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Light-Driven [2 + 2] Cycloaddition Strategies for the Synthesis of Cyclobuta[*b*]indoles and Their Derivatives

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ABSTRACT

The dearomatization of indoles is a powerful strategy for transforming simple substrates into architecturally complex molecular frameworks. This review provides a comprehensive overview of photoinduced methodologies developed for the construction of three-dimensional polycyclic systems bearing indolyl-cyclobutane motifs. We summarize classical ultraviolet(-driven [2 + 2] cycloaddition reactions alongside recent advances in photocatalysis, including sensitizer- or photocatalyst-mediated energy-transfer and single-electron transfer processes. Attention is also given to photoinduced hetero-[2 + 2] cycloadditions, specifically the Büchi and aza-Büchi reactions, as well as photodimerization pathways of indole derivatives. Together, these approaches provide valuable and versatile tools for the rapid assembly of complex molecular architectures and drug-like scaffolds.

1 | Introduction

The indole ring stands out as one of the most important compounds in medicinal chemistry, serving as a versatile molecular scaffold for the synthesis of a plethora of biologically active molecules [1–3]. Nevertheless, a huge number of complex indole-containing therapeutic agents have been identified in plants, animals, and marine organisms [4]. The indole ring is a privileged structural motif in drug discovery, featured in numerous compounds exhibiting anticancer [5], antioxidant [6], antiviral [7, 8], anticonvulsant, antidepressant, antimicrobial [9], and antidiabetic activities [10]. Just to mention some examples (Figure 1), tryptophan is a vital amino acid closely involved in several biological processes [4, 11], the hormone melatonin regulates sleep–wake cycles [12], serotonin, a central neurotransmitter, is involved in the regulation of a wide range of neuropsychological processes and used as a target for the treatment of many psychiatric and neurological disorders [13]. Fused indoles have also been identified in several alkaloids endowed with specific biological activities, such as reserpine [14], isolated from *Rauwolfia Serpentine*, vincristine and vinblastine, obtained from *Catharanthus roseus* [15], and strychnine, extracted from *Strychnos nux-vomica* [16]. Over the past decades, significant effort has been devoted to the synthesis of indole-based compounds [17]. Within this field, the construction of polycyclic derivatives incorporating strained carbocyclic units and in particular cyclobutane moieties is well documented, yet their efficient synthesis remains a significant challenge [18–20]. This difficulty arises from the unique structural and reactive properties imparted by four-membered rings, whose inherent strain and conformational rigidity strongly influence molecular behavior [21–23]. Moreover, several naturally occurring cyclobuta[*b*]indoles have been isolated from diverse biological sources [24, 25].

Over the years, a variety of efficient synthetic strategies have been developed to access cyclopentane- and cyclohexane-fused indoline derivatives [19, 20]. In contrast, methodologies specifically tailored for the preparation of cyclobutane-fused indolines are far less explored and continue to attract considerable interest from synthetic organic chemists [26–31]. Indeed, although numerous effective thermal approaches to these derivatives have been reported [32–38], photoinduced [2 + 2] cycloadditions offer a particularly efficient and environmentally friendly strategy for accessing fused polycyclic frameworks. These photochemical methods enable the construction of complex molecular

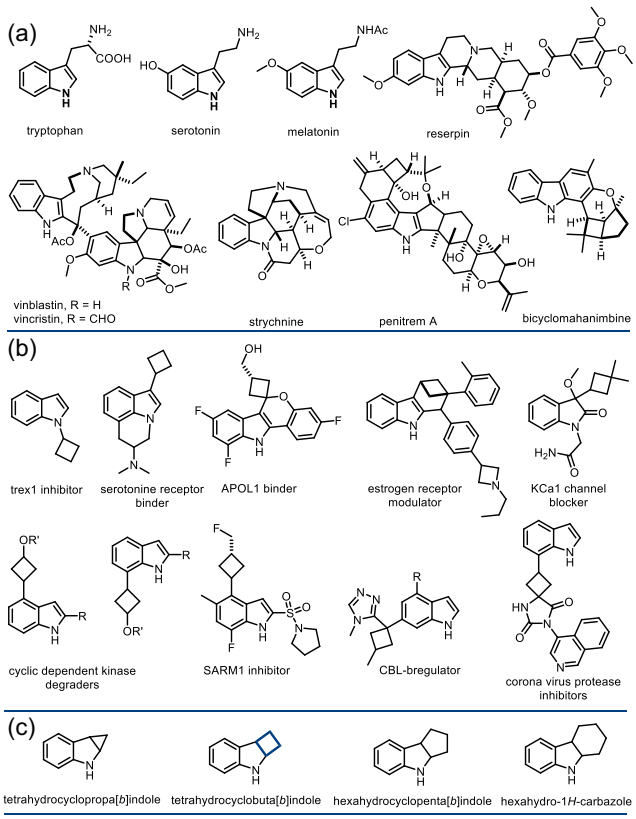


FIGURE 1 | Natural and synthetic bioactive indoles. (a) Natural indole compounds with documented pharmacological activity, (b) cyclobutane-indoles explored as potential lead structures in the development of new therapeutics for human diseases, and (c) nomenclature of cycloalkylindoles used in this review.

architectures that are often difficult to obtain using conventional synthetic routes.

Taken together, these considerations motivate the present review, in which we summarize the most relevant synthetic strategies for the preparation of fused cyclobut[*b*]indoles, with particular emphasis on photoinduced methodologies. Specifically, we focus on:

1. Intermolecular dearomative [2 + 2] cycloaddition of indoles with olefins to afford tricyclic cyclobutane[*b*]indolines;
2. Intramolecular dearomative [2 + 2] photocyclizations leading to polycyclic systems featuring a cyclobutane[*b*]indoline core;
3. [2 + 2] Heterocycloadditions of indoles, including the Paternò–Büchi reaction, and the aza-Paternò–Büchi reaction;
4. [2 + 2] Photodimerization reactions of indole derivatives.

2 | Photochemistry of Indoles

Indoles have been extensively investigated from a photophysical perspective [39], and their properties are now well understood, thanks to comprehensive experimental studies supported by detailed theoretical analyses [40–42]. The absorption and emission spectra of numerous indole derivatives, as well as their corresponding electronic transitions, have been thoroughly characterized [43–47]. Given the ubiquity and importance of the indole scaffold, a wide range of substituted indoles has been examined to elucidate how different functional groups influence their excited-state energies and photophysical behavior. Considerable effort has also been devoted to understanding the effects of solvent interactions [48–50], solid-state environments [51, 52], and incorporation into polymeric matrices [53, 54]. Collectively, these studies have provided a solid foundation for the development of diverse photochemical transformations involving the indole core, including intra- and intermolecular [2 + 2] cycloadditions [55], photodimerization [56], Paternò–Büchi reactions, and other photoinduced functionalization strategies [57].

When an indole derivative in its ground state (S_0) is irradiated in the 240–290 nm range (depending on the solvent), it undergoes excitation to its first singlet excited state (S_1). This absorption band primarily originates from two overlapping $\pi \rightarrow \pi^*$ electronic transitions, conventionally assigned to the ^1L_a and ^1L_b states [39]. Following excitation, indoles may return to the ground state via several pathways. Radiative decay from S_1 produces fluorescence in the 320–340 nm region, whereas nonradiative intersystem crossing (ISC) can populate the triplet excited state (T_1). Subsequent relaxation from T_1 to S_0 results in phosphorescence, typically observed around 400–410 nm (Figure 2). Since its discovery, this behavior has been exploited extensively to investigate protein denaturation, substrate–protein interactions, fluorescence quenching, charge-transfer processes via exciplex formation, as well as energy- and 1,5-hydrogen atom transfer (HAT) mechanisms.

The triplet states of indole are frequently invoked in reaction mechanisms involving olefins and other suitably substituted unsaturated partners, enabling the formation of cycloadducts, most notably in dearomative [2 + 2] cycloadditions. The generation of open-shell diradical intermediates via energy transfer (EnT) has been widely exploited to access complex molecular architectures that are difficult to obtain under thermal conditions or through direct ultraviolet (UV) photoexcitation. However, direct excitation typically requires high-energy UV light, which

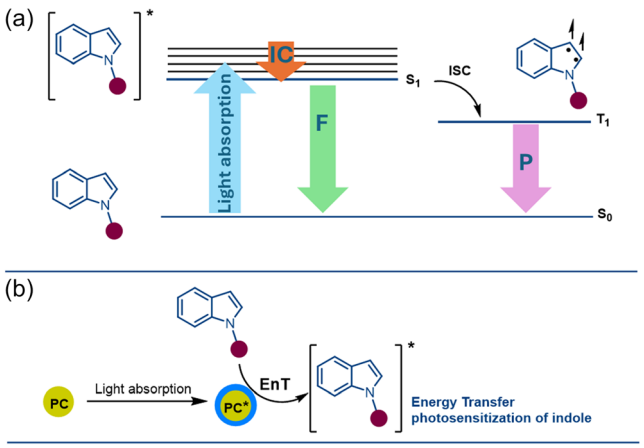


FIGURE 2 | (a) Schematic representation of indole UV excitation to T_1. (b) Schematic representation of indole excitation to T_1 via photocatalytic energy transfer used in this review.

often limits functional-group compatibility. To overcome these constraints, the use of organic and organometallic photosensitizers (PSs) and/or photocatalysts (PCs) capable of absorbing visible light has emerged as a powerful strategy. Upon excitation (PC*), these species can transfer their excited-state energy to the indole substrate, thereby promoting a "sensitized" excitation under significantly milder and more chemoselective conditions. This approach has enabled the development of new synthetic methodologies and photocatalytic processes for assembling complex fused polycyclic structures. In Figure 3, we summarize the PCs employed in the synthesis of cyclobuta[*b*]indole derivatives reported in this review.

Along the years, different luminophores have been investigated as potential candidates for photocatalytic and sensitization applications including both purely organic compounds and organometallic complexes [58–60].

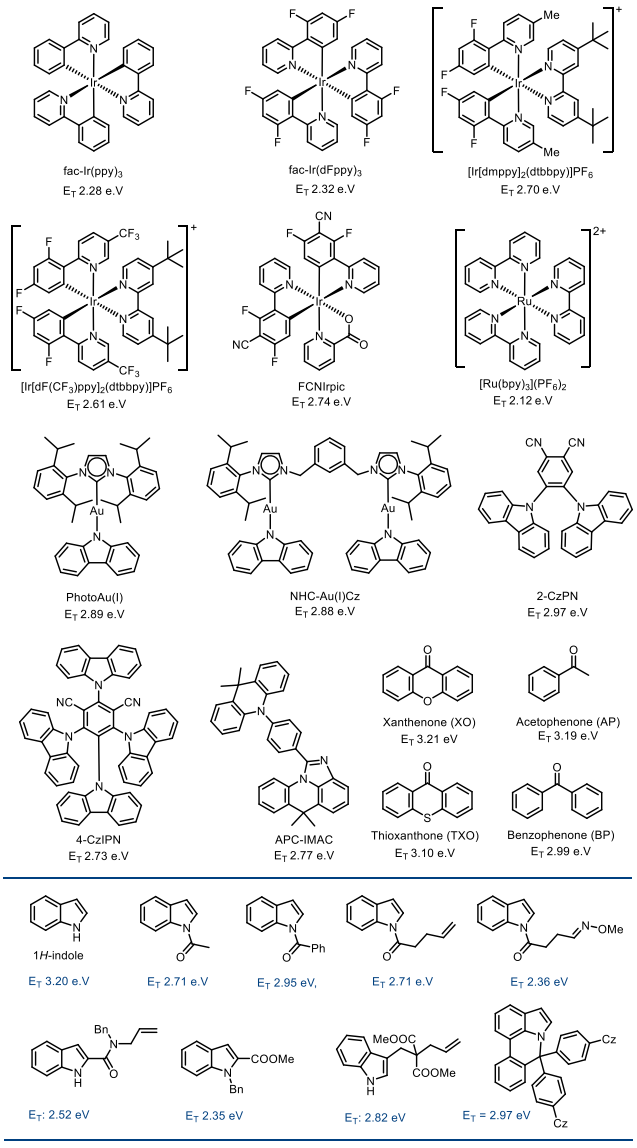


FIGURE 3 | Organometallic complexes and organic compounds used for the sensitization of indole derivatives. The corresponding E_T values are reported. For convenience, the E_T values (eV) of a selection of indoles are also included (in blue).

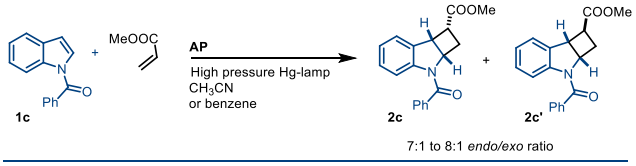
Some of these species are considered classical PSs in photoinduced reactions, including benzophenone, acetophenone (AP), and xanthones, while more recent examples encompass acridines and acridinium salts, carbazole derivatives (e.g., 4-Cz-IPN and 2-Cz-Pn), as well as transition-metal complexes of Ir, Ru, and Au. The selection of an appropriate catalyst in such transformations has been guided by extensive investigations of their photophysical properties (e.g., excited-state lifetimes, λ_{max}, excited-state energies, and chemical stability) and photoredox behavior [61, 62]. Importantly, upon light absorption, both organic and organometallic catalysts can participate in oxidative or reductive pathways, enabling single-electron transfer (SET) to a substrate or promoting EnT processes dictated by electronic reorganization in their excited state [63–65]. Comprehensive mechanistic studies are therefore essential to precisely delineate the role of each catalyst in a given photoinduced transformation.

3 | Photoinduced [2 + 2] Cycloaddition Strategies

Photochemistry is an essential strategy in organic synthesis for the development of unique and complex molecular scaffolds that are otherwise challenging to prepare. Although [2 + 2] intermolecular strategies represent a preferred method for the synthesis of such derivatives, it must be noted that, with respect to intramolecular strategies, they present certain issues such as the potential for homodimerization, generally lower regio- and chemoselectivity and higher competition between different pathways, as will be discussed below.

The [2 + 2] dearomative photocycloaddition of alkenes to indoles represents a fruitful strategy for the preparation of polycyclic architectural structures [66, 67], specifically for the synthesis of cyclobuta[*b*]indole. In 1973, Julian and Foster described the irradiation of *N*-benzoylindoles **1c** in the presence of substituted olefines using a medium-pressure mercury-vapor lamp, in acetonitrile as a solvent and in the presence of AP as a sensitizer (E_T 3.19 eV, 74 kcal/mol), accessing both the *exo*- and *endo*-adducts **2c** and **2c'** benzoyl-2,2a,3,7b-tetrahydro-*1H*-cyclobuta[*b*]indole-1-carboxylates [68] in a 8:1 ratio and generally good yields. Similar results were achieved (*exo/endo* 7:1) when the same reactions were carried out in benzene and without the use of AP as PS. On the other hand, unprotected indole **1a** and *N*-methyl indole **1b** were unreactive in these operational conditions. The authors reported in their work that reactions performed in the presence of electron-deficient olefins (acrylonitrile, methyl vinyl ketone, and acrylic esters) were more efficient to respect other alkenyl derivatives such as vinyl methyl ether, yielding the corresponding tricyclic adducts **2** in good yields. Similar results, carried out in the presence of naphthalene, did not allow the respective cycloaddition products to be obtained, suggesting that the triplet excitation state of benzoyl indole **1c** (E_T 2.95 eV, 68 kcal/mol) [69] was involved in this type of reaction (Scheme 1).

In-depth studies on the [2 + 2] dearomative photocycloaddition of various *N*-acyl indoles were carried out by Weedon and coworkers, revealing the significant influence of photo-Fries acyl-migration processes, which can compete with and parasitize the desired intermolecular [2 + 2] photocyclization with alkenes.

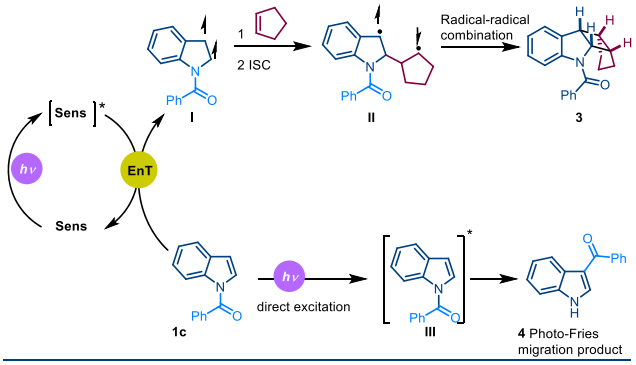


SCHEME 1 | Dearomative [2 + 2] cycloaddition of *N*-benzoyl indole with olefins mediated by acetophenone under UV irradiation.

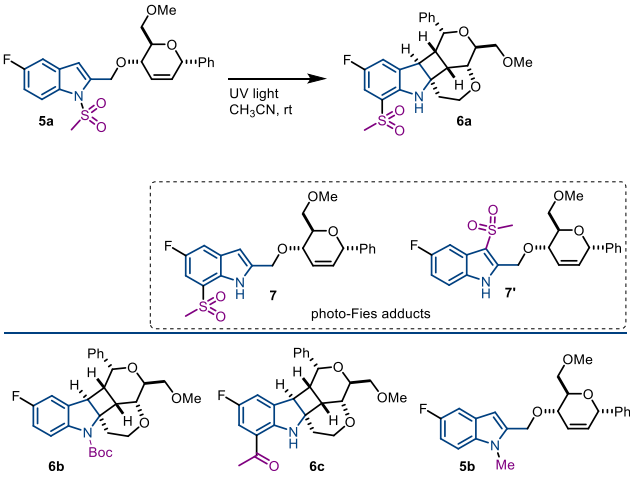
This side reaction becomes particularly evident under direct irradiation of acylindole solutions, where migration of the acyl protecting group to the C3 position of the indole is favored. However, the use of high concentrations of alkene suppresses the photo-Fries pathway in favor of the [2 + 2] photocycloaddition products **3** (Scheme 2). Attempts to reduce the aforementioned acyl migrations also demonstrated that the irradiation wavelength plays a crucial role: reactions performed at progressively longer wavelengths showed a corresponding decrease in the migration products **4** and an increase in the cycloaddition derivatives **3**. These observations suggested that the photo-Fries process could originate from a higher excited state or from a vibrationally hot lowest singlet or triplet state **III** [70]. However, the photo-Fries pathway is completely suppressed when a sensitizer is employed in the photochemical reaction [71].

The competition between the [2 + 2] cycloaddition and the photo-Fries rearrangement was further studied by Beeler and co-workers in 2014 using an automated photochemical microfluidics platform to control all the reaction parameters including irradiation wavelength, nature of the sensitizer, and the role of both temperature and solvent [72]. The intramolecular reaction was carried out using the glycal derived *N*-mesylated indole **5** in acetonitrile, obtaining both the photo-Fries migration products **7** and **7′** and the [2 + 2] cycloaddition compound **6** (Scheme 3).

The authors proved that using an UV filter with a window of 260–300 nm resulted in the exclusive formation of the corresponding photo-Fries products **7**, while irradiating the reaction solution at 290–340 nm favored the [2 + 2] cycloaddition and further photo-Fries migration to the position 7 of the indole scaffold, providing an efficient solution to the issue described in the aforementioned works. Moreover, treating *N*-Boc- and *N*-acetyl-protected indole



SCHEME 2 | Dearomative [2 + 2] cycloaddition of *N*-benzoyl indole with olefins mediated by acetophenone under UV irradiation. Effect of the solvent and irradiation wavelength on the suppression of acyl-group migration.

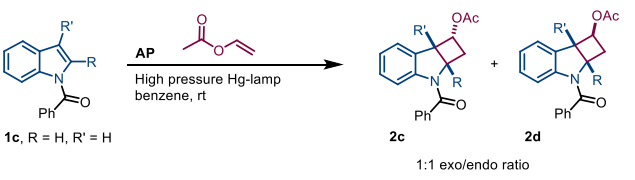


SCHEME 3 | Intramolecular photocyclization of *N*-sulfonylindoles for the synthesis of tetracyclic systems featuring a cyclobuta[*b*]indole core, accompanied by concurrent photo-Fries type migration.

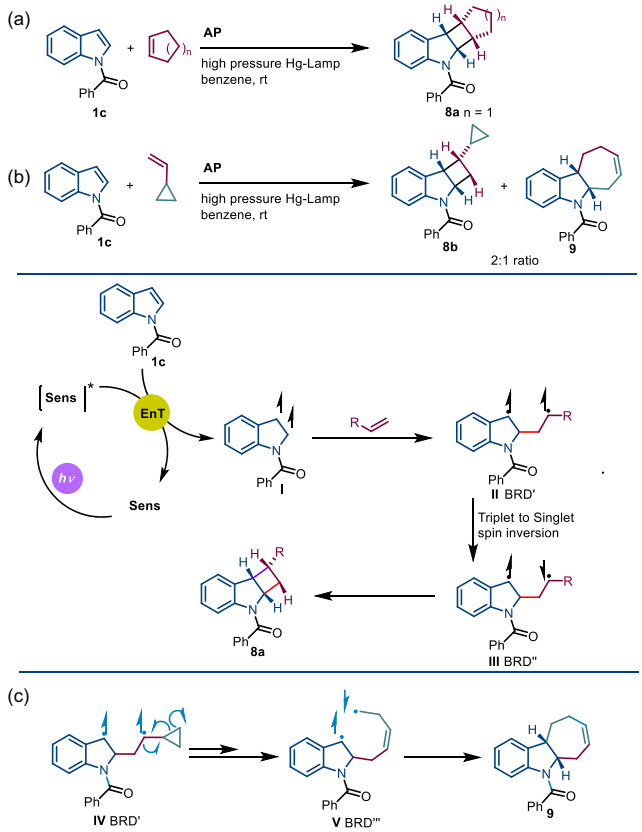
analogs afforded only the corresponding cycloaddition adducts **6b** and **6c**. On the other hand, protection of the nitrogen atom with a methyl group completely inhibits the cycloaddition reaction emphasizing the importance of the nitrogen substitution in [2 + 2] photochemical processes involving indoles.

In 1984, Ikeda and co-workers reported the formation of cyclobuta[*b*]indoles from various 1-benzoylindoles **1c** and vinyl acetate. These experiments were performed in the presence of AP as a triplet sensitizer and UV irradiation with a 350 W high-pressure mercury lamp [73], to afford mixtures of diastereomeric cyclobuta[*b*]indole acetates **2c** and **2d**. This study showed that the addition of vinyl acetate to benzoylindoles bearing an electron-withdrawing group at the 3-position (**1c**) afforded the desired compounds **2c** in high yields and excellent regioselectivity (Scheme 4). However, the stereoselectivity was relatively low, resulting in roughly 1:1 mixtures of the *endo*- and *exo*-isomers. In contrast, reactions with methyl acrylates gave moderate yields but exhibited both high regio- and stereoselectivity, with the *exo*-isomers being predominantly formed.

To better understand the stereochemistry behind the photoinduced [2 + 2] cycloaddition reactions of *N*-benzoylindole **1c**, in 1991, Weedon reported a series of investigations concerning the reaction of **1c** with various alkenes, including cyclic olefins, *cis*- and *trans*-2-butene, 1,6-hexadiene, under UV irradiation, and in the presence of AP (Scheme 5a). In these reaction conditions, [2 + 2] cycloaddition occurs yielding the corresponding *exo*-ciclobuta[*b*]indoles products **8a** in high yields. Moreover, investigations pointed at determining the mechanistic aspects of these



SCHEME 4 | Photoinduced synthesis of cyclobuta[*b*]indoles via dearomative [2 + 2] cycloaddition of acyl indoles and vinyl acetates.



SCHEME 5 | Capture of olefins via the triplet excited state of indoles with: (a) cyclopentene and (b) vinylcyclopropane; (c) rationalization of the formation of biradical intermediates (BRDs) using vinylcyclopropane derivatives prone to ring opening, and the trapping of radical species through a triplet-to-singlet spin inversion mechanism.

transformations revealed that these processes proceed through indole sensitization and excitation to its triplet excited state **I;** then, reaction with olefins would occur via initial bonding between the less substituted alkene terminus and the indole C2 position. The generation of biradical species, depending on the rate of ISC from the triplet biradical (**II**) to the singlet biradical species (**III**) and independently by the substitution in the alkenyl moiety [74], allows rapid formation of the second C—C bond (Scheme 5c), rationalizing the generally observed *cis*-regiochemistry of the [2 + 2] cycloaddition processes of Bz-indoles with monosubstituted alkenes [75]. To confirm the biradical nature of these reaction intermediates, **1c** was also reacted with vinyl cyclopropane, providing the corresponding photoclosure products **8b** and **9** in a 2:1 regioisomeric ratio (Scheme 5b).

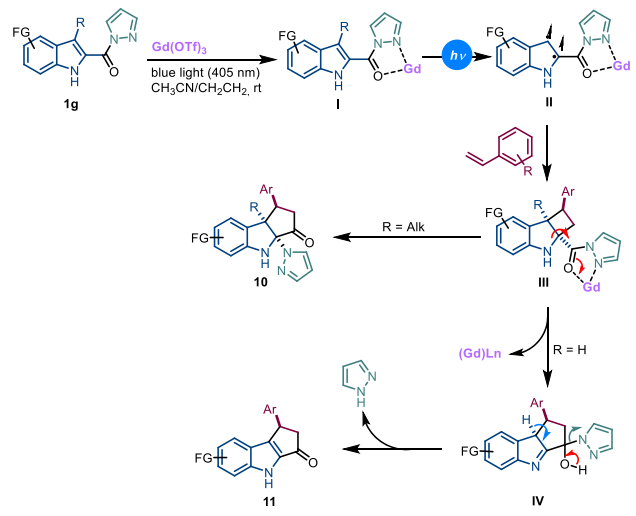
The formation of the tricyclic compound **9** would be generated by ring opening of the cyclopropyl unit, notoriously prone to this type of rearrangement, to furnish the homoallyl 1,7-biradical specie **V** [76, 77]. Triplet-to-singlet spin inversion and the formation of a bond between the two radical carbons finally allow the formation of the indolidine derivatives **9** (Scheme 5c).

The intermediacy of cyclobuta[*b*]indoles has also been evoked by Glorius and co-workers to rationalize a visible light-driven dearomative [2 + 2] cycloaddition/ring-expansion sequence of 2-indolyl pyrazolamides using $Gd(OTf)_3$ as EnT PS to access fused cyclopentanone indoles [78]. As depicted in Scheme 6, coordination of the 2-indole amide **1g** with $Gd(OTf)_3$, (**I**) followed by excitation using visible light, generates a long-lived excited-state intermediate **II**. This species undergoes a stepwise [2 + 2] cycloaddition with various styrene derivatives, forming the corresponding cyclobuta[*b*]indoles **III**.

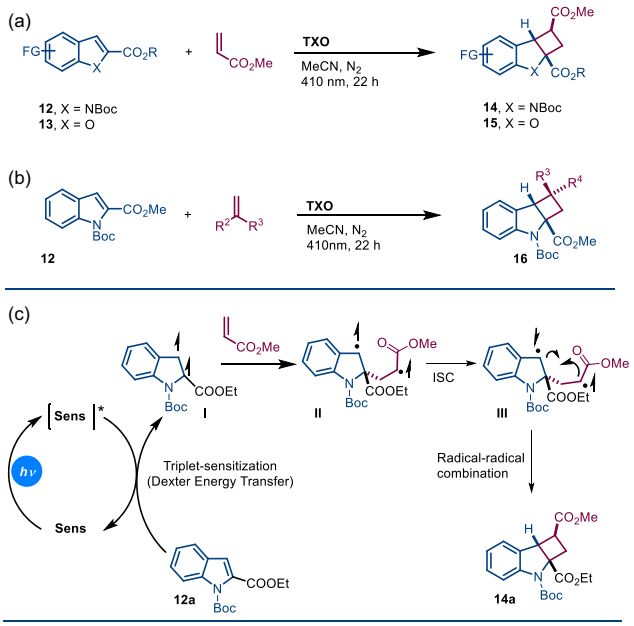
The tricyclic intermediate then undergoes a spontaneous semipinacolic ring expansion, leading to the formation of the desired cyclopentanone product **11** (*R*' = H). On the other hand, when the indole is functionalized with an alkyl group in position 3, migration of the pyrazole moiety and nucleophilic attack on the benzopyrroline yields the 2-pyrazolyl indole **10** [79].

Another example of dearomative [2 + 2] cycloaddition was reported in a recent study by Cui and co-workers [80], who described an efficient and environmentally friendly approach to cyclobutene-fused indolines. This transformation employs thioxanthone (TXT, E_T: 3.10 eV, 71.4 kcal/mol) as a metal-free triplet PS and delivers the desired products with good to excellent stereoselectivity along with high regioselectivity (Scheme 7). According to their report, the mechanism proposed starts with the excitation of the tioxanthone to a singlet state (S_1) by light absorption, followed by a rapid ISC to its triplet state (T_1). Subsequent EnT from the triplet state of the PS to the indole **12** leads to the formation of the triplet 1,2-diradical intermediate **I** whose C2 carbon radical is captured by an olefin, leading to the triplet 1,4-diradical **II**. At this point, ISC and following intramolecular radical–radical coupling led to the formation of the product **14**.

Wei and Shi in 2018 [81] developed a tandem [2 + 2] thermally assisted cycloaddition between 2-(cyclopropylidene-(phenyl) methyl)aniline **18** and diethyl acetylene dicarboxylate **19**, under air conditions at 80°C, followed by a photoinduced ring expansion by irradiating the reaction mixture with visible light. In the reported mechanism, the indoline moiety is generated by the intramolecular nucleophilic attack of an arylamine fragment

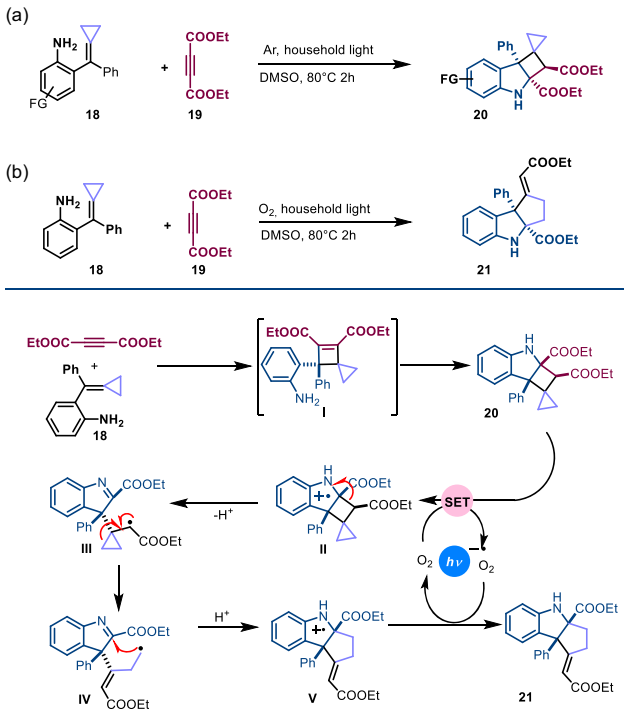


SCHEME 6 | In situ generated 2-indolyl pyrazolamide–Gd complexes enable energy-transfer-driven tandem photodearomatization and semipinacol ring expansion of the indole core, yielding cyclopenta[*b*]indol-3(2H)-ones.



SCHEME 7 | TXO-mediated [2 + 2] indole cycloaddition. (a) general reaction pathway using acrylates. (b) General reaction pathway using other olefins. (c) reaction mechanism.

to the cyclobutene scaffold **I**, leading to the formation of the spiro-cyclobutaindole adduct **20** (Scheme 8). In these reaction conditions, compound **20** is prone to radical ring opening, affording the corresponding cyclopenta[*b*]indole derivative **21** in good chemical yields.

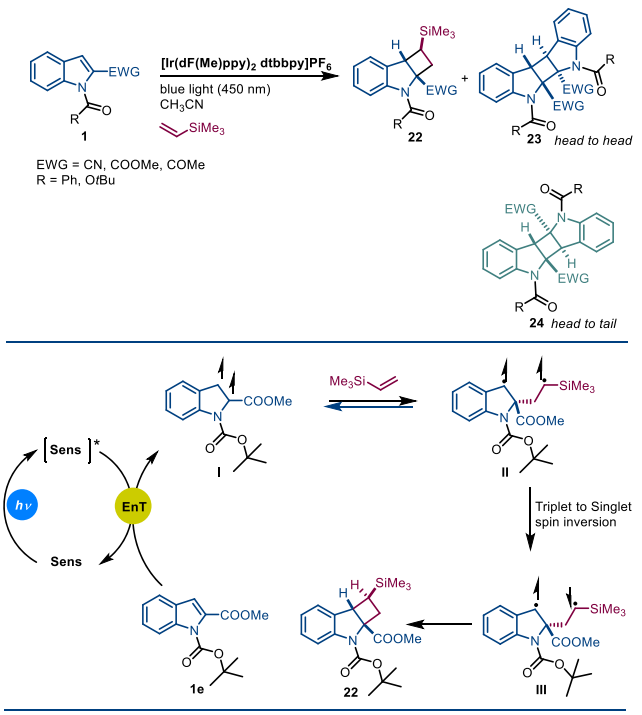


SCHEME 8 | Tandem thermal [2 + 2] cycloaddition and photoinduced ring-expansion of alkylidene cyclopropanes, affording. (a) spiro[2.3]hexane indoles and, (b) cyclopentane-fused indolines via transient cyclobuta[*b*] indole intermediates.

Moreover, Oderinde and co-workers [82] developed a photoinduced dearomative [2 + 2] intermolecular cycloaddition between 2-substituted indoles with a broad range of substituted alkenes and using $[Ir(dF(Me)ppy)_2dtbbpy]PF_6$ as a PS (E_T: 2.61 eV, 60.2 kcal/mol) under blue light irradiation (450 nm). In these conditions, reaction of the Boc-protected indole-2-carboxyesters **1e** with vinyl trimethylsilane afforded the desired product **22** in high yields, with excellent regio- and high *trans*-diastereoselectivity. The authors thoroughly investigated this system to minimize the formation of head-to-head and head-to-tail homodimers **23** and **24**, which arise in the reaction environment depending on whether the indole derivatives exist in long- or short-lived excited states.

Furthermore, the steric hindrance exerted by the substituents in position 2 of the indoles **1e** appears to be responsible both for the *trans* stereochemistry of the final products **22** and for the production of the above described homodimers. The regiochemistry of the reaction, as well as its mechanistic rationalization, has also been studied through quantum mechanical calculations, corroborated by experimental measurements, finally proposing the reaction mechanism reported in Scheme 9. Encouraged by these results, the authors extended this procedure to other substrates including azaindoles, benzofurans, thianaphthenes, and pyrrolo[2,3-d]-pyrimidines, providing the corresponding cycloadducts in good to high yields [82].

"On-water" dearomative [2 + 2] cycloaddition of *N*-Boc indole 26 was reported by Bae and co-workers in a more general study concerning the cycloaddition of various benzofused heterocyclic compounds with a series of 2-phenylethene-1-sulfonyl fluoride derivatives 25 to achieve the corresponding cyclobutene-fused

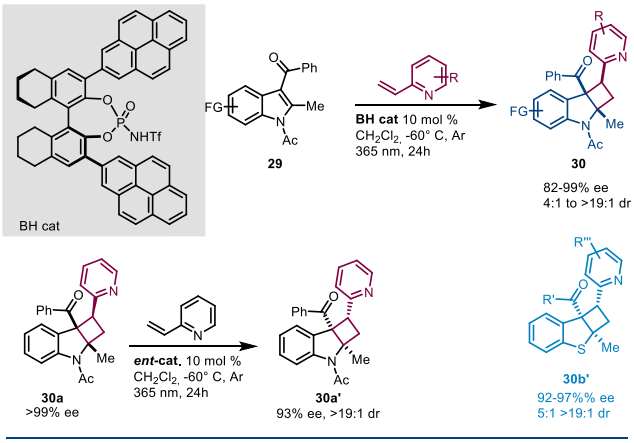


SCHEME 9 | Dearomative [2 + 2] intermolecular cycloaddition of 2-substituted *N*-Boc indoles and vinyl silanes.

derivatives, using 4-Cz-IPN as a PC under blue light irradiation (456 nm).

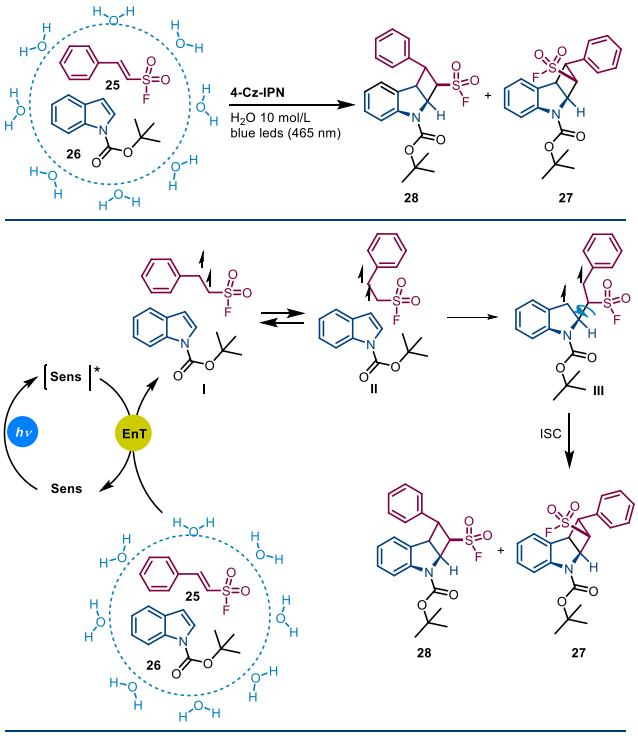
Under these reaction conditions, the Boc-protected cyclobuta[*b*] indoles 27 and 28 were isolated in 73% yield as a *exo/endo* 67:33 mixture of diastereoisomers (Scheme 10). The authors report that the acqueous medium accellerates this proces and propose a Dexter-type energy transfer from 4-CzIPN (ET = 2.73 eV, 62.9 Kcal/mol) to 2-phenylethene-1-sulfonylfluoride. Upon promotion to its triplet state (I) the latter reacts with the substrate through a two-step addition process [83].

An enantioselective, photoinduced synthesis of cyclobuta[*b*] indoles was recently reported by Jiang and co-workers. This transformation, carried out in the presence of a chiral 1,1′-bi-2-naphthol (BINOL)-derived *N*-triflylphosphoramide at −60°C [84, 85], exploits the photocycloreversion of in situ generated cyclobuta[*b*]indoles **30** bearing azaarene substituents, particularly 2-pyridyl derivatives. Upon interaction with the chiral Brønsted acid, these adducts undergo a selective, photoinduced cycloreversion process, leading to deracemization. As described by the authors, the process involves two reversible events: (a) the photoinduced formation of two C—C bonds via triplet state excitation of indole **29**, typically with low levels of enantioselectivity, and (b) the subsequent highly enantioselective dissociation (reversion) of the C—C bonds, which concurrently generates enantioenrichment at all stereocenters. The process has been thoroughly studied and later extended to thionaphthene derivatives, demonstrating a broad substrate scope tolerance. Whether applied to indole-derived compounds or their thionaphthene congeners, the reaction consistently achieves very high levels of enantio- and diastereoselectivity, often exceeding 99%, along with excellent chemical yields (Scheme 11).

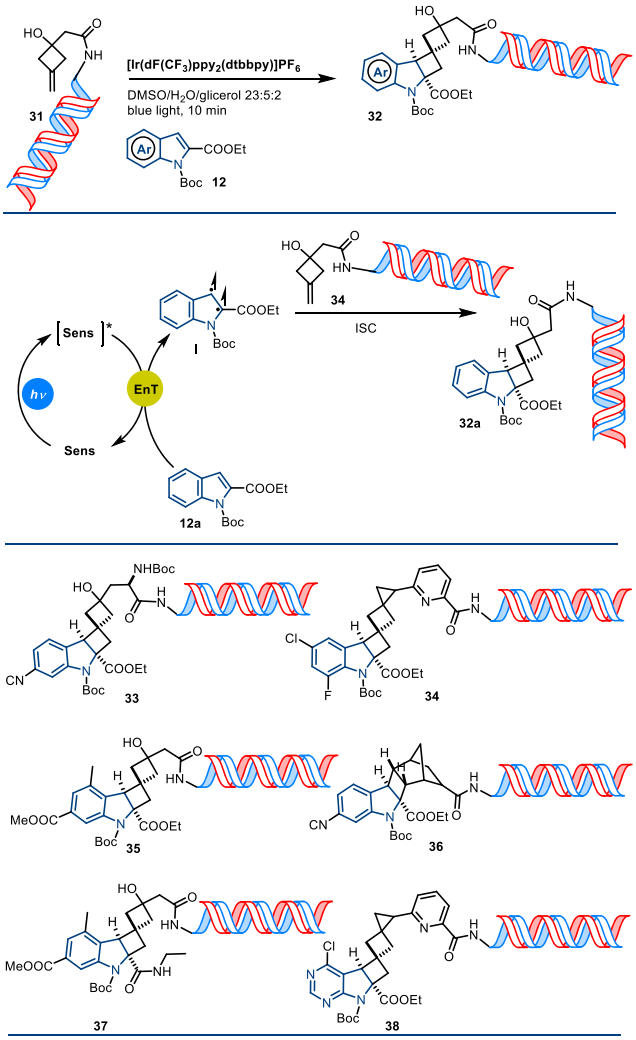


SCHEME 11 | Enantioselective dearomative [2 + 2] cycloaddition of indoles with vinyl pyridines via stereocontrolled cycloreversion and deracemization of preformed cyclobuta[*b*]indoles.

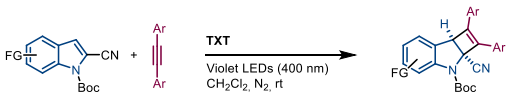
With the aim of developing new DNA-encoded libraries as powerful tools in drug discovery [86], Crane and Molander [87] reported a dearomative intermolecular [2 + 2] photocycloaddition of indoles **12** with a variety of alkylidene cyclobutanes **31** for the construction of C(sp^3)-rich heterospirocycles **32** on DNA (Scheme 12a). This



SCHEME 10 | On-water dearomative [2 + 2] cycloaddition of *N*-Boc indoles and 2-phenylethene-1-sulfonyl fluoride.



SCHEME 12 | DNA tagging via photoinduced EnT [2 + 2] cycloaddition of *N*-Boc indoles with cyclobutylidene derivatives.

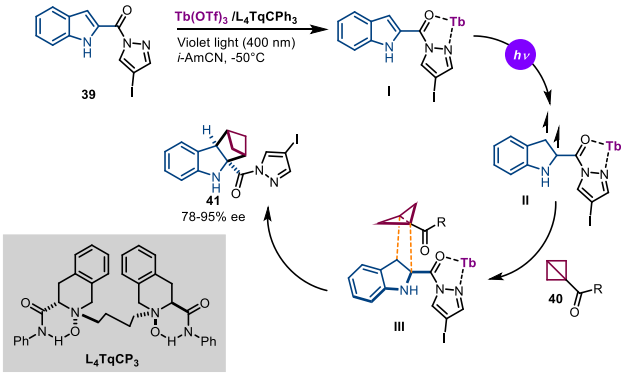


SCHEME 13 | Dearomative [2 + 2] cycloaddition of indoles with diaryl alkynes.

scalable (10–100 nM) approach employs $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ as a sensitizer, which, upon blue light excitation, engages in EnT with *N*-Boc indoles. The resulting triplet excited state of the indole **I** is then able to react with a selection of three-dimensional (3D) olefins. This strategy has also been extended to both activated and unactivated alkenes, producing a wide array of chemically diverse DNA-tagged polycyclic indoles and azaindoles (**33**-**38**) in generally good to excellent yields (Scheme 12b).

To conclude this section, we highlight a recent study reported by Cui and co-workers [88], which enables the synthesis of cyclobutene-fused indolines through a TXT-mediated photoinduced reaction between 2-cyano-*N*-Boc-protected indoles and diaryl alkynes in generally good to excellent yields, as depicted in Scheme 13.

Although this final example extends beyond the strategies discussed above, it is worth highlighting an elegant enantioselective dearomative [2 + 2] photocycloaddition of indole derivatives leading to polycyclic cyclobutane-indole fused frameworks, as reported by Dong and co-workers [89]. As already illustrated in Scheme 6, indoles appropriately functionalized at the C2 position with substituents capable of coordinating rare-earth elements can be efficiently photoexcited upon irradiation with visible light. In this case, a Tb salt fulfills a dual role: it acts both as a PS and as a Lewis acid, thereby enabling the formation of a chiral complex between the indole substrate, the rare-earth metal center, and a chiral *ligand* ($L4TqCPh_3$). Owing to a heavy-atom effect, here associated with the presence of an iodine atom on the azole unit, this substituent enhances the phosphorescence intensity of intermediate **I**, thereby promoting ISC and facilitating access to the corresponding triplet excited state **II**. This reactive triplet species subsequently engages in a [2 + 2] cycloaddition with a bicyclobutane derivative, affording product **41** with a high degree of regioselectivity and excellent enantiomeric excess (Scheme 14).

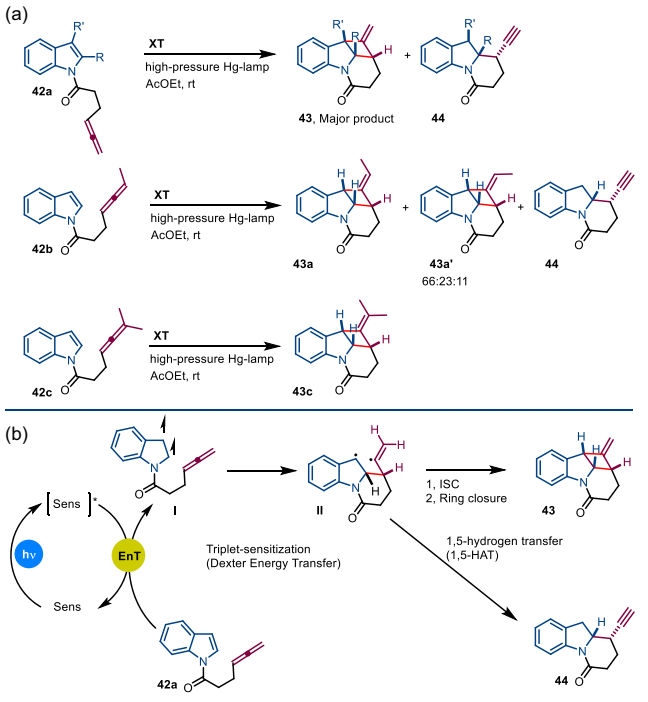


SCHEME 14 | Tb-mediated enantioselective dearomative [2 + 2] cycloaddition of 2-indole pyrazolamides with bicyclobutane derivatives.

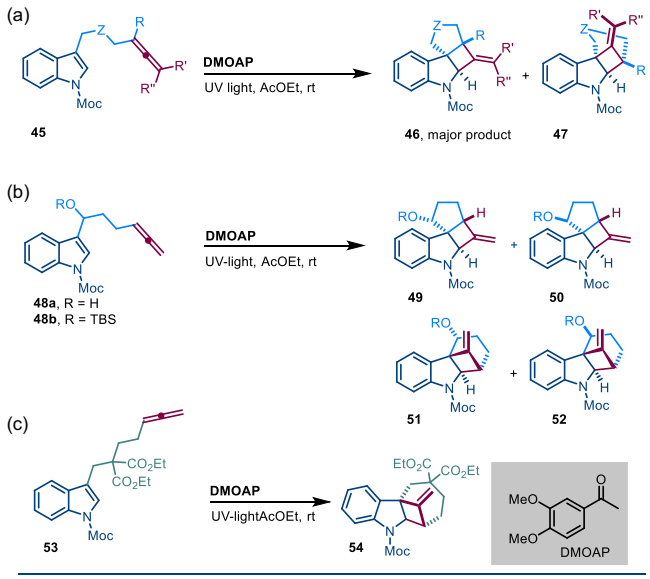
4 | [2 + 2] Photoinduced Intramolecular Cycloaddition Strategies for the Synthesis of Polycyclic Indolines

In 2019, Arai and Ohkuma reported the synthesis of polycyclic cyclobuta[*b*]indole derivatives via an intramolecular [2 + 2] cycloaddition strategy using *N*-functionalized allenyl indoles **42** [90, 91]. Their initial studies focused on the reaction of 1-(hexa-4,5-dienoyl)indole **42a** in the presence of xanthone as a triplet sensitizer under high-pressure mercury lamp irradiation in EtOAc. In these operational reaction conditions, fused tetracyclic cyclobuta[*b*]indoles **43** were obtained in good yields when the allene moiety carried two methyl substituents (**42c**). In contrast, unsubstituted or monomethyl-substituted allenes resulted in *E*/*Z*-regiomeric mixtures of the corresponding products **43a** and **43a'**. The authors also reported the formation of a tricyclic side product (**44**), whose origin was rationalized as illustrated in Scheme 15.

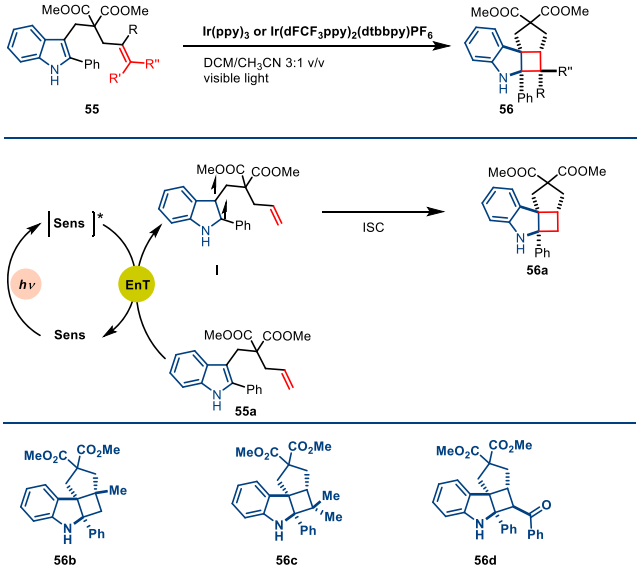
Under similar reaction conditions, relocation of the allene moiety to the C3 position of the indole and the use of 3,4-dimethoxyacetophenone as the sensitizer led predominantly to the formation of the angular tetracyclic indoline **46** starting from Moc-protected indoles **45**, while a bridged minor product was later identified as compound **47** (Scheme 16a). The efficiency and outcome of the photocyclization are strongly influenced by the presence of substituents along the indole side chain (Scheme 16b). This variation results in the formation of the corresponding tetracyclic compounds **49** and **50**, which are accompanied by regioisomeric structures of type **51** and **52** (*R* = TBS). Further elongation of the alkyl chain bearing the terminal allenyl group, combined



SCHEME 15 | Preparation of ethynyl-8,9-dihydropyrido[1,2-a]indolones and benzo[*b*]cyclobutaindolizinones via EnT photoactivation of *N*-acylindoles. (a) general reaction pathway to access the tetracyclic compounds. (b) meaction mechanism.



SCHEME 16 | Regioselective synthesis of angular tetracyclic spiroindolines via EnT photoactivation of 3-(hexa-3,4-dien-yl)-indoles. (a) general pathway using tetrasubstituted allenes. (b) general reaction pathway using monosubstituted allenes. (c) synthesis of cycloepta[*b*]indole derivatives.

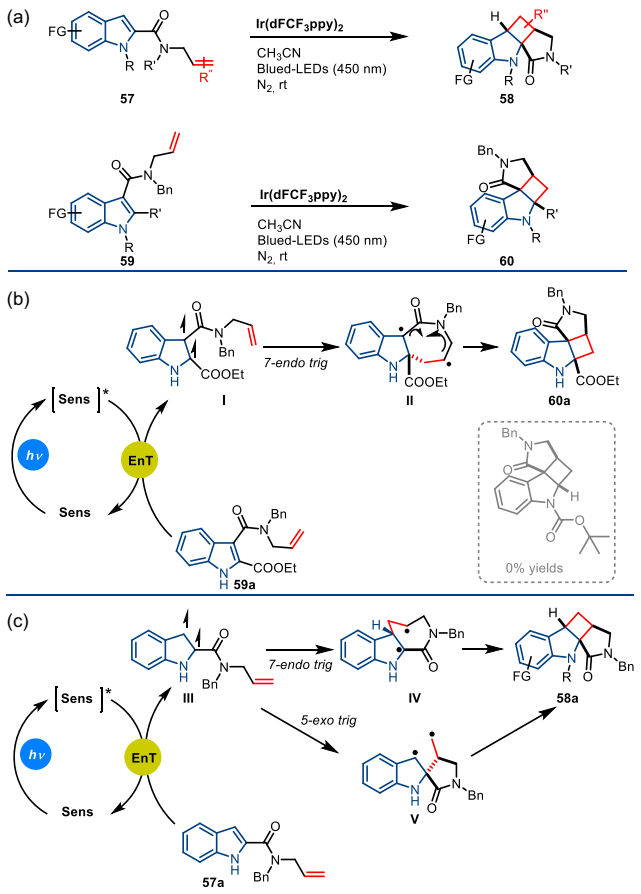


SCHEME 17 | Stereoselective preparation of tetracyclic cyclobuta[*b*] indole derivatives via intramolecular [2 + 2] photocyclization of 3-substituted alkenyl indoles.

with the introduction of two bulky substituents on the same side chain, enables the direct conversion of indoles **53** into fused cyclobutane adducts **54** in good chemical yields (Scheme 16c).

In a separate study, Zhu and co-workers reported a visible-light-promoted intramolecular [2 + 2] cycloaddition of indoles bearing various alkenyl substituents, affording cyclobutane-fused angular tetracyclic spiroindolines **56** in excellent yields with remarkable stereoselectivity under mild conditions [92]. Their investigation began with dimethyl 2-((1H-indol-3-yl)methyl)-2-allylmalonate **55** (E_T: 2.82 eV, 58.2 kcal/mol), under irradiation with 24 W blue LEDs at room temperature in an inert atmosphere. These studies revealed that *fac*-Ir(ppy)$_3$ (E_T: 2.28 eV, 52.6 kcal/mol) and Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (E_T: 2.61 eV, 60.1 kcal/mol) were the most effective PSs when used in a DCM/MeCN (3:1) mixture, delivering the desired product **56a**. Under the optimized conditions, the authors expanded the substrate scope to other indole derivatives, obtaining the corresponding tetracyclic products **56b-d** in consistently good to excellent yields (Scheme 17).

Fused tetracyclic cyclobutane-pyrrolidinone compounds can be also obtained through photochemical [2 + 2] cycloaddition from 2-carboxamido-allyl indole derivatives **57** and **59** (E_T: 2.52 eV, 58.2 kcal/mol) as recently reported by Oderinde [93]. In this study (Scheme 18a), the intramolecular [2 + 2] photocycloaddition process was performed in CH$_3$CN using Ir-based PSs *fac*-Ir(dFppy)$_3$ (E_T: 2.32 eV, 53.5 kcal/mol) under irradiation with 450 nm blue LEDs. The rational mechanism purposed by the authors is based on a first sensitization of the indole **59a** by the Ir-species, followed by *7-endo-trig* rearrangement **II** that generates a biradical spiro-adduct **III** and radical–radical ring closure to access the tetracyclic derivatives **60a** (Scheme 18b). Alternatively, starting from 2-substituted indoles **57**, *5-exo-trig* rearrangement would lead to a spiranyl tricyclic biradical intermediate **V** that would rearrange via ring closure step to form the

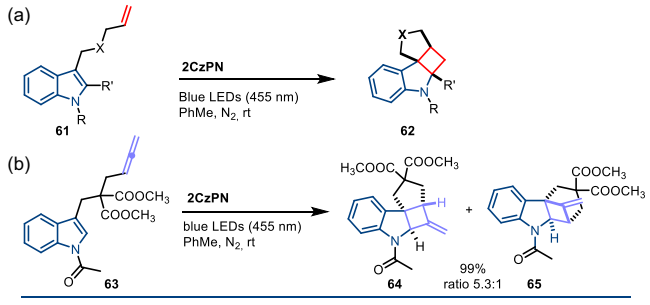


SCHEME 18 | Stereoselective synthesis of tetracyclic cyclobuta[*b*] indoles via intramolecular [2 + 2] photocyclization of 2-carboxamido-allyl indole derivatives. (a) synthesis of cyclobuta[1,2-*b*]indolones. (b) Proposed reaction mechanism to access cyclobuta[1,2-*b*]indolones starting from 2-amidoindoles. (c) reaction mechanism for the synthesis of cyclobuta [1,2-*b*]indolones starting from 3-amidoindole derivatives.

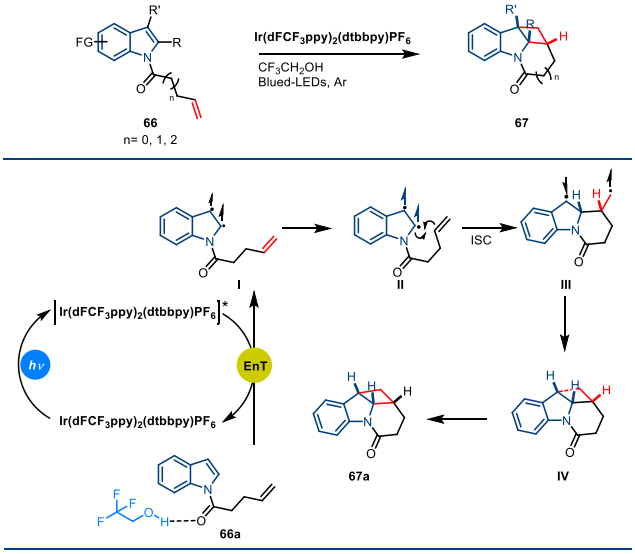
compounds **58**. Using these optimized conditions, a series of fused cyclobuta[*b*]indoles were obtained with high control of the stereochemistry and in high chemical yields (Scheme 18c). Unlike traditional UV-based methods, photocatalytic approaches using Iridium catalysts typically operate under milder conditions (visible light, room temperature), while still achieving high to excellent yields. Furthermore, the formation of by-products is significantly reduced in comparison, and greater control over regioselectivity is achieved.

On the other hand, Rolka and co-workers reported the dearomative intramolecular [2 + 2] photocyclization of a series of 3-substituted indole derivatives **61** or **63** using 1,2-bis(carbazol-9-yl)–4,5-dicyanobenzene (2CzPN) as an organic PS (E_T: 2.97 eV, 68.5 kcal/mol) instead of the most common Ir-catalysts [94], performing their reactions in toluene, under blue light irradiation (455 nm). With this setup, the authors obtained the corresponding fused cyclobuta[*b*]indoles **62** avoiding the need for metal catalysts, in high yields with high degree of regio- and stereochemical control (Scheme 19a). Moreover, the efficacy of 2CzPN in promoting these reactions was also tested using allene-based indoles to obtain highly strained methylencyclobutane adducts **64** accompanied by the regioisomeric products **65** (Scheme 19b).

In 2020, Zhang and co-workers reported the [2 + 2] photocyclization of 1-(1H-indol-1-yl)pent-4-en-1-ones [95]. Generally, indole derivatives functionalized with *N*-acyl olefins possess relatively high triplet excited-state energies compared to those of the PS, which hampers the reaction (Figure 3). To address this challenge, the authors first examined the reactivity of *N*-(ω-alkenoyl) indoles **66** using Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ as the PS (E_T: 2.61 eV, 60.1 kcal/mol) under visible-light irradiation. They found that aprotic solvents were inefficient, whereas trifluoroethanol efficiently promoted the reaction, yielding the cyclized products **67** in near-quantitative yield. The authors proposed that the oxygen atom of the amide forms a hydrogen bond with the hydroxyl group of trifluoroethanol (**66a**), lowering the triplet excited-state energy of the substrate (**I**). This hydrogen-bonding system proves to be an effective strategy for functionalized or more "challenging" polar substrates, as it can stabilize the excited triplet states and thus expand the range of products that can be obtained in terms of group tolerance, while maintaining the efficiency and selectivity of EnT methods, operating in the visible-light range. This hypothesis was supported by Nuclear Magnetic Resonance (NMR) experiments, in which varying amounts of trifluoroethanol



SCHEME 19 | 3-alkenyl and 3-allenyl indoles intramolecular dearomative [2+2] photocyclization using 2CzPN as a photosensitizer. (a) intramolecular photocyclization of 3-substituted alchenyl indoles. (b) photocyclization of 3-allenyl *N*-acyl indoles.

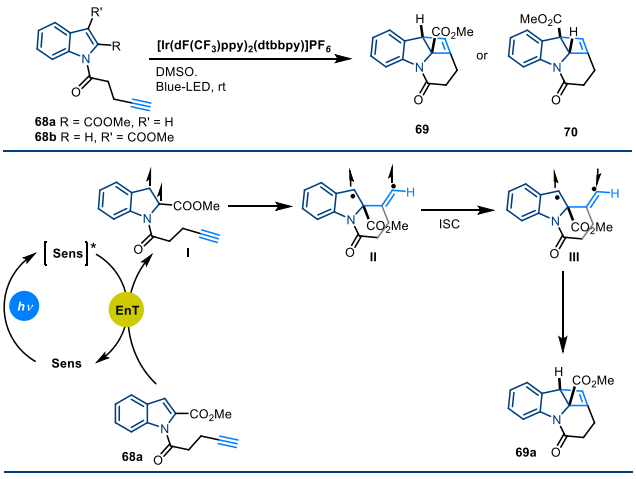


SCHEME 20 | *N*-acyl alkenyl indoles intramolecular dearomative [2 + 2] photocyclization using trifuluoroethanol as a solvent.

were added to a $CDCl_3$ solution of *N*-(ω-alkenoyl)indole, resulting in a chemical shift of the carbonyl carbon due to deshielding from hydrogen-bond formation. Using these optimized conditions, a series of indole derivatives was evaluated, affording 31 analogs with substitutions at the 4-, 5-, and 6-positions of the indole core (Scheme 20).

Dearomative photocyclization of indoles bearing *N*-acylated terminal alkynes **68** was also reported by Zhang, Zheng, and You in 2020 [96]. The reaction proceeds through a [2 + 2] cycloaddition triggered by [Ir(dF(CF$_3$)ppy)$_2$dtbbpy]PF$_6$ photosensitization in DMSO under blue LED irradiation. The reaction was also extended to other alkenyl derivatives affording the corresponding tetracyclic indolidine cyclobutens **69** or **70** in good to excellent yields with full control of the products stereochemistry (Scheme 21).

Remarkably, Zhu and co-workers prepared a wide array of polycyclic indoline derivatives via intramolecular double

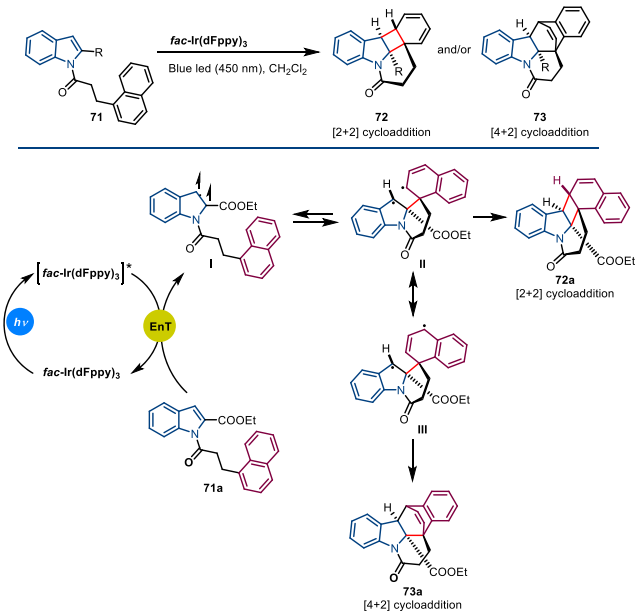


SCHEME 21 | *N*-acyl alkynyl indoles intramolecular dearomative [2 + 2] photocyclization.

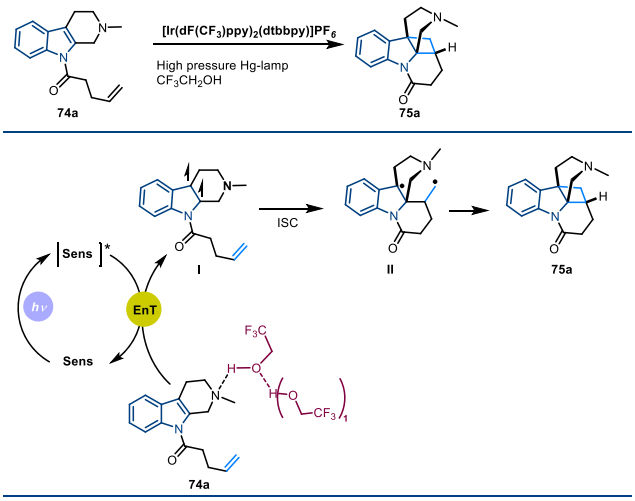
dearomative cycloaddition of arenes [97]. The reaction was developed using ethyl 1-(3-(naphthalen-2-yl)propanoyl)-1H-indole-2-carboxylate **71** as a model substrate, which was irradiated with blue LEDs in the presence of *fac*-Ir(dFppy)$_3$. Reactions carried out in dichloromethane afforded the desired polycyclic compounds **72** and/or **73** in good yields, demonstrating the compatibility of various substitution patterns on the indole moiety. The increased molecular complexity in these substrates was achieved through a stereoselective [4 + 2] cycloaddition, rationalized as follows: the indolyl derivative **71a** is excited to its first triplet state **I** via EnT from the Ir-PS, enabling a first [2 + 2] cycloaddition. This is followed by ISC to generate a common open-shell singlet diradical species with two unpaired electrons (**II**). Two competitive pathways were proposed to explain the experimental outcomes reported in Scheme 20: (a) reversible [2 + 2] cycloaddition and (b) irreversible [4 + 2] cycloaddition, leading, respectively, to compound **72a** and to adduct **III**. This would further evolve into the more stable compound **73a** (Scheme 22).

Yi, Zhang, and Fu [98] reported the synthesis of aliphatic-amine-containing cyclobutane-fused indolines **75** *via* photoinduced dearomative [2 + 2] cyclization using [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ as the PS. The reaction efficiently furnished the desired photocyclization products in generally good yields, regardless of whether the aliphatic ring contained electron-donating or electron-withdrawing substituents.

In this study, the authors highlighted the crucial role of hydrogen-bonding networks between the nitrogen atom of the terminal indole amines **74** and the solvent (trifluoroethanol or hexafluoro-2-propanol) in achieving full stereochemical control. A reaction mechanism was proposed (Scheme 23), starting from compound **74a**, which is excited to the triplet state to form the intermediate **I** via EnT process. The formation of a C—C bond between the C2 position of the indole and the alkene moiety is followed by ISC, generating an open-shell singlet 1,4-diradical



SCHEME 22 | Photoinduced intramolecular double dearomative cycloaddition of arenes for the synthesis of [2 + 2] and [4 + 2] polycyclic indoline adducts.

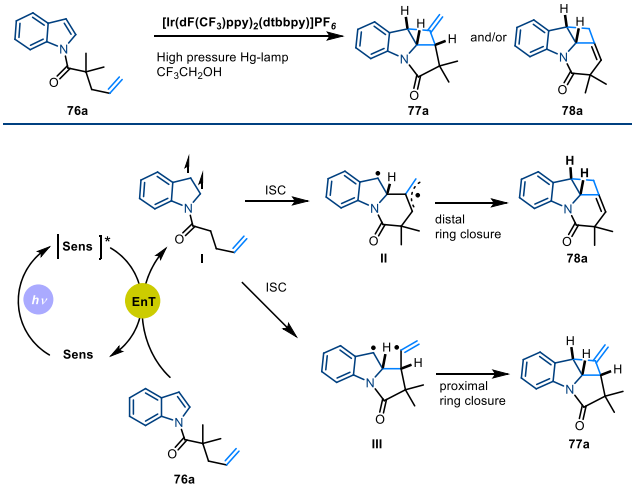


SCHEME 23 | Photoinduced intramolecular [2 + 2] cycloaddition of tetrahydro-1H-pyrido[3,4-*b*]indole derivatives for the synthesis of tetracyclic cyclobutene-fused compounds.

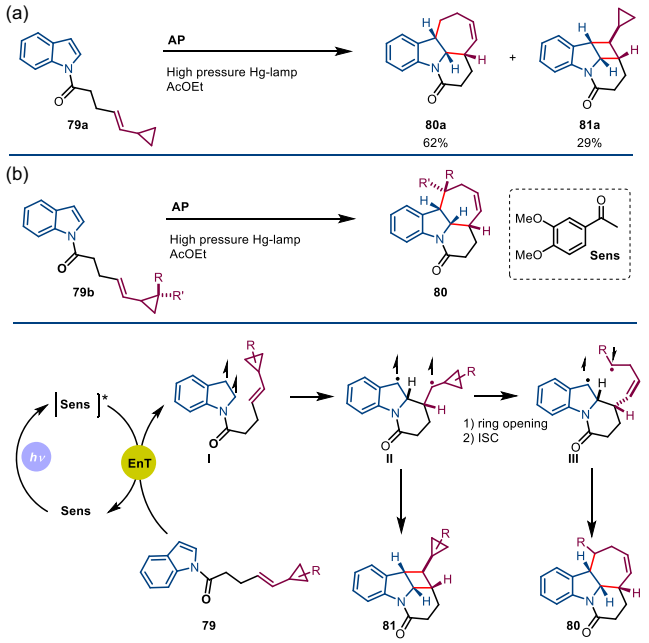
intermediate **II**. This intermediate undergoes radical–radical recombination to furnish the cyclobutane-fused product **75**.

Arai [99] investigated the formation of *anti*-Bredt-type azabicyclo[4.2.0]octene scaffolds through photoinduced intramolecular [2 + 2] cycloaddition, irradiating 1-(penta-3,4-dienoyl)indole derivatives **76** using a high-pressure mercury lamp and methylenedioxy acetophenone as PS. In this process, two different tetracyclic indoline derivatives, **77a** and **78a**, were generated along the photocyclization process with the predominant formation of the compound **77**. A variety of functional groups is tolerated by the reaction conditions, obtaining generally good yield and excellent diasteroselectivity. The proposed mechanism for this transformation is reported in Scheme 24.

The same group also reported the photoinduced synthesis of cycloheptene-fused indolines **80** from precursor **79**. This tetracyclic derivative is generally accompanied by the corresponding [2 + 2] cycloaddition products **81**, indicating that the



SCHEME 24 | Synthesis of *anti*-Bredt-type azabicyclo[4.2.0]octenes via EnT [2 + 2] dearomative photocyclization.



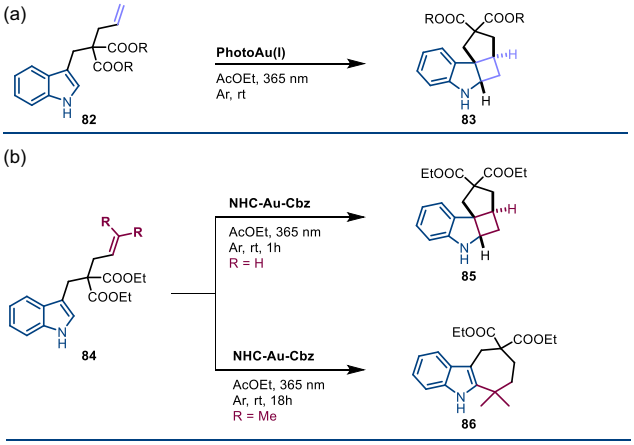
SCHEME 25 | Biradical-driven formation of tetracyclic cyclobuta[*b*]indole derivatives versus remote cyclopropyl-ring opening and strain-release pathways leading to indolylcycloheptene derivatives. (a) intramolecular photocyclization of alkenylcyclopropyl acylindoles. (b) Selective photocyclization of substituted alkenylcyclopropyl acylindoles leading to the synthesis of cycloeptaindolizinones.

cycloheptane frameworks may arise from a subsequent structural rearrangement of the carbon skeleton of **81**-*type* intermediates [100]. Indeed, irradiation of substituted vinylcyclopropyl derivatives **79b**, which are capable of generating more stable biradical intermediates **III**, provides selective access to cycloheptenyl cycloaddition products **80** in high yields when AP is employed as the photosensitizer (Scheme 25).

The successful use of gold-based PS for the synthesis of fused cyclobuta[*b*]indoles has been reported by Nolan and co-workers [101]. In this work, the intramolecular [2 + 2] cycloaddition reaction was performed using the PhotoAu(I) sensitizer (E_T: 2.89 e.V, 66.6 kcal/mol) in EtOAc under UV irradiation (365 nm). Substrate scope investigations disclosed large applicability of this protocol, leading to the desired compounds **83** in high yield and in short reaction time (Scheme 26a).

The same research group in 2023 reported the preparation of other dinuclear NHC-Au(I)-amido complexes [102], which were employed in EnT-photoinduced dearomative processes to achieve similar molecular architectures **85** (R = H). Moreover, reactions performed with trisubstituted alkenes (R = Me) seem to contrast the [2 + 2] intramolecular cycloaddition leading to the synthesis of cyclohepta[*b*]indole motifs **86** in 64% yield (Scheme 26b).

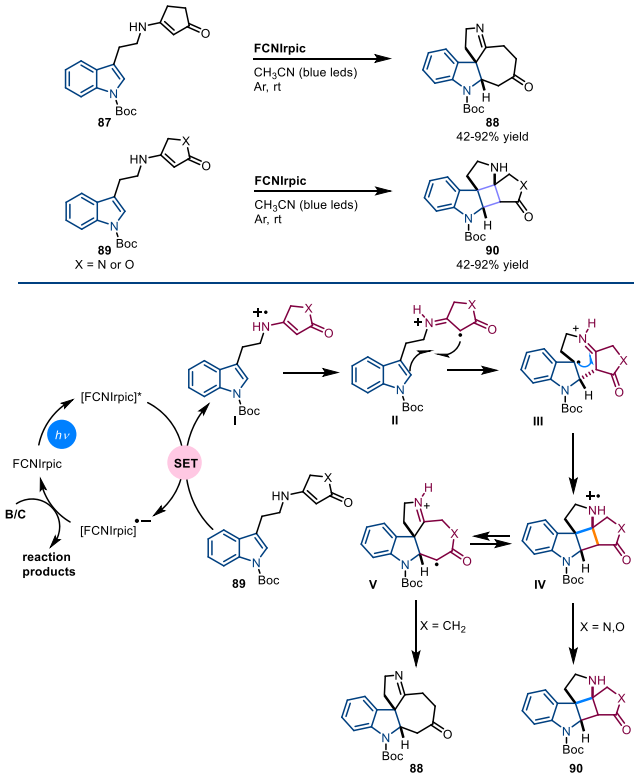
Another stereoselective synthesis of structurally diverse tetracyclic cyclohepta[*b*]indoles and cyclobutene-fused indoles via a SET-initiated process was developed using FCNIrpic (PC^*/PC^- = +1.24 V) as the PC [103–105]. This transformation was achieved by reacting tryptamine-derived imino-enones **87** or **89**. Specifically, cyclic imino-enones bearing lactone or lactam



SCHEME 26 | Influence of terminal-olefin substitution on the Au(I)-photosensitized intramolecular [2 + 2] cycloaddition of 3-functionalized indoles.

moieties undergo photooxidation to their corresponding radical cation species (**I**), triggering an intramolecular dearomative [2 + 2] cycloaddition that affords the cyclobutane-fused indolines **90** in moderate to good yields, as shown in Scheme 27.

Compared with the EnT processes described above, this SET-type strategy features lower chemoselectivity and requires more accurate reaction design. Computational studies were performed to identify the key transition states, thereby rationalizing the divergent reaction pathways. The proposed mechanism involves single-electron oxidation of the substrate by the excited FCNIrpic PC, followed by dearomative [2 + 2] cyclization to generate the



SCHEME 27 | Synthesis of tetracyclic cyclohepta[*b*]indoles and cyclobutane-fused indolines via a SET process.

cyclobutyl radical cation intermediate **IV**. Fragmentation of this intermediate via a retro-Mannich-type process would lead to a seven-membered ring **V**, which subsequently undergoes single-electron reduction and proton transfer to furnish the final cyclohepta[*b*]indole products **88**. In contrast, when a heteroatom is present on the enone moiety, stabilization of the cyclobutene intermediate occurs, allowing isolation of cyclobuta[*b*]indole derivatives **90**.

In 2022, Oderinde and Hudson reported the use of imidazoacridine-based thermally activated delayed fluorescence (TADF) materials in visible-light-mediated photocatalysis [106], presenting them as viable alternatives to traditional Ir- and Ru-based PSs. TADF compounds are typically designed with a twisted donor–acceptor architecture, which increases the spatial separation between the highest occupied molecular orbital and the lowest unoccupied molecular orbital. This separation reduces the electronic exchange interaction between the frontier orbitals, thereby facilitating efficient ISC between singlet and triplet excited states [94, 107, 108]. TADF materials that exhibit deep-blue fluorescence and high triplet excited-state energies are particularly well suited to promoting photochemical transformations via EnT mechanisms [109]. In this context, the authors demonstrated that ACR-IMAC ($E_T = 2.77$ eV, 63.9 kcal/mol) functions as an effective PS for [2 + 2] cycloaddition reactions, enabling access to strained cyclobuta[*b*]indole families **14′** and **92** in near-quantitative yields. Notably, both dearomative intramolecular and intermolecular [2 + 2] cycloadditions of functionalized indoles and azaindoles proceeded with high regio- and diastereoselectivity, as summarized in Scheme 28.

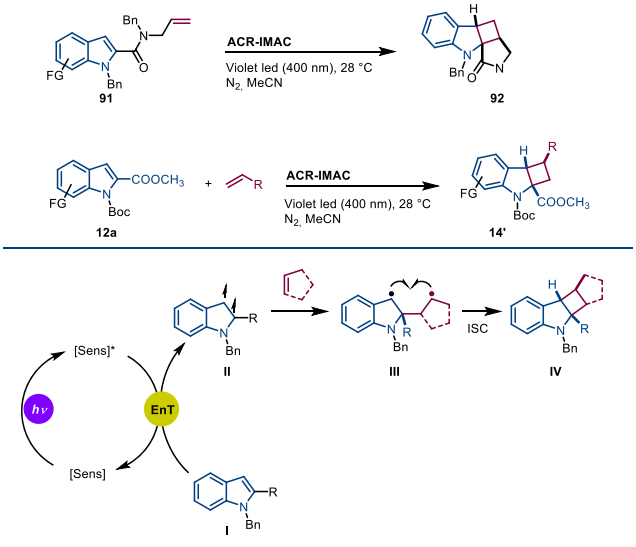
A study by Wang, Cao, and Yin introduced new strategies for the intramolecular [2 + 2] dearomative cycloaddition of a wide range of aryl and heterocyclic substrates, including 2-functionalized indoles conjugated with cinnamamide moieties [110]. In this work, EnT from an excited PS, either 4CzIPN or TXT, to the conjugated *α*,*β*-unsaturated amides **93** or **96** promotes these substrates to their singlet excited state, which subsequently undergoes ISC to access the corresponding triplet excited state **I**.

The resulting triplet species is capable of initiating a biradical addition of the cinnamyl unit onto the indole (or heteroaryl) core via intermediate **II**. The newly formed biradical then undergoes a *5-exo-trig* cyclization, ultimately affording polycyclic products bearing cyclobutane units **97** with excellent diastereoselectivity (>20:1).

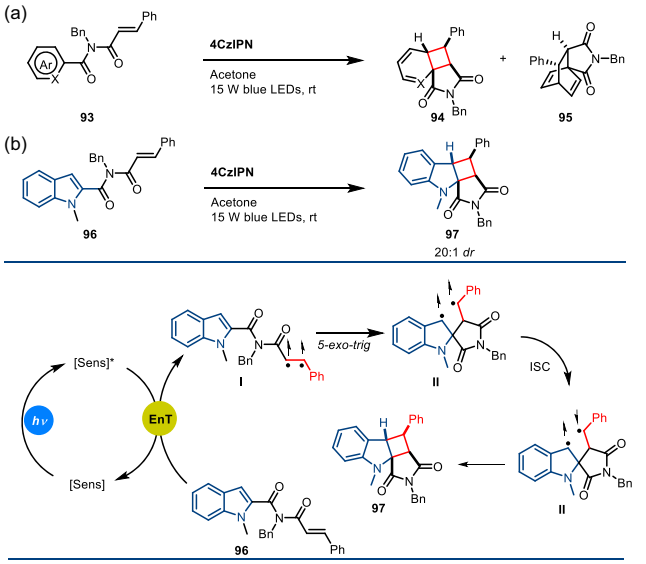
In addition, photosensitization of substrate **93** leads to fused cyclobutane derivatives **94**, which are often accompanied by bridged bicyclic structures **95**, as summarized in Scheme 29.

Furthermore, Wang and co-workers reported the synthesis of a series of cyclobutane-fused polycyclic compounds featuring multiple contiguous quaternary stereocenters through an intramolecular, light-induced catalytic [2 + 2] cycloaddition [111]. The authors evaluated both Ru- and Ir-based PSs, identifying $Ru(bpy)_3(PF_6)_2$ as the most effective EnT-sensitizer. Using blue LED irradiation in acetone, the reaction delivered a broad panel of products in yields of up to 96% and 20:1 diastereoselectivities (Scheme 28b). Mechanistic investigations revealed that *α*,*β*-unsaturated carbon–carbon double bond of the dienamide substrate was selectively activated via an EnT process, generating a biradical intermediate **I** that undergoes an uncommon *7-endo* cyclization to access compounds **101**. Under these conditions, cyclobuta[*b*]indole derivatives were obtained in up to 73% yield with a diastereomeric ratio of 16:1 (Scheme 30).

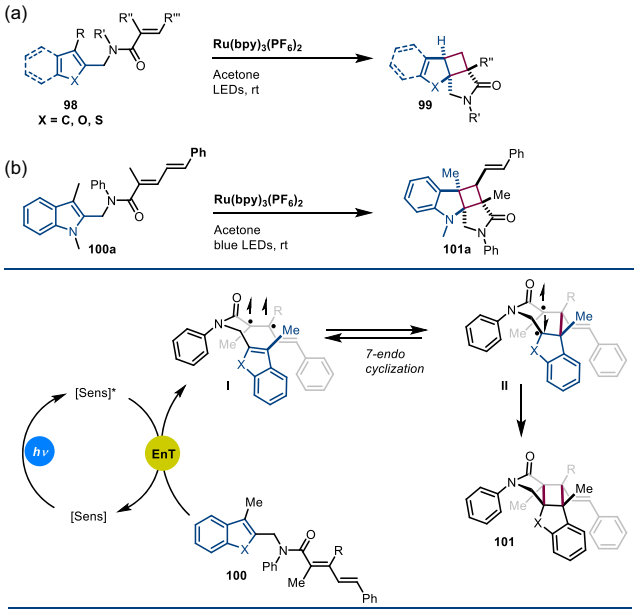
A diradical-mediated *ipso*-cyclization leading to a double dearomative [2 + 2] cycloaddition of *N*-acyl 2-amidosulfonyl indoles was developed by Wang, Cao, and Yin [112], enabling access to an extensive library of fused pentacyclic indolyl scaffolds (Scheme 31a). This photocyclization is initiated via an EnT



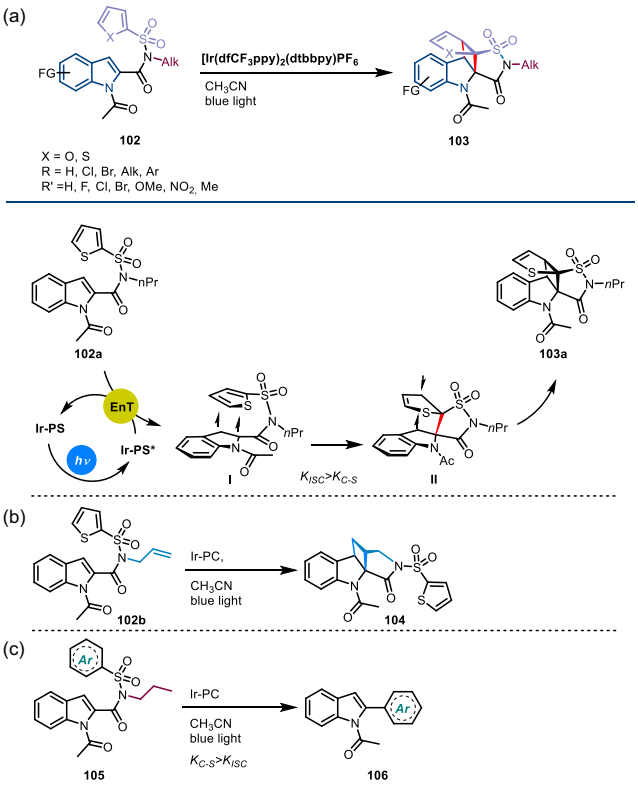
SCHEME 28 | Use of ACR-IMAC TADF sensitizers in the synthesis of cyclobuta[*b*]indole derivatives via EnT [2 + 2] dearomative intra- and intermolecular cyclization.



SCHEME 29 | Energy-transfer-driven intramolecular [2 + 2] cyclization of indolylcinnamamides to access cyclobuta[*b*]indole derivatives. (a) Photocyclization of heteroaryl cinnamamides. (b) Intramolecular cyclization of indolylcinnamamides to afford tetracyclic cyclobuta[*b*]indole derivatives.

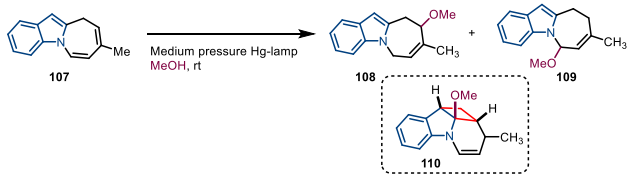


SCHEME 30 | Energy-transfer-driven intramolecular dearomative [2 + 2] cyclization of dienamides. (a) General intramolecular cyclization of benzofused dienamides. (b) Intramolecular cyclization of indole dienamides.



SCHEME 31 | Diradical-mediated ipso-cyclization leading to a double dearomative [2 + 2] cycloaddition of *N*-acyl 2-amidosulfonyl indoles. (a) general reaction scheme. (b) intramolecular cyclization of *N*-acyl-2-allylamidosulfonyl indoles. (c) Transposition of aryl during the intramolecular photocyclization of *N*-acyl-2-alkylamidosulfonyl indoles.

mechanism from the photoexcited $[Ir(dfCF_3ppy)_2(dtbbpy)]PF_6$ complex to the *N*-acylindole substrate **102**. Upon population of its triplet excited state, the *N*-acylindole undergoes an

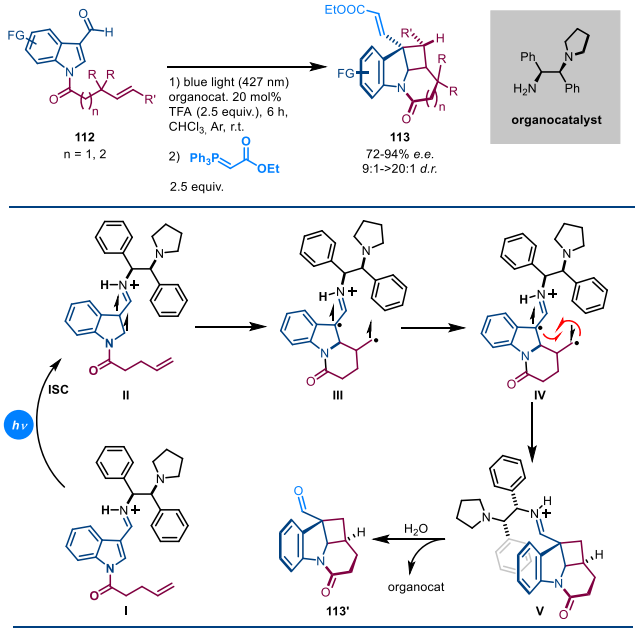


SCHEME 32 | Photoinduced rearrangement of 1-hydroxyazepino[1,2-a]indole derivatives: access to cyclobuta[*b*]indole scaffolds.

intramolecular reaction with a tethered thiophene moiety, leading to the formation of a spiro indoline–isothiazolidin-3-one 1,1-dioxide **II** biradical intermediate. Rapid radical recombination then furnishes the corresponding fused pentacyclic product **103** [113]. In contrast, substitution of the *N*-alkyl group with an *N*-allyl substituent (**102b**) diverts the reaction pathway, resulting in the formation of a hexahydro-1H-pyrrolo[3,4:1,4]cyclobuta[1,2-b]indol-1-one (Scheme 31b) derivative **104**. This outcome arises from a competing intramolecular reaction involving the alkenyl group and proceeds through a more conventional [2 + 2] cycloaddition manifold. Notably, replacement of the thiophene unit with an aryl substituent (**105**) suppresses the double photoinduced dearomatization [114], instead yielding 2-arylindoles **106** via C—S bond cleavage (Scheme 31c). This divergence was attributed by the authors to the substantial difference between the rate constants for C—S bond cleavage and ISC in benzenoid derivatives, which display greater kinetic resistance toward [2 + 2] cycloaddition pathways.

The synthesis of polycyclic cyclobuta[*b*]indole derivatives was already reported in the 1980s by Hayes and Jones [115], who explored the photochemical response of 1-hydroxyazepino[1,2-a]indole **107**. Upon irradiation with a Hanovia medium-pressure mercury lamp in methanol, these substrates afforded three distinct isomers, as depicted in Scheme 32. The authors observed that photoactivation of the azepine adduct partially led to the formation of allylic systems in which a molecule of MeOH was incorporated into the scheletal framework, yielding a mixture of methoxyallyl regioisomers **108** and **109**, along with a third product that was later identified as the fused cyclobuta[*b*]indole derivative **110**. The formation of these products was rationalized by invoking a cationic cyclopropyl intermediate, which evolves into the corresponding cyclobutane derivative through an initial 1,2-cyclopropane ring expansion followed by nucleophilic attack by the alcohol species.

During the preparation of this review, Dell'Amico and co-workers reported a novel approach based on the photoexcitation of a chiral iminium ion to achieve the intramolecular radical dearomatization of 3-carboxyindoles **112** [116]. While photoexcited iminium ions typically exhibit S_1-state reactivity, modulation of their photophysical properties through conjugation with a heteroaromatic ring was shown to overcome this limitation, thereby enabling access to T_1-state reactivity. Specifically, condensation of 3-indolecarbaldehydes **112** with a chiral amine catalyst generates the corresponding chiral iminium ion **I**, which upon photoexcitation is promoted to the singlet excited state and subsequently undergoes ISC to the triplet manifold **II**. In its triplet state, this intermediate engages in an intramolecular, stereoselective dearomative [2 + 2] cycloaddition via a diradical



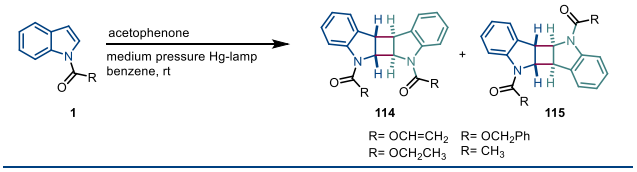
SCHEME 33 | [2 + 2] intramolecular dearomative photocyclization of chiral iminium indoles.

coupling pathway (**IV** → **V**). Subsequent hydrolysis releases the corresponding indolyl-cyclobutane derivatives **113** in good yields, with high enantioselectivity and excellent diastereoselectivity (Scheme 33).

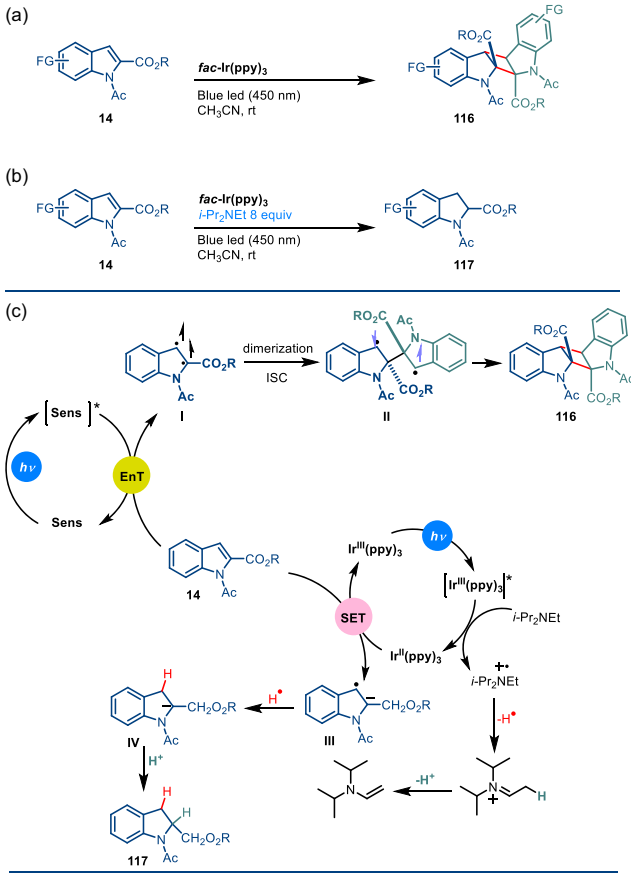
5 | [2 + 2] Photodimerization Processes

In 1993, Oldroyd and co-workers investigated the selective photodimerization of acylindoles **1** in the presence of AP as a triplet sensitizer under UV irradiation [56]. Under these conditions, the photodimerization was significantly accelerated compared to the uncatalyzed process, while competing photo-Fries rearrangement pathways were effectively suppressed. The methodology was subsequently extended to a range of *N*-protected indoles, including *N*-ethoxycarbonylindole, *N*-benzyloxycarbonylindole, *N*-phenoxycarbonylindole, and *N*-acetylindole, providing the corresponding head-to-head **114** and head-to-tail dimers **115** in moderate to good yields (Scheme 34).

A visible-light-induced divergent dearomatization of indoles was also reported by Huang and Zhang, who achieved the formation of cyclobutane-fused pentacyclic derivatives **116** with an *anti* head-to-head configuration [117] using Ir(ppy)$_3$ as PS, under blue light irradiation (Scheme 35a). Moreover, when the reaction was conducted in the presence of *N*, *N*-diisopropylethylamine as an



SCHEME 34 | Photoinduced head-to-head and head-to-tail dimerization of acylindoles.



SCHEME 35 | Head-to-head photodimerization of *N*-acyl indoles catalyzed by *fac*-Ir(ppy)$_3$ complexes. (a) General *N*-acylindoles dimerization. (b) Isolation of *N*-acylindoles under the operational reaction conditions. (c) Proposed reaction mechanism.

additive, a catalytic reduction pathway became operative, enabling access to 2-substituted indolines **117**.

To rationalize these divergent outcomes, the authors proposed two distinct reaction mechanisms. In the photodimerization manifold, an EnT process was invoked (Scheme 35c), whereas in the reductive pathway a SET mechanism accounts for the formation of the reduced products **117**.

6 | [2 + 2] Heterocycloadditions of Indoles

The Paternò–Büchi reaction represents one of the most efficient and well-established synthetic strategies for the construction of oxetane derivatives since its discovery [118]. This transformation relies on the photoexcitation of carbonyl compounds (aldehydes or ketones), which are promoted from the ground state to the singlet excited state ($n \rightarrow \pi^*$). In this excited state, carbonyl compounds readily react with variously substituted alkenes, leading to the formation of four-membered oxygen-containing heterocycles with a high degree of stereo- and regioselectivity.

Alternatively, carbonyl compounds may undergo ISC from their short-lived singlet excited state (S_1) to the corresponding triplet excited state (T_1), generating biradical species with significantly longer lifetimes [119]. In addition, relatively stable exciplexes can

form upon interaction between an excited carbonyl compound and an alkene C═C double bond. In such cases, the reaction proceeds via a stepwise mechanism: initial formation of a new C—O bond generates a 1,4-biradical intermediate, which then undergoes spin inversion followed by C—C bond formation to furnish functionalized oxetanes.

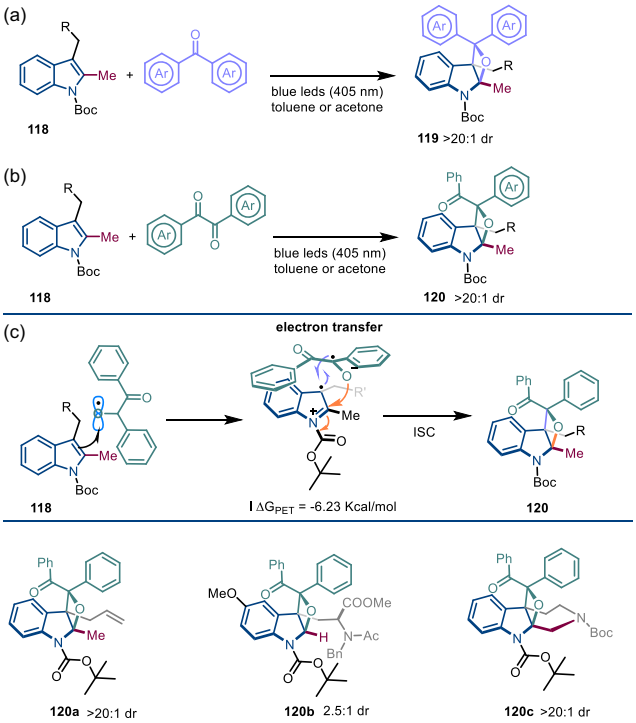
The regioselectivity of the Paternò–Büchi reaction is strongly influenced by the electronic properties of the alkene. Carbonyl compounds in their $n \rightarrow \pi^*$ excited state display amphoteric character: population of the π^* orbital renders the π system relatively electron-rich, while the nonbonding (n) orbital on oxygen remains electron-deficient [120, 121]. Consequently, electron-rich and electron-poor alkenes exhibit distinct regioselectivity patterns. Furthermore, a series of studies have demonstrated that both temperature and solvent effects play a crucial role in controlling the reaction outcome, enabling access to novel molecular architectures with moderate to high levels of stereo- and regioselectivity.

In recent years, the Paternò–Büchi reaction has experienced a renaissance, with several important extensions reported. These include the development of highly enantioselective variants [122], as well as the replacement of carbonyl compounds with imides (aza-Paternò–Büchi) [123–125] or thioketones (thia-Paternò–Büchi) [126, 127] to access structurally complex 3D frameworks. These transformations, activated either directly by light or through photosensitization, provide efficient routes to azetidine and thietane scaffolds. Although indoles readily engage in photoinduced reactions with carbonyl and imine derivatives, enabling a variety of [2 + 2] dearomative cycloaddition strategies, no examples of fused thienyl-indole systems have been reported to date.

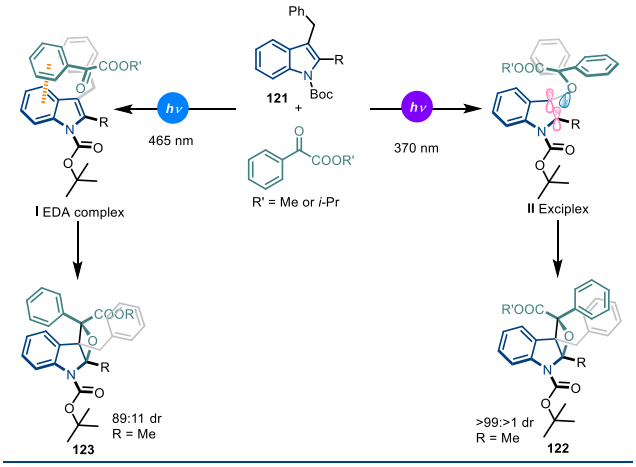
In this context, light-driven Paternò–Buchi [128, 129] [2 + 2] dearomative heterocycloadditions of indoles with ketones have been investigated by Companyó and Dell'Amico [130]. In their study, they revealed that both regio- and diastereoselection can be imposed during the cycloaddition process using mild visible-light conditions and accessing to a variety of polycyclic compounds in excellent yields and high diastereoselectivity (Scheme 36).

These results have been rationalized by evoking a photoelectron transfer (PET) process from the indole 118 to the excited diarylketone (or diaril diketone). These would generate biradical species that interacting with the indole would lead to the formation of *cis*-oxetanes 119 or 120. Moreover, the distereoselectivity of this photochemical process is strongly dependent on the steric relationships between the reagents and by π–π interactions between the aromatic moieties of both indole and the ketones.

Further investigations in this domine from the same research group [131, 132] concerning the reactivity of functionalized indoles with α-ketoesters highlighted that diastereoselection in [2 + 2] dearomative Paternò–Buchi-type reactions can be imposed during the cycloaddition process by modulating the light source (Scheme 37). Reactions performed at 390 nm proceed by the photoexcitation of the ketone to its triplet state by ISC and generating a biradical species, classically elicited in this kind of reactions. Formation of an exciplex between the indole 121 and the carbonyl compound through n_p–π interactions is responsible



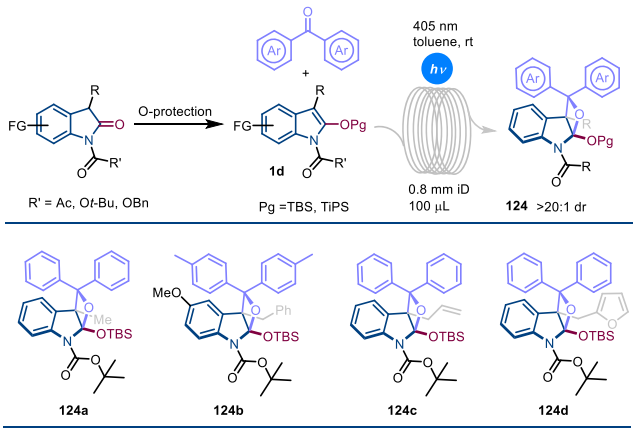
SCHEME 36 | Light-driven Paternò–Buchi [2 + 2] dearomative heterocycloadditions of indoles and ketones via photoelectron transfer (PET).



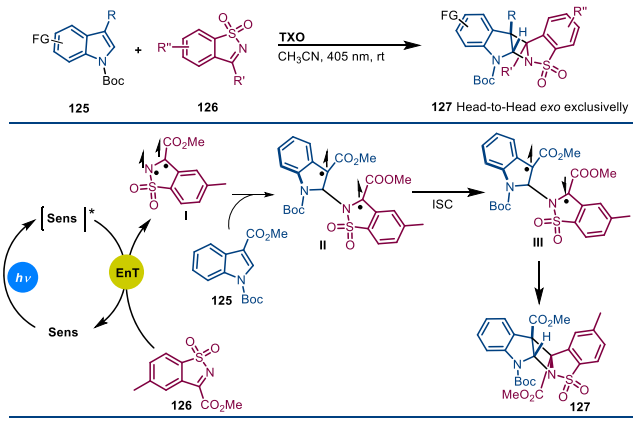
SCHEME 37 | Light irradiation-dependent regio- and diastereoselective Paternò–Buchi [2 + 2] dearomatization of *N*-Boc indoles.

to access in good yields, tricyclic oxetane indole-2-carboxylates 122 with high diastereoselectivity (>99:<1) driven by steric effects. On the other hand, reactions carried out under visible light (465 nm) favor the excitation of a *N*-Boc-idole and the PET to the ketone. As reported above [131], this process would allow rapid [2 + 2] cycloaddition of the two reaction partners via EDA-complex, reducing erosion of the stereochemistry and accessing to derivatives 123.

The extension of this reaction to oxindole enol-ethers and aromatic ketones under microfluidic conditions was also reported, enabling access to a series of novel polycyclic oxetane scaffolds **124** via Paternò–Büchi [2 + 2] dearomatization with high stereoselectivity (>20:1) and excellent yields (up to 98%) [132]. The use



SCHEME 38 | Continuous flow diastereoselective Paternò–Buchi [2 + 2] dearomatization of 2-O protected *N*-acyl indoles.

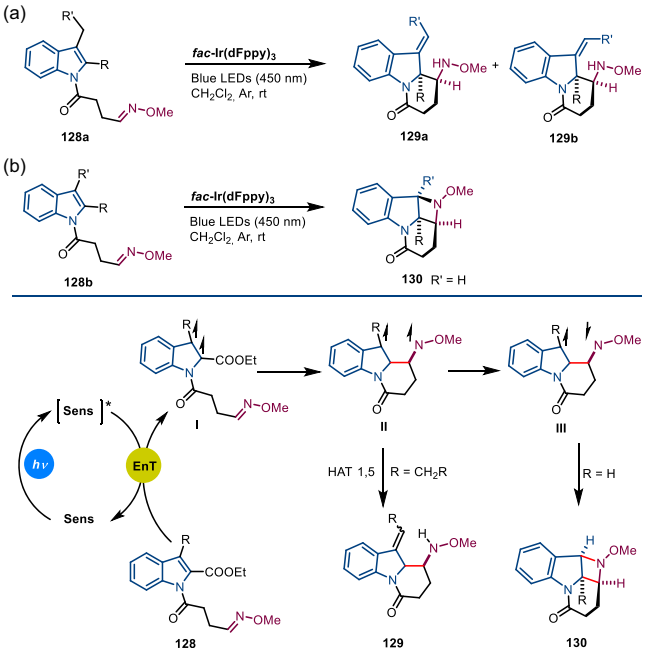


SCHEME 39 | Potoinduces head-to-head cycloaddition of Boc indoles with isothiazole derivatives.

of visible light (405 nm) in combination with continuous-flow technology allowed the authors to drastically suppress the formation of benzophenone homodimers, which arise from the triplet excited state of benzophenone, while maximizing productive cross-reactivity between the indole-derived substrate and the ketone. On the other hand, this approach afforded clean, safe, highly reproducible, and efficient transformations. Notably, the process could be readily scaled up to gram scale providing difunctionalized oxindole products without loss of efficiency. Moreover, an efficient two-step telescoped version of this synthetic strategy, starting directly from oxindole, was developed, as illustrated in Scheme 38.

A straightforward intermolecular aza-Paternò–Büchi [133–135] [2 + 2] dearomative photocycloaddition of indoles **125** with benzo[*d*]isothiazole derivatives **126** has been reported by Liao and Zhong [136]. This transformation is initiated by the photoexcitation of TXT [137] that promoted to its triplet state is enrolled in an EnT to the benzoisothiazole. The benzothiazole biradical species **I** reacts with the indole through the formation of a C—N bond step **II,** which is followed by ISC. Further radical coupling give access to a large number of ladder-shape azetidine-fused indoline pentacycles **127** with *exo*-stereoselectivity and divergent head-to-head/head-to-tail regioselectivity as reported in Scheme 38. In deep quantum mechanical calculations and control experiments were performed to elucidate both the reaction mechanism and the origin of the selectivity. This protocol was also extended to other aza-Paternò–Büchi dearomative [2 + 2] photocyclizations by substituting the indole scaffold **125** with benzofuran, thionaphthene, and indenyl derivatives, accessing the corresponding fused pentacyclic compounds in good yields and selectivity (Scheme 39).

An alternative intramolecular [2 + 2] dearomative cycloaddition of indole-functionalized O-methyl oximes **128** (E_T: 2.36 eV, 54.4 kcal/mol) was reported by You and co-workers in 2020 [138]. The reaction is initiated by light absorption of *fac*-Ir(dFppy)$_3$ and proceeds through an EnT process, generating intermediate **I**, which subsequently evolves into **II**. ISC followed by spin reversion and radical coupling enables access to indolyl azetidines **130** when the C3 position of the indole bears a hydrogen atom. The process is characterized by high levels of diastereoselectivity and generally affords tetracyclic derivatives in excellent yields.



SCHEME 40 | Dearomative intramolecular [2 + 2] cycloaddition of indole tethered O-methyl oximes. (a) intramolecular photocyclization of 3-alkylindoles leading to the formation of tricyclic alkylidene indolone oximes. (b) Synthesis of tetracyclic azetidin-indolidin derivatives.

In contrast, when the C3 position is substituted with a methyl or other alkyl groups, formation of the bond between the C2 carbon of the indole and the sp^2 carbon of the oxime unit is followed by a HAT rearrangement, leading exclusively to derivatives **129**, as shown in Scheme 40.

7 | Authors' Perspective and Closing Remarks

The use of light as a traceless reagent for the construction of complex molecular architectures has reached a remarkable level of sophistication and selectivity. This evolution has been driven by the development of advanced photophysical tools enabling detailed interrogation of excited states, alongside their broad adoption within the synthetic community. Together, these

advances have enabled robust, scalable, and environmentally benign methodologies [139], providing access to molecular frameworks that are often difficult or impossible to achieve through thermal approaches [140]. In parallel, the design of increasingly efficient organic PSs has begun to rival the performance of traditional transition-metal complexes, significantly reducing reliance on scarce and toxic elements [141, 142]. Coupled with the widespread availability of tunable LED light sources [143, 144] and the emergence of enabling technologies such as continuous-flow photochemistry [145], modern photocatalysis has evolved into a powerful and practical platform for synthesis. Within this context, the photoinduced dearomative [2 + 2] cycloaddition of indoles has matured into a versatile strategy for the rapid construction of cyclobutane-fused indoline architectures. The transition from UV-driven processes to visible-light-mediated EnT catalysis represents a decisive conceptual advance, enabling precise control over chemo-, regio-, and stereoselectivity while minimizing undesired side reactivity. Crucially, it is now evident that reactivity in these systems is governed less by substrate structure alone than by the careful orchestration of photophysical parameters. Matching sensitizer and substrate triplet energies, selecting appropriate irradiation wavelengths, and tuning the reaction environment have collectively transformed these transformations into predictable and programmable processes. In this regard, visible-light EnT catalysis most commonly mediated by Ir- and Ru-based complexes remains the most general and reliable platform, typically delivering high yields and selectivities under mild conditions. However, a critical analysis of the reaction landscape reveals that optimal performance is highly condition-dependent and far from universal. With regard to catalyst design, organic sensitizers including carbazole-based systems, TXT derivatives, and emerging TADF materials have demonstrated increasingly competitive performance, in some cases matching metal-based systems in efficiency and selectivity. Nevertheless, their broader applicability is often constrained by narrower energetic windows and reduced tolerance to structural variation, indicating that no truly universal sensitizer platform has yet emerged. Regarding the indole reactivity, substrate activation through *N*-protection is often indispensable, with acyl- and carbamate-protected indoles displaying markedly superior reactivity compared to unprotected or *N*-alkyl analogs, which are frequently unreactive. Similarly, electron-deficient olefins are consistently preferred partners, highlighting an intrinsic limitation in substrate scope for intermolecular variants. Reaction media also exert a noninnocent role: hydrogen-bonding solvents such as fluorinated alcohols can modulate triplet-state energetics, enabling transformations that are otherwise inaccessible, whereas "on-water" conditions can significantly accelerate reactivity. Selectivity remains a central challenge. From a scope perspective, intramolecular [2 + 2] cycloadditions generally offer superior levels of regio- and stereocontrol, enabling efficient access to highly complex polycyclic architectures. In contrast, intermolecular processes, while conceptually more versatile, remain more sensitive to competing pathways and substrate-dependent effects. Despite substantial progress, the field still shows a pronounced bias toward activated indoles and electronically predisposed reaction partners, leaving unactivated systems largely underexplored. Looking forward, several key challenges must be addressed to unlock the full potential of this chemistry. The development of general catalyst selection principles based on predictive triplet-energy relationships, rather than empirical screening, would represent a major conceptual advance. Likewise, the realization of cascade and multicomponent photochemical processes currently rare in this area could dramatically enhance molecular complexity generation and synthetic efficiency. Continued progress in catalytic enantioselective variants, particularly those not relying on highly specialized architectures, will also be essential for broader application. At the interface of synthesis and engineering, emerging technologies are poised to play a decisive role. Continuous flow photochemistry, microfluidic platforms, and solvent-minimized or mechanochemical approaches offer clear advantages in scalability and sustainability. In particular, photo-mechanochemical strategies, which could eliminate solvents entirely, represent an intriguing yet largely unexplored direction [146, 147]. Ultimately, indole dearomatization via [2 + 2] photocycloaddition has evolved far beyond a niche photochemical transformation. It now stands as a powerful strategy for converting simple aromatic precursors into 3D, functionally rich architectures. Continued progress driven by advances in catalyst design, reaction engineering, and photophysical understanding will not only expand the scope of this methodology but also contribute to defining more sustainable paradigms in synthetic organic chemistry.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

References

1. A. Dorababu, "Indole – A Promising Pharmacophore in Recent Antiviral Drug Discovery," *RSC Medicinal Chemistry* 11 (2020): 1335–1353.

2. A. Kumari, and R. K. Singh, "Medicinal Chemistry of Indole Derivatives: Current to Future Therapeutic Prospectives," *Bioorganic Chemistry* 89 (2019): 103021.

3. N. Chadha and O. Silakari, "Indoles as Therapeutics of Interest in Medicinal Chemistry: Bird's Eye View," *European Journal of Medicinal Chemistry* 134 (2017): 159–184.

4. M. M. Heravi, Z. Amiri, K. Kafshdarzadeh, and V. Zadsirjan, "Synthesis of Indole Derivatives as Prevalent Moieties Present in Selected Alkaloids," *RSC Advances* 11 (2021): 33540–33612.

5. M. Géraldy, M. Morgen, P. Sehr, et al., "Selective Inhibition of Histone Deacetylase 10: Hydrogen Bonding to the Gatekeeper Residue Is Implicated," *Journal of Medicinal Chemistry* 62 (2019): 4426–4443.

6. M. Demurtas, A. Baldisserotto, I. Lampronti, et al., "Indole Derivatives as Multifunctional Drugs: Synthesis and Evaluation of Antioxidant, Photoprotective and Antiproliferative Activity of Indole Hydrazones," *Bioorganic Chemistry* 85 (2019): 568–576.

7. M. Hassam, A. E. Basson, D. C. Liotta, L. Morris, W. A. L. van Otterlo, and S. C. Pelly, "Novel Cyclopropyl-Indole Derivatives as HIV Non-Nucleoside Reverse Transcriptase Inhibitors," *ACS Medicinal Chemistry Letters* 3 (2012): 470–475.

8. A. Citarella, D. Moi, M. Pedrini, et al., "Synthesis of SARS-CoV-2 M^{pro} Inhibitors Bearing a Cinnamic Ester Warhead with *In Vitro* Activity against Human Coronaviruses," *Organic & Biomolecular Chemistry* 21 (2023): 3811–3824.

9. T. Saini, S. Kumar, and B. Narasimhan, "Central Nervous System Activities of Indole Derivatives: An Overview," *Central Nervous System Agents in Medicinal Chemistry* 16 (2015): 19–28.

10. Y. Y. Li, H. S. Wu, L. Tang, et al., "The Potential Insulin Sensitizing and Glucose Lowering Effects of a Novel Indole Derivative In Vitro and In Vivo," *Pharmacological Research* 56 (2007): 335–343.

11. M. Z. Zhang, N. Mulholland, D. Beattie, et al., "Synthesis and Antifungal Activity of 3-(1,3,4-Oxadiazol-5-Yl)-Indoles and 3-(1,3,4-Oxadiazol-5-Yl)methyl-Indoles," *European Journal of Medicinal Chemistry* 63 (2013): 22–32.

12. B. L. Diss, S. D. Robinson, Y. Wu, S. Fidalgo, M. S. Yeoman, and B. A. Patel, "Age-Related Changes in Melatonin Release in the Murine Distal Colon," *ACS Chemical Neuroscience* 5 (2013): 879–887.

13. I. Yalug, A. E. Tufan, and L. Kayaalp, "Quetiapine May Be Associated With New-Onset Seizures in Patients With Seizurogenic Conditions," *The Journal of Neuropsychiatry and Clinical Neurosciences* 19 (2007): 341–342.

14. S. Sagi, B. Avula, Y. H. Wang, and I. A. Khan, "Quantification and Characterization of Alkaloids from Roots of Rauwolfia Serpentina Using Ultra-High Performance Liquid Chromatography-Photo Diode Array-Mass Spectrometry," *Analytical and Bioanalytical Chemistry* 408 (2016): 177–190.

15. K. Pathak, M. P. Pathak, R. Saikia, et al., "Cancer Chemotherapy via Natural Bioactive Compounds," *Current Drug Discovery Technologies* 19 (2022): 1–20.

16. N. K. Kaushik, N. Kaushik, P. Attri, et al., "Biomedical Importance of Indoles," *Molecules* 18 (2013): 6620–6662.

17. R. J. Sundberg, *Indoles*, (Academic Press, 1996). 1–171.

18. M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes, and D. Blanco-Ania, "Cyclobutanes in Small-Molecule Drug Candidates," *ChemMedChem* 17, no. 9 (2022): e202200020.

19. F. Turnu, A. Luridiana, A. Cocco, et al., "Catalytic Tandem Friedel–Crafts Alkylation/C4–C3 Ring-Contraction Reaction: An Efficient Route for the Synthesis of Indolyl Cyclopropanecarbaldehydes and Ketones," *Organic Letters* 21, no. 18 (2019): 7329–7332.

20. S. Porcu, C. A. Rodriguez, A. Frongia, and F. Secci, "A Catalytic One-Pot Synthesis of Indolyl Cyclobutanones," *Synthesis* 53 (2021): 925–932.

21. A. M. Bernard, A. Frongia, F. Secci, and P. P. Piras, "2,2-Dimethyl Cyclopentanones by Acid Catalyzed ring Expansion of Isopropenylcyclobutanols. A Short Synthesis of (±)-α-Cuparenone and (±)-Herbertene," *Chemical Communications* (2005): 3853–3855.

22. A. M. Bernard, A. Frongia, R. Guillot, P. P. Piras, F. Secci, and M. Spiga, "L -Proline-Catalyzed Direct Intermolecular Asymmetric Aldol Reactions of 1-Phenylthiocycloalkyl Carboxaldehydes with Ketones. Easy Access to Spiro- and Fused-Cyclobutyl Tetrahydrofurans and Cyclopentanones," *Organic Letters* 9 (2007): 541–544.

23. D. J. Aitken, A. M. Bernard, F. Capitta, et al., "Very High Stereoselectivity in Organocatalyzed Desymmetrizing Aldol Reactions of 3-Substituted Cyclobutanones," *Organic & Biomolecular Chemistry* 10 (2012): 5045–5048.

24. B. J. Wilson, C. H. Wilson, and A. W. Hayes, "Tremorgenic Mycotoxins Produced by Strains of Penicillium Spp. Isolated from Toxic Poa Huecu Parodi," *Nature* 1968 (2020): 77–78.

25. A. A. El-Banna and L. Leistner, "Production of penitrem A by Penicillium crustosum isolated from foodstuffs," *International Journal of Food Microbiology* 7 (1988): 9–17.

26. B. M. Trost and J. Quancard, "Palladium-Catalyzed Enantioselective C-3 Allylation of 3-Substituted-1 *H*-Indoles Using Trialkylboranes," *Journal of the American Chemical Society* 128 (2006): 6314–6315.

27. H. Ishikawa, D. A. Colby, S. Seto, et al., "Total Synthesis of Vinblastine, Vincristine, Related Natural Products, and Key Structural Analogues," *Journal of the American Chemical Society* 131 (2009): 4904–4916.

28. T. Bach and J. P. Hehn, "Photochemical Reactions as Key Steps in Natural Product Synthesis," *Angewandte Chemie, International Edition* 50 (2011): 1000–1045.

29. L. Jiao, E. Herdtweck, and T. Bach, "Pd(II)-Catalyzed Regioselective 2-Alkylation of Indoles via a Norbornene-Mediated C–H Activation: Mechanism and Applications," *Journal of the American Chemical Society* 134 (2012): 14563–14572.

30. G. Yang, P. Lindovska, D. Zhu, et al., "Pd(II)-Catalyzed *meta* -C–H Olefination, Arylation, and Acetoxylation of Indolines Using a U-Shaped Template," *Journal of the American Chemical Society* 136 (2014): 10807–10813.

31. K. Liu, W. Song, Y. Deng, et al., "Electrooxidation Enables High Regioselective Dearomative Annulation of Indole and Benzofuran Derivatives," *Nature Communications* 11 (2020): 1–11.

32. L. Zhang, "Tandem Au-Catalyzed 3,3-Rearrangement−[2 + 2] Cycloadditions of Propargylic Esters: Expeditious Access to Highly Functionalized 2,3-Indoline-Fused Cyclobutanes," *Journal of the American Chemical Society* 127 (2005): 16804–16805.

33. D. Zhao, J. Zhang, and Z. Xie, "Dearomative [2 + 2] Cycloaddition and Formal C–H Insertion Reaction of *o*-Carboryne with Indoles: Synthesis of Carborane-Functionalized Heterocycles," *Journal of the American Chemical Society* 137 (2015): 9423–9428.

34. T. Miyoshi, Y. Aoki, Y. Uno, et al., "Michael Addition–Aromatization Reaction of Dienylimines Bearing a Leaving Group and Its Application to the Preparation of Thiol-Selective Labeling Reagents Capable of Forming Strong Carbon–Sulfur Bonds," *The Journal of Organic Chemistry* 78 (2013): 11433–11443.

35. R. Ocello, A. De Nisi, M. Jia, et al., "Gold(I)-Catalyzed Dearomative [2 + 2]-Cycloaddition of Indoles with Activated Allenes: A Combined Experimental–Computational Study," *Chemistry – A European Journal* 21 (2015): 18445–18453.

36. M. Jia, M. Monari, Q.-Q. Yang, and M. Bandini, "Enantioselective gold catalyzed dearomative [2 + 2]-cycloaddition between indoles and allenamides," *Chemical Communications* 51 (2015): 2320–2323.

37. R. K. Nandi, R. Guillot, C. Kouklovsky, and G. Vincent, "Synthesis of 3,3-Spiroindolines via $FeCl_3$-Mediated Cyclization of Aryl- or Alkene-Containing 3-Substituted N–Ac Indoles," *Organic Letters* 18 (2016): 1716–1719.

38. R. M. Neyyappadath, M. D. Greenhalgh, D. B. Cordes, A. M. Z. Slawin, and A. D. Smith, "Synthesis of Fused Indoline-cyclobutanone Derivatives Via an Intramolecular [2 + 2] Cycloaddition," *European Journal of Organic Chemistry* 31 (2019): 5169–5174.

39. A. Weedon, "The Photochemistry of Indoles," *Advances in Photochemistry* (Wiley, 1997), 22.

40. C. G. Chen, M. Giustini, M. D'Abramo, and A. Amadei, "Unveiling the Excited State Dynamics of Indole in Solution," *Journal of Chemical Theory and Computation* 19, no. 13 (2023): 4114–4124.

41. A. Giussani, M. Merchán, D. Roca-Sanjuán, and R. Lindh, "Essential on the Photophysics and Photochemistry of the Indole Chromophore by

Using a Totally Unconstrained Theoretical Approach," *Journal of Chemical Theory and Computation* 7, no. 12 (2011): 4088–4096.

42. D. C. Neckers and A. H. A. Tinnemans, "Photochemical Addition Reactions in the Benzo[b]Thiophene, Benzo[b]Furan, and Indole Series," in *Synthetic Organic Photochemistry*, ed. W. M. Horspool (Springer, 1984).

43. H. Cao, J. Hall, and R. Hille, "Substrate Orientation and Specificity in Xanthine Oxidase: Christal Structures of the Enzyme in Complex with Indole-3-acetaldehyde and Guanine," *Biochemistry* 53, no. 3 (2014): 533–554.

44. J. Catalán, "The First UV Absorption Band for Indole Is Not due to Two Simultaneous Orthogonal Electronic Transitions Differing in Dipole Moment," *Physical Chemistry Chemical Physics* 17 (2015): 12515–12520.

45. A. Chrostowska, S. Xu, A. Mazière, et al., "UV-Photoelectron Spectroscopy of BN Indoles: Experimental and Computational Electronic Structure Analysis," *Journal of the American Chemical Society* 136, no. 33 (2014): 11813–11820.

46. R. Ragone, G. Colonna, L. Servillo, and G. Irace, "Resolution of Overlapping Bands in the Near-UV Absorption Spectrum of Indole Derivatives," *Photochemistry and Photobiology* 42, no. 5 (1985): 505–508.

47. E. H. Strickland, J. Horwitz, and C. Billups, "*Near-Ultraviolet Absorption Bands of Tryptophan. Studies Using Indole and 3-Methylindole as Models*," 9, no. 25 (1970): 4914–4921.

48. A. Peralta Conde, V. Ovejas, R. Montero, F. Castaño, and A. Longarte, "Influence of Solvation on the Indole Photophysics: Ultrafast Dynamics of Indole–Water Clusters," *Chemical Physics Letters* 530 (2012): 25–30.

49. B. L. van Duuren, "Solvent Effects in the Fluorescence of Indole and Substituted Indoles[1]," *The Journal of Organic Chemistry* 26, no. 8 (1961): 2954–2960.

50. M. Krishnamurthy, A. K. Mishra, and S. K. Dogra, "Solvent Effects on the Electronic Absorption and Fluorescence Spectra of Indole-4-Carboxylic Acid: Prototropic Equilibria in Aqueous Solutions," *Photochemistry and Photobiology* 45, no. 3 (1987): 359–364.

51. C. J. Fischer, A. Gafni, D. G. Steel, and J. A. Schauerte, "The Triplet-State Lifetime of Indole in Aqueous and Viscous Environments: Significance to the Interpretation of Room Temperature Phosphorescence in Proteins," *Journal of the American Chemical Society* 124, no. 35 (2002): 10359–10366.

52. O. Younis, M. Sayed, A. A. K. Mohammed, et al., "Solid-State Luminescent Materials Containing both Indole and Pyrimidine Moieties: Design, Synthesis, and Density Functional Theory Calculations," *ACS Omega* 7, no. 17 (2022): 15016–15026.

53. Y. Chen, J. Xie, Z. Wang, et al., "Highly Efficient Bipolar Host Material Based-on Indole and Triazine Moiety for Red Phosphorescent Light-Emitting Diodes," *Dyes and Pigments* 124 (2016): 188–195.

54. G. Chang, L. Yang, S. Liu, X. Luo, R. Lin, and L. Zhang, "Synthesis of Indole-Based Functional Polymers with Well-Defined Structures via a Catalyst-Free C—N Coupling Reaction," *RSC Advances* 4 (2014): 30630–30637.

55. B. Baruah, C. D. Pegu, and M. L. Deb, "Indole as a Versatile Building Block in Cycloaddition Reactions: Synthesis of Diverse Heterocyclic Frameworks," *Topics in Current Chemistry* 382 (2024): 18.

56. D. L. Oldroyd, N. C. Payne, J. J. Vittal, A. C. Weedon, and B. Zhang, "Photochemical Dimerization Reactions of N-Acylindoles," *Tetrahedron Letters* 34, no. 7 (1993): 1087–1090.

57. D. R. Julian and G. D. Tringham, "Photoaddition of Ketones to Indoles: Synthesis of Oxeto[2,3-b]Indoles," *Journal of the Chemical Society, Chemical Communications* (1973): 13–14.

58. M. V. Bobo, J. J. Kuchta, and A. K. Vannucci, "Recent Advancements in the Development of Molecular Organic Photocatalysts," *Organic & Biomolecular Chemistry* 19 (2021): 4816–4834.

59. Y. Du, R. M. Pearson, C.-H. Lim, et al., "Strongly Reducing, Visible-Light Organic Photoredox Catalysts as Sustainable Alternatives to Precious Metals," *Chemistry–A European Journal* 23, no. 46 (2017): 10962–10968.

60. R. Ballardini, G. Varani, M. T. Indelli, F. Scandola, and V. Balzani, "Free Energy Correlation of Rate Constants for Electron Transfer Quenching of Excited Transition Metal Complexes," *Journal of the American Chemical Society* 100, no. 23 (1978): 7219–7223.

61. J. K. Matsui, S. B. Lang, D. R. Heitz, and G. A. Molander, "Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development," *ACS Catalysis* 7, no. 4 (2017): 2563–2575.

62. C. K. Prier, D. A. Rankic, and D. W. C. MacMillan, "Visible light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis," *Chemical Reviews* 113, no. 7 (2013): 5322–5363.

63. F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer, and F. Glorius, "Energy Transfer Catalysis Mediated by Visible Light: Principles, Applications, Directions," *Chemical Society Reviews* 47 (2018): 7190–7202.

64. S. Dutta, J. E. Erchinger, F. Strieth-Kalthoff, R. Kleinmans, and F. Glorius, "Energy Transfer Photocatalysis: Exciting Modes of Reactivity," *Chemical Society Reviews* 53 (2024): 1068–1089.

65. F. Strieth-Kalthoff and F. Glorius, "Triplet Energy Transfer Photocatalysis: Unlocking the Next Level," *Chem* 6, no. 8(2020): 1888–1903.

66. M. H. Shaw, J. Twilton, and D. W. C. MacMillan, "Photoredox Catalysis in Organic Chemistry," *The Journal of Organic Chemistry* 81 (2016): 6898–6926.

67. H. Cui, B. An, and X. Zhang, "Photosensitized Dearomatizations of (Hetero)Arenes," in *Dearomatizations*, ed. D. Sarlah (Thieme, 2025), https://doi.org/10.1055/sos-SD-245-00122.

68. D. R. Julian and R. Foster, "Photoaddition of Olefins to Indoles: Synthesis of Tetrahydro-1H-Cyclobut[b]indoles," *Journal of the Chemical Society, Chemical Communications* 1 (1973): 311–312.

69. B. W. Disanayaka and A. C. Can Weedon, "Charge Transfer Fluorescence of some N-Benzoylindoles," *Journal of Chemistry* 65 (1987): 245–250.

70. H.-N. Na, M. Kim, L.-I. Shen, and J. H. Jeong, "Introduction of the Acyl Group at the C7 Position of Indole via *N* -Acyl Indole Photo-Fries Rearrangement Under UV-C," *Journal of Heterocyclic Chemistry* 62, no. 11 (2025): 1834–1839.

71. A. C. Weedon and B. Zhang, "Removable Groups for Activation of Indole Photochemistry," *Synthesis* 1992, no. 01/02 (1992): 95–100.

72. V. I. Martin, J. R. Goodell, O. J. Ingham, J. A. Porco Jr, and A. B. Beeler, "Multidimensional Reaction Screening for Photochemical Transformations as a Tool for Discovering New Chemotypes," *The Journal of Organic Chemistry* 79 (2014): 3838–3846.

73. J. P. Benner, G. B. Gill, S. J. Parrott, and B. Wallace, "Some Aspects of the Chemistry of 1,1,1-trihalogenoalk-4-en-2-ols," *Journal of the Chemical Society, Perkin Transactions* 1 (1984): 331–342.

74. M. B. Zimmt, C. Doubleday Jr., I. R. Gould, and N. J. Turro, "Nanosecond Flash Photolysis Studies of Intersystem Crossing Rate Constants in Biradicals: Structural Effects Brought about by Spin-Orbit Coupling," *Journal of the American Chemical Society* 107, no. 23 (1985): 6724–6726.

75. D. J. Hasting and A. C. Weedon, "Structures and Lifetimes of 1, 4-Biradical Intermediates in the Photochemical Cycloaddition Reactions of N-Benzoylindole with Alkenes," *Journal of Organic Chemistry* 56 (1991): 6326.

76. P. J. Wagner, K. C. Liu, and Y. Noguchi, "Monoradical Rearrangements of the 1, 4-Biradicals Involved in Norrish Type II Photoreactions," *Journal of the American Chemical Society* 103 (1981): 3837–3841.

77. A. J. Castellino and T. C. Bruice, "Intermediates in the Epoxidation of Alkenes by Cytochrome P-450 Models. 2. Use of the Trans-2, Trans-3-Diphenylcyclopropyl Substituent in a Search for Radical Intermediates," *Journal of the American Chemical Society* 110 (1988): 7512–7519.

78. X. Han, H. Li, R. P. Hughes, and J. Wu, "Gallium(III)-Catalyzed Three-Component (4 + 3) Cycloaddition Reactions," *Angewandte Chemie, International Edition* 51, no. 41 (2012): 10390–10393.

79. J. Ma, F. Schäfers, C. Daniliuc, K. Bergander, C. A. Strassert, and F. Glorius, "Gadolinium Photocatalysis: Dearomative [2 + 2] Cycloaddition/Ring-Expansion Sequence with Indoles," *Angewandte Chemie, International Edition* 59 (2020): 9639–9645.

80. Z. Han, L. Wang, Y. Luo, and X. Cui, "Photocatalytic Intermolecular [2 + 2] Cycloaddition/Dearomatization of Indoles: Easy Access to Cyclobutane-Fused Indolines," *Organic Chemistry Frontiers* 12 (2025): 3177–3183.

81. B. Cao, Y. Wei, and M. Shi, "An Atmosphere and Light Tuned Highly Diastereoselective Synthesis of Cyclobuta/Penta[*b*]indoles from Aniline-Tethered Alkylidenecyclopropanes with Alkynes," *Chemical Communications* 54 (2018): 2870–2873.

82. M. S. Oderinde, A. Ramirez, T. G. M. Dhar, et al., "Photocatalytic Dearomative Intermolecular [2 + 2] Cycloaddition of Heterocycles for Building Molecular Complexity," *The Journal of Organic Chemistry* 86 (2021): 1730–1747.

83. S. B. Kim, D. H. Kim, and H. Y. Bae, ""On-Water" Accelerated Dearomative Cycloaddition via Aquaphotocatalysis," *Nature Communications* 15 (2024): 3876, https://doi.org/10.1038/s41467-024-47861-w.

84. D. Parmar, E. Sugiono, S. Raja, and M. Rueping, "Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates," *Chemical Reviews* 114, no. 18 (2014): 9047–9153.

85. J. Wang, Q. Fu, S. Cao, et al., "Enantioselective [2 + 2] Photocycloreversion Enables De Novo Deracemization Synthesis of Cyclobutanes," *Journal of the American Chemical Society* 146, no. 32 (2024): 22840–22849.

86. D. K. Kölmel, A. S. Ratnayake, M. E. Flanagan, M.-H. Tsai, C. Duan, and C. Song, "Photocatalytic [2 + 2] Cycloaddition in DNA-Encoded Chemistry," *Organic Letters* 22, no. 8 (2020): 2908–2913.

87. L. Li, B. Matsuo, G. Levitre, et al., "Dearomative Intermolecular [2 + 2] Photocycloaddition for Construction of C(sp^3)-Rich Heterospirocycles on-DNA," *Chemical Science* 14 (2023): 2713–2720.

88. Y. Luo, C. Wang, Z. Han, J. Chen, and X. Cui, "Photocatalyzed Dearomative [2 + 2] Cycloaddition of Indoles with Alkynes to Access Cyclobutene-Fused Indolines," *Organic Letters* 27, no. 45 (2025): 12639–12644.

89. J. Yang, L. Yang, Y. Zhao, et al., "Asymmetric Dearomative [2 + 2] Photocycloaddition of Quinoline and Indole Derivatives with Bicyclo[1.1.0]butanes," *Journal of the American Chemical Society* 147, no. 39 (2025): 35755–35766.

90. N. Arai and T. Ohkuma, "Stereoselective Construction of Methylenecyclobutane-Fused Indolines through Photosensitized [2 + 2] Cycloaddition of Allene-Tethered Indole Derivatives," *Organic Letters* 21 (2019): 1506–1510.

91. N. Arai and T. Ohkuma, "Stereoselective Preparation of Methylenecyclobutane-Fused Angular Tetracyclic Spiroindolines via Photosensitized Intramolecular [2 + 2] Cycloaddition with Allene," *Tetrahedron Letters* 60 (2019): 151252.

92. M. Zhu, C. Zheng, X. Zhang, and S.-L. You, "Synthesis of Cyclobutane-Fused Angular Tetracyclic Spiroindolines via Visible-Light-Promoted Intramolecular Dearomatization of Indole Derivatives," *Journal of the American Chemical Society* 141 (2019): 2636–2644.

93. M. S. Oderinde, E. Mao, A. Ramirez, et al., "Synthesis of Cyclobutane-Fused Tetracyclic Scaffolds via Visible-Light Photocatalysis for Building Molecular Complexity," *Journal of the American Chemical Society* 142 (2020): 3094–3103.

94. A. B. Rolka and B. Koenig, "Dearomative Cycloadditions Utilizing an Organic Photosensitizer: An Alternative to Iridium Catalysis," *Organic Letters* 22 (2020): 5035–5040.

95. Z. Zhang, D. Yi, M. Zhang, et al., "Photocatalytic Intramolecular [2 + 2] Cycloaddition of Indole Derivatives via Energy Transfer: A Method for Late-Stage Skeletal Transformation," *ACS Catalysis* 10 (2020): 10149–10156.

96. M. Zhu, X.-L. Huang, H. Xu, X. Zhang, C. Zheng, and S.-L. You, "Visible-Light-Mediated Synthesis of Cyclobutene-Fused Indolizidines and Related Structural Analogs," *CCS Chemistry* 3 (2021): 652–664.

97. M. Zhu, H. Xu, X. Zhang, C. Zheng, and S. L. You, "Visible-Light-Induced Intramolecular Double Dearomative Cycloaddition of Arenes," *Angewandte Chemie, International Edition* 60 (2021): 7036–7040.

98. H. Li, Y. He, D. Zhang, et al., "Hydrogen Bond Serving as a Protecting Group to Enable the Photocatalytic [2 + 2] Cycloaddition of Redox-Active Aliphatic-Amine-Containing Indole Derivatives," *Chemical Communications* 58 (2022): 3194–3197.

99. N. Arai, "Formation of Anti-Bredt-Type Azabicyclo [4.2.0] Octene Frameworks through Photochemical Intramolecular [2 + 2] Cycloaddition between Indole and a Distal Double Bond of Allene," *Journal of Heterocyclic Chemistry* 60 (2023): 219–231.

100. N. Arai and T. Ohkuma, "Stereoselective Construction of Cycloheptene-Fused Indoline Frameworks through Photosensitised Formal [5 + 2] Cycloaddition," *Tetrahedron Letters* 88 (2022): 153588.

101. E. A. Martynova, V. A. Voloshkin, S. G. Guillet, et al., "Energy Transfer (EnT) Photocatalysis Enabled by Gold-N-Heterocyclic Carbene (NHC) Complexes," *Chemical Science* 13 (2022): 6852–6857.

102. X. Ma, V. A. Voloshkin, E. A. Martynova, et al., "Novel Dinuclear NHC-Gold (I)-Amido Complexes and Their Application in Energy Transfer Photocatalysis," *Catalysis Science & Technology* 2023 (13): 4168–4175.

103. M. E. Thompson, P. Djurovich, and R. Kwong, "Organic Light Emitting Materials and Devices," WO2004/016711 (2004).

104. M. E. Thompson, P. Djurovich, R. Kwong, et al., "Organometallic Complexes for Optoelectronic Applications," US2004/0121184 (2004).

105. X.-P. Mu, Y.-H. Li, N. Zheng, et al., "Stereoselective Synthesis of Cyclohepta[b] Indoles by Visible-Light-Induced [2 + 2]-Cycloaddition/Retro-Mannich-Type Reactions," *Angewandte Chemie, International Edition* 60, no. 20 (2021): 11211–11216.

106. E. R. Sauvé, D. M. Mayder, S. Kamal, M. S. Oderinde, and Z. M. Hudson, "An Imidazoacridine-Based TADF Material as an Effective Organic Photosensitizer for Visible-Light-Promoted [2 + 2] Cycloaddition," *Chemical Science* 13 (2022): 2296–2302.

107. M. A. Bryden, and E. Zysman-Colman, "Organic Thermally Activated Delayed Fluorescence (TADF) Compounds Used in Photocatalysis," *Chemical Society Reviews* 50 (2021): 7587–7680.

108. A. Cocco, S. Paniziutti, C. Olla, et al., "Design, Synthesis, and Photophysical Characterization of Biocompatible Thermally Activated Delayed Fluorescent Carbazole-Coumarins for Sensing Applications," *Chemistry – A European Journal* 30 (2024): e202401263.

109. Q. Q. Zhou, Y. Q. Zou, L. Q. Lu, and W. J. Xiao, "Visible-Light-Induced Organic Photochemical Reactions through Energy-Transfer Pathways," *Angewandte Chemie, International Edition* 58 (2019): 1586–1604.

110. G. Zhen, G. Zeng, F. Wang, X. Cao, and B. Yin, "Direct Construction of Fused/Bridged 3D Rings via Visible-Light Induced Dearomative Cycloaddition of Arenes," *Advanced Synthesis & Catalysis* 365 (2023): 43–52.

111. X. Wang, F. Liu, and T. Xu, "Catalytic Diastereoselective Construction of Multiple Contiguous Quaternary Carbon Stereocenters

via [2 + 2] Cycloaddition and Mechanistic Insight," *Chinese Chemical Letters* 34 (2023): 107624.

112. G. Zhen, G. Zeng, K. Jiang, F. Wang, X. Cao, and B. Yin, "Visible-Light-Induced Diradical-Mediated *ipso*-Cyclization towards Double Dearomative [2 + 2]-Cycloaddition or Smiles-Type Rearrangement," *Chemistry – A European Journal* 29 (2023): e202203217.

113. M. Abe, "Diradicals," *Chemical Reviews* 113, no. 9 (2013): 7011–7088.

114. M. Zhu and C. Zheng, "Post-Spin Crossing Dynamics Determine the Regioselectivity in Open-Shell Singlet Biradical Recombination," *Organic Chemistry Frontiers* 9 (2022): 995–1003.

115. P. C. Hayes and G. Jones, "New Photochemistry of Cyclic Dienes - the Reaction between 1OH-Azepino[1,2-a]indoles and Methanol," *Tetrahedron Letters* 22 (1981): 3897–3900.

116. V. Corti, G. Simionato, L. Rizzo, et al., "Triplet State Reactivity of Iminium Ions in Organocatalytic Asymmetric [2 + 2] Photocycloadditions," *Nature Chemistry* 18 (2026): 189–197, https://doi.org/10.1038/s41557-025-01960-3.

117. W. Zhuang, Y. Z. Cheng, X. L. Huang, O. Huang, and X. Zhang, "Visible-Light Induced Divergent Dearomatization of Indole Derivatives: Controlled Access to Cyclobutane-Fused Polycycles and 2-Substituted Indolines," *Organic Chemistry Frontiers* 8 (2021): 319–325.

118. G. Büchi, C. G. Inman, and E. S. Lipinsky, "Light-Catalyzed Organic Reactions. I. The Reaction of Carbonyl Compounds with 2-Methyl-2-Butene in the Presence of Ultraviolet Light," *Journal of the American Chemical Society* 76, no. 17 (1954): 4327–4331.

119. N. J. Turro, J. C. Dalton, K. Dawes, et al., "Molecular Photochemistry. L. Molecular Photochemistry of Alkanones in Solution.alpha.-Cleavage, Hydrogen Abstraction, Cycloaddition, and Sensitization Reactions," *Accounts of Chemical Research* 5 (1972): 92–101.

120. M. Fréneau and N. Hoffmann, "The Paterno-Buchi Reaction-Mechanisms and Applications to Organic Synthesis," *Journal of Photochemistry and Photobiology C: Photochemistry Reviews* 33 (2017): 83–108.

121. J. Mateos, S. Cuadros, A. Vega-Penaloza, and L. Dell'Amico, "Unlocking the Synthetic Potential of Light-Excited Aryl Ketones: Applications in Direct Photochemistry and Photoredox Catalysis," *Synlett* 33 (2022): 116–128.

122. J. B. Kidd, T. A. Fiala, W. B. Swords, et al., "Enantioselective Paternò–Büchi Reactions: Strategic Application of a Triplet Rebound Mechanism for Asymmetric Photocatalysis," *Journal of the American Chemical Society* 146, no. 22 (2024): 15293–15300.

123. R. Sakamoto, T. Inada, S. Sakurai, and K. Maruoka, "[2 + 2] Photocycloadditions Between the Carbon-Nitrogen Double Bonds of Imines and Carbon-Carbon Double Bonds," *Organic Letters* 18, no. 24 (2016): 6252–6255.

124. D. E. Blackmun, S. A. Chamness, and C. S. Schindler, "Intramolecular, Visible-Light-Mediated Aza Paternò-Büchi Reactions of Unactivated Alkenes," *Organic Letters* 24, no. 16 (2022): 3053–3057.

125. X. Li, J. Großkopf, C. Jandl, and T. Bach, "Enantioselective Visible Light Mediated Aza Paternò-Buchi Reaction of Quinoxalinones," *Angewandte Chemie, International Edition* 60, no. 5 (2021): 2684–2688.

126. A. F. Kassir, R. Guillot, M.-C. Scherrmann, T. Boddaert, and D. J. Aitken, "Formation of Tetrahydrothiophenes via a Thia-Paternò–Büchi-Initiated Domino Photochemical Reaction," *Organic Letters* 22, no. 21 (2020): 8522–8527.

127. J. He, Z.-Q. Bai, P.-F. Yuan, L.-Z. Wu, and Q. Liu, "Highly Efficient Iridium-Based Photosensitizers for Thia-Paternò–Büchi Reaction and Aza-Photocyclization," *ACS Catalysis* 11, no. 1 (2020): 446–455.

128. E. Paternó and G. Chieffi, "Sintesi in Chimica Organica per Mezzo Della Luce. Nota II. Composti Degli Idrocarburi Non Saturi Con Aldeidi e Chetoni," *Gazzetta Chimica Italiana* 39 (1909): 341–361.

129. G. Büchi, G. Inman, and E. S. Lipinsky, "Photochemistry in Pharmaceutical Development: a Survey of Strategies and Approaches to Industry-wide Implementation," *Journal of the American Chemical Society* 76 (1954): 4237–4331.

130. J. Mateos, A. Vega-Peñaloza, P. Franceschi, et al., "A Visible-Light Paternò–Büchi Dearomatisation Process towards the Construction of Oxeto-Indolinic Polycycles," *Chemical Science* 11 (2020): 6532–6538.

131. J. Mateos, F. Rigodanza, P. Costa, et al., "Unveiling the Impact of the Light Source and Steric Factors on [2 + 2] Heterocycloaddition Reactions," *Nature Synthesis* 2 (2023): 26–36.

132. P. Franceschi, J. Mateos, A. Vega-Peñaloza, and L. Dell'Amico, "Microfluidic Visible-Light Paternò–Büchi Reaction of Oxindole Enol Ethers," *European Journal of Organic Chemistry* 2020, no. 43 (2020): 6718–6722.

133. A. Padwa, "Photochemistry of the Carbon-Nitrogen Double Bond," *Chemical Reviews* 77, no. 1 (1977): 37–68.

134. E. R. Wearing, Y.-C. Yeh, G. G. Terrones, et al., *Science* 384 (2024): 1468–1476.

135. M. R. Becker, E. R. Wearing, and C. S. Schindler, "Synthesis of Azetidines via Visible-Light-Mediated Intermolecular [2 + 2] Photocycloadditions," *Nature Chemistry* 12 (2020): 898–905.

136. J. Huang, T.-P. Zhou, N. Sun, et al., "Accessing Ladder-Shape Azetidine-Fused Indoline Pentacycles through Intermolecular Regiodivergent Aza-Paternò–Büchi Reactions," *Nature Communications* 15 (2024): 1431.

137. E. Kumarasamy, S. K. Kandappa, R. Raghunathan, S. Jockusch, and J. Sivaguru, "Realizing an Aza Paternò–Büchi Reaction," *Angewandte Chemie, International Edition* 56, no. 25 (2017): 7056–7061.

138. M. Zhu, X. Zhang, C. Zheng, and S.-L. You, "Visible-Light-Induced Dearomatization via [2 + 2] Cycloaddition or 1,5-Hydrogen Atom Transfer: Divergent Reaction Pathways of Transient Diradicals," *ACS Catalysis* 10, no. 21 (2020): 12618–12626.

139. E. G. Moschetta, G. C. Cook, L. J. Edwards, et al., "Photochemistry in Pharmaceutical Development: A Survey of Strategies and Approaches to Industry-Wide Implementation," *Organic Process Research & Development* 28, no. 4 (2024): 831–846.

140. H. E. Bonfield, T. Knauber, F. Lévesque, E. G. Moschetta, F. Susanne, and L. J. Edwards, "Photons as a 21st Century Reagent," *Nature Communications* 11 (2020): 804, https://doi.org/10.1038/s41467-019-13988-4.

141. Y. Xue and D. Chao, "Organic and Non-Precious Metal Photosensitizers for Photocatalytic CO2 Reduction," *ChemPhotoChem* 8, no. 12 (2024): e202400246.

142. C. Michelin and N. Hoffmann, "Photosensitization and Photocatalysis—Perspectives in Organic Synthesis," *ACS Catalysis* 8, no. 12 (2018): 12046–12055.

143. W.-K. Jo and R. J. Tayade, "New Generation Energy-Efficient Light Source for Photocatalysis: LEDs for Environmental Applications," *Industrial & Engineering Chemistry Research* 53, no. 6 (2014): 2073–2084.

144. T. M. Masson, S. D. A. Zondag, J. H. A. Schuurmans, and T. Noël, "Open-source 3D-printed Reactors for Reproducible Batch and Continuous-flow Photon-Induced Chemistry," *Reaction Chemistry & Engineering* 9 (2024): 2218–2225.

145. K. Donnelly and M. Baumann, "Advances in the Continuous Flow Synthesis of 3- and 4-Membered Ring Systems," *Chemistry – A European Journal* 30, no. 32 (2024): e202400758.

146. F. Millward and E. Zysman-Colman, "Mechanophotocatalysis: A Generalizable Approach to Solvent-Minimized Photocatalytic Reactions for Organic Synthesis," *Angewandte Chemie, International Edition* 63, no. 13 (2024): e202316169.

147. D. Kong, L. Yi, A. Nanni, and M. Rueping, "A Scalable Photo-Mechanochemical Platform for Sustainable Photoredox Catalysis by Resonant Acoustic Mixing," *Nature Communications* 16 (2025): 3983, https://doi.org/10.1038/s41467-025-59358-1.

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