Review

Visible-Light-Induced Dearomative Annulation of Indoles toward Stereoselective Formation of Fused- and Spiro Indolines

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ABSTRACT: Dearomatization approaches are attractive for their abilities to transform simple, planar arenes into complex, three-dimensional architectures. In particular, visible-light driven dearomatization strategies are significant because of their mild, green, and sustainable nature, enabling the fabrication of new chemical bonds via an electron transfer or energy transfer process. Indole compounds, being potentially bioactive and readily accessible, can be employed efficiently as building blocks for constructing diverse annulated frameworks under photocatalysis. Highly stereoselective radical cascade reactions of appropriate indole systems can provide complex cyclic scaffolds bearing multiple stereocenters. In fact, the past few years have witnessed the renaissance of dearomative cycloadditions of indoles via visible-light-induced photocatalysis. The present review highlights recent advances (2019−mid 2024) in visible-light-driven dearomative annulation of indoles leading to formation of polycyclic indolines, including angularly fused and spiro indolines.

Most of the reactions described in this review are simple, providing quick access to the desired products. Additionally, characteristic reaction mechanisms are offered to provide an understand of how indole scaffolds show distinctive reactivity under photocatalytic conditions.
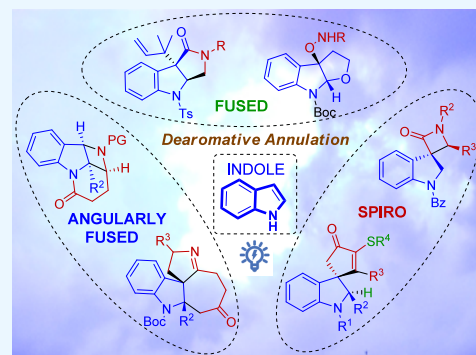
1. INTRODUCTION

Indoles are privileged heterocyclic scaffolds widely distributed in naturally occurring and synthetic bioactive molecules.[1−6] In fact, indolines, the dearomatized form of indoles, are frequently found in various alkaloid natural products, pharmaceutics, and agrochemicals. For example (Figure 1), (−)-isatisine A extracted from the leaves of *Isatis indigotica* is typically used for the

treatment of viral diseases, such as influenza, mumps and hepatitis.[7] Physostigmine is derived from *Myxococcus xanthus* and used as an anti-cholinergic drug.[8] Aspidospermidine collected from the leaves and skin of *Apocynaceae* plants displays respiratory stimulant and antibiotic activities,[9] whereas, Alstonlarsine A, obtained from *Alstonia scholaris*, exhibits DRAK2 inhibitory activity.[10] Ajmaline, isolated from the plant *Rauvolfia serpentina*, is employed as an antiarrhythmic drug,[11] while tubifolidine, a strychnos alkaloid, is a useful antioxidant.[12] Likewise, (+)-hinckdentine A, (+)-glioclodine C, spirobacillene B, and vindoline are significant indoline containing molecules present in natural alkaloids.[13−16] Moreover, these kinds of molecules have ample applications in materials sciences,[17,18] sensing,[19] and bioimaging.[20]

Rapid access to sp³-rich three-dimensional motifs with stereochemical diversity can regulate target oriented synthesis in drug discovery research.[21−24] Indole skeletons, incidentally, can be employed as useful building blocks for diverse dearomatized annulated architectures.[25−30] Although catalytic
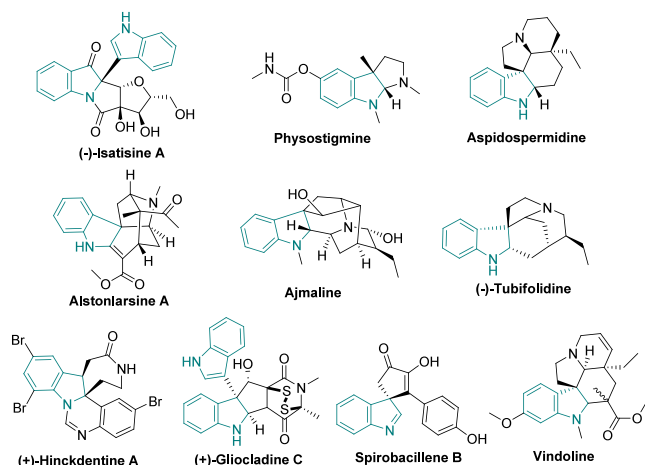

Figure 1. Representative examples of natural products containing an indoline skeleton.

dearomative cyclization of indoles comprises one of the most efficient methods for synthesizing indoline annulated scaffolds,[31−42] however, sustainable synthesis of this type of molecules is highly demanding from a green chemistry perspective. In this regard, a visible-light driven dearomatization strategy meets the goal hugely because of its mild, green, and sustainable nature, enabling the fabrication of new chemical bonds via a single electron transfer or energy transfer process.[43−48] The use of visible light energy led to enormous potential for excited state reactivity. The excited triplet state population could be attained by triplet energy transfer from the suitable photosensitizer to the substrate.[49−51]

In 2021, Zheng and Guo surveyed photocatalyzed synthesis of indole compounds and their modifications.[52] Van der Eycken, in 2019, published a review article on the visible-light-mediated chemistry of indoles and related heterocycles.[53] However, the past few years have witnessed the renaissance of dearomative cycloadditions of indoles via visible-light-induced energy transfer catalysis. The present review focuses on recent (2019−mid 2024) advancement in visible-light-driven dearomative annulation of indoles leading to the stereoselective formation of polycyclic indolines. The reactions are categorized according to the construction of (1) simple fused indolines, (2) angularly fused indolines, and (3) spirocyclic indolines. The formation of different types of annulated indolines via suitable reactions discussed in this review is summarized in Figure 2.

2. FORMATION OF FUSED INDOLINE SCAFFOLDS

2.1. Heterocycle Fused Indolines. Synthesis of heterocyclic compounds using blue LEDs has become a powerful tool in synthetic organic chemistry.[54−56] In 2022, Tong, Xia and coworkers devised a visible-light driven reaction between tryptamines 1 and alkynyl sulfones 2 for obtaining pyrroloindoline

Figure 2. Visible-light-induced formation of fused, angularly fused, and spiro-indolines from indole derivatives.

scaffolds.[57] This reaction offered a straightforward approach for alkynylation of tryptamines to accomplish C3-alkynyl pyrroloindoline derivatives 3. The authors employed an iridium-based photocatalyst (**PC-1**) under 462 nm LEDs in the presence of Cs_2CO_3. Both aromatic and aliphatic alkynyl sulfones responded well to the reaction. The authors suggested the reaction mechanism depicted in Scheme 1. The process was anticipated

Scheme 1. Visible-Light-Driven Reaction between Tryptamines and Alkynyl Sulfones to Afford Pyrroloindoline Scaffolds in the Presence of Ir-Photocatalyst
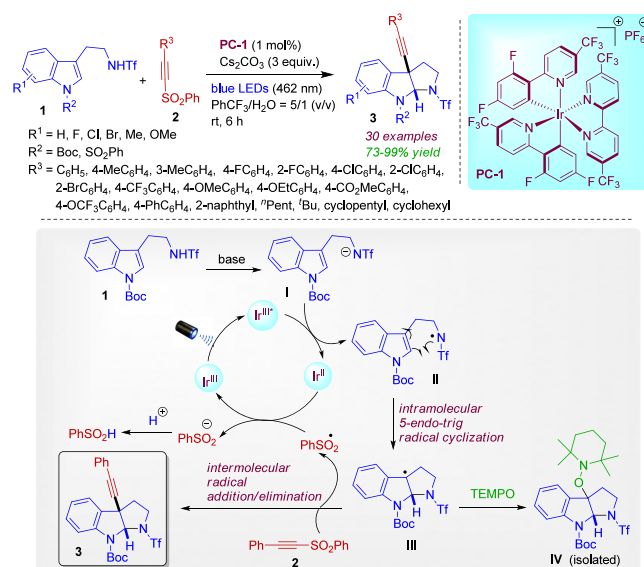
to commence with blue LED-triggered irradiation of the Ir(III)-photocatalyst to the excited Ir(III)*. In the meantime, base-promoted deprotonation of Tf-protected tryptamine 1 produced intermediate **I**, which could be oxidized by Ir(III)* to generate N-centered sulfamidyl radical **II** along with the formation of Ir(II) via a single electron transfer (SET) process. Radical **II** underwent an intramolecular *5-endo-trig* radical cyclization resulting in C3-centered pyrroloindoline radical **III**. Eventually, intermolecular radical reaction with alkynyl sulfone **2** delivered pyrroloindolines **3** via an addition/elimination process with extrusion of phenyl sulfonyl radical ($PhSO_2^{\bullet}$), which would regenerate the photocatalyst Ir(III) species. Finally, the resulting $PhSO_2^{-}$ was protonated to provide benzene sulfinic acid ($PhSO_2H$). The formation of C3-centered pyrroloindoline radical **III** could be realized by trapping with the radical inhibitor TEMPO (isolable compound **IV**).

Dearomatization of electron-deficient indoles via a photoredox-catalyzed hydroalkylation was realized by You et al.[58] The organic compound 4CzIPN flawlessly worked as a photocatalyst for accessing substituted indolines 6 from readily accessible C-2 substituted indoles 4 and glycines 5. Here, glycine derivatives acted as the hydrofunctionalization reagents. This strategy provided 1,2-disubstituted indolines 6 in excellent yields with *trans*-selectivity (>20:1 dr). Notably, treatment of indolines 6 with DBU delivered lactam-fused indoline 7. A plausible mechanism is depicted in Scheme 2. At first, photoexcitation of 4CzIPN led to excited 4CzIPN*, which underwent SET reduction of indole 4 to form radical anion **I** and radical cation 4CzIPN•+. While protonation of **I** produced radical **II**, 4CzIPN•+ triggered SET oxidation of glycine **5** to regenerate 4CzIPN and α-amino radical **III** with release of CO_2. Finally,
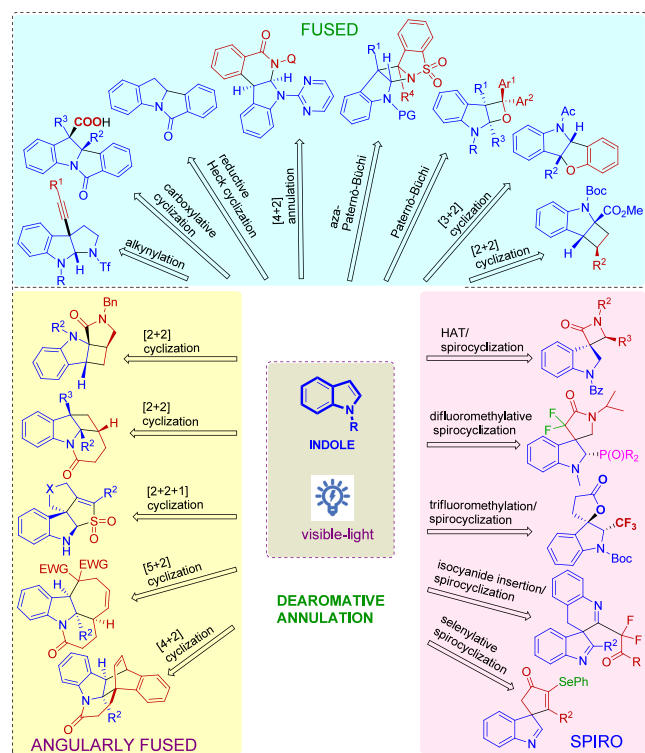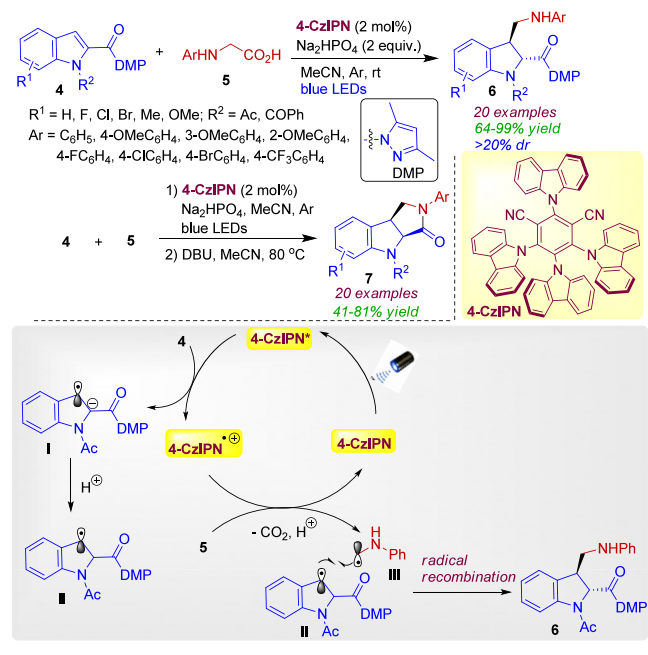
Scheme 2. Light-Induced Assembly of Electron-Deficient Indoles and Glycines toward Lactam-Fused Indolines in the Presence of an Organic Photocatalyst


Scheme 3. Visible-Light Photocatalyzed Intermolecular A-Aminomethyl/Carboxylative Dearomatization of Indoles with CO_2 and Radical Precursors

cross-coupling of the two radical species **II** and **III** afforded indoline **6**.

Very recently, Sun et al. realized intermolecular α-aminomethyl/carboxylative dearomatization of indoles with CO_2 and radical precursors in the presence of Ir-based photocatalyst (PC).[59] The reaction of indole **7** with tertiary aminomethyl radical precursors **8** and CO_2 delivered indoline-3-carboxylic acids **9**. Under similar conditions, the use of secondary aminomethyl radical precursors (glycine derivatives) **10** led to the formation of indoline-fused lactams **11**. As depicted in Scheme 3, the reductive quenching of the photoexcited Ir-catalyst by α-aminomethyl radical precursor **8/10** would produce the α-aminomethyl radical species **I**. Radical addition of **I** to the 2-position of indole **7** generated radical **II**. Subsequent SET reduction of **II** produced corresponding anion **III**, and the following nucleophilic addition to CO_2 provided indoline-3-carboxylic acids **9**. In the case of the free N–H motif of the amino moiety ($R^2 = H$), intramolecular lactamization occurred to yield indoline-fused lactams **11**.

Development of stereoselective methods for accessing structurally diverse prenylated indolines is a challenging task. Feng, Liu, and co-workers endeavored to continue the field and introduced intermolecular dearomative prenylation of electron deficient indoles **12** via tandem Giese radical addition/Ireland–Claisen rearrangement.[60] Here, tertiary α-silylamines **13** were employed as radical precursors in the presence of an photocatalyst 4CzIPN to deliver 2,3-disubstituted indolines **14** with excellent diastereoselectivity (>20:1 dr). However, the use of secondary α-silylamines **15** led to prenylated lactam-fused indolines **16**. Mechanistic studies revealed that the reaction proceeded via an initial photoredox-SET process (**I → II**), followed by the generation of silylketene acetals (**III → IV**) and subsequent [3,3]-rearrangement to afford richly decorated indolines (Scheme 4). Importantly, some of the indolines displayed anticancer activity.
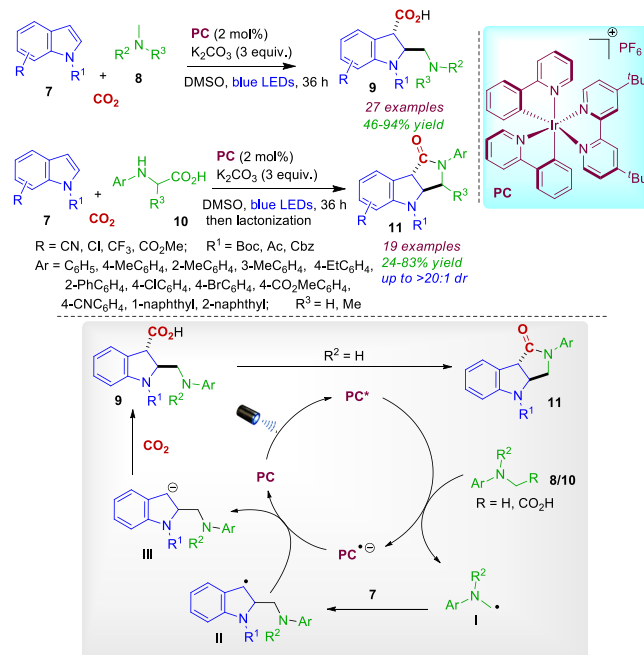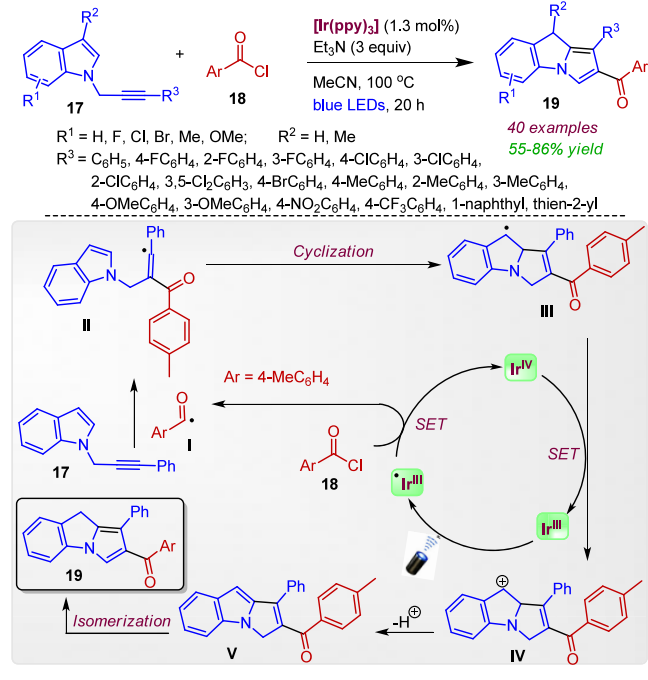
Scheme 4. Photocatalytic Synthesis of Prenylated Indolines from α-Silylamines and Indoles
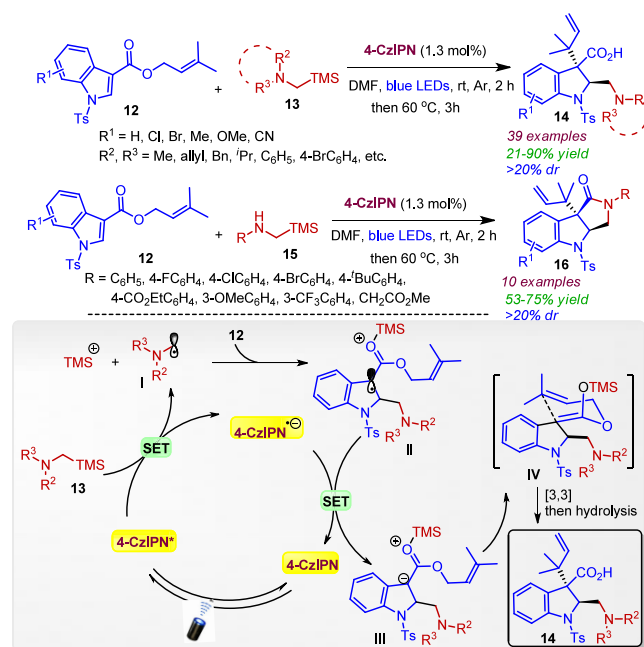
N-Propargylindoles have the ability to capture free radicals for the cascade cyclization process. In 2020, Liu, Xie, Tang, and co-workers reported light-mediated tandem cyclization of *N*-propargylindoles and acyl chlorides for obtaining pyrrolo[1,2-*a*]indolines.[61] *N*-Propargylindoles **17** bearing electron withdrawing groups at the phenyl ring of terminal triple bonds gave lower yields than those of electron donating substituents. Moreover, naphthyl- or thienyl-substituted *N*-propargylindoles responded well under optimized conditions. The use of photocatalyst [Ir(ppy)$_3$], base (Et$_3$N), and a blue LED was

found to be essential for this conversion. As depicted in Scheme 5, visible-light-triggered conversion of $Ir^{III}(ppy)_3$ into
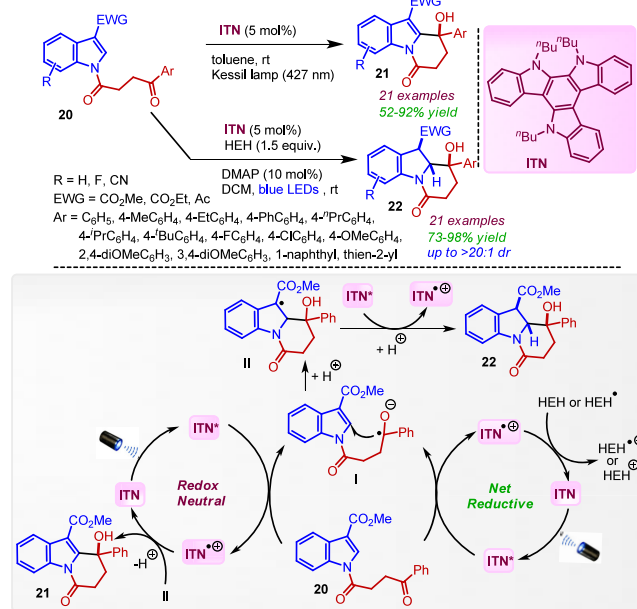
Scheme 5. Rapid Access to Pyrroloindolines from *N*-Propargylindoles and Acyl Chlorides under Photocatalysis

*MeCN, 100 °C
blue LEDs, 20 h*

R^1 = H, F, Cl, Br, Me, OMe; R^2 = H, Me
R^3 = C_6H_5, 4-FC_6H_4, 2-FC_6H_4, 3-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 3,5-$Cl_2C_6H_3$, 4-BrC_6H_4, 4-MeC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 4-$OMeC_6H_4$, 3-$OMeC_6H_4$, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 1-naphthyl, thien-2-yl

*40 examples
55–86% yield*

*$Ir^{III}(ppy)_3$ and reduction of acyl chloride **18** via the SET process generated acyl radical **I**. The latter would attack the C–C triple bond of **17**, resulting in stable benzyl radical **II**, which underwent intramolecular cyclization to form intermediate **III**. Subsequent oxidation by $Ir^{IV}(ppy)_3$ produced carbocation **IV** with regeneration of the catalyst $Ir^{III}(ppy)_3$. Deprotonation and isomerization delivered the desired fused indolines (**V → 19**). However, use of external oxidant (TBHP) could accomplish the corresponding aromative annulation product.[62]

Very recently, Zheng, You, Zhang, and co-workers reported a photocatalytic approach for selective C-H functionalization and dearomatization by operating a distinct mechanism.[63] Starting from the same indole-tethered ketones **20**, intramolecular alkylation and reductive dearomatization were realized under redox-neutral and net-reductive conditions, respectively. The visible-light-induced C-2 alkylation proceeded in the presence of photocatalyst isoazatruxene (ITN) in toluene, resulting in polycyclic indole **21** (rearomatized product). However, the use of 4-methylaminopyridine (DMAP) and Hantzsch ester (HEH) as the reductant in dichloromethane afforded dearomatized product **22** with excellent diastereoselectivity (up to >20:1 dr). A plausible mechanism for the photocatalytic reaction is illustrated in Scheme 6. Initially, the photoexcitation of ITN led to excited ITN*. Oxidative quenching of ITN* by indole derivative **20** produced ITN•+ and the corresponding ketyl radical **I**, which underwent addition to electron-deficient indole to form intermediate **II**. After protonation, intermediate **II** proceeded diversely in two conversions. In the C-H functionalization reaction, single electron oxidation of **II** by ITN•+ furnished aromatization product **21** upon deprotonation, thereby completing the catalytic cycle. Regarding the dearomatization process, single electron reduction of **II** by excited state ITN* occurred, affording the benzannulated indolizine **22** after

Scheme 6. Tunable Photocatalytic C-H Functionalization and Dearomative Annulation Involving Indole-Tethered Ketones

R = H, F, CN
EWG = CO_2Me, CO_2Et, Ac
Ar = C_6H_5, 4-MeC_6H_4, 4-EtC_6H_4, 4-PhC_6H_4, 4-$^nPrC_6H_4$, 4-$^iPrC_6H_4$, 4-$^tBuC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, 2,4-$diOMeC_6H_3$, 3,4-$diOMeC_6H_3$, 1-naphthyl, thien-2-yl

21 *21 examples
52–92% yield*

22 *21 examples
73–98% yield
up to >20:1 dr*


protonation. ITN•+ could be further converted back to ITN with external reductant. Notably, the C-H functionalization is a redox-neutral transformation, and dearomatization is a net-reductive process requiring a stoichiometric external reductant to turn over the photocatalytic cycle.

Visible-light-driven palladium-catalyzed conversions offer efficient strategies for building C-C and C-N bonds under mild reaction conditions. Indole dearomatization via palladium-catalyzed photoredox reactions was reported by Sharma's group for the construction of isoindoloindoline scaffolds **25** starting from functionalized *N*-(2-bromobenzoyl)indoles **23** and styrenes **24**.[64] The indole substrates bearing a fluoro, chloro, bromo, methyl, methoxy, and nitro group at the phenyl ring afforded the desired products in moderate yields with good diastereoselectivity (up to 20:1 dr). Mechanistically it was conceivable that (Scheme 7) the transfer of a single electron from the photoexcited state of the Pd-complex to *N*-(2-bromobenzoyl)-indoles **23** produced aryl radical **I**. Intramolecular radical addition led to benzyl radical **II**, and subsequent intermolecular radical addition to alkene **24** afforded Pd(I) radical species **III** (remained in equilibrium with alkyl Pd(II) species **III'**). Eventually, *β*-H elimination gave isoindoloindoline **25** with regeneration of Pd(0) catalyst.

In 2020, Yu's team introduced the strategy of successive single electron transfer (SSET) for the tandem reductive annulation of indoles with carbon dioxide (CO_2).[65] This is a typical example of dearomative arylcarboxylation of indoles which produced (isoindolo)indoline-3-carboxylic acids **28** with high selectivity (up to 19:1 dr). A variety of ester groups and amide groups at the C2 position of indoles underwent the reaction well, resulting in desired indoline-3-carboxylic acids in high yields. The authors suggested a mechanism as depicted in Scheme 8. The reductive quenching of photoactivated 4CzIPN by DIPEA produced radical cation DIPEA•+ and the radical anion 4CzIPN•−. The latter performed single electron reduction of aryl bromide **26** to generate radical anion **I** with the regeneration of 4CzIPN and completed one catalytic cycle. Concomitant release of bromide

Scheme 7. Visible-Light-Promoted Palladium-Catalysis of N-(2-Bromobenzoyl)indoles and Alkenes to Access Fused Indolines
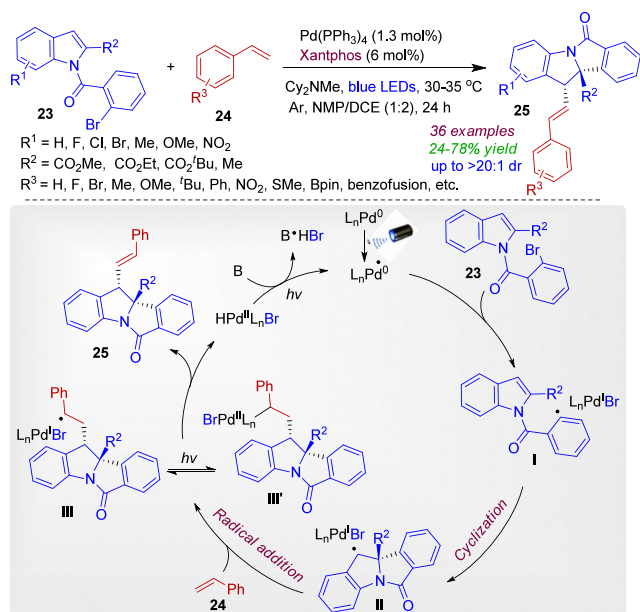
Scheme 8. Photocatalytic Dearomative Arylcarboxylation of Indoles for Accessing Indoline-3-Carboxylic Acid Derivatives
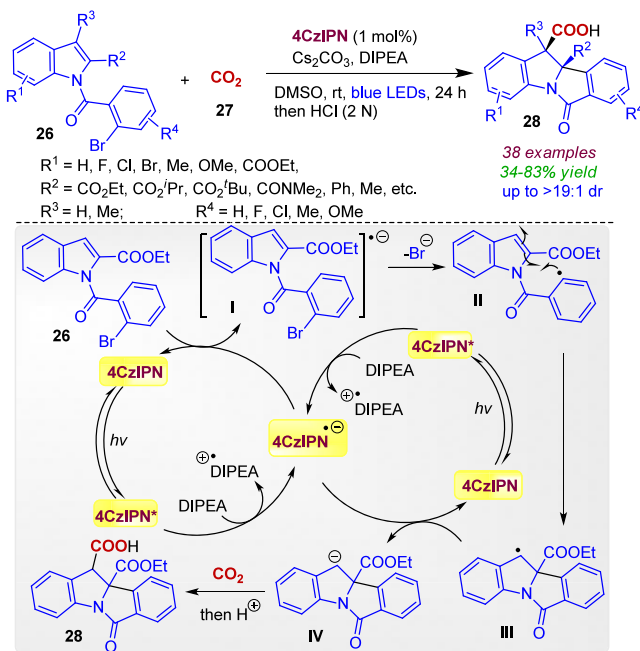

anion would form intermediate **II**, and ensuing intramolecular radical cyclization provided benzyl radical **III**. The second SET process afforded anion **IV**. Nucleophilic addition with CO_2 (**27**) followed by protonation delivered the dearomative arylcarboxylation product **28**.

Photoinduced cleavage of $C(sp^2)$–Cl bonds usually requires the use of UV light and photocatalysts. A direct photoinduced reductive Heck cyclization reaction of indole derivatives without using any photocatalyst or photosensitizer was developed by Che's group.[66] Indole-tethered benzoyl moieties **29** possessing electron donating (OMe, NHAc) and electron withdrawing

groups (F, Cl, CF_3) were well tolerated to deliver isoindoloindolines **30** in good yields (50−88%). The mechanism of photoinduced electron transfer between indole and DIPEA is depicted in Scheme 9. The long-lived excited state of N-(2-

Scheme 9. Direct Photoinduced Reductive Heck Cyclization of Indoles to Obtain Indolino-Isoindolones
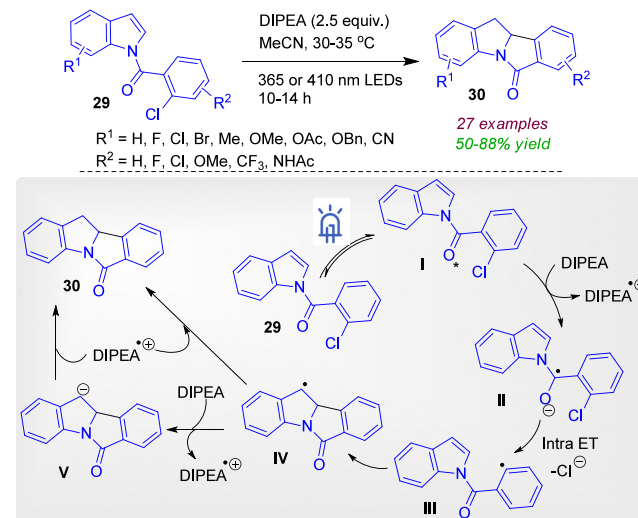

chlorobenzoyl)indole, **I**, experienced bimolecular redox reaction with the reductant (amine) affording radical anion **II**. Subsequent $C(sp^2)$–Cl bond activation followed by fragmentation provided phenyl radical **III** and chloride ion. Intramolecular radical addition to the indole moiety of **III** furnished benzyl radical **IV**. Ultimately, the hydrogen atom abstraction involving DIPEA$^{•+}$ (or reduction of **IV** to carbanion **V**) following protonation yielded final product **30**.

McDaniel and Jui discovered a radical−polar crossover strategy for intramolecular cyclization of indole compounds under mild photoredox conditions.[67] The organic donor−acceptor cyanoarene (**P3**) was the best chosen photocatalyst in the presence of tributylamine (reductant) to attain intramolecular dearomatization of pyridine-tethered indoles **31** affording fused indoline derivatives **32**. The use of toluene as cosolvent (25% v/v) improved the photocatalyst solubility and reaction reproducibility. Both bromopyridines and iodopyridines served as effective radical precursors. Based on isotope labeling experiments, the authors proposed the radical−polar crossover mechanism (Scheme 10). The electron transfer from amine reductant to **P3*** would generate cyanoarene radical anion (**P3**$^{•−}$) and amine radical cation (Bu$_3$N$^{•+}$). Subsequent SET of **31** and loss of bromide afforded radical **I**. Intramolecular cyclization via the 5-exo mode led to benzylic radical **II**. Finally, radical termination via HAT from the amine radical cation furnished final product **32** (path a). Alternatively (path b), reduction of **II** to the corresponding anion **III** would precede protonation to afford **32**. The authors performed a deuterium labeling experiment in support of the radical−polar crossover mechanism (path b).

Using a benzothiolate containing electron donor−acceptor (EDA) complex, the Song group developed reductive dearomatization of N-(o-haloarylformyl)indoles **33** under blue LEDs.[68] Control experiments ensured that base (DIPEA), thiophenol, and blue light are essential for accessing corresponding isoindoloindoline derivatives **34**. In contrast to

Scheme 10. Dearomative Photoredox Radical–Polar Crossover Reaction of Pyridine-Tethered Indoles toward Fused Indoline Motifs
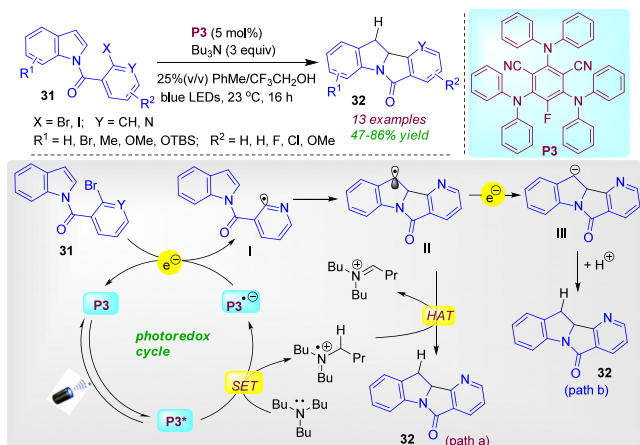
the previous approach, this method proceeded via a concerted HAT pathway of benzyl radical formation from ArSH and an amine rather than a stepwise reduction/protonation process. Mechanistic investigation revealed that photoinduced electron transfer from benzenethiolate to the *o*-haloarylformyl moiety triggered a radical reaction to produce 2-arylindoline and that the radical termination occurred via a concerted HAT process (Scheme 11).

Liu et al. explored a novel metallophotoredox dearomatization of indoles for direct entry to indoloisoquinolinones through a benzamide empowered [4 + 2] annulation.[69] The reaction comprised regioselective C-2 and C-3 dual functionalization of

Scheme 11. Visible-Light-Assisted Dearomatization of *N*-(*o*-Haloarylformyl)indoles in an EDA Complex of Thiophenol for Accessing Indoline Derivatives
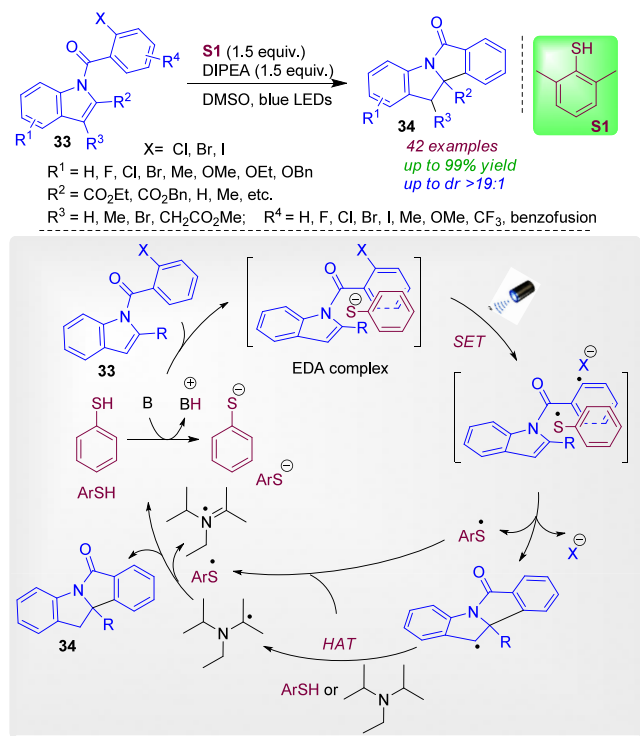
indoles **35** via coupling with *N*-quinolylbenzamide **36** to result in indolo[2,3-*c*]isoquinolinone **37** in an atom and step economical approach. Involvement of Co(OAc)₂, benzoylacetone (bzacH), Ir(bt)₂(acac), visible light, and air were crucial for this transformation. The mechanism of dual cobalt/photocatalysis is depicted in Scheme 12. Initially, Co(II)-triggered

Scheme 12. Metallophotoredox Dearomatization of Indoles for Facile Entry to Indolo[2,3-*c*]isoquinolin-5-ones
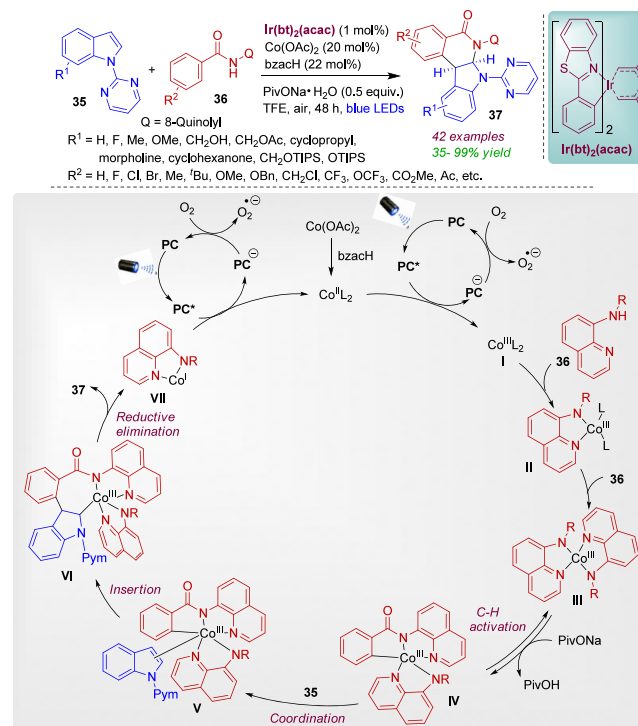
ligand exchange followed by single electron oxidation generated Co(III) complex **I**, which experienced continuous *N,N′*-coordination of benzamide **36** to afford the intermediate **III** (via **II**). Afterward, directed C–H activation of Co(III) complex **III** through a concerted metalation deprotonation furnished cobaltacycle **IV**. Regioselective insertion of indole **35** provided a seven-membered intermediate (**V → VI**). At the final step, reductive elimination delivered desired product **37** along with release of Co(I) species **VII**. Oxidation of **VII** occurred in the presence of blue light, air, and Ir(bt)₂(acac) for sustaining the continuity of the catalytic cycle.

Liao, Zhong, and co-workers carried out an intermolecular aza-Paternò–Büchi reaction of indoles **38/41** and *N*-sulfonylimines **39**, which provided direct access to azetidine-fused pentacyclic indolines in the presence of thioxanthone (TXO) photocatalyst.[70] The heterocycloaddition reactions exhibited exclusive *exo* stereoselectivity and divergent regioselectivity, leading to head-to-head (H-H*exo*) and head-to-tail (H-T*exo*) cycloadducts **40/42**. While the use of N-protected 3-substituted indoles **38** afforded H-H*exo* product **40**, N-protected 3-substituted indoles **41** gave H-T*exo* adduct **42** exclusively. The mechanism followed energy transfer catalysis (Scheme 13). The reaction started with the population of the triplet state of TXO upon excitation and intersystem crossing (ISC). Energy transfer of TXO with imine **39** would promote the latter into its triplet state **39***. Next, the triplet intermediate **39*** and indole **38/41** underwent C-N coupling to produce triplet **I** (H-H) and triplet

Scheme 13. Intermolecular Aza-Paternò−Büchi Reaction of Indoles and *N*-Sulfonylimines Leading to Azetidine-Fused Pentacyclic Indolines


Scheme 14. Photocatalyst-Free Paternò−Büchi Reaction of Indoles and Aromatic Ketones for Affording Oxeto[2,3-*b*]indoles
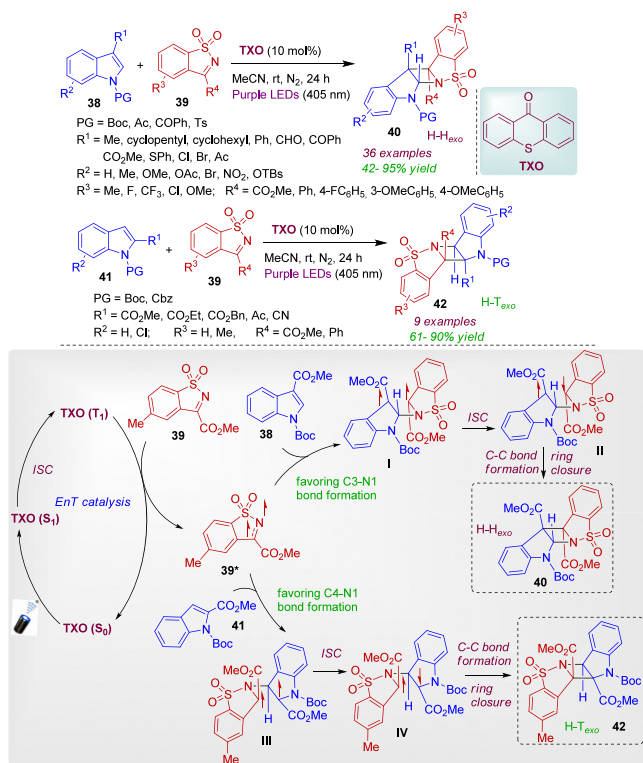
III (H-T), respectively. Upon ISC, open-shell singlet intermediates **II** and **IV** were produced, which finally experienced radical recombination to form azetidines **40** and **42**.

Construction of oxetane-based polycyclic scaffolds remains a formidable challenge because of high ring strain, and this could be attained via the Paternò-Büchi reaction. In 2020, a photocatalyst-free Paternò-Büchi reaction for the dearomatization of indoles was designed by Companyó and Dell'Amico.[71] A large variety of tetrahydrooxeto[2,3-*b*]indoles **46/47** was prepared from readily available indoles **43** and aromatic ketones **44/45** with excellent regio- and diastereoselectivity (>20:1). This could be accomplished by the careful tuning of visible light source (405 or 465 nm), which enabled complete shutting down of the ketone dimerization side reaction. The mechanism for the photoinduced electron transfer (PET) process is presented in Scheme 14. After the initial PET from **43** to **44***, a reactive radical ion pair **I** was formed, which collapsed into final product **46**. Of note, intermediate **I** might be stabilized by favorable π−π stacking between two aromatic rings.

[3 + 2] annulation of phenols with indoles in the presence of light-excited Ag_3PO_4 nanoparticles (NPs) was studied by Wang et al.[72] A set of structurally diverse benzofuroindolines **50** was accomplished via the oxidative radical cross-coupling/cyclization of indoles **48** and functionalized phenols **49** (Scheme 15). Importantly, Ag_3PO_4 extended the lifetime of the radical intermediates, thereby facilitating the reaction. It should be mentioned that sunlight could serve as sustainable light source for this conversion. The reaction was additive-free and scalable using reusable heterogeneous Ag_3PO_4 NPs.

In order to obtain enantioenriched furoindolines, You's group employed indole derivatives (e.g, tryptophol) as electrophiles.[73] The transformation could be assisted by a combined catalyst
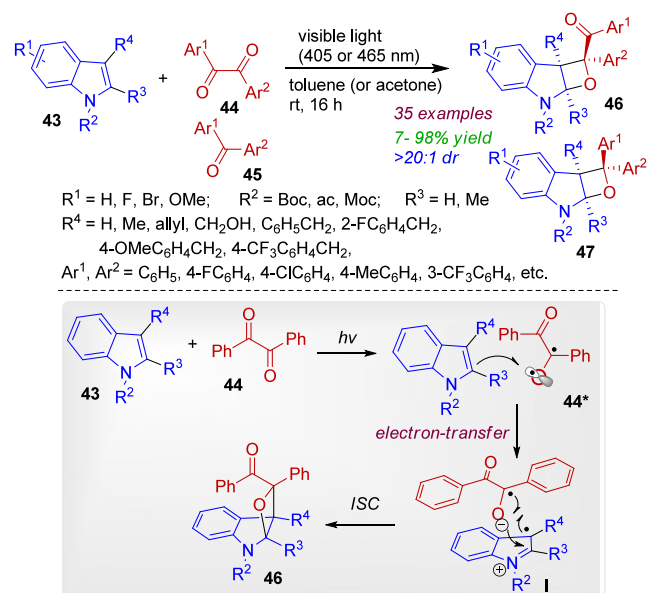
Scheme 15. Visible-Light Excited Ag_3PO_4 (NPs) Assisted Synthesis of Benzofuroindolines
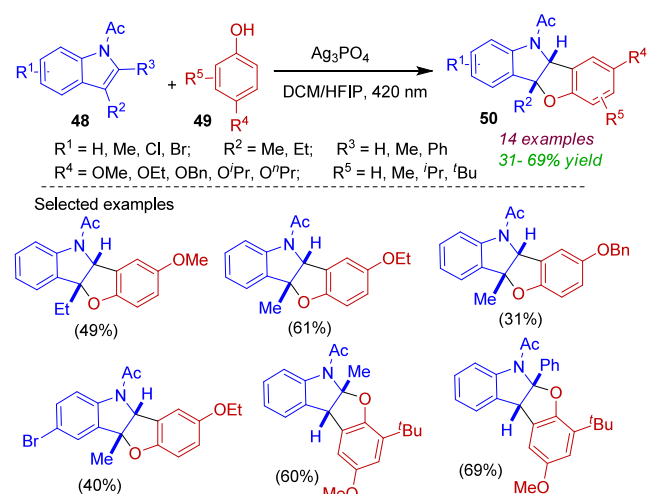
(photocatalyst Ir[dF(CF$_3$)ppy]$_2$(bpy)PF$_6$ and chiral phosphoric acid **53**) under light and air. The dual catalysis unlocked the umpolung reactivity of indoles, enabling the enantioselective dearomatization of indole derivatives **51** with *N*-hydroxycarbamates **52**. Mechanistically (Scheme 16) it was conceivable that indole substrates could be converted into configurationally biased carbocation intermediates after two successive SET oxidations under visible light. The short-lived electrophilic species then reacted with *N*-hydroxycarbamates **52** to form furoindoline scaffolds **54**. Notably, due to instability of some dearomative products, N-protection with Boc was performed before final isolation of the desired compound.

2.2. Carbocycle Fused Indolines. Cyclobutane-fused heterocyclic skeletons are synthetically important because of high strain energy and conformational rigidity imposed by the cyclobutane ring. To attain this type of skeleton, Oderinde and Hudson employed an imidazoacridine-based compound (ACR-

Scheme 16. Photoredox Asymmetric Dearomatization of Indole Derivatives with *N*-Hydroxycarbamates Promoted by Ir/CPA Dual Catalysis
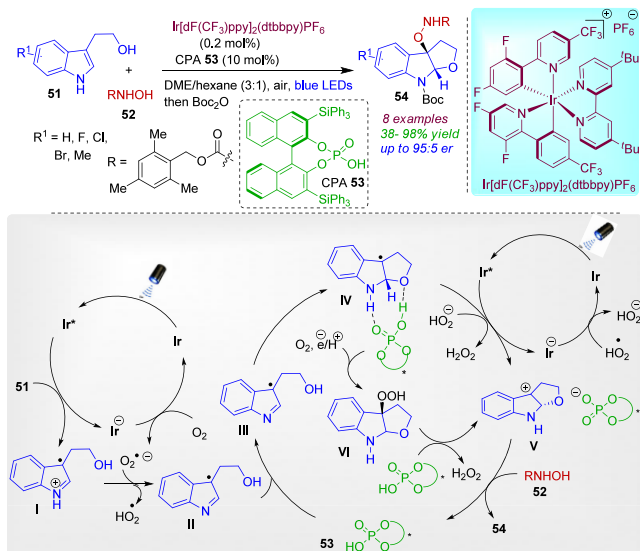
IMAC) as effective high-energy photosensitizer (PS) for promoting $[2\pi + 2\pi]$ cycloadditions.[74] Actually, the high energy efficiency of ACR-IMAC as a triplet photosensitizer comprised a suitable organic replacement for metal-based photocatalysts.[75] Using this strategy, cyclobutane-fused indolines **57** were successfully prepared from functionalized indoles **55** and alkenes **56** via dearomative intermolecular $[2 + 2]$ photocycloadditions. A plausible mechanism for the photocycloaddition via the energy transfer process is illustrated in Scheme 17.

Scheme 17. Imidazoacridine-Based Photosensitizer (ACR-IMAC) for $[2 + 2]$ Photocycloaddition of Indoles and Olefins Resulting in Cyclobutane-Fused Indolines
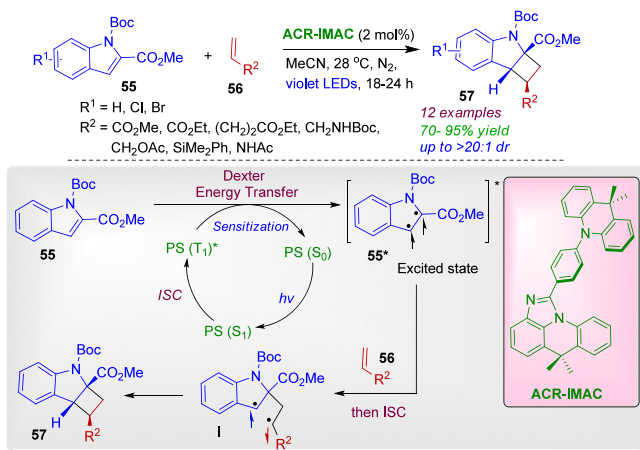
Light absorption would excite the PS to its S_1 state, which underwent rapid ISC to the T_1 state. Intermolecular energy transfer from the PS to substrate **55** afforded a diradical based triplet excited state **55***. As expected, the two electrons mainly populated at the C2 and C3 positions of the indole ring. Subsequently, regioselective attachment with olefin **56** produced a 1,4-diradical intermediate **I**, which experienced a quick radical−radical combination to deliver cyclobutane-fused indolines **57** with high diastereocontrol.

The Glorius group reported an unprecedented intermolecular $[2 + 2]$ photocycloaddition that involved bicyclo[1,1,0]butanes as 2σ-electron reactants.[76] This strain-release-driven $[2\pi + 2\sigma]$-photocycloaddition reaction was realized by visible-light-induced triplet energy transfer catalysis. Various C2 and C3 substituted indoles **58** smoothly reacted with bicyclo[1,1,0]-butanes **59** in the presence of thioxanthone (TXO) photocatalyst, resulting in bicyclo[2,1,1]hexanes **60** with diastereoselectivity (Scheme 18).

Scheme 18. $[2\pi + 2\sigma]$-Photocycloaddition Reaction of Indoles with Bicyclo[1,1,0]butanes Affording Bicyclo[2,1,1]hexanes
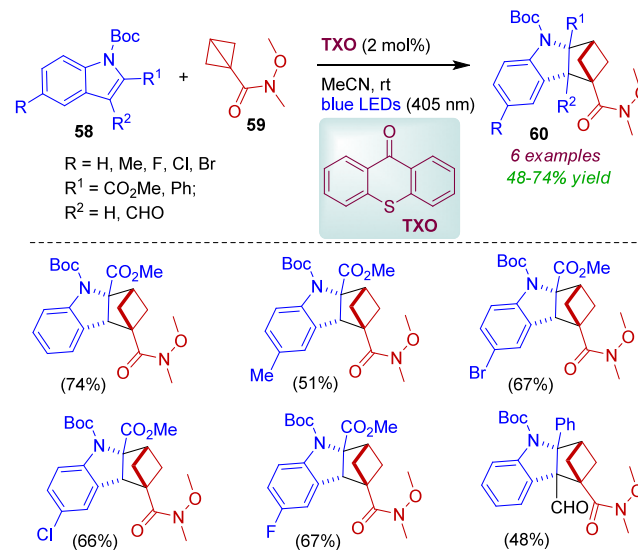
However, a dearomative $[3 + 2]$ photocycloaddition reaction between indoles and vinyldiazo reagents was developed by the Ferreira group to accomplish cyclopentene fused indolines (yield 57−96%).[77] This transformation was enabled by a novel oxidizing Cr^{III} photocatalyst (**PC-2**) under visible light (23 W CFL). Mechanistically (Scheme 19), oxidation of indole **61** by excited Cr(III) would generate radical cation **61**[•+], which combined with vinyldiazo compound **62**, resulting in intermediate **I**. Subsequent ring closure (**II**) and reduction by

Scheme 19. Cr^{III}-Photocatalyzed Dearomative $[3 + 2]$ Cycloaddition between Indoles and Vinyldiazo Compounds to Afford Cyclopentene Fused Indolines
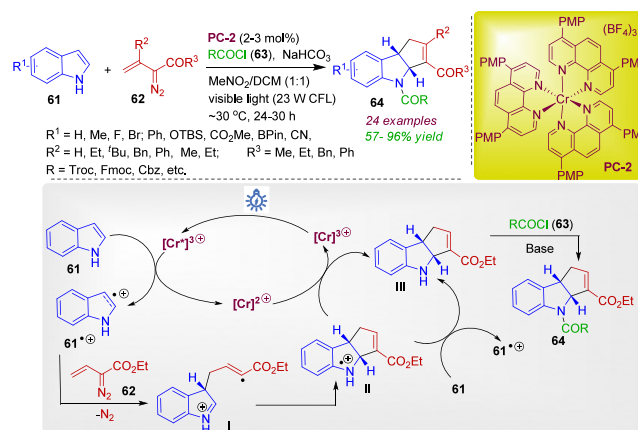
either Cr^{II} or the indole substrate afforded fused indoline **III**. Finally, acylation by RCOCl (**63**) in the presence of base delivered indoline **64**. It is noteworthy that the in situ N-substitution (by RCOCl) would be essential for this process; otherwise, the indoline product would be susceptible to oxidation.

In 2020, Glorius and co-workers introduced the use of gadolinium photocatalyst for the formation of C−C bonds, developing an efficient [2 + 2] cycloaddition/ring expansion strategy with indoles and alkenes.[78] The author employed commercially available Gd(OTf)$_3$ salt as photocatalyst to synthesize cyclopenta[b]indoles **67** from pyrazole pendant indoles **65** and alkenes **66**. However, use of 3-alkylindole derivatives **65** (R = alkyl) and isoprene regioselectively delivered cyclopenta[b]indolines **68** with moderate diastereoselectivity (75:25 dr). As depicted in Scheme 20, bidentate coordination of

Scheme 20. Gd(III)-Photocatalysis Enabled a Dearomative [2 + 2] Cycloaddition/Ring Expansion Sequence with Indoles toward Cyclopenta[b]indolines
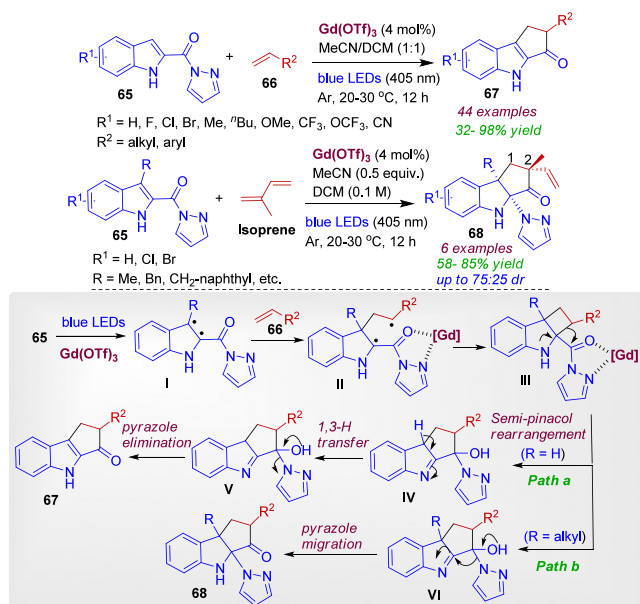
indole **65** to Gd(OTf)$_3$ and concomitant visible light excitation produced long-lived excited state intermediate **I**. The latter would experience [2 + 2] cycloaddition with alkene **66** to afford the cyclobutane **III** (through **II**). Intermediate **IV** was obtained via semi-pinacol rearrangement. Afterward, 1,3-H transfer (**V**) and pyrazole elimination delivered rearomatization product **67** (path a). In contrast, installation of an alkyl group at the 3-position of the indole substrate furnished cyclopenta[b]-indolines **68** via migratory addition of the pyrazole moiety to imine **VI** (path b).

An interesting stereoselective intramolecular radical cascade reaction of tryptophans **69** and acrylamides **70** via photoredox catalysis was reported by Zhuo's group.[79] The desired radical cascade cyclization product, *trans* fused hexahydrocarbazoles, was achieved under the assistance of Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)-PF$_6$ photocatalyst, Na$_2$CO$_3$ base, and blue LEDs. Importantly, the synthesized hexahydrocarbazoles **71** contained multiple chiral centers; two of them were quaternary ones. Based on some control experiments, the authors suggested a mechanism (Scheme 21). Initially, the α-aminoalkyl radical **I** (produced

Scheme 21. Ir-Photoredox Catalyzed Stereoselective Synthesis of Hexahydrocarbazoles from Tryptophans and Acrylamides
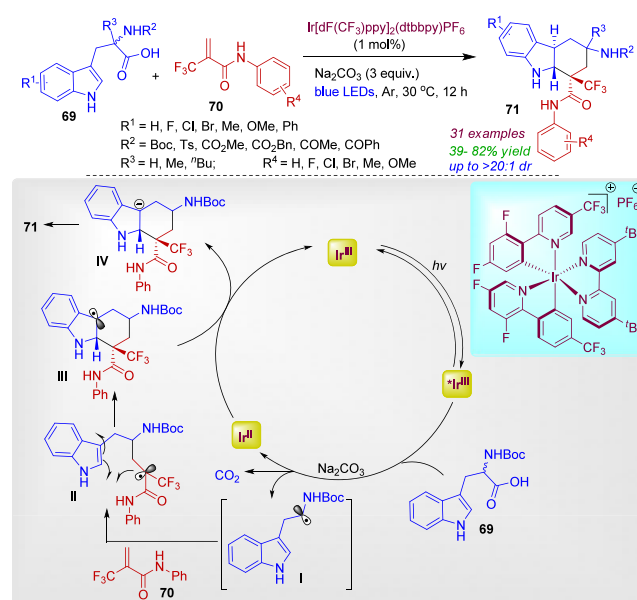
by photoinduced decarboxylation of **69**) combined with amide **70** to generate radical intermediate **II**. Radical cyclization onto the indole ring offered radical intermediate **III**, which after reduction by Ir(II) gave anion intermediate **IV**. At last, protonation provided hexahydrocarbazoles **71**.

Meanwhile, Zhang et al. reported the synthesis of two sets of indole-based scaffolds via a photocatalytic divergent dearomatization of indoles selectively by manipulating the reaction parameters.[80] This is a fascinating example of dearomative dimerization of indoles to afford cyclobutane-fused indolines **73** bearing two contiguous quaternary stereocenters. Surprisingly, the use of ^{i}Pr$_2$NEt as additive led to the formation of 2-substituted indoles **74**. A plausible reaction mechanism is offered in Scheme 22. In the absence of ^{i}Pr$_2$NEt, Ir^{III}(ppy)$_3$ acted as a triplet sensitizer. Energy transfer from *Ir^{III}(ppy)$_3$ to **72** would promote it to its triplet state **72***, which immediately underwent [2 + 2] cycloaddition with another ground state

Scheme 22. Synthesis of Cyclobutane-Fused Indolines via Photocatalytic Divergent Dearomatization of Indoles
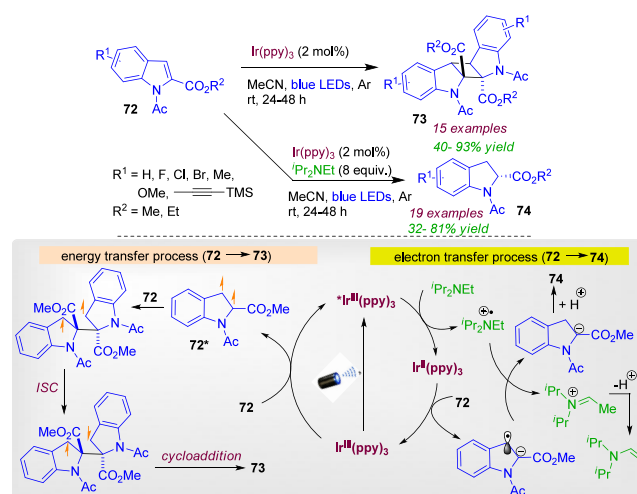
indole **72**, yielding cyclobutane-fused indoline dimer **73**. On the other hand, in the presence of $^{i}Pr_2NEt$, the reaction was triggered by SET from $^{i}Pr_2NEt$ to $*Ir^{III}(ppy)_3$. Next, the reduced species $Ir^{II}(ppy)_3$ served as a reducing agent for **72**, thereby generating the corresponding radical anion **72**$^{•-}$. Subsequent hydrogen transfer and protonation from the iminium ion delivered indoline product **74**.

3. FORMATION OF ANGULARLY FUSED INDOLINES

Angularly fused polycyclic compounds comprise core units of many natural products and bioactive molecules,[81,82] and some of them displayed promising photophysical properties.[83,84] Construction of highly strained angularly fused skeletons containing an indole moiety is a new direction in heterocyclic chemistry. To achieve this, indoles tethered with an alkene/alkyne/allyl moiety were subjected to visible-light-induced intramolecular [2 + 2] cycloaddition, which occurred via an energy transfer process. In 2019, You's group successfully conducted dearomatization of allylic tethered indole derivatives **75** to access cyclobutane-fused angular tetracyclic indolines **76** via an intramolecular [2 + 2] cycloaddition strategy.[85] Cyclobutane fused angular tetracyclic indolines, which were inaccessible under thermal conditions, could be readily obtained in excellent yields and diastereoselectivity (>20:1 dr) with the aid of an iridium photosensitizer (Scheme 23). This protocol was amenable to varied substitution

Scheme 23. Visible-Light-Induced Intramolecular Dearomatization of Indole Derivatives to Access Cyclobutane-Fused Angular Tetracyclic Indolines
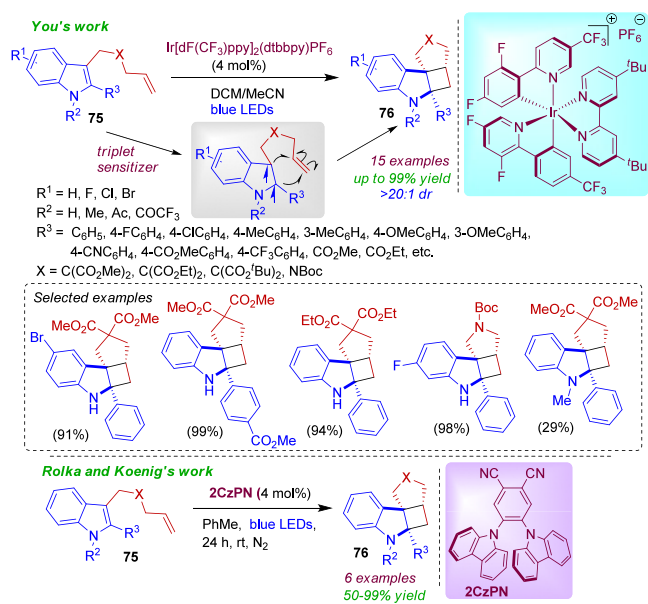
patterns on the indole ring. One year later, Rolka and Koenig synthesized the similar indoline products **76** using organic photosensitizer 2CzPN instead of an Ir-based photosensitizer.[86]

Synthesis of methylenecyclobutane fused angular tetracyclic indolines was reported by Arai and Ohkuma via a 3,4-dimethoxy acetophenone sensitized [2 + 2] photocyclization of 3-(hexa-4,5-dienyl)indoles.[87] The reaction with appropriate indole substrates **77** in the presence of a high pressure mercury lamp delivered methylenecyclobutane fused angular tetracyclic indolines **78** as major product (Scheme 24). The reaction comprised triplet sensitization of indole substrates followed by ring formation through a biradical intermediate.

Scheme 24. [2 + 2] Photocyclization of 3-(Hexa-4,5-dienyl)indoles Sensitized by 3,4-Dimethoxy Acetophenone to Form Methylenecyclobutane Fused Angular Tetracyclic Indolines
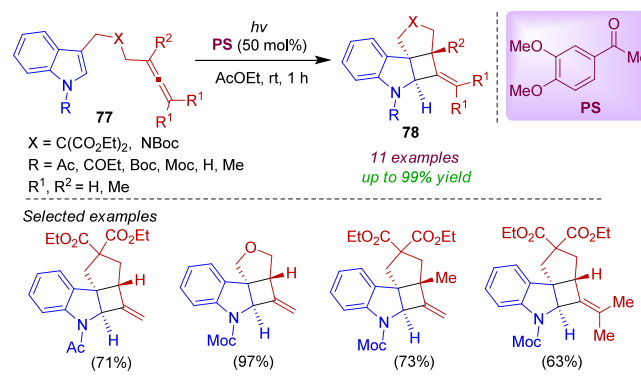
In 2020, Oderinde and Dhar devised an intramolecular [2 + 2] cycloaddition with concomitant dearomatization of indole derivatives **79** through an energy transfer process promoted by an Ir-based photosensitizer $Ir(dFppy)_3$.[88] The indoline embedded cyclobutane-fused pyrrolidinones **80** could be accomplished in good yields and excellent diastereoselectivity (>99:1 dr). This intramolecular [2 + 2] photocycloaddition was believed to proceed through light absorption and excitation of photosensitizer (PS) to its triplet excited state (via ISC) and subsequent energy transfer to substrate **79** to give the corresponding diradical-based triplet excited state **79***. The diradical species might attack the C2 carbon-centered radical (5-exo-trig) to form intermediate **I**, or the C3- carbon-centered radical (7-endo-trig) to provide intermediate **II**. Finally, rapid radical−radical combination furnished fused tetracyclic scaffold **80** (Scheme 25). Later on, Hudson's group efficiently conducted

Scheme 25. Intramolecular [2 + 2] Photocycloaddition of Indole Derivatives toward Indoline Embedded Cyclobutane-Fused Pyrrolidinones Using $Ir(dFppy)_3$ or Organic Photosensitizer
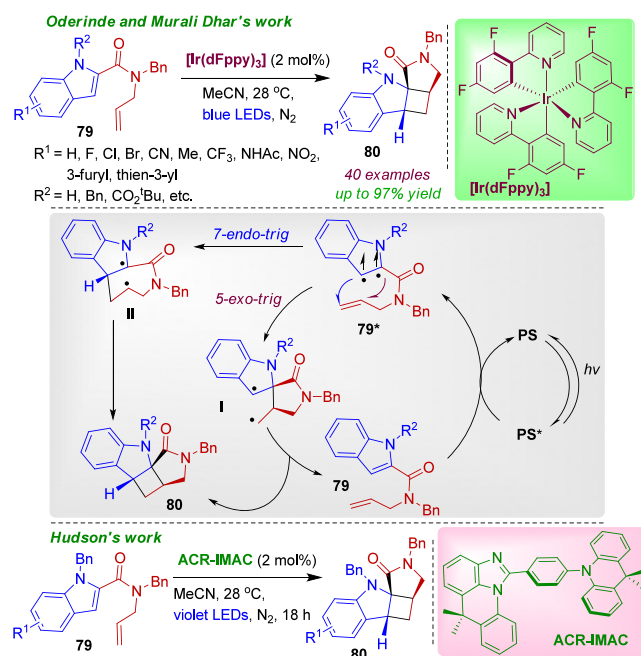
the same transformation using a novel imidazoacridine-based thermally activated delayed fluorescence (TADF) material (ACR-IMAC) as organic photosensitizer.[74]

To prepare angularly fused cyclohepta[*b*]indoles in a stereoselective manner, Yang's group conducted a formal photoredox-catalyzed [2 + 2] cycloaddition of enaminone tethered indoles using Ir-based photocatalyst (FCNIrPic).[89] The reaction was initiated by single electron oxidation of the enaminone moiety (indole substrate **81**) by excited Ir-photocatalyst, followed by stepwise cyclization (via **I** and **II**) to generate an unstable cyclobutane species **III**. Rapid fragmentation of radical cation **III** led to seven membered ring **IV**, which underwent single electron reduction (**V**) and proton transfer to furnish desired product **82** (Scheme 26).

Scheme 26. Photoredox-Catalyzed [2 + 2] Cycloaddition of Enaminone Tethered Indoles to Furnish Cyclohepta[*b*]indoles
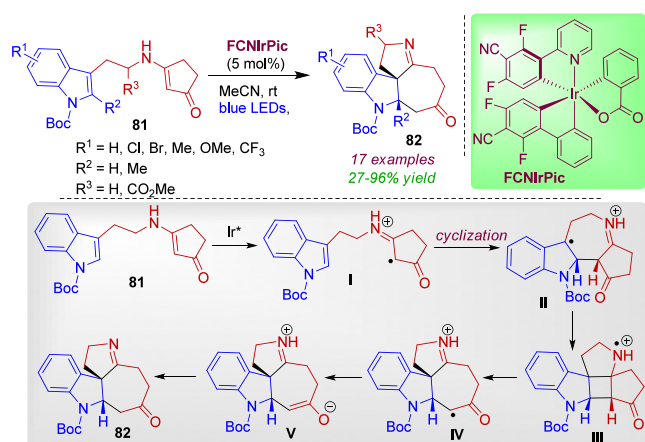
Employing an acridine-based photocatalyst (Acr-Mes+ClO4−), Cao and Yin investigated visible-light-mediated [2 + 2+1] dearomative cyclization of indole propargyl compounds with simple NaHSO3.[90] Indole-alkyne **83** containing both alkyl and aryl moieties responded to the reaction to provide a range of strained indoline fused sulfonyl polycycles **84** in moderate to good yields. According to their strategy, the alkenyl radical formed by intramolecular addition was intercepted by SO2 which was generated from NaHSO3. The plausible mechanism is illustrated in Scheme 27. In the presence of photocatalyst, the indole substrate **83** was first oxidized to intermediate **I** via intramolecular photoinduced electron transfer (PET). Next, alkenylative dearomatization involving radical cation **I** led to the formation of spiro radical cation intermediate **II**, or it was reduced to substrate by PC radical via a back electron transfer (BET) process. SO2 might be captured by intermediate **II** to produce intermediate **III**. Finally reduction by PC delivered strained indoline fused polycycle **84**.

Photochemical transformation of allene tethered indoles into tetracyclic cyclobutane-fused indoline scaffolds could be realized with the aid of an aromatic ketone photosensitizer. Arai and Ohkuma, in 2019, irradiated 1-(hexa-4,5-dienonyl)-indoles **85** with 3′,4′-dimethoxyacetophenone (PS) by a high-pressure mercury lamp through Pyrex glass to prepare skeletally distinct *all-cis*-fused methylenecyclobutane derivatives **86**.[91] The perfect diastereoselection of this [2 + 2] cycloaddition reaction is the main feature of the reaction. Notably, during this process, a small amount of alkyne pendant fused tricyclic compounds **87** was

Scheme 27. Photocatalytic Cyclization of Indole-Alkyne Compounds with NaHSO3 Leading to Indoline Fused Sulfonyl Polycycles
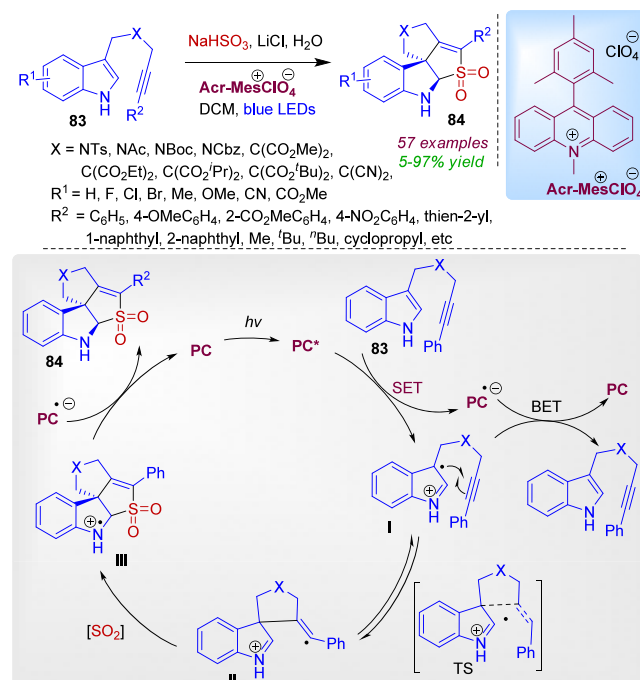
also produced via 1,5-hydrogen transfer of the biradical intermediate **I** (Scheme 28).

Scheme 28. Photochemical Transformation of Allene Tethered Indoles into Tetracyclic Cyclobutane-Fused Indoline Scaffolds Using an Aromatic Ketone Photosensitizer
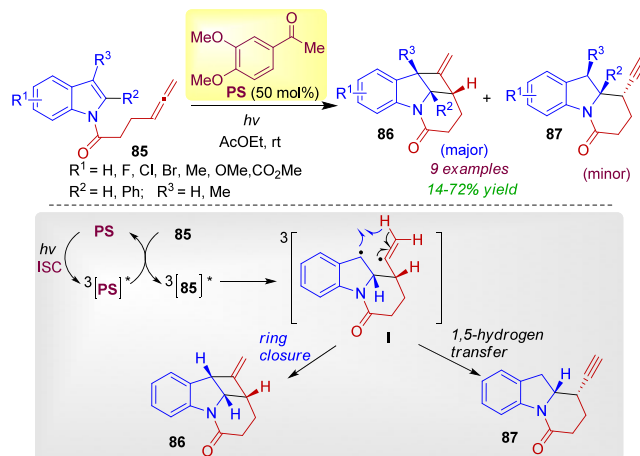
In the next year, Wei and Fu reported a dearomative [2 + 2] cycloaddition of olefin-tethered indoles **88** for affording cyclobutane fused polycyclic indolines **89** with excellent diastereoselectivities (>99:1).[92] The efficiency of the strategy could be greatly enhanced with trifluoroethanol (TFE) solvents by the H-bonding interaction. The authors suggested a mechanism as described in Scheme 29. Initially, the substrate **88** was excited to the triplet state, producing triplet intermediate **88T1** in the presence of Ir[III] photosensitizer after irradiation via energy transfer (EnT). The two electrons mostly populated at the C2 and C3 positions of the indole moiety. Subsequently

Scheme 29. Visible-Light-Promoted Dearomative Cyclization of Olefin-Tethered Indoles Process to Prepare Cyclobutane Fused Polycyclic Indolines
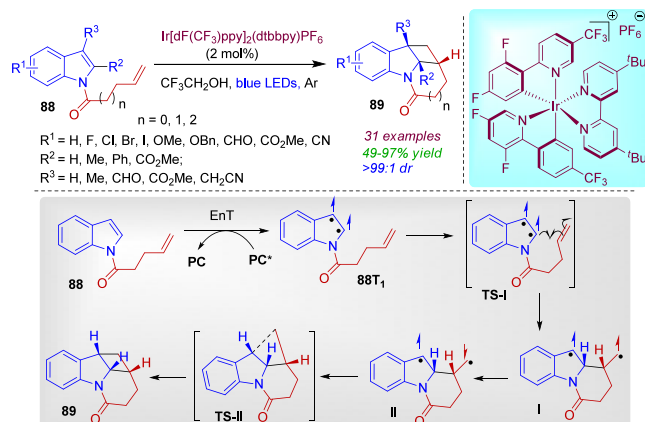

"tail-to-tail" attack (via **TS-I**) led to the formation of intermediate **I**, which gave corresponding open shell singlet state counterpart **II**. The final product **89** was obtained through radical−radical recombination (**TS-II**).

Zhang and You endeavored to continue the field and designed a dearomative [2 + 2] cycloaddition of indole-tethered alkynes **90** with an Ir-based photosensitizer.[93] A wide array of cyclobutene-fused indolizidines **91** were accomplished in high yields and diastereoselectivity (>20:1 dr). This method could be extended to the synthesis of cyclobutane-fused indolizidines and related structural analogues **92**. By choosing an appropriate substrate with an extended linkage, a seven-membered ring lactam could be incorporated. The authors efficiently carried out both experimental and DFT analyses in support of an energy-transfer mechanism. As depicted in Scheme 30, the first C−C bond formation occurred at the C2 position of the indole ring via the triplet state **90T1**. The subsequent spin inversion followed by radical−radical recombination on the open-shell singlet states through **TS-II** led to final product **91**.

The use of an H-bond as a protecting group for allowing the construction of aliphatic amine-containing cyclobutane-fused

Scheme 30. Dearomative [2 + 2] Cycloaddition of Indole-Tethered Alkynes with an Ir-Based Photosensitizer for the Synthesis of Cyclobutene-Fused Indolizidines
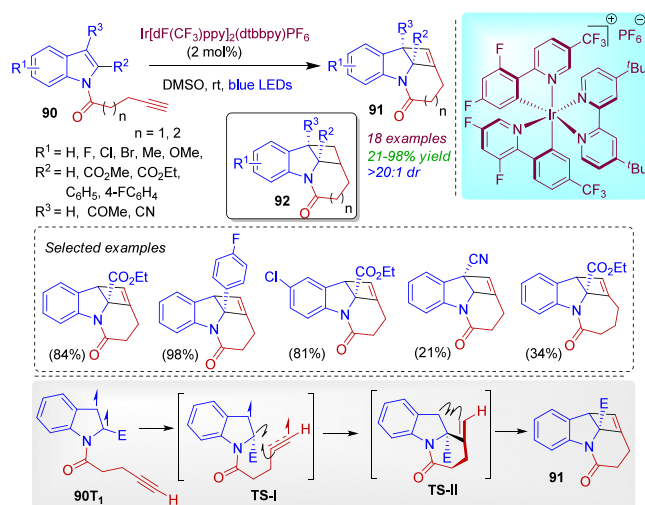
polycyclic indolines was investigated by Li, Zhang, and Fu.[94] In this work, redox-sensitive aliphatic amine bearing indoles **93** could be selectively transformed into the desired strained indoline scaffolds **94** via photocatalytic [2 + 2] cycloaddition of olefin-tethered indoles in fluorinated alcohol solvent (TFE or HFIP). The success of the approach relied on the formation of H-bonds between the N-atom and alcohol proton, thereby preventing the single electron transfer and enabling the energy transfer process (Scheme 31). In the presence of visible light and

Scheme 31. Photocatalytic [2 + 2] Cycloaddition of Aliphatic Amine Bearing Indoles toward Strained Indolines
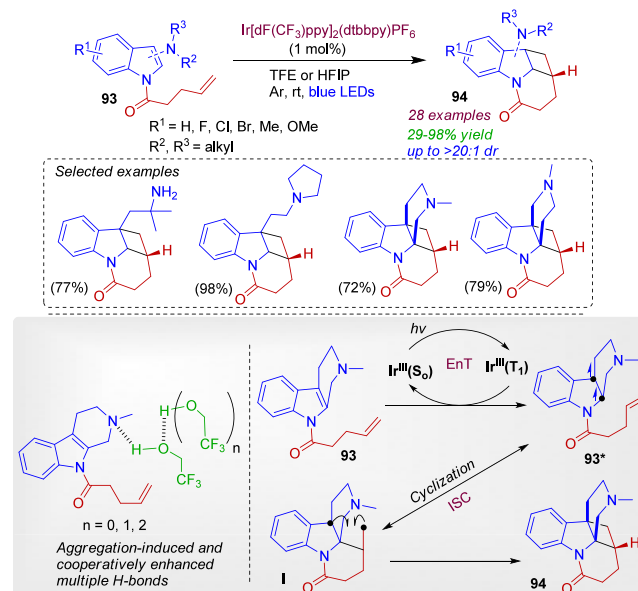

Ir-photocatalyst, substrate **93** is excited to triplet state **93*** through EnT. The formation of the first C−C bond followed by intersystem crossing (ISC) provided the open-shell singlet 1,4-diradical intermediate **I**. The final product **94** was formed by radical−radical combination. It is worth noting that tetrahydro carboline derivatives smoothly delivered corresponding bridged products obeying this protocol.

Dearomatization of indole-tethered O-methyl oximes was devised by You to access indoline-fused azetidine derivatives or benzindolizidines via an energy transfer mechanism with the help of Ir(dFppy)₃ photocatalyst.[95] Importantly, by tuning the substitution patterns of the indole substrates, two reaction pathways of the open shell singlet diradical species **I** could be regulated. When C3-unsubstituted indole derivatives **95** was exposed under blue LEDs, indoline-fused azetidines **96** were formed via [2 + 2] cycloaddition (Scheme 32). However, the presence of an alkyl substituent at the C3-position of the indole ring might interrupt the [2 + 2] cycloaddition process and force the reaction toward 1,5-hydrogen atom transfer to deliver benzindolizidine core **97**. Mechanistically, the switch of the reaction pathways for the open shell singlet diradical intermediates **I** was realized to afford products **96/97** (via TS-I/TS-II).

Vinylcyclopropanes (VCPs) can function as versatile radical acceptors and find wide applications in radical clock experiments.[96] In 2021, You's team employed indole-tethered VCPs with suitable substitutions at the indole moiety for rapid building up of molecular complexity via the visible-light energy transfer strategy.[97] They observed that C3-unsubstituted indole-VCPs

Scheme 32. Photocatalytic Dearomative [2 + 2] Cycloaddition of Indole-Tethered O-Methyl Oximes to Achieve Indoline-Fused Azetidines
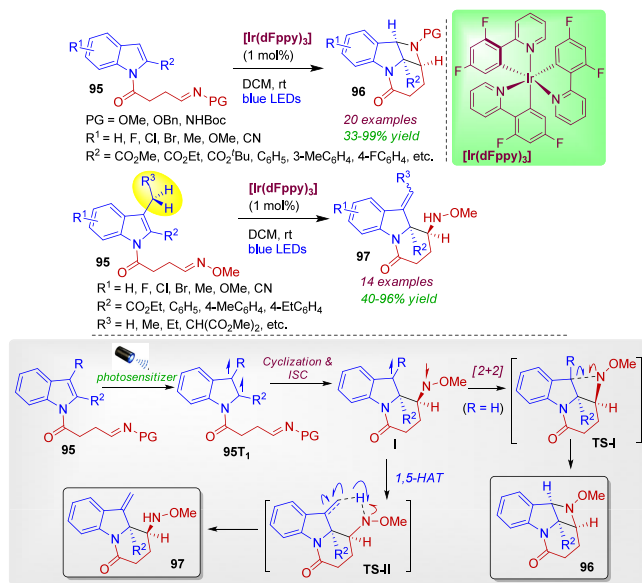
98 in the presence of Ir-photosensitizer furnished cycloheptane-fused indolines **99** via [5 + 2] cycloaddition under blue LEDs. The reaction tolerated a large variety of indole-tethered VCP substrates with diverse substitution patterns. On the other hand, C3-substituted indole-VCPs provided corresponding cyclobutane-fused scaffolds **100** through the [2 + 2] pathway under optimized conditions. The formation of products could be explained on the basis of open-shell singlet 1,4- and 1,7-biradical intermediates, as shown in Scheme 33.

Visible-light-mediated intramolecular double dearomative cycloaddition of arene-tethered indoles was realized for the

Scheme 33. Visible-Light-Mediated [5 + 2]/[2 + 2] Cycloaddition Involving Indole-Tethered VCPs toward Cycloheptane/Cyclobutane-Fused Indolines
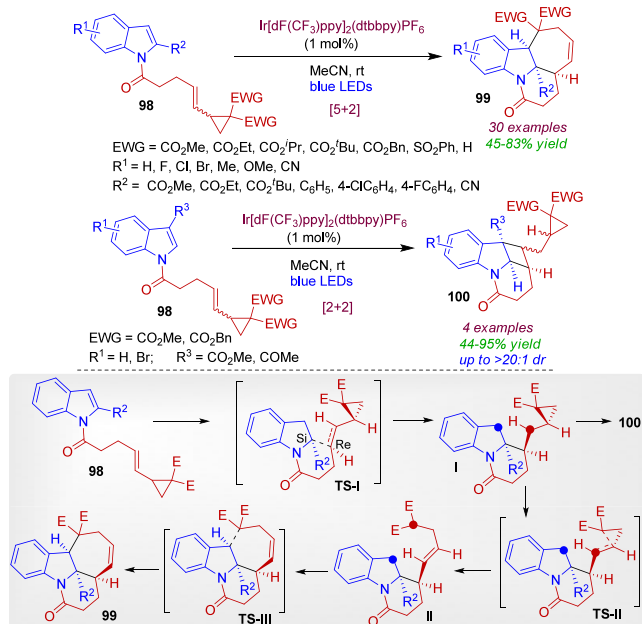
construction of bridged cyclic indoline derivatives.[98] A variety of C2-substituted indoles **101** was introduced to afford complex indoline architectures **102** with excellent yields and diastereoselectivity (up to 97% yields, >20:1 dr). As depicted in

Scheme 34. Visible-Light-Driven Double Dearomative Cycloaddition of Arene-Tethered Indoles for the Construction of Bridged Cyclic Indolines
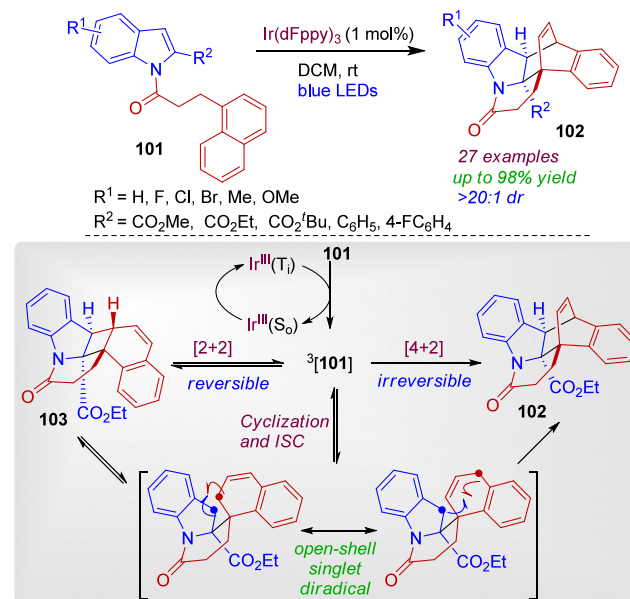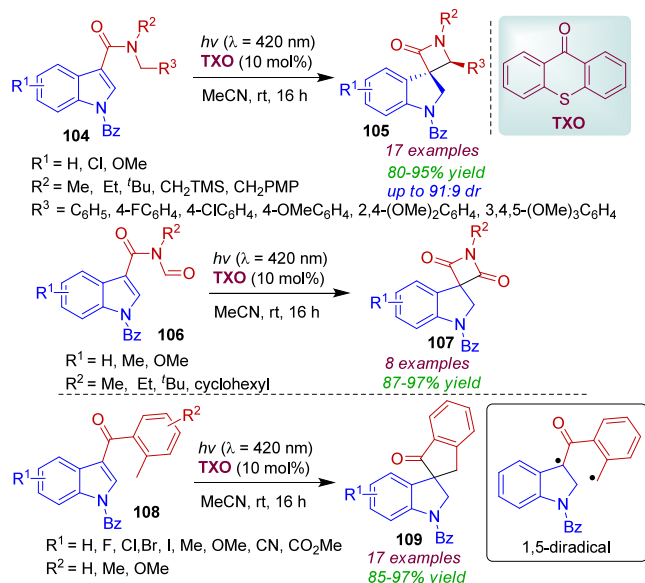

Scheme 34, the substrate **101** was excited to its first triplet state ^{3}[**101**] with the aid of an Ir-based photosensitizer and visible light via an energy transfer process. The first C−C bond formation at the C2 position of the indole moiety and ISC would generate the open shell singlet diradical species. Next, two competitive pathways, reversible [2 + 2] and irreversible [4 + 2] additions, provided structurally diverse indolines **102** and **103**, respectively.

4. FORMATION OF SPIRO INDOLINES

Synthesis of spirocyclic indolines is of great interest in organic and medicinal chemistry because of their medicinal value as well as frequent natural occurrence.[99,100] However, spirocyclization of indoles under the influence of visible-light irradiation has attracted immense attention due to rapid fabrication under mild conditions. In 2022, Bach's team synthesized spiroazetidine indoline scaffolds **105/107** (via HAT/cyclization cascade) starting from simple 3-substituted indoles **104/106** upon irradiation (λ = 420 nm) using thioxanthone (TXO) sensitizer.[101] Under similar reaction conditions, 3-(2′-methyl-benzoyl)-substituted indoles **108** smoothly delivered the corresponding spiroindane indolines **109** in good yields (Scheme 35). The authors claimed that the triplet state of the indoles not only acted as the intermediate for the photocycloaddition reactions but also served as the recipient of hydrogen atoms by intramolecular HAT. The 1,4- or 1,5-diradical intermediates were generated by excited state HAT from suitable alkyl groups within the C3-substituent to the indole C2 carbon atom. Then, the diradicals underwent ring closure to form a 4- or 5-membered spirocyclic scaffold with good diastereoselectivity.

Scheme 35. Light-Induced Dearomative Spirocyclization of Indoles toward Spiroazetidine/Spiroindane Indolines

104
R^1 = H, Cl, OMe
R^2 = Me, Et, ^{t}Bu, CH$_2$TMS, CH$_2$PMP
R^3 = C$_6$H$_5$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-OMeC$_6$H$_4$, 2,4-(OMe)$_2$C$_6$H$_3$, 3,4,5-(OMe)$_3$C$_6$H$_2$

105
17 examples
80-95% yield
up to 91:9 dr

106
R^1 = H, Me, OMe
R^2 = Me, Et, ^{t}Bu, cyclohexyl

107
8 examples
87-97% yield

108
R^1 = H, F, Cl,Br, I, Me, OMe, CN, CO$_2$Me
R^2 = H, Me, OMe

109
17 examples
85-97% yield

1,5-diradical

Construction of 3,3′-spirocyclic indolines bearing fluorine atom is a challenging task in organic synthesis. In 2019, Wang et al. devised a photoredox-catalyzed one-pot protocol for the synthesis of 3,3′-spirocyclic indolines via sequential difluoromethylative dearomatization, hydroxylation, and substitution reaction of indole-derived bromodifluoroacetamide **110**.[102] The use of diarylphosphine oxide as a nucleophile afforded the corresponding phosphine-tethered spirocyclic product **111** (Scheme 36)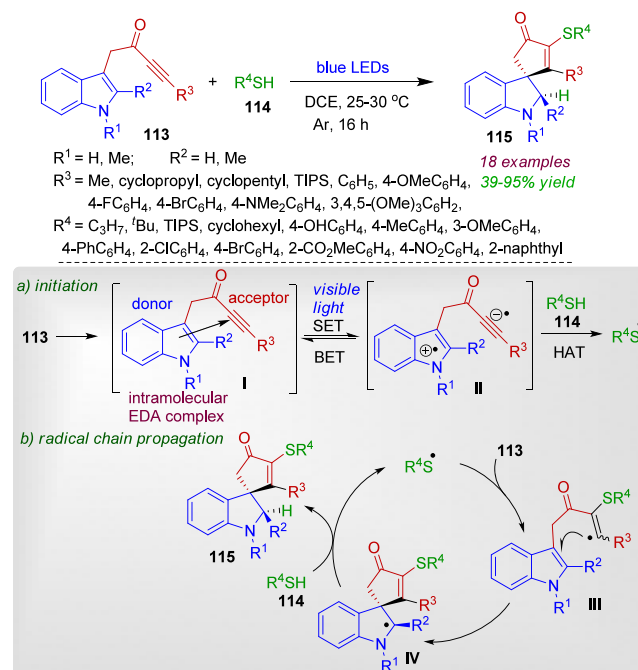. In all the cases, a single diastereoisomer was formed under optimized condition. When the nucleophile was indole, the reaction yielded indole-substituted spiroindolines **112** (54−99%). Some of the synthesized phosphine oxide- and indole-substituted spiroindolines displayed promising fungicidal activity. These are typical examples of difluoromethylative spirocyclization for the stereoselective synthesis of spiroindoles.

A unique intramolecular electron donor−acceptor (EDA) complexation/charge transfer strategy was reported in 2020 by

Scheme 36. Photoredox-Catalyzed Reaction of Indole-Substituted Bromodifluoroacetamide and Phosphine Oxide toward Synthesis of Spiroindolines

110
R^1 = H, F, Cl, Br, Me
R^2 = OEt, C$_6$H$_5$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$

111
15 examples
39-95% yield

110
R^1 = H, F, Cl, Br, Me
X = H, F, Cl, Br, Me, OMe, CN

112
16 examples
54-99% yield

Taylor and Unsworth.[103] The novel dearomative spirocyclization of indole-ynones **113** and thiols **114** was catalyst-free and self-initiated by the ynone substrates under visible light to accomplish sulfur-containing spirocyclic indolines **115**. According to the mechanism (Scheme 37), EDA complex **I** absorbed

Scheme 37. Light-Promoted Catalyst-Free Dearomative Spirocyclization of Indole-Tethered Ynones and Thiols to Access Sulfur-Containing Spirocyclic Indolines
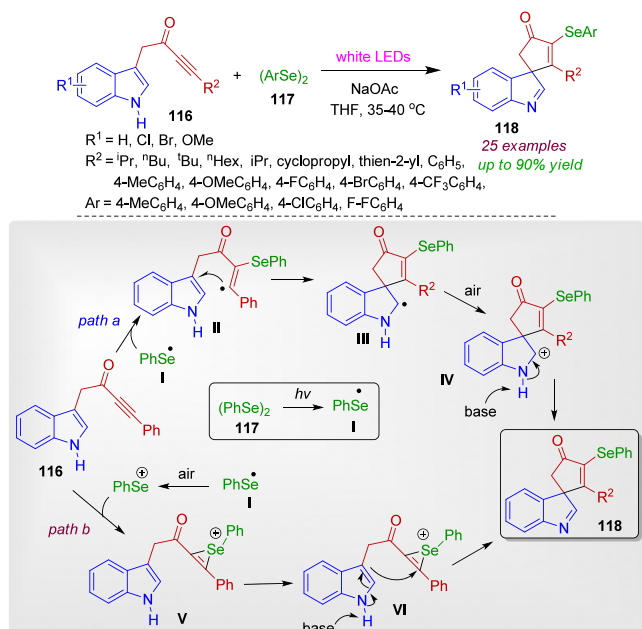

113
R^1 = H, Me; R^2 = H, Me
R^3 = Me, cyclopropyl, cyclopentyl, TIPS, C$_6$H$_5$, 4-OMeC$_6$H$_4$,
4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NMe$_2$C$_6$H$_4$, 3,4,5-(OMe)$_3$C$_6$H$_2$,
R^4 = C$_3$H$_7$, ^{t}Bu, TIPS, cyclohexyl, 4-OHC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-OMeC$_6$H$_4$,
4-PhC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-CO$_2$MeC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-naphthyl

115
18 examples
39-95% yield

a) initiation
b) radical chain propagation

visible light to form photoexcited state (charge transfer complex) **II**. The latter might simply relax to reform EDA complex **I** via BET, or alternatively, the open shell excited state **II** would abstract a hydrogen atom from the thiol **114**, thereby producing the thiyl radical. Subsequently, the addition of thiyl radical to the ynone (**113 → III**), spirocyclization (**III → IV**), and hydrogen atom transfer from thiol **114** delivered final dearomatized product **115**.

Immediately after, Chen, Xu, and co-workers prepared 3-selenospiroindolines **118** via visible-light-mediated selenylative spirocyclization of indole tethered ynones **116** with diselenides **117** under metal-free conditions.[104] The use of NaOAc in THF under air conditions provided the best result. The reaction was fruitful for diaryldiselenides; however, 1,2-dimethyldiselenides failed to provide the desired product. The authors suggested two possible pathways (Scheme 38). According to path a, phenylselenyl radical **I** added to the alkyne moiety of **116** to form an alkenyl radical **II**, following cyclization at the 3-position of indole, resulting in spiro radical intermediate **III**. Oxidation of **III** in air would provide cation intermediate **IV**, which experienced dehydrogenation under basic conditions to offer spiroindoline **118**. Alternatively (path b) oxidation of the phenylselenyl radical in air gave PhSe$^+$, which reacted with the alkyne moiety of **96** to afford bridged selenium ion **V**. Base-promoted cyclization yielded the spiro product (**VI → 118**).
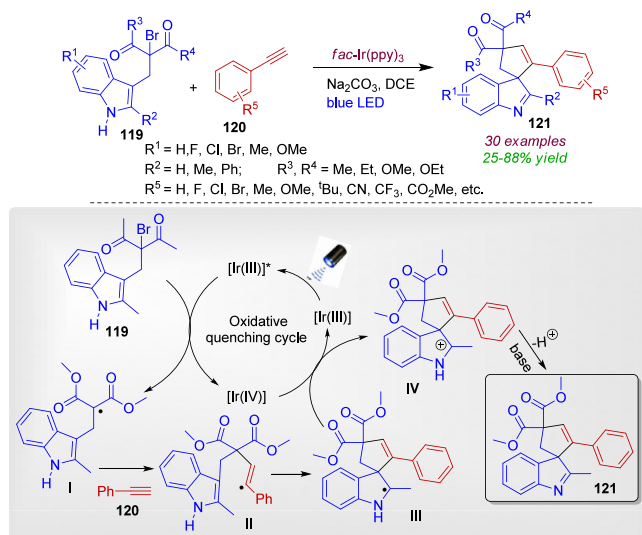
In 2020, intermolecular dearomative cyclization of indole-derived bromides with alkynes was reported to afford spiroindolines.[105] The reaction was performed under blue LED with iridium photocatalyst in the presence of the base Na$_2$CO$_3$. The

Scheme 38. Visible-Light-Mediated Spirocyclization of Indole Ynones with Diselenides to Obtain 3-Selenospiroindolines

R¹ = H, Cl, Br, OMe
R² = ⁱPr, ⁿBu, ᵗBu, ⁿHex, iPr, cyclopropyl, thien-2-yl, C₆H₅,
   4-MeC₆H₄, 4-OMeC₆H₄, 4-FC₆H₄, 4-BrC₆H₄, 4-CF₃C₆H₄,
Ar = 4-MeC₆H₄, 4-OMeC₆H₄, 4-ClC₆H₄, F-FC₆H₄

25 examples
up to 90% yield

alkynes bearing halogens and electron-donating (Me, OMe, ᵗBu) and electron-withdrawing (CF₃, CN, CO₂Me) groups at the phenyl ring smoothly proceeded to furnish the corresponding spiroindolines **121** in moderate to good yields (25−88%). However, the reaction was unsuccessful for the aliphatic alkynes. As mentioned in Scheme 39, the reaction started with visible-

Scheme 39. Photocatalytic Intermolecular Dearomative Cyclization of Indole-Derived Bromides with Alkynes Affording Spiroindolines

R¹ = H,F, Cl, Br, Me, OMe
R² = H, Me, Ph;   R³, R⁴ = Me, Et, OMe, OEt
R⁵ = H, F, Cl, Br, Me, OMe, ᵗBu, CN, CF₃, CO₂Me, etc.
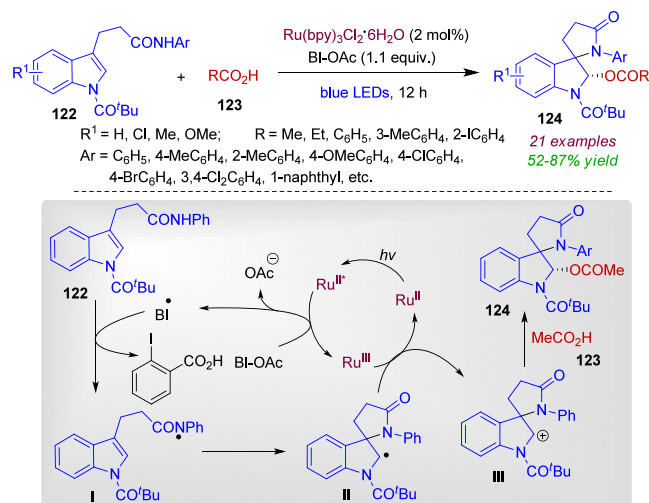
30 examples
25-88% yield

light-induced excitation of the Ir(III) photocatalyst to form excited Ir(III)*. Single electron transfer (SET) with indole derivative **119** would form radical **I**, which underwent rapid addition with alkyne **120** to generate radical intermediate **II**. Intramolecular cyclization afforded spiro radical **III**, followed by SET to provide carbocation **IV** with regeneration of Ir(III)

photocatalyst. Eventually, deprotonation of **IV** under basic conditions resulted in spiro indoline **121**.

In the same year, Wang's group explored dearomative oxamination reaction of anilide-tethered indoles for stereo-selective formation of spiroindolines.[106] The reaction of indoles **122** with aliphatic or aromatic carboxylic acids **123** in the presence of Ru(bpy)₃Cl₂·H₂O photocatalyst and acetoxyben-ziodoxole (BI-OAc) oxidant efficiently produced spiro compound **124** bearing an ester moiety at the C2-position. The step-economical strategy comprised C−N and C−O bond formation with exclusive diastereoselectivity. Mechanistically (Scheme 40), the reaction was triggered by photoexcited Ruᴵᴵ* to BI-OAc

Scheme 40. Visible-Light-Initiated Dearomative Oxamination Reaction of Anilide-Tethered Indoles toward Spiroindolines

R¹ = H, Cl, Me, OMe;   R = Me, Et, C₆H₅, 3-MeC₆H₄, 2-IC₆H₄
Ar = C₆H₅, 4-MeC₆H₄, 2-MeC₆H₄, 4-OMeC₆H₄, 4-ClC₆H₄,
   4-BrC₆H₄, 3,4-Cl₂C₆H₄, 1-naphthyl, etc.

21 examples
52-87% yield

via the SET process to generate BI radical. The latter would oxidize **122** to produce radical **I**, which experienced *5-exo* cyclization affording spiroindoline radical **II**. Oxidation of radical **II** by Ruᴵᴵᴵ resulted in cation intermediate **III**, and concomitant nucleophilic attack by carboxylic acid **123** from the less hindered face of **III** delivered final spiro product **124**.

A red-light-induced cascade trifluoromethylation/spirocyclization of indole derivatives **125** with Umemoto's reagent **126** was investigated by Gianetti's group.[107] The authors employed *N*,*N*′-dipropyl-1,13-dimethoxyquinacridinium (ⁿPr-DMQA⁺) tetrafluoroborate as an effective photocatalyst for this radical-mediated dearomatization furnishing CF₃-containing 3,3′-spirocyclic indolines **127**. Various indoles with carboxylic acid pendants bearing different substituents at the aromatic ring worked well under the optimized reaction conditions. Furthermore, indole-tethered *N*-tosylamines were compatible with this protocol. The mechanism of the *anti*-selective cyclization process is depicted in Scheme 41. In the presence of red light, ⁿPr-DMQA⁺ was excited to ⁿPr-DMQA⁺*, which would reduce the Umemoto's reagent **126** to generate CF₃ radical via oxidative quenching. Next, addition of CF₃• to indole substrate **105** furnished dearomatized benzyl radical **I**, and a subsequent SET process involving ⁿPr-DMQA•⁺⁺ afforded benzyl carbocation intermediate **II**. Intermediate **II-a** would be more favored because of steric repulsion between CF₃ and the dangling CO₂H group in **II-b**. Therefore, single *anti*-diastereomer **127** was formed via intramolecular nucleophilic attack involving CO₂H. It should be noted that a rapid

Scheme 41. Red-Light-Induced Cascade Trifluoromethylation and Dearomatization of Indole Derivatives with Umemoto's Reagent to Access 3,3′-Spirocyclic Indolines
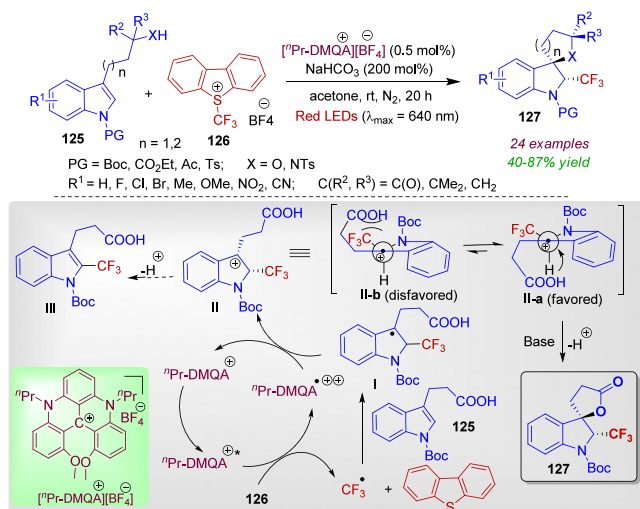
aromatization of **II** might occur to produce unexpected C2-trifluoromethylated adduct **III**.

Meanwhile, Wang's group introduced a radical isocyanide insertion/spirocyclization reaction between 3-(2-isocyanobenzyl)-indoles **128** and bromodifluoroacetates **129** under visible-light irradiation with the aid of *fac*-Ir(ppy)₃ photocatalyst.[108] Interestingly, bromodifluoroacetates bearing azacyclic substituents (morpholinyl, piperazinyl, isoquinolinyl, etc.) responded well. A library of spiro[indole-3,3′-quinoline] derivatives **130** was produced under this condition in moderate to good yields (34−91%). The authors proposed a radical mechanism based on some radical inhibition experiments (Scheme 42). Initially, [*fac*-Ir^III(ppy)₃], under visible light, was excited to [*fac*-Ir^III(ppy)₃]*, which was oxidized by ethylbromodifluoroacetate **129** to form

Scheme 42. Photocatalytic Radical Insertion Reaction of 3-(2-Isocyanobenzyl)-Indoles and Bromodifluoroacetates to Offer Spiro[indole-3,3′-quinoline] Derivatives
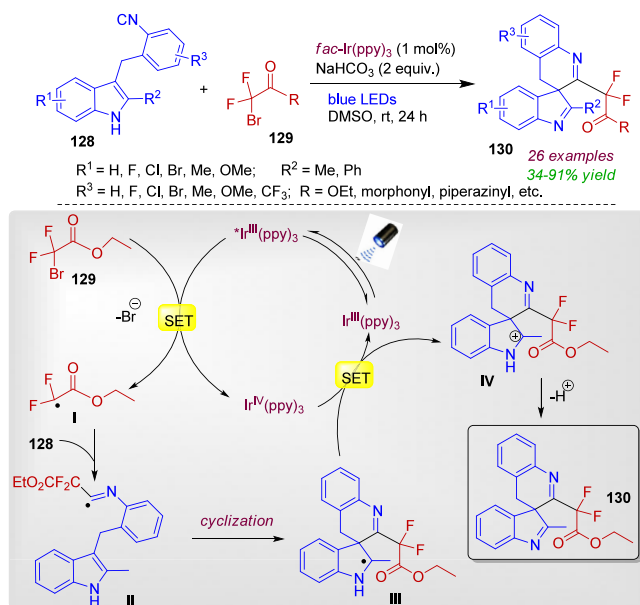
radical **I**. Next, addition of radical **I** on the isocyanide moiety of indole **128** offered intermediate **II**, which underwent *6-exo-trig* cyclization to generate spiro intermediate **III**. The latter was oxidized by [*fac*-Ir^IV(ppy)₃] to afford intermediate **IV**, which after deprotonation in the presence of a base (NaHCO₃) yielded spiro quinolone indoline **130**.

Very recently, visible-light-induced selenylative spirocyclization of 3-(2-isocyanobenzyl)-indoles **131** with diselenides **132** has been developed by Qi, Wang, and co-workers.[109] Various dialkyl- and diarylselenides efficiently reacted under blue LEDs, leading to the formation of selenyl spiro[indole-3,3′-quinoline] derivatives **133** (Scheme 43). The selenyl free radical **I** produced

Scheme 43. Visible-Light-Induced Spirocyclization of 3-(2-Isocyanobenzyl)-Indoles with Diselenides, Affording Selenyl Spiro[indole-3,3′-quinoline] Derivatives
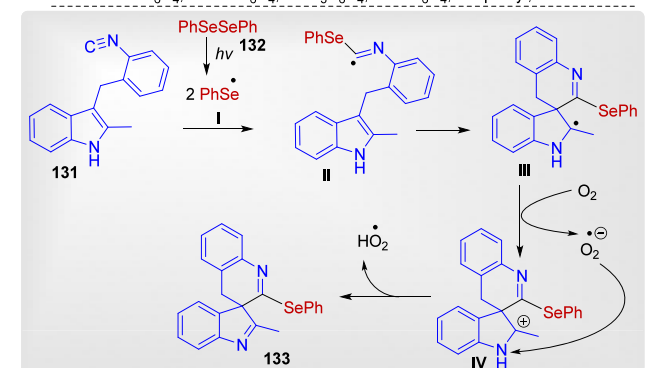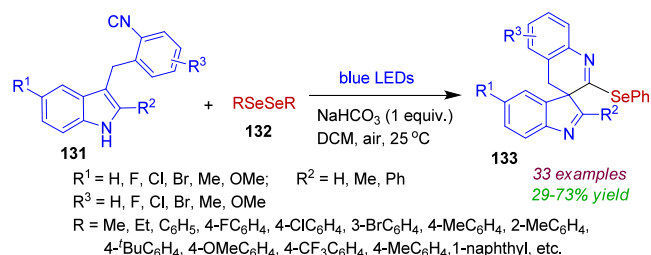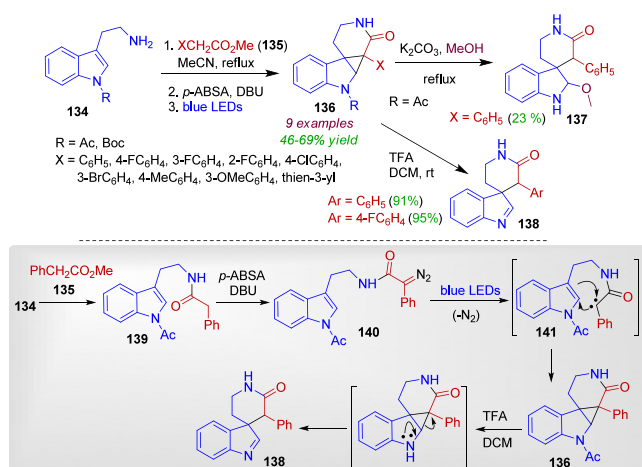

from **132** underwent addition with isocyanide **131**, affording radical intermediate **II**. Subsequent *6-exo-trig* cyclization (**III**) followed by oxidation produced intermediate **IV**. Lastly, proton abstraction by the anion radical O₂^•− furnished the desired spiroindole-3,3′-quinolines **133**.

Sen et al. devised blue LED enabled intramolecular C-H functionalization and cyclopropanation of tryptamine derivatives to afford polycyclic indoline scaffolds.[110] When tryptamine derivatives **134** was treated with arylacetates **135** in refluxing acetonitrile, compound **139** could be obtained satisfactorily (Scheme 44). Treatment of **139** with *p*-acetamido benzenesulfonyl azide (*p*-ABSA) and DBU afforded diazo intermediate **140**. Irradiation of the latter under blue LEDs would produce cyclopropane-fused indoline scaffold **136** via the formation of carbene intermediate **141**. N-Acetyl and N-Boc tryptamines delivered the corresponding cyclopropane-fused indolines in acceptable yields (46−69%). Under basic/acid conditions, cyclopropane-fused indolines **136** afforded spiropiperidino indolines **137/138** through the cyclopropane ring opening process.

5. CONCLUSION

Indolines, the dearomatized form of indoles, are ubiquitous in alkaloid natural products that display diverse pharmacological

Scheme 44. Synthesis of Spiropiperidino Indolines via Blue LED Driven Cyclopropanation of Tryptamine Derivatives

Notes

The author declares no competing financial interest.

Biography

Suven Das obtained his B.Sc., M.Sc., and Ph.D. Degrees (2007) in Chemistry from the University of Calcutta, India. In 2007 he joined as Lecturer in Chemistry at Rishi Bankim Chandra College for Women, Naihati, India. After his post doctoral research at the National Tsing Hua University, Taiwan (2009), he returned to India and joined as Assistant Professor in the same college to start his independent research career. He is a member of the Royal Society of Chemistry. He has published several research articles including some review articles in journals of international repute. His research interests cover the areas of synthetic methodology, catalysis, indanone chemistry, and heterocycles.

■ ACKNOWLEDGMENTS

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