsulfonylation of diazo compounds.

99.3a–c in satisfactory yields by using H-phosphorus oxides **99.2a–c** as the coupling partner. The suggested mechanism again highlighted the role of a photogenerated siloxycarbene **99.4** as the key intermediate.[322]

6.7. *Via* ketenes

When coloured α-diazo ketones are used in place of the corresponding esters, a new chemistry appears due to the conversion of the photogenerated α-ketocarbenes (upon nitrogen loss) into electrophilic ketenes *via* Wolff rearrangement.[323] One of the possible pathways for the ketenes (*e.g.*, **100.3**) is the



Scheme 95 Dihydropyrido[2,1-*c*][1,4]thiazine derivatives *via* photogenerated carbenes.

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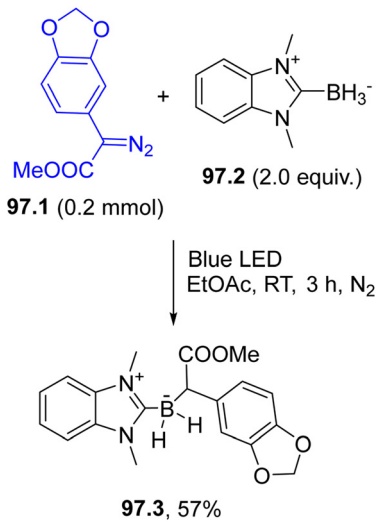
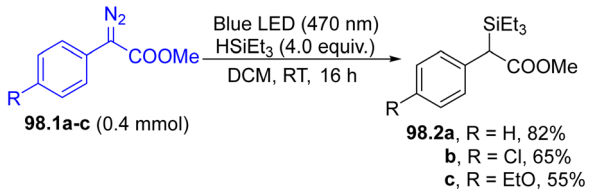
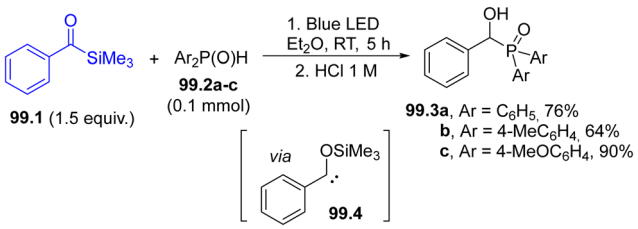


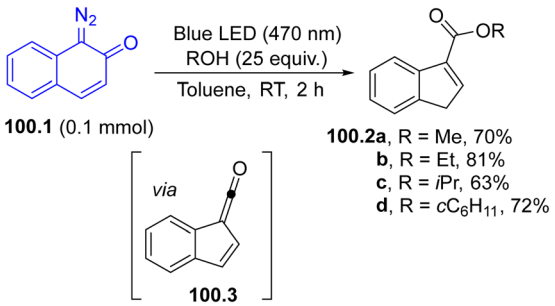
Scheme 97 B–H Insertion in NHC-boranes.



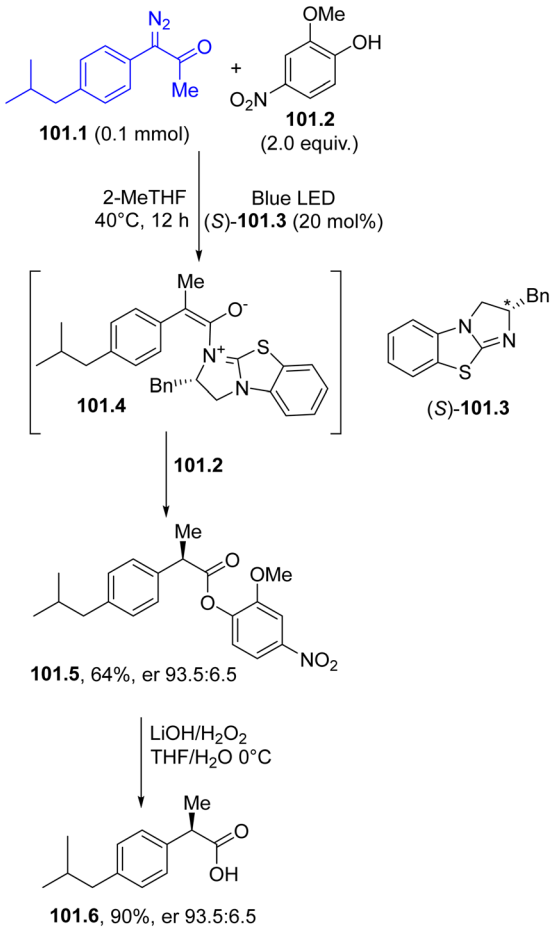
Scheme 98 Visible-light mediated synthesis of α-trialkylsilyl esters.



Scheme 99 C–P bond formation in the synthesis of α-hydroxy-phosphorus oxides.



Scheme 100 Alcohols as nucleophiles in the synthesis of 1*H*-indene-3-carboxylates.



Scheme 101 Photochemical synthesis of (*R*)-ibuprofen.

nucleophile addition, as exemplified in Scheme 100. Thus, differently substituted 1*H*-indene-3-carboxylates (**100.2a–d**) were produced in discrete to good yields *via* visible-light mediated Wolff rearrangement of 1-diazonaphthalen-2(1*H*)-one **100.1** in the presence of different alcohols as nucleophilic additives.[324]

Apart from alcohols, even phenols (*e.g.*, **101.2**) may be used to obtain esters with the help of a benzotetramisole-type chiral catalyst such as (*S*)-**101.3**, acting as the nucleophilic catalyst (Scheme 101). Thus, the ketene formed through the visible-light irradiation of α-diazoketone **101.1** was trapped by (*S*)-**101.3**, forming ammonium enolate **101.4**, which upon protonation and nucleophilic attack of the resulting phenate yielded α,α-disubstituted carboxylic ester **101.5** with a good enantiomeric ratio, which on subsequent hydrolysis yielded (*R*)-ibuprofen **101.6** in 90% yield.[325]

A similar approach was exploited in the enantioselective preparation of α-chlorinated carboxylic acid esters from α-diazoketones by reaction with *N*-chloro succinimide (NCS) as the electrophilic chlorine source mediated by an isothiourea-based chiral catalyst.[326] The nucleophile can be a primary amine and the presence of a chiral phosphoric acid in the double role of accelerating the ketene capture by amines and

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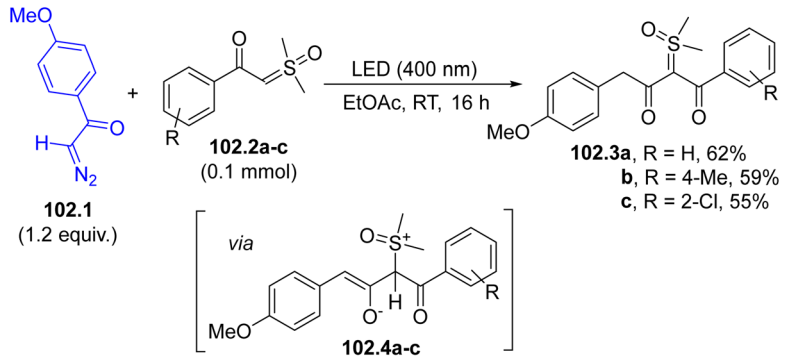


Scheme 102 Synthesis of 1,3-dicarbonyl sulfoxonium ylides *via* photogenerated ketenes.

promoting an enantioselective proton-transfer led to the formation of an enantioenriched chiral amide.[327]

1,3-Dicarbonyl sulfoxonium ylides **102.3a–c** were prepared *via* purple light irradiation of azoketone **102.1** in the presence of sulfoxonium ylides **102.2a–c** as the nucleophiles (Scheme 102).[328,329] The process relied on the nucleophilic addition of the ylide onto the photogenerated ketene to give intermediates **102.4a–c** that ultimately led to the formation of compounds **102.3a–c** upon proton transfer. Notably, the process has been also optimized under continuous flow conditions, allowing for a decrease in the reaction time (t_r = 28 min) and an improvement of the overall yields.[328]

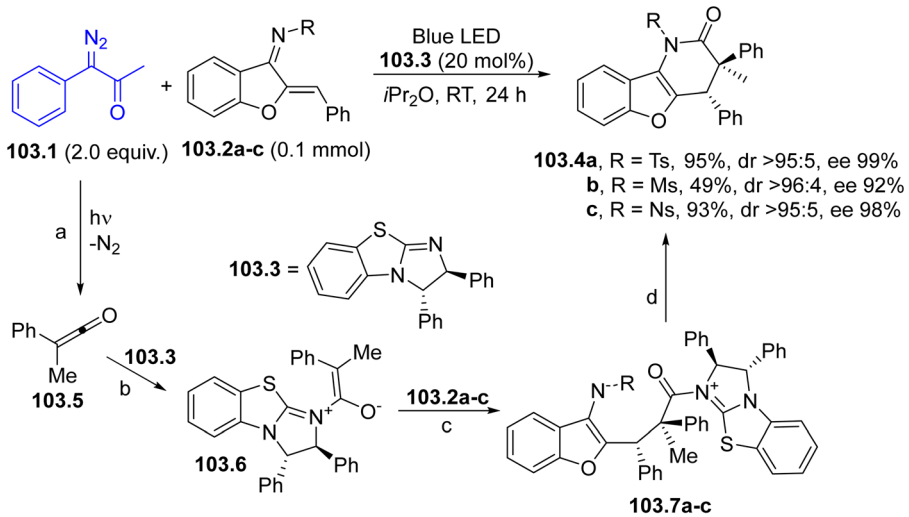
Again, an ammonium enolate intermediate was the key compound for the synthesis of 3,4-dihydrobenzofuro[3,2-*b*]pyridin-2(1*H*)-ones **103.4a–c** (Scheme 103).[330] These heterocycles were obtained *via* [4+2] annulation of a photogenerated ketene **103.5** with the aurone derived α,β-unsaturated imines **103.2a–c** in the presence of a chiral isothiourea **103.3** as the catalyst.[330] In detail, ketene **103.5** (from path a) coupled with the chiral catalyst **103.3** to form ammonium enolate **103.6** (path b), which in turn acted as a nucleophile towards the Michael acceptors **103.2a–c** (path c). The resulting intermediates **103.7a–c** then underwent intramolecular amidation, yielding the desired products **103.4a–c**. An analogous [4+2] cyclization was employed in the preparation of substituted benzothiazolopyrimidines from 2-benzothiazolimines and α-diazo ketones.[331]

Moreover, a chiral NHC may function as an organocatalyst for the stereoselective construction of a six-membered ring between 3-alkylenyloxindole **104.2** and α-diazoketone **104.1** under visible-light irradiation (Scheme 104). Thus, triazolium salt **104.3** may release the corresponding NHC under basic conditions and the consecutive addition of the ketene and **104.2** enabled the *enantio* and stereoselective preparation of tetrahydropyrano[2,3-*b*]indoles (*e.g.*, **104.4**) bearing an all-carbon quaternary stereocenter.[332]

In a similar fashion, the reaction of ketene with sultam-fused dihydropyridinones has been performed *via* dual light driven/NHC catalyzed asymmetric [4+2] annulation of saccharine-derived azadienes and α-diazoketones.[333]

Photogenerated ketenes have also been efficiently employed as a partner in cycloaddition reactions.

Scheme 105 illustrates an example where this approach was included in a multicomponent process. Thus, the ketene 3-component Staudinger reaction (K-3CSR) for the synthesis of



Scheme 103 Enantioselective preparation of 4-dihydrobenzofuro[3,2-*b*]pyridin-2(1*H*)-ones.

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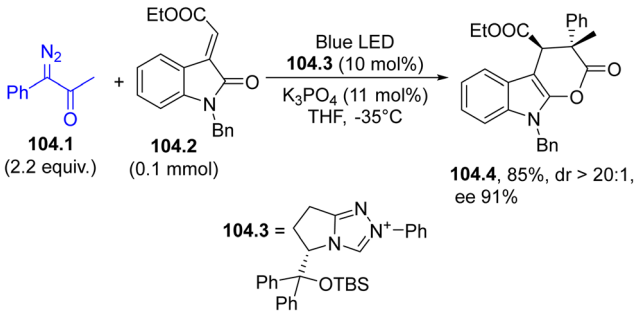
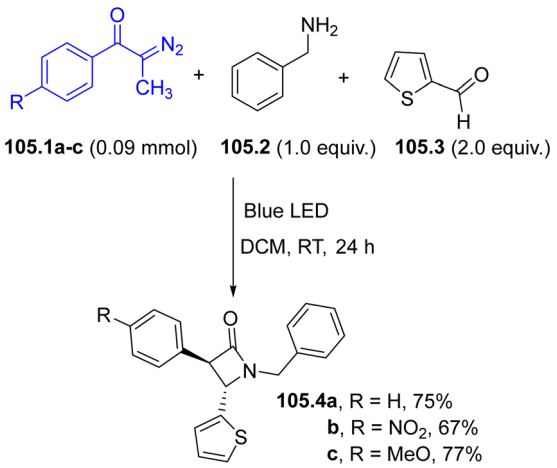


Scheme 104 NHC catalyzed preparation of tetrahydropyrano[2,3-*b*]indoles.

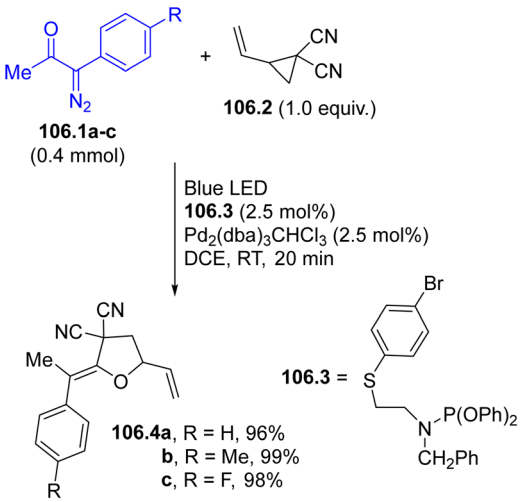


Scheme 105 Visible-light promoted ketene 3-component Staudinger reaction.

β-lactams **105.4a–c** was devised starting from α-diazoketones **105.1a–c**, a primary amine **105.2** and an aldehyde **105.3**. The first step of the reaction (the *in situ* formation of the imine intermediate) proceeded in dark, whereas the generation of the ketene (*via* Wolff rearrangement of **105.1a–c**) occurred under visible-light irradiation.[334] Analogously, a sequential Wolff rearrangement of diazoketones and Staudinger cycloaddition of the photogenerated ketenes onto pyrazolone ketimines led to the formation of spiro-pyrazolone-β-lactams in more than 90% yield in several cases.[335]

A powerful [4+2] annulation strategy was adopted for the construction of dihydroquinolinone derivatives. The reaction took place through visible-light irradiation of a mixture of an α-diazoketone and *ortho*-amino Morita–Baylis–Hillman (MBH) carbonate in the presence of DMAP as the Lewis base catalyst. An initial S_N2' reaction promoted by the addition of the base onto the unsaturated system of the MHB-carbonate was followed by ketene addition and an intramolecular ring-closure.[336]

Alternative kinds of cycloaddition reactions may be promoted by Pd catalysis. The Pd-catalyzed [3+2] cycloaddition of ketenes with vinyl cyclopropanes **106.2** in the presence of a hybrid P,S-ligand **106.3** was found to yield a wide range of



Scheme 106 Visible-light mediated, Pd-catalyzed preparation of tetrahydrofurans.

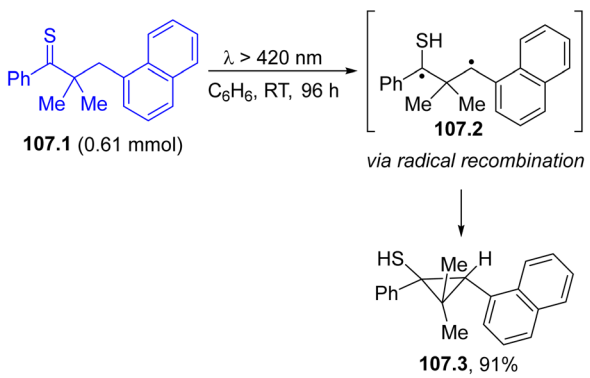
substituted tetrahydrofurans **106.4a–c** *via* a tandem C–C/C–O bond formation (Scheme 106). The role of Pd(0) here was to convert the vinyl cyclopropane into a reactive ring opened Pd-containing 1,3-dipolar intermediate.[337] Similarly an enantioselective [8+2] cycloaddition was carried out between a ketene and a Pd-containing 1,8-dipole (in turn generated from a vinyl carbamate derivative) to afford a 10-membered nitrogen-based heterocycle.[338]

7. Reactions *via* other intermediates

7.1. Biradicals

Typical reactions belonging to this class are Norrish-type I or II reactions. Thiones underwent an intramolecular hydrogen atom transfer reaction when excited with visible-light.[52] As shown in Scheme 107, irradiation of β-substituted arylalkyl thione **107.1** in benzene triggered a Norrish-type II reaction forming the 1,3-biradical **107.2,** which upon radical recombination afforded the cyclopropyl thiol **107.3** in a good yield.[339,340]

α-Diketones are well-known substrates for visible-light-induced photochemical reactions. As an example, the irradiation



Scheme 107 Intramolecular hydrogen transfer in thioketones.

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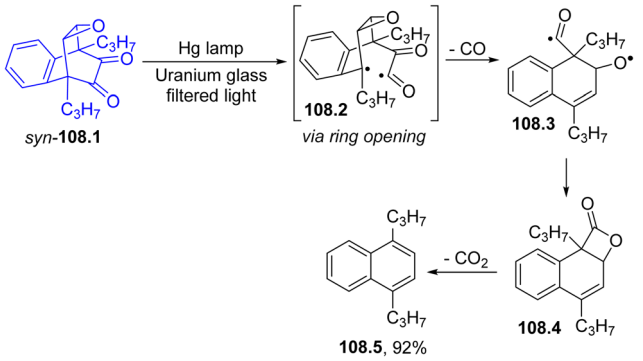
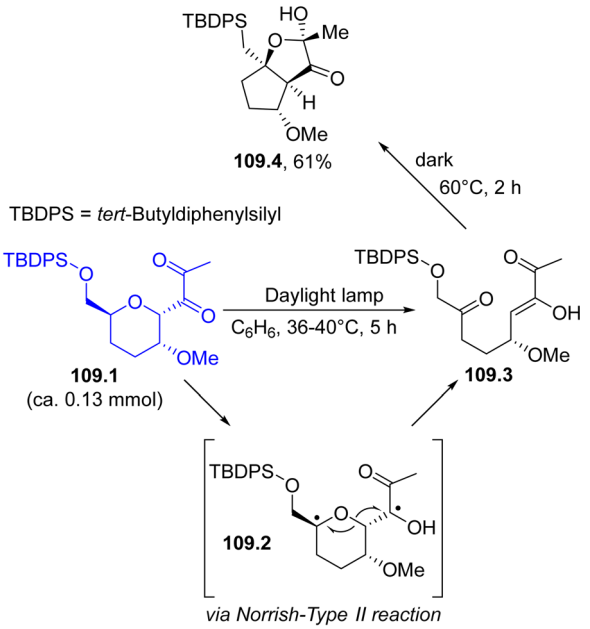


Scheme 108 Norrish-type I cleavage in α-diketones.

of *syn*-9,10-epoxy-1,4-dihydro-1,4-dipropyl-1,4-ethanonaphthalene-2,3-dione (*syn*-**108.1**) resulted in the efficient formation of 1,4-di-*n*-propylnaphthalene (**108.5**, Scheme 108). In the suggested mechanism, a Norrish-type I homolytic cleavage led to the formation of biradical **108.2**. This biradical, in turn, upon losing carbon monoxide, led to the formation of intermediate **108.3**, which upon radical recombination and fast carbon dioxide loss from lactone **108.4**, produced naphthalene **108.5** in more than 90% yield.[341]

A visible-light triggered Norrish-type II intramolecular hydrogen abstraction reaction on 1,2-diketones has also been reported. As a matter of fact, the exposure of compound **109.1** to a daylight lamp prompted the hydrogen abstraction from one of the two carbonyls groups, targeting the hydrogen located adjacent to the oxygen atom of the ring (Scheme 109). The so obtained biradical **109.2** fragmentated, releasing *Z* photoenol **109.3** which upon heating underwent an intramolecular aldol reaction affording the final product **109.4**.[342,343] This approach



Scheme 109 Synthesis of functionalized cyclopentitols.

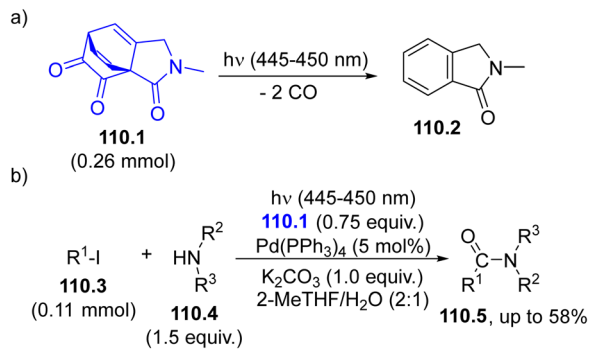
was a simple route to achieve the synthesis of densely functionalized cyclopentitols starting from pyranoses exhibiting a surprisingly diastereoselectivity.

When the structure of the starting carbohydrate containing a 1,2-diketone moiety was converted to 1-glycosyl-2,3-butanodiones, the occurrence of the Norrish-type II reaction led to a biradical that cyclized, accessing chiral 1-hydroxy-1-methyl-5-oxaspiro[3.5]nonan-2-ones (bearing the 1-hydroxy-1-methyl-2-cyclobutanone moiety).[344] A Norrish–Yang cyclization reaction was instead proposed as the strategy to prepare a potent inhibitor of the 20S proteasome, (+)-lactacystin, starting from a tetrahydro-3*H*,5*H*-pyrrolo[1,2-*c*]oxazol-5-one.[345] The photochemically induced cyclization of 1,2-ketones for the preparation of functionalized 2-hydroxycyclobutanones was likewise performed with blue LED radiation under flow conditions.[346]

The photoreactivity of 1,2-diketones has also been exploited for the release of smaller chemical entities, which can be used *in situ* for other chemical transformations. For instance, the visible-light exposure of 2-methyl-1,6-dihydro-3a,6-ethanoisoindole-3,8,9(2*H*)-trione **110.1** resulted in the liberation of two equivalents of carbon monoxide along with the formation of lactam **110.2** (Scheme 110a). Thus, the CO liberated in the process was successfully combined with palladium catalysis for the coupling of non-activated alkyl iodides **110.3** with amines **110.4**, yielding amides **110.5** (Scheme 110b).[347]

α-Ketoamides (see, for instance, 1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione **111.1** in Scheme 111) upon photolysis with blue light underwent a Norrish–Yang type II reaction, giving access to α-hydroxy-β-lactam **111.3** *via* biradical **111.2**.[348] The reaction was performed on a film of the starting compound **111.1** applied to the glass surface of a 20 mL vial, under solvent-free conditions.

Recently, a peculiar aspect of the pyrazolo[1,2-*a*]pyrazolones **112.1** photoreactivity has been highlighted (Scheme 112a). Under exposure to visible-light in neat DCM, these compounds experience the homolytic cleavage of the C_5–N_4 and/or C_1–N_8 bonds, furnishing substituted pirazoles **112.2** or diazepines **112.3**, respectively. Remarkably, a selective photochemical ring-opening process could be achieved using different additives. For instance, when pyrazolo[1,2-*a*]pyrazoles were



Scheme 110 Visible-light fragmentation of diketone **110.1** for (a) the carbon monoxide release to be used in (b) the synthesis of amides.

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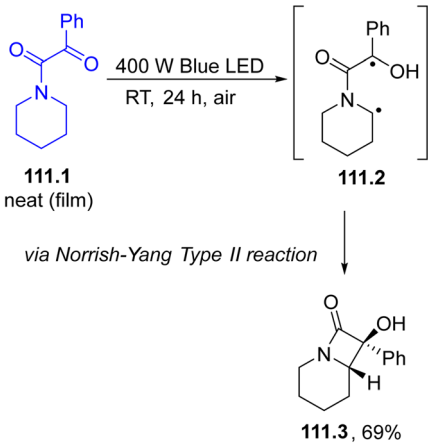
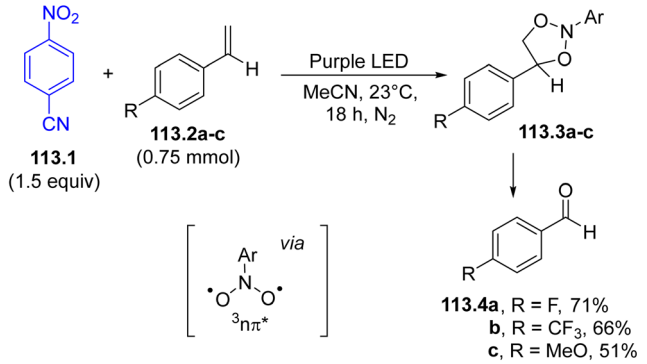


Scheme 111 Norrish–Yang type II reaction of α-ketoamides.



Scheme 113 Oxidative cleavage of alkenes promoted by excited nitroarenes.

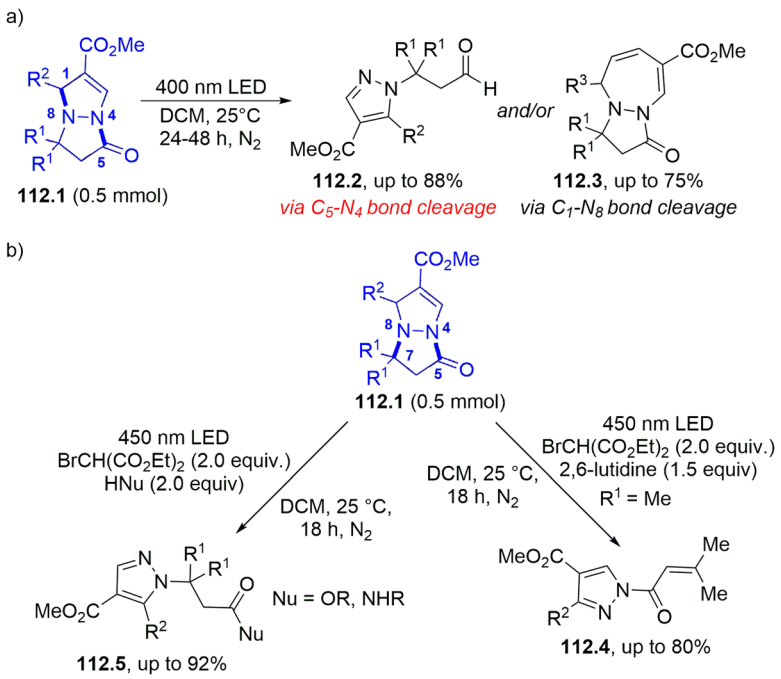
irradiated in the presence of diethyl bromomalonate and 2,6-lutidine yielded after C_7–N_8 cleavage *N*-acryloyl-substituted pyrazoles **112.4** (Scheme 112b). On the other hand, shifting to other nucleophilic species (*e.g.*, alcohols and amines), induced the photochemical C_5–N_4 photocleavage, resulting in the formation of functionalized pyrazoles **112.5** (Scheme 112b).[349]

The latter example deals with the use of a nitroarene as oxygen transfer. Excitation of **113.1** populates the triplet nπ* state, allowing it to readily add to an electron-rich C=C bond in styrenes **113.2a–c**, yielding a biradical intermediate that smoothly cyclized to the short-lived 1,3,2-dioxazolidine intermediates **113.3a–c** that underwent fragmentation to the corresponding carbonyl products **113.4a–c** (Scheme 113). This nonstereospecific radical cycloaddition of nitroarenes onto an alkene was the key for a mild alternative oxidative cleavage protocol, such as ozonolysis.[350] A related oxidative cleavage made use of 3,5-dinitrobenzotrifluoride as the oxidant.[351]

7.2. Radical ions and ions

Cyanoarenes were known for having a good reactivity towards electron donors[352] under visible-light irradiation promoting a photoaddition/photosubstitution on the aromatic ring.[353] For example, the reaction between **114.1** and the α-silyl amine **114.2** was fueled by an initial electron transfer; the subsequent loss of the trimethylsilyl cation from the radical cation **114.2**$^{\bullet+}$ followed by radical–radical anion recombination yielded dinitrile **114.3** (Scheme 114). In some cases, the substitution occurred on the *ipso* position upon cyanide anion loss.[354]

Visible-light was successfully applied in the arylation of substituted arenaz-2-(2-nitro)-propanes **115.1**. These compounds in aqueous HCl are able to absorb purple light,



Scheme 112 Photochemical reaction of pyrazolo[1,2-*a*]pyrazolones.

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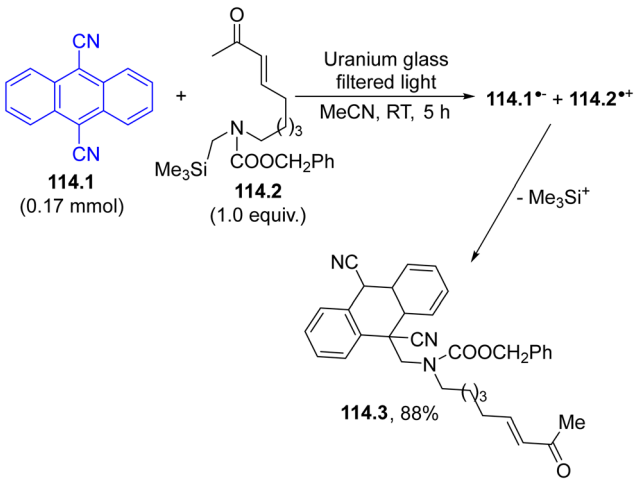
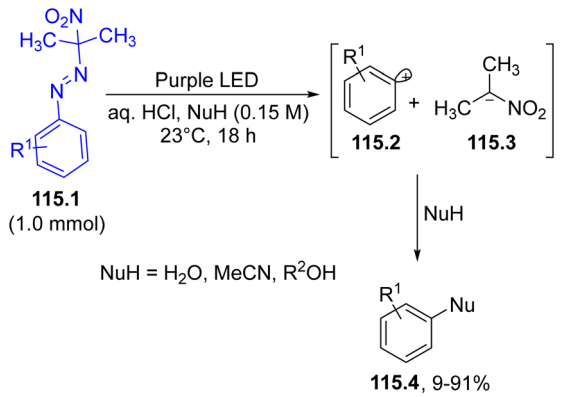


Scheme 114 Visible-light functionalization of cyanoarenes.



Scheme 115 Photochemically induced synthesis of $C(sp^2)$–X bonds.

promoting the nitrogen loss and releasing a singlet aryl cation **115.2** which was immediately trapped by a variety of nucleophiles NuH (Scheme 115). The cation **115.2** was stabilized by the *in situ* photochemically generated counter ion **115.3**, avoiding any intersystem crossing or single electron transfer processes. This approach was a good strategy for the formation of $C(sp^2)$–X bonds, allowing for the synthesis of compounds **115.4**.[355]

8. Conclusions and outlook

Although most organic compounds are not able to absorb in the visible-light region, the use of an expensive high-energy UV-photons source,[13] has been mainly avoided by utilizing photocatalytic strategies that employ low-energy demanding LED lamps covering the entire visible-light region (Scheme 1a). Despite its fast development, this strategy (still the main used) is often hindered by the cost of the (metal-based) photocatalyst used, and a rather limited number of approaches for the activation of the starting substrates.

In this context, the conversion of a photoreactive coloured compound into the desired product is the preferred option for exploiting visible photons in synthesis, thus behaving as the ideal promoting reagents, and several classes of organic molecules can be photochemically activated by visible-light-photons without the need for promoters or catalysts. These compounds can absorb coloured radiation related to a specific transition ($\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ or $n \rightarrow \sigma^*$) due to a given chromophore (in 1,2-diketones, diazo compounds, dichalcogenides, *etc.*). However, the application of these compounds in synthetic strategies remains quite limited, and, apart from their use in carbene generation from diazo compounds,[37] there has been little advancement in the last 10–15 years. This demonstrated that there is still a hard work to do for the satisfying exploitation of the photoconversion of known classes or coloured organic compounds following the strategy depicted in Scheme 1g.

As an example, nitroaromatics (apart those having benzylic hydrogens in the *ortho* position) were always considered photochemically unreactive and unimportant in synthesis due to the short lifetime of their excited states.[356] However, these arenes are recently becoming interesting substrates for the photogeneration of nitrenes by tuning the right reaction conditions.[224,225] Moreover, due to the recent development of visible LEDs technology it is possible to carry out reactions on coloured compounds, previously promoted by multichromatic sources which mostly emit in the UV region. The easy accessibility to these sources allowed for the discovery of new processes on known chromophores.

Along with this traditional and re-discovered approach, alternative strategies may be adopted for the *in situ* formation of the coloured species or the installation of a new devised photoreactive chromophore by a functional group interconversion on colourless derivatives. The latter case belongs to the dyedauxiliary groups strategy[35] (Scheme 1f) as in the cases of arylazo sulfones, dihydropyridines and Barton esters. The use of such compounds in organic synthesis can take advantage of their visible-light photoactivity since they generate reactive intermediates without the need for harsh conditions (transition metal chemistry, high temperatures, strong bases, *etc.*). In doing so, these kinds of processes become appealing from the industrial point of view due to the low operational cost, leaving open the possibility of using known dyedauxiliary groups for the release of new intermediates (*e.g.*, carbon or heteroatom-based radicals). Alternatively, the development of of new dyedauxiliary groups may open up fascinating new routes for the photogeneration of reactive intermediates, although it would require a chemical step to install the photoreactive chromophore. However, this strategy, together with the largely unexplored *in situ* chromophore activation (Scheme 1b and c) or the nucleophilic activation (Scheme 1e) could represent a significant advancement in the near future, paving the way for a new era for visible photons based on a photocatalyst-free chemistry.

Conflicts of interest

There are no conflicts to declare.

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