# Strategic Use of Visible-Light Photoredox Catalysis in Natural Product Synthesis

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**ABSTRACT:** Recent progress in the development of photocatalytic reactions promoted by visible light is leading to a renaissance in the use of photochemistry in the construction of structurally elaborate organic molecules. Because of the rich functionality found in natural products, studies in natural-product total synthesis provide useful insights into functional group compatibility of these new photocatalytic methods as well as their impact on synthetic strategy. In this review, we examine total syntheses published through the end of 2020 that employ a visible-light photoredox catalytic step. To assist someone interested in employing the photocatalytic steps discussed, the review is organized largely by the nature of the bond formed in the photocatalytic step.

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## 1. INTRODUCTION

### 1.1 Introductory Comments

Photochemical reactions brought about by high-energy UV light have played a role in organic synthesis for over a century.[1,2] The extensive recent progress in the development of photocatalytic reactions promoted by visible light is leading to a renaissance in the use of photochemistry in the construction of organic molecules, including structurally elaborate natural products. The mechanistic underpinnings and scope of recent advances in visible-light photoredox catalysis are discussed in many excellent reviews and monographs[3-13], including reviews published in this issue of *Chemical Reviews*.

One indication of the impact of these recent developments is the increasing use of photocatalytic reactions in the total synthesis of natural products. Because of the rich functionality found in structurally elaborate natural products, such studies provide useful insights into functional group compatibility of visible-light photocatalytic methods as well as their impact on synthetic strategy. In this review, we examine total syntheses published through the end of 2020 that have a visible-light photoredox catalytic step. Aspects of these developments have been treated in earlier reviews of this general topic.[14-16]

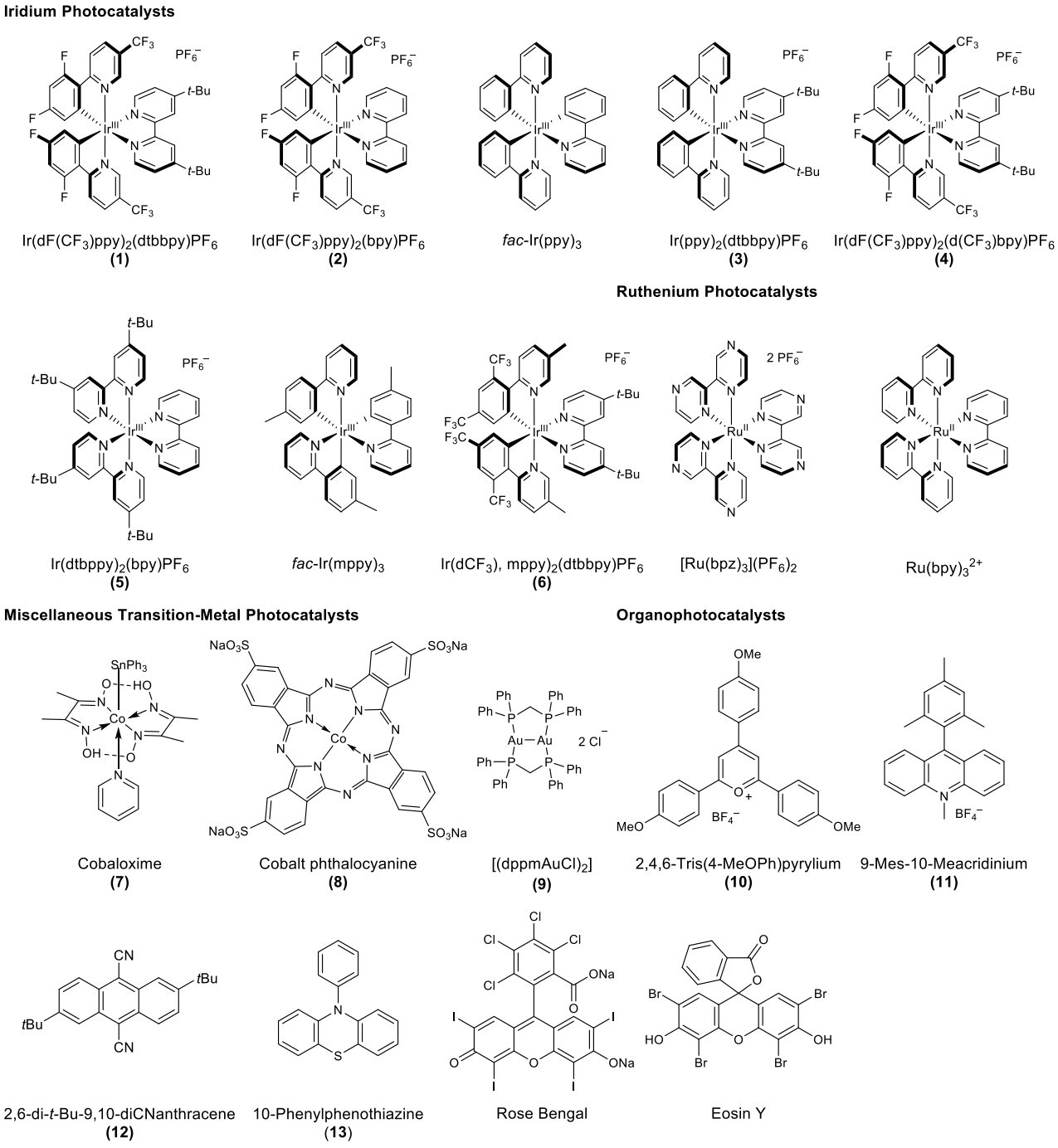



Figure 1. Structures of photocatalysts that were employed in the total syntheses.

1.2 Photocatalysts Employed in the Total Syntheses and Comments on Choosing an Appropriate Photocatalyst

Figure 1 depicts the various photocatalysts (PCs) that were employed in the total syntheses highlighted in this review. With such a wide array of photocatalyst options now available, how does one approach choosing a photocatalyst for a given application? There are several factors that should be considered. For instance, the photocatalyst should not absorb in the same region as any of the reagents and the desired product to prevent unwanted side reaction and product decomposition. It is here where visible light absorbing photocatalysts are advantageous, as organic compounds generally do not absorb in this region. Therefore, photocatalysts with high extinction coefficients at wavelengths > 400 nm are particularly well-suited for synthetic applications. Nevertheless, it should be noted that UV-irradiation can also lead to efficient and selective photocatalyzed reactions if care is taken to ensure there is no absorption of the reaction components in the region of irradiation.[17-19]

It is also important to know whether the desired single-electron transfer (SET) event from the excited state photocatalyst to the reactant is thermodynamically feasible, as this is the first step in the photoredox catalytic cycle. This analysis is readily accomplished by determining the Gibbs free energy for the SET process ($\Delta G_{SET}$). For an excited state process, one

can employ the Rehm–Weller equation[20] (eq 1) for calculating $\Delta G_{SET}$:

$$\Delta G_{\mathrm{SET}} = E_{1/2}^{ox}(\mathrm{D}) - E_{1/2}^{red}(\mathrm{A}) - E^{*}(\mathrm{D\ or\ A}) + \Delta E_{\mathrm{Coulombic}} \quad (1)$$

where $E_{1/2}^{ox}(\mathrm{D})$ is the oxidation potential of the electron donor, $E_{1/2}^{red}(\mathrm{A})$ is the reduction potential of the electron acceptor, $E^{*}$ (D or A) is the excited state energy of the excited donor or acceptor, and $\Delta E_{\mathrm{Coulombic}}$ is the measure of the interaction between charged ions in the dielectric constant of the reaction's solvent. From eq 1, one can infer that choosing photocatalysts with higher excited state energies will increase the probability that the desired SET event will be favored.

Finally, when choosing a photocatalyst for a given application, one should also be mindful of the excited state kinetics, as even though a SET event may be thermodynamically feasible, it may not necessarily occur owing to time constraints and competition from other reagents. In this regard, choosing a photocatalyst with a high quantum yield of formation for the triplet excited state is beneficial, as triplet states possess relatively long lifetimes since relaxation back to the singlet ground state is spin forbidden.[21] A longer excited-state lifetime increases the probability of SET quenching events, leading to increased efficiencies in photoredox catalyzed reactions. Furthermore, it can also be important to modify reaction conditions to suppress competitive quenching events. For example, removal of oxygen from a triplet photocatalyst-mediated reaction often increases reaction efficiency, as molecular oxygen is a potent quencher of triplet excited states.

### 1.3 Organization of the Review

We have organized the review in the way we believe will be most useful for someone interested in employing the photocatalytic steps discussed. Thus, most of the review (Sections 2–4) is organized by the nature of the bond formed in the photocatalytic step. For some of the less common photocatalytic transformations, key intermediates are depicted; however, catalytic cycles are not provided, as these are described in detail in the general reviews cited earlier. To give the reader an impression of the conciseness of the total syntheses covered, synthetic schemes typically begin with the commercially available starting material the authors employed, or if not commercially available, its origin is mentioned in the text.

We have limited our treatment to completed total syntheses, so publications reporting studies toward a natural product target are not presented, nor are syntheses of simple α-amino acids. Total syntheses whose only photocatalytic step is generation of singlet oxygen are also not covered.

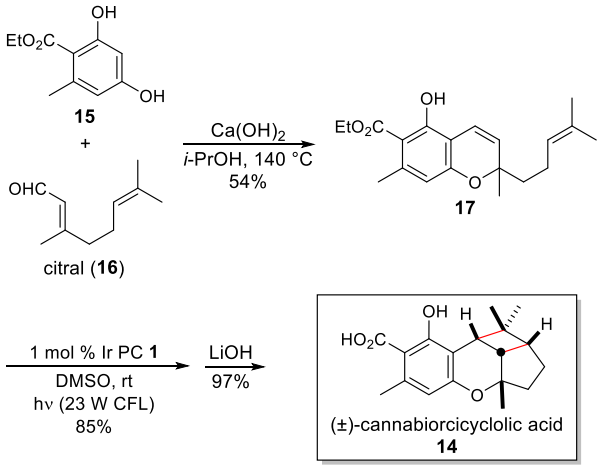
## 2. CARBON-CARBON BOND FORMATION

### 2.1 Cycloadditions

**2.1.1. [2+2] Cycloadditions.** Cyclobutane rings are prominent structural features of a wide variety of natural products, and photochemistry has long played a prominent role in their synthesis. Until recently, such constructions required high-energy UV light and nearly always used an enone as one of the cycloaddends.[1] Photocatalysis now allows a variety [2+2] cycloadditions to be accomplished using visible light, which greatly broadens the functionality that can be present in the cycloaddends and the product. In addition, the ability of visible-light photocatalysis to initiate [2+2] cycloadditons by either photoreduction or photooxidation to generate radical anion or radical cation intermediates, or by energy transfer to form a triplet intermediates, expands significantly the types of alkenes that can be used. These recent advances and their mechanistic underpinnings are described in many reviews.[22,23]

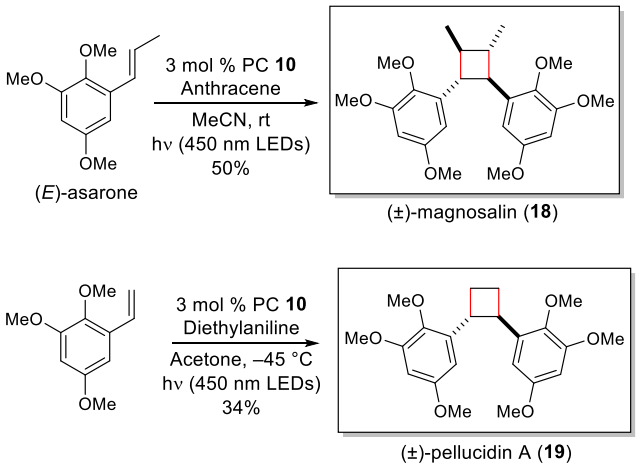
An early contribution to this area from the Yoon group reported intramolecular cycloadditions of a styrene and an alkene to form polycarbocyclic and heterocyclic products harboring cyclobutane rings.[24] These cycloadditions used the fluorinated PC Ir[(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (**1**), whose emission maximum at 470 nm corresponds approximately to the triplet energy of a styrene (61 kcal/mol). This method was exemplified in a short total synthesis of (±)-cannabiorcicyclolic acid (**14**), one of several cyclobutane-containing cannabinoids (Scheme 1). The synthesis starts with base-promoted condensation of resorcinol **15** with citral (**16**) to give chromene **17**. Irradiation of a DMSO solution of this intermediate with visible light at room temperature produced the cyclobutane-containing cycloadduct in high yield; saponification of the ester substituent then yielded (±)-cannabiorcicyclolic acid (**14**).

**Scheme 1.**

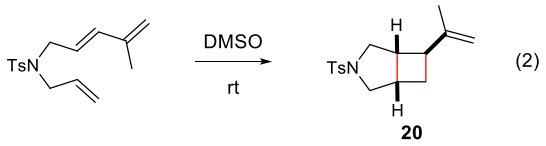



Visible-light photocatalysis can be used to form cyclobutanes by [2+2] cycloadditions of electron-rich styrenes in two ways. In the first method reported by Yoon, the photocatalytic cycle generates radical cation intermediates, which were well known to yield [2+2] cycloadducts when generated using stoichiometric one-electron oxidants. To render such cycloadditions irreversible, the PC is chosen so the catalytic photooxidant can oxidize the styrene, but not the cycloadduct.[24] An alternative method to achieve this selectivity, reported by Nicewicz, employs an electron relay which is oxidized by pyrilium salt **10** and subsequently catalyzes photodimerization by oxidation of the styrene.[25] This method was used to synthesize the lignan natural products (±)-magnosalin (**18**) and (±)-pellucidin A (**19**), (Scheme 2). The dimerization of unsubstituted styrenes is especially challenging, as they are prone to polymerization. As a result, the synthesis of (±)-pellucidin A (**19**) was carried out at low temperature and was less efficient. The critical role played by the relay oxidant was highlighted by resubjecting the cyclodimer to photocatalytic conditions and observing that it suffered significant cycloreversion if anthracene was omitted.

**Scheme 2.**




Diene-alkene cyclizations have rarely been used in natural products total synthesis because of the high energy required for direct excitation of a 1,3-diene. The UVC light (240–265 nm) required for such reactions has limited compatibility with many functional groups. To overcome this restriction, Yoon and co-workers reported the use of Ir PC **1** under visible-light irradiation.[26] In the example depicted in eq 2, visible-light photocatalysis conditions provided photo cycloadduct **20** in high efficiency, whereas direct excitation using UVC light failed to yield any of the [2+2] photoadduct.

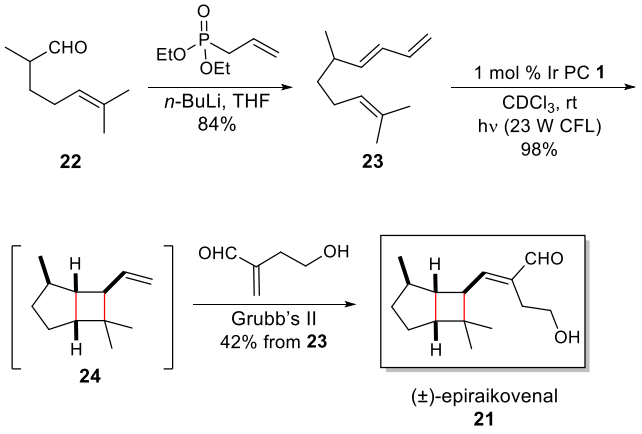



hν (UVC), 30 min: 100% conversion, 0% yield

1 mol% **1,** hν (CFL bulb), 15 h:100% conversion, 89% yield

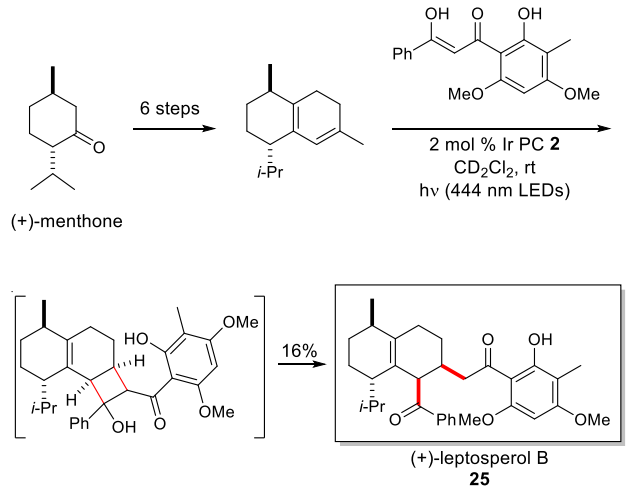
These authors went on to utilize this approach in a short synthesis of (±)-epiraikovenal (**21**), the natural levorotatory enantiomer of which was isolated from a marine ciliate. The synthesis begins with aldehyde **22**, which was olefinated in standard fashion to give triene **23** (Scheme 3). In the presence of 1 mol % of Ir PC **1**, intramolecular [2+2]-cycloadduct **24** was formed in nearly quantitative yield under visible-light irradiation. In the same flask, this crude cycloadduct was elaborated by cross metathesis to give racemic epiraikovenal (**21**) in 42% yield from triene **23**.

**Scheme 3.**




Intermolecular diene-alkene [2+2] cycloadditions were employed by Wang and co-workers to prepare two phloroglucinols, leptosperols A and B (**25**).[27] In these syntheses, a β-hydroxyenone was used and retro-aldolization followed the cycloaddition step, as summarized for the synthesis of (+)-leptosin B (**25**) in Scheme 4. In this way, the stereoselective photoredox-catalyzed cycloaddition was used to fashion *cis*-vicinal side chains on a six-membered ring.

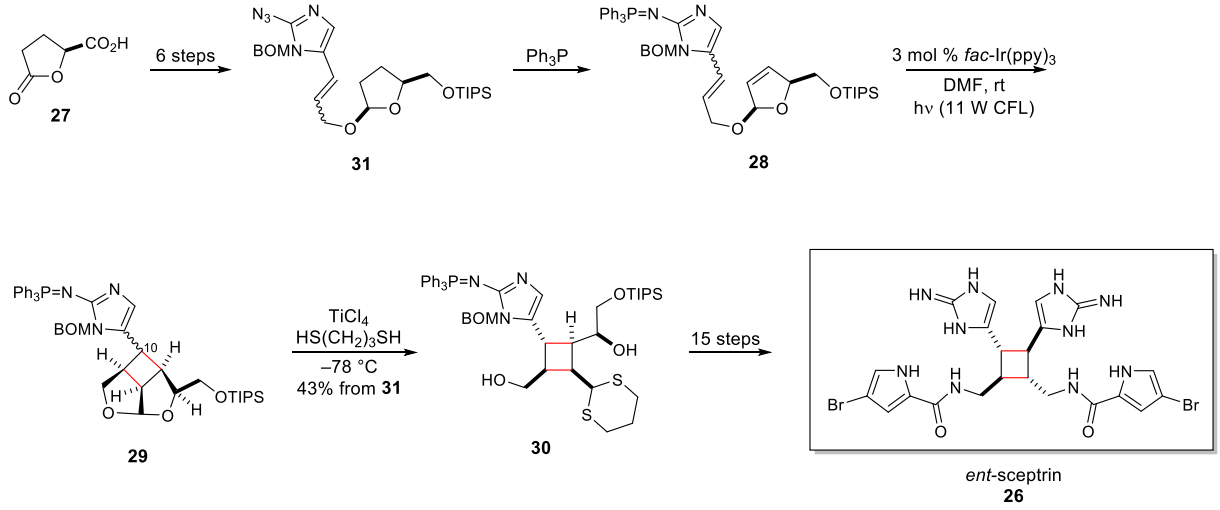
**Scheme 4.**




The dimeric pyrrole-imidazole alkaloids are complex marine metabolites having an unusually high heteroatom to carbon ratio and a variety of unique structures. The cyclobutane-containing alkaloid sceptrin is proposed to be the precursor of several more-elaborate members of this family. In an investigation that established the absolute configuration of sceptrin and the more complex pyrrole-imidazole alkaloid massadine, Chen and co-workers carried out an enantioselective total synthesis of *ent*-sceptrin (**26**) (Scheme 5).[28] The synthesis begins with the L-glutamic acid-derived lactone acid **27**, which was elaborated in seven steps to cyclization precursor **28**. The reaction of **28** with several stoichiometric single-electron oxidants resulted in complete decomposition. Employing Yoon's photoredox method, however, cycloadduct **29** was formed in useful yield as a 1:1.8 mixture of C-10 epimers. After acetal to thioacetal exchange, *ent*-sceptrin precursor **30** was obtained in 43% overall yield from intermediate **31**. This sequence was subsequently used by Chen and co-workers to prepare natural sceptrin.[29]

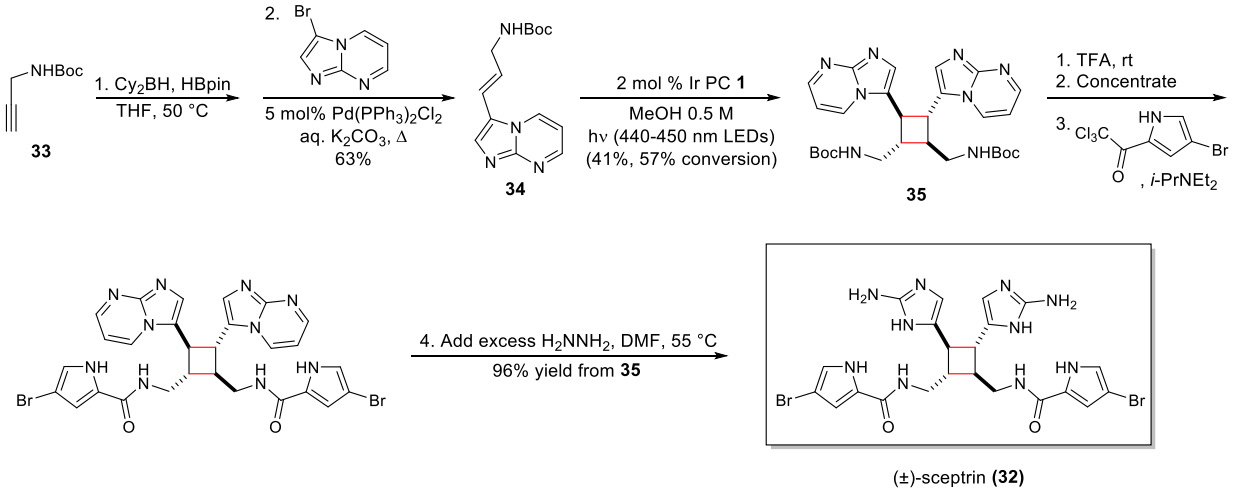
The presumed biosynthetic precursor of sceptrin is the acyclic alkene marine metabolite hymenidin. To no surprise, constructions of sceptrin by head-to-head dimerization of hymenidin or related structures has been investigated for some time.[30-32] In 2020, this general strategy was reduced to practice in a short synthesis of (±)-sceptrin (**32**) by Nguyen and Jamison (Scheme 6).[33] Starting with *tert*-butoxycarbonyl (Boc)-protected propargylamine **33**, cycloaddition precursor **34** having the 2-aminoimidazole fragment protected with a trimethine unit[32] was prepared by Suzuki-Miyaura cross-coupling. Irradiation of **34** and 2 mol % of Ir PC **1** in methanol with blue LEDs gave dimer **35** in 41% yield (57% conversion). In four carefully orchestrated steps, **35** was transformed to (±)-sceptrin (**32**) in high yield. The selectivity of this dimerization is remarkable as the formation of ten racemic isomers is possible. Since the Ir PC **1** is not sufficiently oxidizing in its excited state to generate a radical cation from **34**, the dimerization is presumed to proceed via a triplet energy transfer mechanism.

**Scheme 5.**




27 31 28 29 30 **26**

**Scheme 6.**




**33** **34** **35** (±)-sceptrin **(32)**

**2.1.2. [4+2] Cycloadditions.** Since thermal [4+2]-cycloadditions are allowed by the Woodward-Hoffman rules, photochemistry typically has played little role in natural product syntheses featuring such bond constructions. As photoaddends can be activated by forming radical cation or radical anion intermediates using photoredox catalysis, there are now several examples where visible-light photocatalysis has played a decisive role in promoting [4+2]-cycloadditions in the synthesis of natural products.

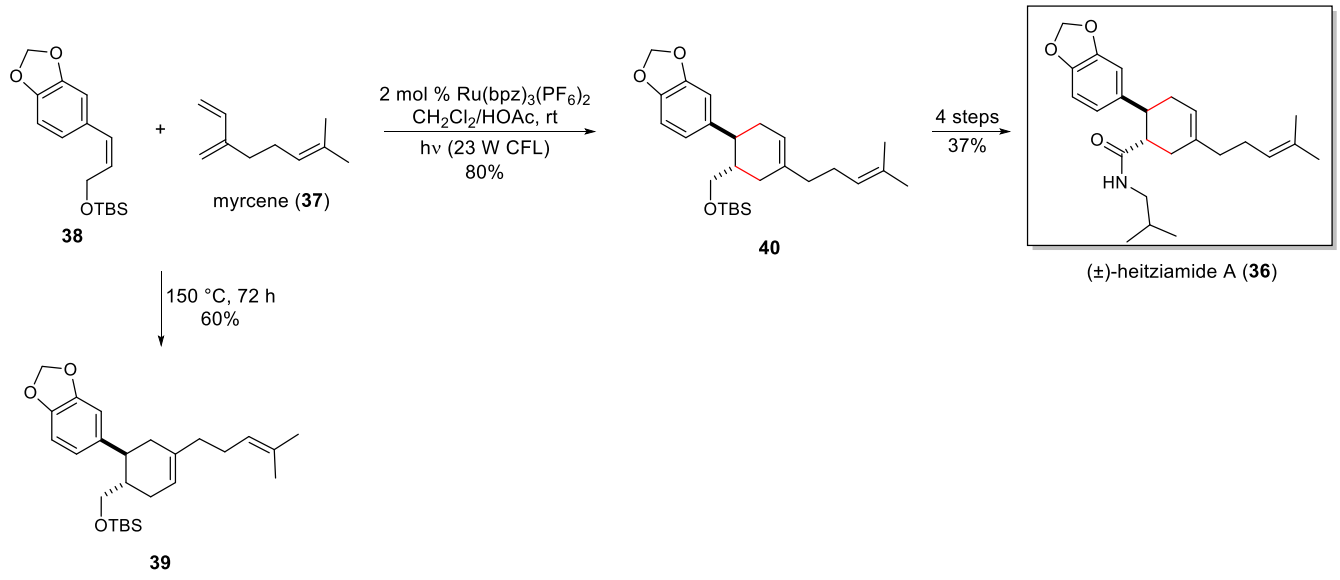
An early report by the Yoon group highlights the potential advantages of this approach (Scheme 7).[34] Heitziamide A (**36**) is a cyclohexenamide natural product isolated from an African medicinal plant. Whereas thermal cycloaddition of myrcene

(**37**) and styrene **38** provides Diels–Alder adduct **39**, photocatalytic one-electron oxidation using $Ru(bpz)_3(PF_6)_2$ under visible light irradiation delivers the regioisomeric cycloadduct **40** in 80% yield. The authors report that none of the isomeric cycloadduct **39** was detected in the photocatalytic reaction, nor could an aminium radical cation promote the cycloaddition. In four straightforward steps, **40** was elaborated to (±)-heitziamide A (**36**).

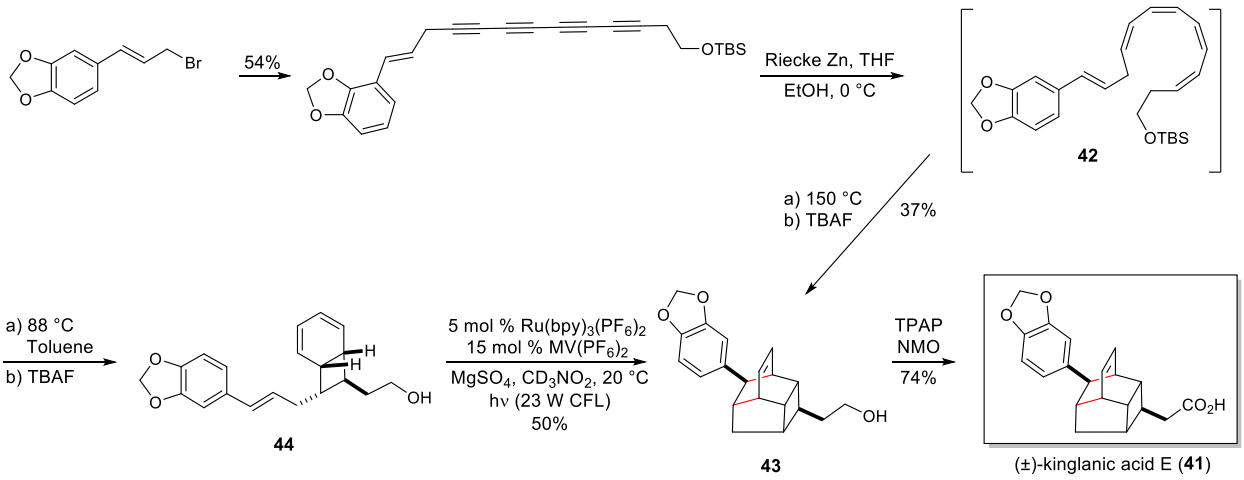
Kinglanic acid E (**41**) is exemplary of a family of natural products isolated from *Endiandra kingiana* whose structures are distinct from the endiandric acids originally isolated from these plants by Black, Banfield and co-workers.[35] In the recent inaugural synthesis of (±)-kinglanic acid E (**41**) by Sherburn and co-workers, the tetracyclic framework of kinglanic acid E was viewed as the result of a Black-Banfield-type domino 8π-6π electrocyclization/intramolecular Diels–Alder sequence,[35] albeit with the diene and dienophile reversed from that giving rise to the endiandric acids.[36] Sherburn and co-workers reported the five-step synthesis of (±)-kinglanic acid E (**41**) in which the electrocyclization/cycloaddition cascade of pentaene **42** to form tetracyclic product **43** after desilylation was accomplished thermally at 150 °C (Scheme 8). The 8π-6π electrocyclization of **42** could be achieved at lower temperature, but not the final intramolecular Diels–Alder reaction of bicyclic triene **44**. Nevertheless, this final step could be accomplished photocatalytically by visible-light irradiation of **44** in the presence of $Ru(bpy)_3(PF_6)_2$ and methyl viologen as a co-oxidant, giving **43** in 50% yield.

In 2017, the use of the highly oxidizing Fukuzumi acridinium PC **11**[37] and a hydrogen-atom transfer co-catalyst to promote [4+2] cycloaddition of electron-rich styrenes to form 1-aryltetralins was reported by Nicewicz and Huang.[38] In a recent disclosure, Zhu and co-workers describe the use of this method to synthesize six aryltetralin cyclic ether lignans, exemplified by syntheses of (±)-aglacin B (**45**) and (±)-aglacin C (**46**), (Scheme 9).[39] The use of an oxidizing PC capable of promoting a retro-[2+2]cycloaddition by oxidizing the corresponding [2+2] cycloadduct and thiophenol as the hydrogen-atom transfer co-catalyst were essential for success. With substrates having different aryl groups, as illustrated in the synthesis of (±)-aglacin C (**46**), the more electron-rich styrene served as the diene unit for the cycloaddition.

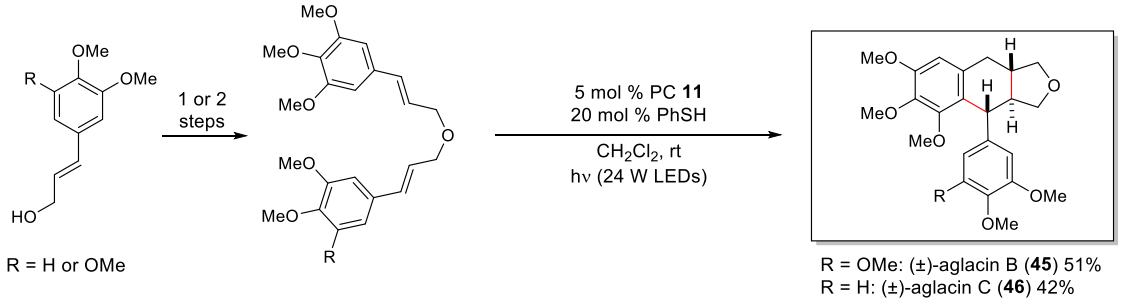
**Scheme 7.**



**Scheme 8.**




**Scheme 9.**



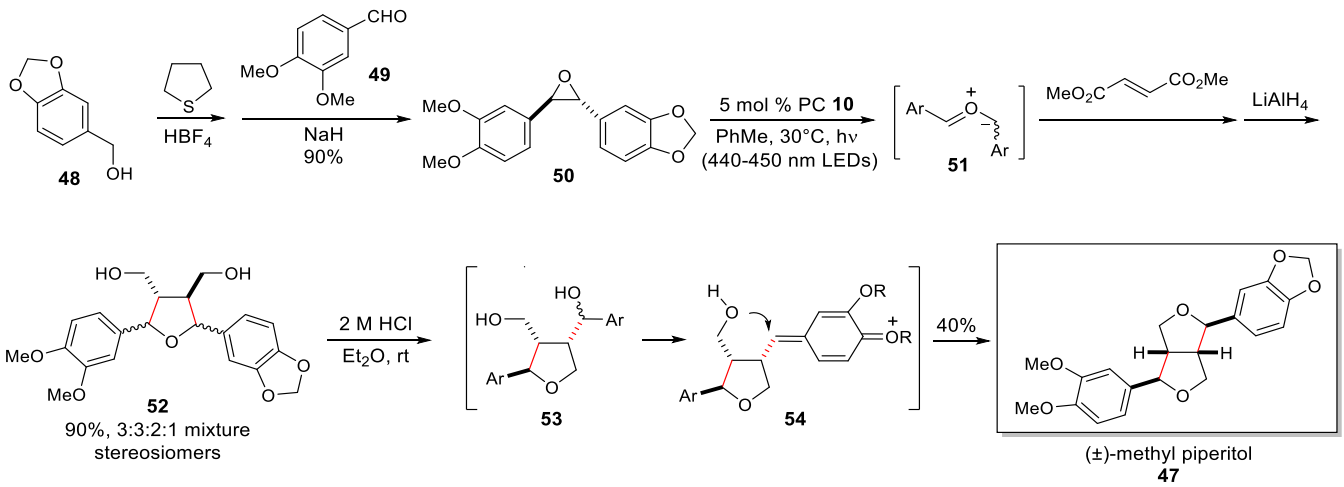

**2.1.3. [3+2] Cycloadditions.** As first reported by Whiting in 1990, acyclic carbonyl ylides can be generated from epoxides upon radiation with UV light in the presence of the PC 9,10-dicyanoanthracene and trapped with electron-deficient dipolarophiles.[40] In 2017, Beeler and co-workers reported that such reactions could be accomplished more efficiently using visible light and 2,6-di-*tert*-butyl-9,10-dicyanoanthracene (**12**) as the PC.[41]

This method was used by the Beeler group to prepare representative members of six subtypes of classical lignans, Illustrated by the four-step synthesis of (±)-methyl piperitol (**47**) summarized in Scheme 10.[42] The synthesis begins with piperonyl alcohol (**48**) which in a one-pot reaction was converted to a sulfonium ylide that was allowed to react with aldehyde **49** to give *trans*-epoxide **50** in high yield. Generation of the carbonyl ylide **51** from **50** and its [3+2] cycloaddition with dimethyl fumarate was brought about by irradiation with blue LEDs in the presence of sterically encumbered dicyanoanthracene PC **12**.[36] After reduction of the crude diester product with $LiAlH_4$, tetrahydrofuran **52** was formed in 90% yield as a mixture of four stereoisomers. Upon exposure to 2 M HCl, **52** was transformed via intermediates **53** and **54** to (±)-methyl piperitol (**47**) in 40% yield. An additional 33% of **47** could be obtained by subjection of the recovered mixture of diol stereoisomers to acidic equilibration. In a publication last year, the Beeler group reported that tetrahydrofuran cycloadducts like **52** can be elaborated to the aryltetralin lignans pycnanthulignene B and C and justicidin E.[43]

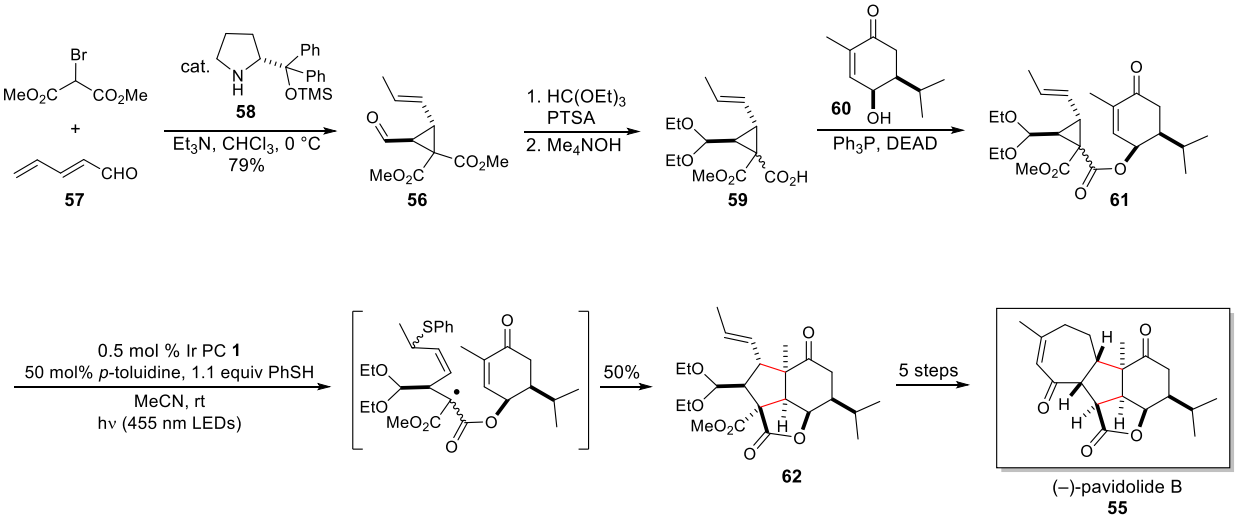
Five-membered carbocyclic rings of natural products have often been formed by [3+2]-cycloadditions of vinylcyclopropanes that proceed by radical intermediates.[44] Yang and co-workers used a photocatalytic version of this strategy in a short enantioselective total synthesis of the marine natural product (–)-pavidolide B (**55**, Scheme 11).[45,46] As the cyclopentane ring of **55** is *cis* to the isopropyl group of the cyclohexanone fragment, an intramolecular [3+2]-cycloaddition approach was pursued. When early model studies showed that related Pd(0)-catalyzed cycloadditions were not successful, the authors turned to an established strategy wherein a radical cascade is promoted by addition of a thiolate radical to the vinyl substituent.[44] In the successful approach, vinylcyclopropane **56** was assembled in enantioenriched fashion from dimethyl bromomalonate and 2,4-pentadienal (**57**) by Michael addition/alkylation catalyzed by proline catalyst **58**. Subsequent transformation of **56** to vinylcyclopropane carboxylic ester **59** and its Mitsunobu coupling with enantiopure hydroxycyclohexenone **60** provided cyclization precursor **61**. The pivotal intramolecular [3+2]-cycloaddition of **61** could be accomplished in classical thermal fashion using thiophenol and AIBN. Nevertheless, the yield was improved when the thiol radical catalyst was generated by a visible-light photocatalytic method first described by Yoon.[47] In this way, **62** was formed with high stereoselectivity in 50% yield from **61**. The origin of stereoselection and details of the formal [3+2]-cycloaddition process have been discussed in detail.[45] Employing ring-closing metathesis to fashion the cycloheptene ring, **62** was elaborated in five additional steps to (–)-

pavidolide B (**55**), completing a concise ten-step enantioselective synthesis of this diterpenoid.

**Scheme 10.**



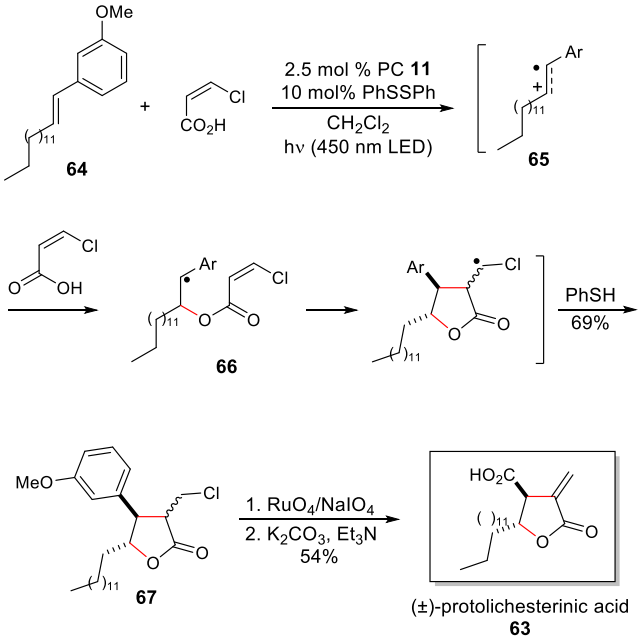

**Scheme 11.**




In an early contribution to expanding the scope of photoredox-catalyzed transformations, Nicewicz and co-workers reported the anti-Markovinikov addition of nucleophiles to oxidizable alkenes using the Fukuzumi acridinium PC **11** and a redox-active hydrogen-atom donor.[48] This approach was used subsequently to achieve a [3+2]-type assembly of butyrolactones, as exemplified in a short synthesis of (±)-protolichesterinic acid (**63**) (Scheme 12).[49] The cycloaddition step is proposed to take place by single-electron photooxidation of styrene **64** to form the electrophilic radical cation **65**, followed by its regioselective trapping by the carboxylic acid to form radical intermediate **66**, which is poised to undergo 5-*exo*-trig cyclization to ultimately yield **67**. The authors found that either an aromatic thiol or an aromatic disulfide could function as the co-catalyst.

**2.1.4. [2+2+2] Cycloadditions.** Photocatalytic [2+2+2]-cycloadditions of oxygen and electron-rich styrenes to give 1,2-dioxanes was reported by Gollnick and co-workers in 1984 using using 9,10-dicyanoanthracene as the PC.[50] Using the approach described by Nicewicz in which triarylpyrilium salts are used as the PC,[51] George and co-workers accomplished short biomimetic total syntheses of several meroterpenoids that had been isolated as scalemic mixtures from a Chinese rhododendron (Scheme 13).[52] The syntheses begin with chromene **68**, which is available in two steps from orcinol and citral. Irradiation of **68** in the presence of oxygen and the triarylpyrilium PC **10** gave as the kinetic product the [2+2]-photocyclic adduct **69**. Under extended reaction times this product was converted to 1,2-dioxane **70**. Under these conditions, the [2+2]-photocycloaddition was reversible and **70** is ultimately produced by [2+2+2]-cycloaddition, as signaled by epimerization of the C-11 stereocenter in the **69** → **70** conversion. Desilylation of these products produced racemic nyingchinoids D (**71**) and B (**72**) in high yields. Further rearrangement of nyingchinoids B (**72**) under acidic conditions yielded (±)-nyingchinoid A (**73**).

**Scheme 12.**



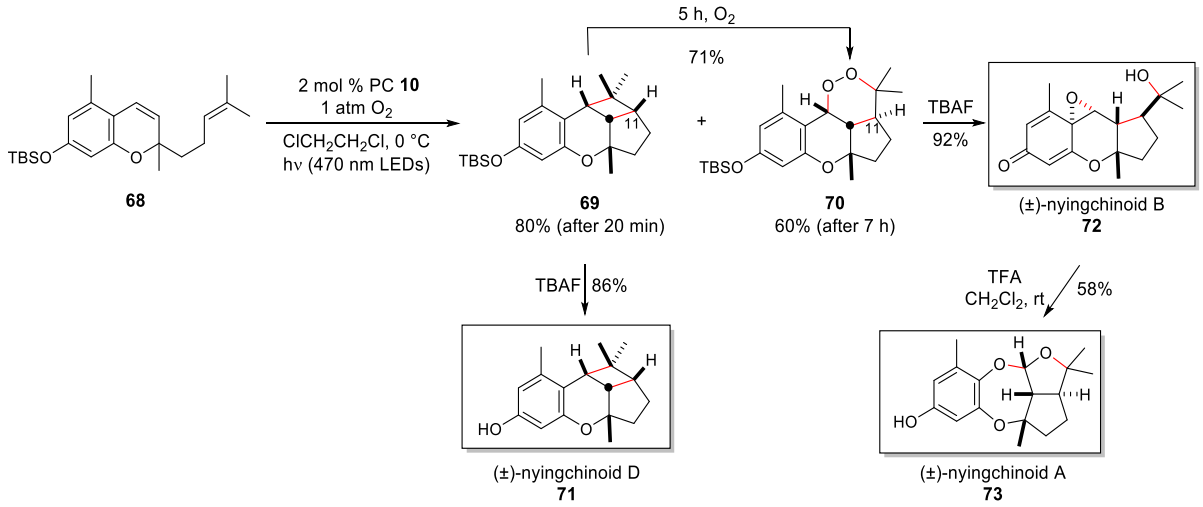

A second example of a formal photoredox-catalyzed [2+2+2] cycloaddition having oxygen as one component was reported by Gao and co-workers in their synthesis of (+)-fusarisetin A (**74**) (Scheme 14).[53] Employing an intramolecular Diels–Alder strategy, this group first developed a concise enantioselective total synthesis of equisetin (**75**). To pursue its potential biomimetic oxidative conversion to (+)-fusarisetin A (**74**), synthetic equisetin was irradiated at room temperature with blue LEDs (or sunlight) in the presence of 5 mol % $Ru(bpy)_3Cl_2$, oxygen and triethylamine to give **76**, the peroxy analogue of fusarisetin A, and its C-5 epimer in a ratio of 2:1. A similar yield was obtained using methylene blue as the PC. A stepwise mechanism having superoxide as an intermediate was proposed for this formal [2+2+2]-cycloaddition. Reduction of these peroxide intermediates with Zn and acetic acid ultimately yielded a mixture of (+)-fusarisetin A (**74**) and **77**.

## 2.2. Carbon-Centered Radical Alkene Coupling

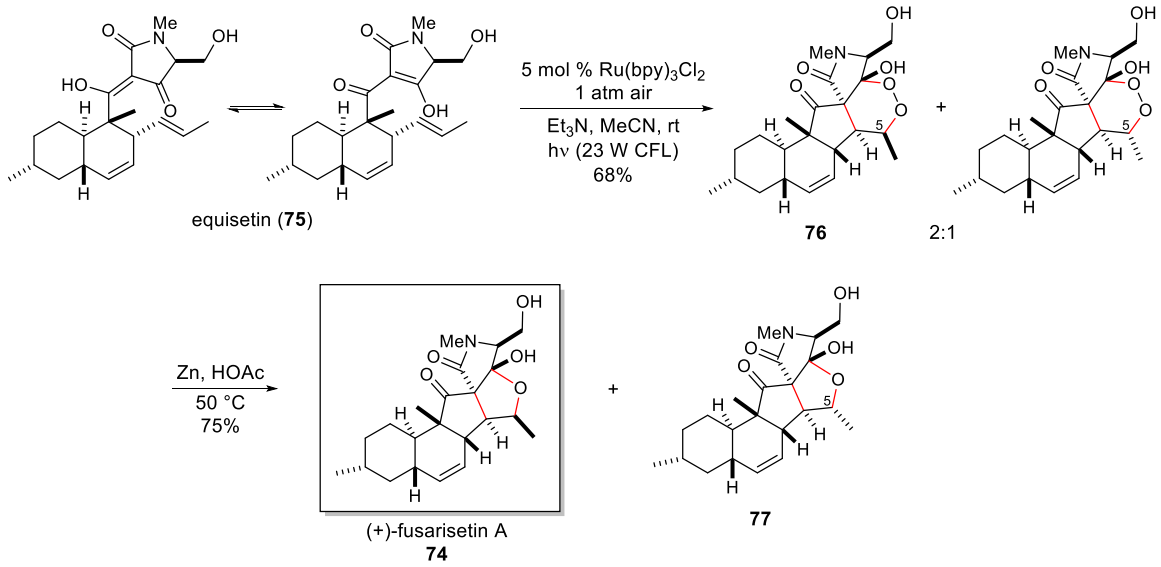
Carbon-centered radicals are fundamental intermediates in organic synthesis.[54-57] The development of myriad ways for forming carbon-centered radicals under mild, environmentally benign conditions using visible-light photocatalysis[58,59] has been central to the recent renaissance in using free radical chemistry in the synthesis of natural products.[60-63] Early investigations by Barton, Giese, Curran and others showed that the addition of carbon-centered radicals to alkenes had significant potential for chemical synthesis outside the polymer arena.[54,64] Trends in reactivity and selectivity of carbon-radical alkene couplings can be described using frontier orbital theory: for nucleophilic radicals the dominant interactions are those between radical SOMO's and alkene LUMO's, and for electrophilic radicals those between radical SOMO's and alkene HOMO's.[65] The total syntheses discussed in this section will be organized by the extent of carbon substitution of the carbon radical. This organization has been adopted because retrosynthetic disconnection of a C–C σ-bond to a carbon-centered radical/alkene coupling immediately raises the question of what would be a viable precursor of the carbon radical.

**2.2.1. Primary Carbon Radicals.** The synthesis of (+)-daphmanidin E (**78**), reported by Weiss and Carreira in 2011, is one of the earliest uses of visible-light photoredox-catalysis in the total synthesis of a complex natural product (Scheme 15).[66] In this synthesis, a carbon radical/alkene coupling was used to form the seven-membered ring of the hexacyclic daphmanidin skeleton. The synthesis began with $C_2$-symmetric bicyclo[2.2.2]octadiione **79**, which was obtained by resolution of the racemate, which in turn was available in one-step from diethyl succinate. In five steps, **79** was transformed to the tricyclic ketone **80**. The third quaternary carbon stereocenter (C-8) of this natural product target was then installed by sequential Claisen rearrangement of allyl vinyl ethers formed from *O*-allylation of lithium enolates generated from the sterically hindered ketone **80** to give **81**. In eight subsequent steps, **81** was elaborated to enone primary iodide intermediate **82**. To fashion the seven-membered ring of (+)-daphmanidin E, potential cyclizations of the iodide side chain of **82** promoted by $SmI_2$ or several Pd- and Cr-mediated alternatives were investigated without success. Ultimately, the desired transformation was realized by employing a Co-mediated alkyl Heck reaction.[67] The desired transformation to tetracyclic product **83** was accomplished in 93–95% yield using either stoichiometric conditions (irradiation of **82** and 1.2 equiv of cobaloxime **7** with a sunlamp), or in low-turnover, catalytic fashion by irradiation of an acetonitrile solution of **82**, 25 mol % of cobaloxime **7**, and 1.5 equiv of *i*-$PrNEt_2$ with blue LEDs. In six subsequent steps, **83** was elaborated to (+)-daphmanidin E (**78**).

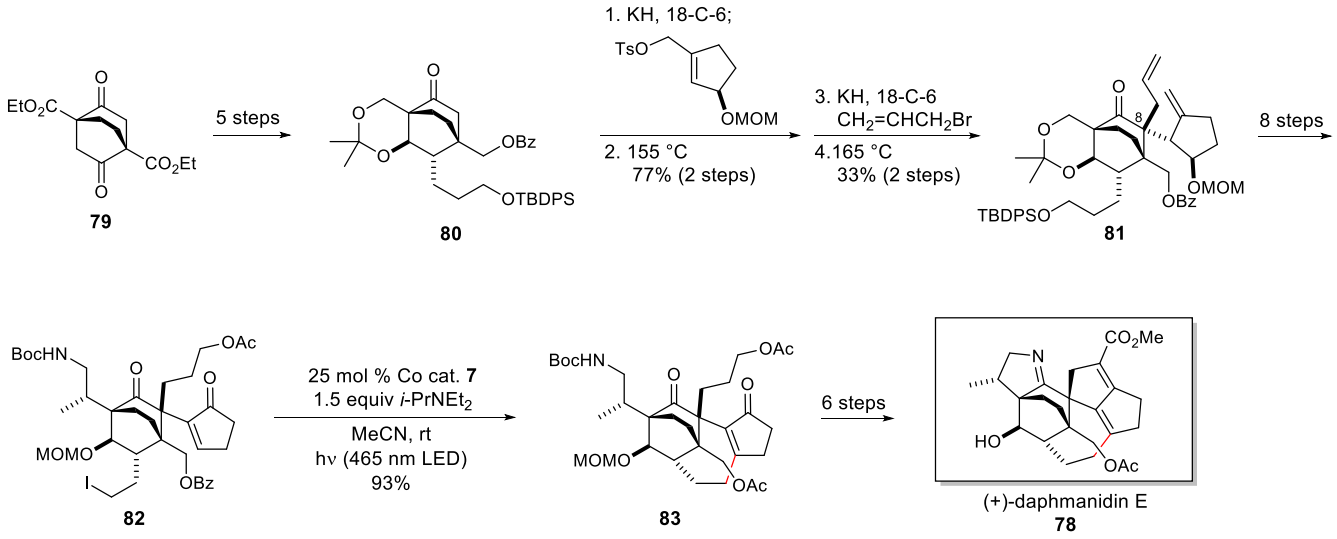
**Scheme 13.**




**Scheme 14.**

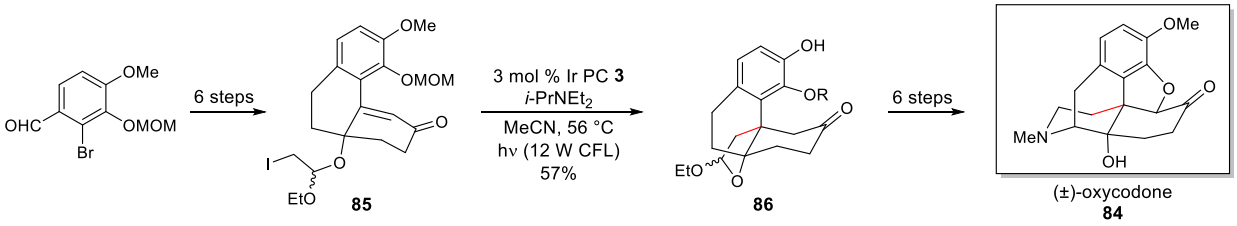



**Scheme 15.**



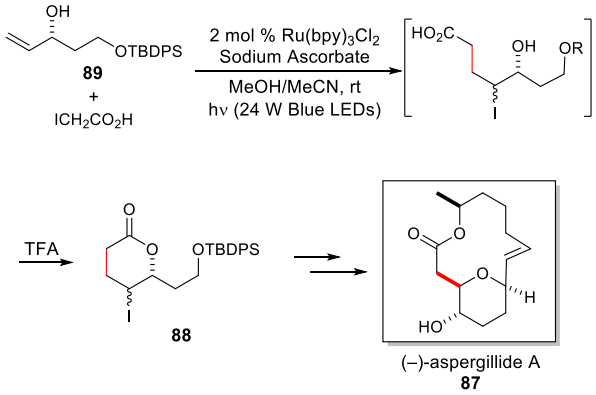
Two additional examples of the coupling of primary carbon radicals with alkenes are summarized in Schemes 16 and 17. In the synthesis of racemic oxycodone (**84**),[68] Chen and co-workers employed a Stork-Ueno radical cyclization to form the quaternary carbon stereocenter of this opium alkaloid analogue (Scheme 16).[69] The conversion of iodoacetal **85** to **86** could be accomplished in classical fashion (*n*-$Bu_3SnH$, $Et_3B$),[70] or in similar yield and avoiding tedious removal of tin byproducts by using 3 mol % of $Ir(ppy)_2(dtbbpy)PF_6$ (**3**), *i*-$PrNEt_2$, and visible light irradiation.

**Scheme 16.**



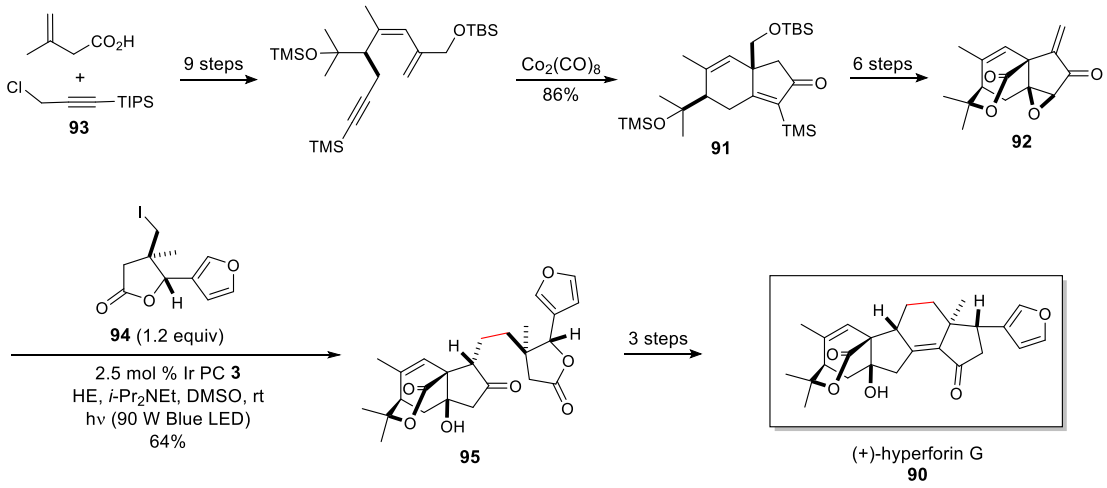

A similar benefit of using photoredox catalysis is seen in the synthesis of (–)-aspergillide A (**87**), reported by Mateus-Ruiz and Cordero-Vargas (Scheme 17).[71] In an early step in this synthesis, hydropyran **88** is fashioned by atom-transfer radical addition (ATRA) of iodoacetic acid to allylic alcohol **89**, followed by an acid-catalyzed cyclization. This C–C bond-forming step could be achieved under classical ATRA conditions (lauroyl peroxide, refluxing 1,2-dichloroethane) or under visible-light mediated photoredox conditions using 2 mol % of $Ru(bpy)_3Cl_2$. The authors report identical yields under both conditions; however, the reaction was cleaner and the product easier to isolate in pure form using the photoredox-catalyzed method.

**Scheme 17.**



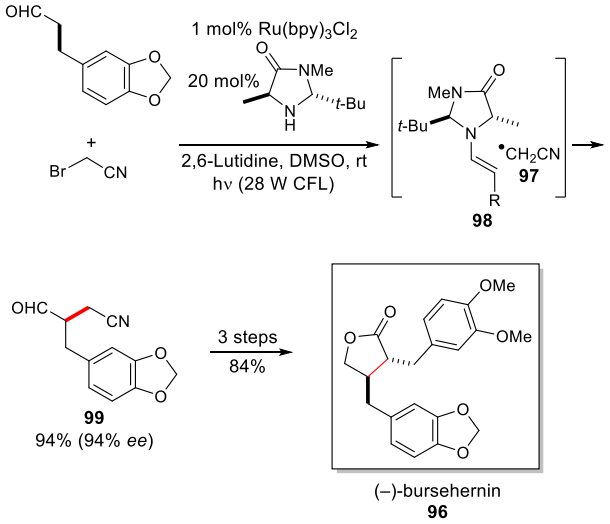

The recent total synthesis of the limonoid tetranorditepenoid (+)-hyperforin G (**90**) by Chen, Yang and co-workers provides a particularly good example of the advantages of using photoredox catalysis in the coupling of structurally complex fragments by a Giese reaction (Scheme 18).[72] In a multistep sequence featuring an intramolecular Paulson-Kahn reaction to form **91**, the tricyclic α-methylene cyclopentanone **92** was assembled from 3-methyl-3-pentenoic acid and propargyl chloride **93**. The authors initially tried without success to unite enone **92** with the primary carbon radical derived from iodide **94** using standard *n*-$Bu_3SnH$/AIBN conditions. In contrast, the desired Giese coupling of the primary radical generated from **94** and enone **92** to form product **95** was accomplished in 64% yield using a photoreductive catalytic cycle. As expected, under these strongly reducing conditions, the α-ketoepoxide was cleaved to introduce the angular hydroxyl substituent of **95**. In three additional steps, this intermediate was advanced to complete a 20-step enantioselective total synthesis of (+)-hyperforin G (**90**).

**Scheme 18.**



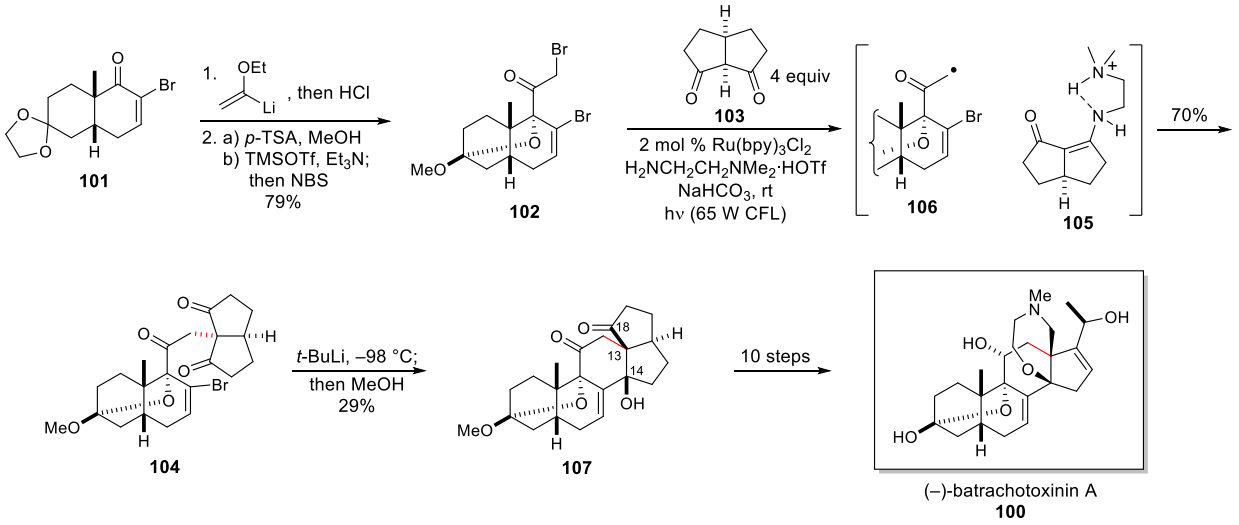

An important recent development in photoredox catalysis has been the merging of photoredox catalysis with other catalytic cycles.[13,73-75] In a seminal report in 2008, Nicewicz and MacMillan reported the merging of organocatalysis with photoredox catalysis to accomplish the direct enantioselective alkylation of aldehydes.[76] This method, in which stereocontrolled C–C bond formation results from the addition of an electron-deficient carbon radical to an *in situ*-generated enamine, was later used by the MacMillan group to accomplish a short enantioselective synthesis of the cytotoxic lignan (–)-bursehernin (**96**, Scheme 19).[77] In the key step of the merged catalytic cycles, the primary radical **97** generated for bromoacetonitrile adds from the *Si* face to the oxazolidone-derived enamine intermediate **98** to form α-alkylated aldehyde **99** in high yield and high enantioselectivity. Intermediate 99 could be elaborated to (–)-bursehernin (**96**) in three additional steps and 84% yield.

**Scheme 19.**



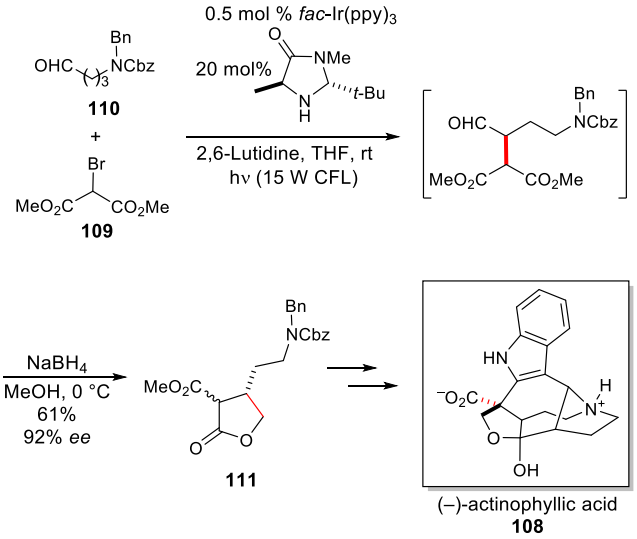

Batrachotoxin, a highly toxic alkaloid isolated from poison-dart frogs is often isolated together with the less potent alkaloid (–)-batrachotoxinin A (**100**). The latter is readily converted to batrachotoxin by appending a 2,4-dimethyl-3-acylpyrrole fragment to its side chain oxygen substituent. A third total synthesis of (–)-batrachotoxinin A (**100**) was reported last year by the Luo group (Scheme 20).[78] In this concise synthesis, a key C–C σ-bond and the quaternary carbon of the steroidal C ring were formed by photoredox-catalyzed coupling of a primary α-acyl radical with an enamine intermediate. The synthesis begins with the *cis*-decalin derivative **101**, an intermediate in Du Bois's earlier synthesis of **100**.[79] In two steps, **101** was elaborated to tricyclic α-bromoketone **102**. After failing to C-alkylate this intermediate with enolates generated from β-diketone **103**, the desired transformation to form **104** was successfully achieved in 70% yield by visible-light irradiation of an acetonitrile solution of **102**, 4 equiv of diketone **103**, 1 equiv of *N*,*N*-dimethylethane-1,2-diamine, and 2 mol % $Ru(bpy)_3Cl_2$. The authors speculate that hydrogen bonding of the protonated diamine fragment of **105** with the α-acyl group of the primary radical facilitates the C–C bond-forming union of electrophilic radical **106** and the nucleophilic enamine double bond. In one additional step, the steroid skeleton was constructed from **104** by intramolecular cyclization of the vinyl bromide-derived lithium reagent to give the desired intermediate **107** in 29% yield together with 10% of its C-13,C-14 diastereomer and 30% of debrominated **104**. In this total synthesis endeavor, the ability to unite fragments **102** and **103** while forming the hindered C-13 quaternary carbon center is critical in allowing the hidden symmetry in intermediate **104** to be exploited.

**Scheme 20.**




**2.2.2. Secondary Carbon Radicals.** The union of a secondary carbon radical with an alkene was an early step in the formal total synthesis of (–)-actinophyllic acid **108** reported by Qin and co-workers (Scheme 21).[80] Exploiting MacMillan's merged photoredox/organocatalysis method,[76] dimethyl bromomalonate (**109**) and aldehyde **110** were united to form, after hydride reduction of the aldehyde, butyrolactone **111** in 61% yield and 92% *ee*. Advancing intermediate **111** to the primary-alcohol precursor of (–)-actinophyllic acid **108** exploited a second photoredox catalyzed C–C bond formation that will be discussed in section 2.3.1 of this review.

**Scheme 21.**



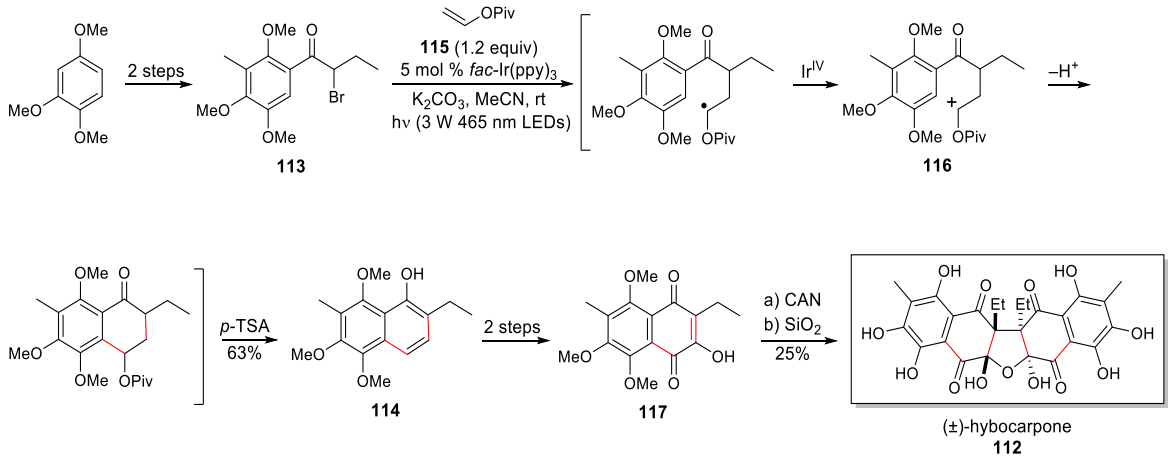

The synthesis of (±)-hybocarpone (**112**), a napthoquinone natural product isolated from lichen, by Gong and co-workers featured a visible-light promoted benzannulation reaction **113** → **114** (Scheme 22).[81] Although the organic PC Eosin Y could be used in the coupling step, the yield was higher using *fac*-Ir(ppy)$_3$. The first step in the photoredox catalyzed annulation sequence undoubtedly involves addition of the electron-deficient secondary carbon radical formed from **113** to enol ether **115** to generate, after SET oxidation, carbonium ion **116**, which cyclizes with the proximal arene to eventually form napthol **114**. The final oxidative dimerization of napthoquinone **117** to form (±)-hybocarpone (**112**) was accomplished using a slight modification of the method used by Nicolaou in the inaugural total synthesis of **112**.[82]

**2.2.3. Tertiary Carbon Radicals.** The use of tertiary carbon radicals to form strategic C–C σ-bonds has played a central role in several recent syntheses of complex natural products. This tactic is notable as it creates a quaternary carbon center as well as a C–C single bond. In this section, we look at total syntheses where the coupling of a tertiary radical and an alkene played a key role.

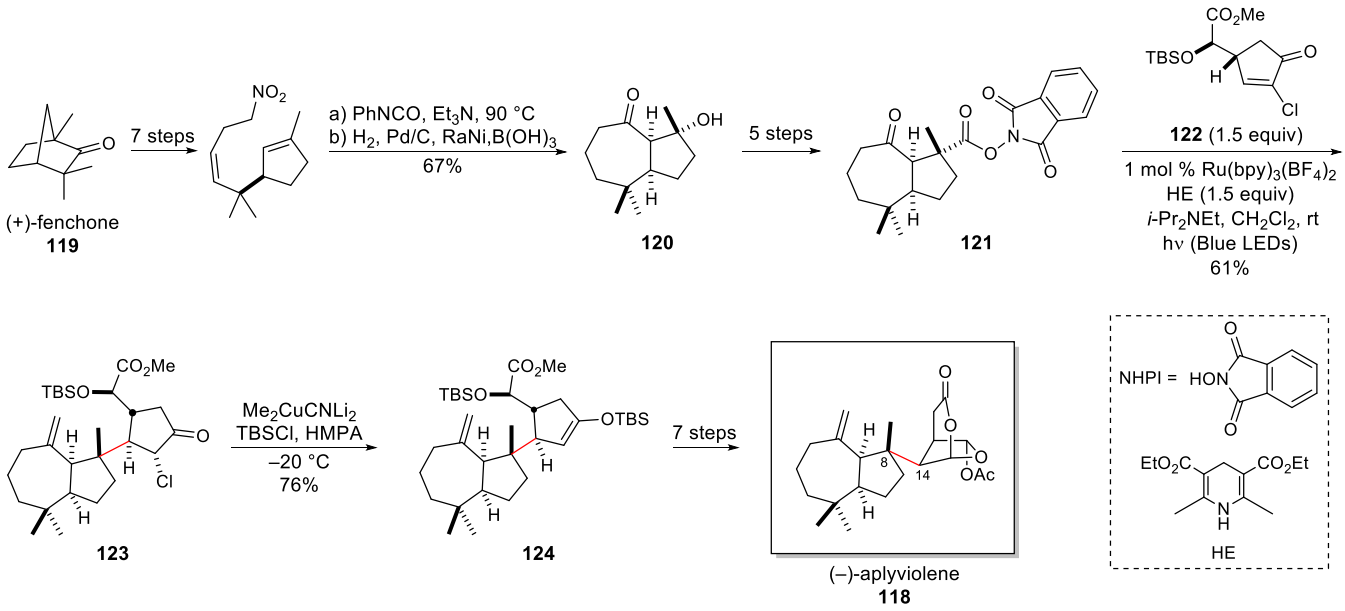
An influential early example was reported in 2012 by the Overman group during studies to synthesize the rearranged spongian diterpenoid (–)-aplyviolene (**118**) (Scheme 23).[83] A central challenge in the synthesis of aplyviolene is fashioning the C-8/C-14 single bond that joins the two freely rotating chiral fragments. Directly linking two enantiopure-chiral fragments is a convergent strategy, whose stereochemical outcome would depend on the facial selectivity of the union of the two reactants. Starting with (+)-fenchone (**119**), *cis*-perhydroazulene alcohol **120** was constructed in nine steps using an intramolecular nitrile oxide cycloaddition to fashion the seven-membered ring. In five steps, this intermediate was advanced to *N*-(acyloxy)phthalimide ester (NHPI ester) **121**. Using a minor modification of conditions first reported by Okada,[84] **121** coupled with α-chlorocyclopentenone **122** upon irradiation with visible light in the presence of 1 mol % of Ru(bpy)$_3$(BF$_4$)$_2$ and an excess of Hantzsch ester (HE) and *i*-Pr$_2$NEt as reductive quenchers. The fragment coupling proceeded with high stereoselectivity from the less-sterically hindered face of each component to form exclusively product **123** in 61% yield. The chlorine substituent in intermediate **123** was exploited subsequently to selectively generate

enoxysilane **124**, whose double bond was cleaved in a key step in the eventual formation of the bridged dioxobicyclooctanone fragment of (–)-aplyviolene (**118**).

**Scheme 22.**



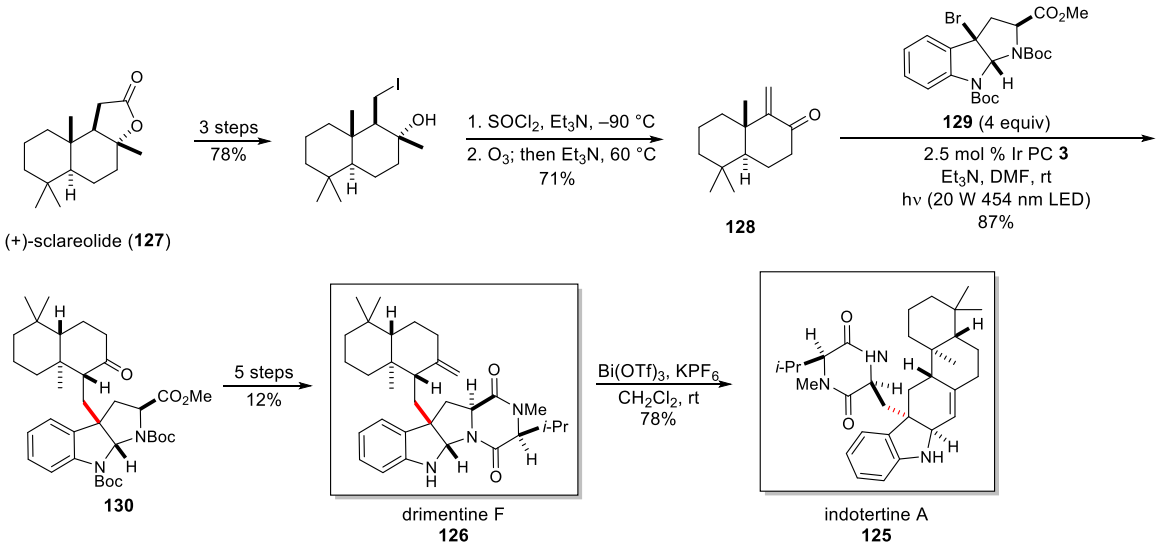

**Scheme 23.**




The high preference for tertiary carbon radicals to react with carbon electrophiles from the radical's sterically most-accessible face observed in this synthesis is an important outcome that will be a feature of other applications of photoredox-catalyzed fragment coupling of tertiary carbon radicals. The importance of this facial preference in nicely illustrated in early studies towards (–)-aplyviolene (**118**), because prior attempts in the Overman laboratory to employ a tertiary cuprate nucleophile in the critical C-8/C-14 coupling step gave nearly exclusively the C-8 epimer of **123**.[83]

Shortly thereafter, Li and co-workers reported enantioselective total syntheses of indotertine A (**125**) and three structurally related pyrrolidinoindoline alkaloids, drimentines A, F (**126**), and G (Scheme 24).[85] These total syntheses begin with (+)-sclareolide (**127**), which in five steps was advanced to α-methylene *trans*-decalone **128**. The pivotal step in the synthesis was the union of this fragment with bromopyrrolindoline **129**, which is readily available from di-Boc (*S*)-tryptophan. Initial attempts to accomplish the Giese coupling of these components using *n*-$Bu_3SnH$ and standard free-radical initiators, or using a Co catalyst, provided none of the desired product. Some success was realized when *n*-$Bu_3SnH$ was slowly added by syringe pump, suggesting that slow generation of the tertiary carbon radical was critical.[86] To pursue this possibility further, photoredox-catalyzed conditions were investigated. Although the use of $Ru(bpy)_3Cl_2$ as the PC and irradiation with blue LEDs in the presence of $Et_3N$ gave only a moderate yield of **130**, the yield was increased to 87% when 2.5 mol % $[Ir(ppy)_2(dtbbpy)PF_6]$ (**3**) was employed. Removing the Boc protecting groups from **130** and standard construction of the diketopiperazine from the resulting α-aminoacid gave drimentine F (**126**) and drimentines A and G, which differ from **126** only in the substituents of the diketopiperidine ring.

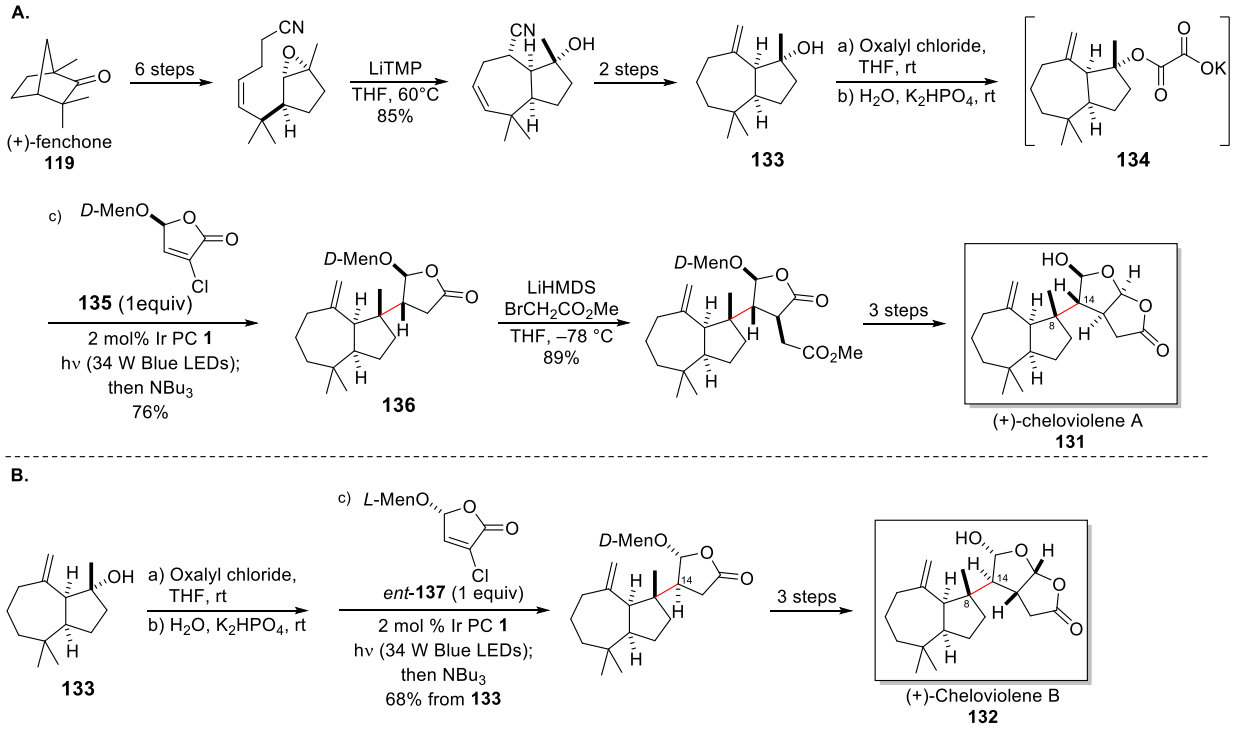
**Scheme 24.**




These authors correctly predicted that the structurally novel, isomeric alkaloid indotertine A (**125**) could be accessed from drimentine F (**126**) by acid-promoted opening of the pyrrolidinoindoline ring followed by intramolecular aza-Prins cyclization of the *exo*-methylene decalin side chain. In the event, the authors used 1 equiv of $Bi(OTf)_3$, which delivered indotertine A (**125**) in 78% yield.[85]

Cheloviolenes A (**131**) and B (**132**) are representative of a group of rearranged spongian diterpenoids that are structurally related to aplyviolene (**118**), however, the lactone fragment in these diterpenoids is a *cis*-2,8-dioxabicyclo[3.3.0]octanone. The syntheses of cheloviolenes A (**131**) and B (**132**) accomplished by Overman and co-workers illustrate a convenient method for directly generating a tertiary carbon radical from a tertiary alcohol precursor (Scheme 25A).[87,88] Beginning with (+)-fenchone (**119**), the enantiopure *cis*-perhydroazulene tertiary alcohol **133** was prepared in nine steps. In a one-step sequence, the tertiary potassium hemioxalate derivative **134** was generated by sequential reaction of a THF solution of alcohol **133** with oxalyl chloride and aqueous $K_2HPO_4$.[89] Addition of 1 equiv of the D-menthol-derived α-chlorobutenolide **135** and 1 mol % of $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**1**), followed by irradiation at room temperature with blue LEDs promoted the fragment coupling. The final step in this sequence, removal of the chlorine substituent that is present to increase the efficiency of the Giese fragment coupling, was accomplished by adding excess tri-*n*-butylamine and continued irradiation to give the coupled product **136** in 76% yield and >20:1 stereoselectivity. In four additional steps, intermediate **136** was advanced to (–)-cheloviolene A (**131**).

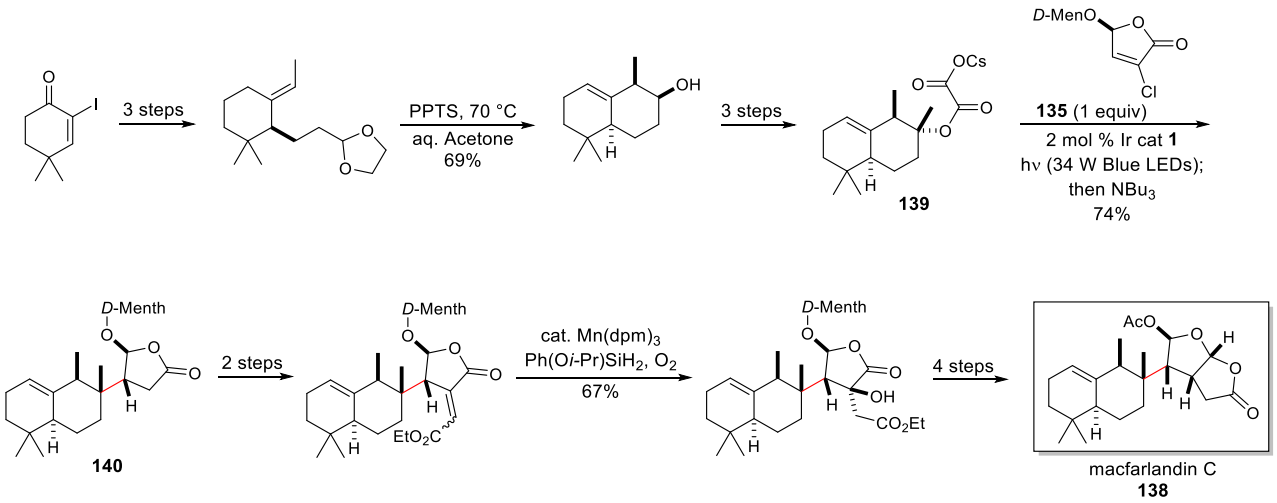
**Scheme 25.**




One feature of synthesis strategies involving the late-stage union of enantiopure chiral fragments is the ease of preparing diastereomers or analogues by varying the structure of the more readily available chiral fragment. This aspect is illustrated in the synthesis of (+)-cheloviolene B (**132**), wherein the butenolide *ent*-**137** was used in the stereoselective fragment coupling step (Scheme 25B).[87]

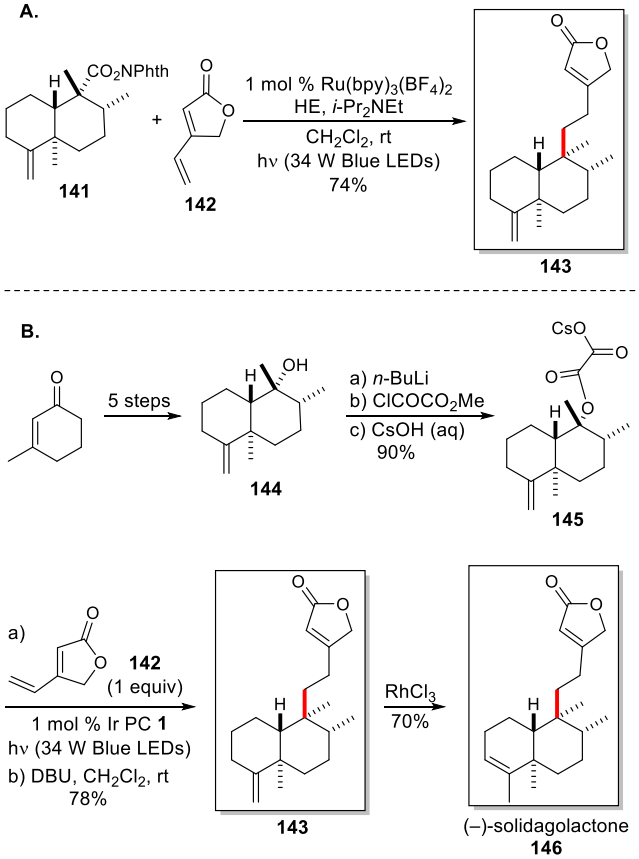
Related examples of the fragment coupling of tertiary carbon radicals generated from alcohol intermediates are found in recently disclosed total synthesis of (–)-macfarlarlandin C (**138**, Scheme 26) and (+)-dendrillolide A by Overman and coworkers.[90,91] These rearranged spongian diterpenoids are representative of a family in which the hydrocarbon fragment resides on the more-hindered concave face of the *cis*-dioxabicyclo]3.3.0]octanone fragment. As in the syntheses of the cheloviolenes, the fragment-coupling step (**139** → **140**) was accomplished in >20:1 stereoselectivity and good yield by irradiation of the coupling partners with blue LEDs in the presence of 1 mol % of Ir PC **1**.

**Scheme 26.**




The 1,6-addition of a tertiary carbon radical to a vinylbutenolide was a key step in several total syntheses of *trans*-clerodane diterpenoids reported from the Overman laboratory. In their first-generation approach, the tertiary radical was generated from NHPI ester **141** using 1 mol % of $Ru(bpy)_3(BF_4)_2$ as the PC (Scheme 27A).[92] As expected, the tertiary *trans*-decalin radical coupled stereoselectivity with vinylbutenolide **142** from its least-hindered face—opposite the angular methyl substituent—to give **143**, a naturally occurring diterpenoid in 74% yield.

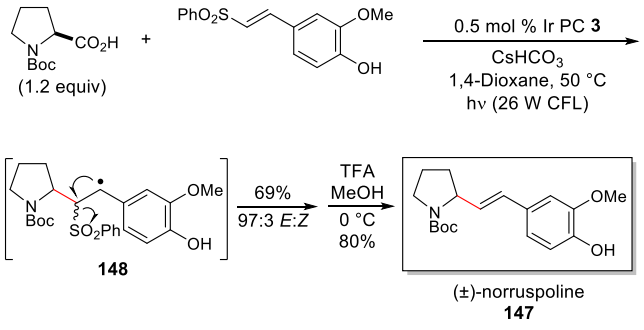
**Scheme 27.**




Their second-generation synthesis of *trans*-cleorodanes exploited the ready availability of *trans*-decalin tertiary alcohol **144**,[93] which was assembled using a catalytic enantioselective variant of a strategy first reported in the racemic series (Scheme 27B).[94] Because of the substantial steric shielding of the axial alcohol substituent in **144**, acylation to introduce the oxalate functionality required preformation of the lithium alkoxide intermediate. Photoredox coupling of oxalate salt **145** and 1 equiv of vinylbutenolide **142** took place in high yield with excellent diastereoselection to afford a mixture of **143** and its β,γ-unsaturated butenolide isomer, which, after exposure to DBU, gave **143** in 78% yield. Isomerization of the exomethylene double bond of **143** then delivered (–)-solidagolactone (**146**).

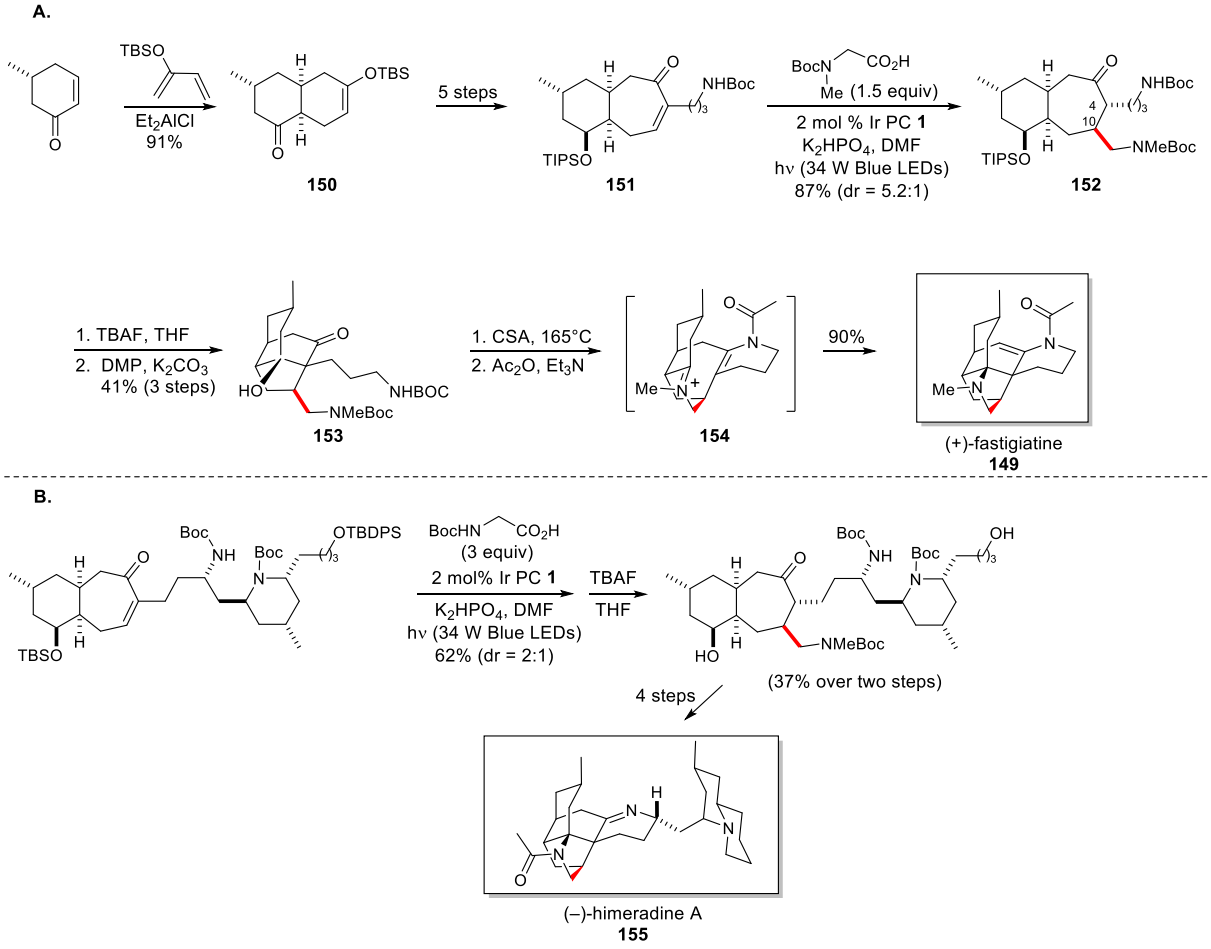
**2.2.4. α-Heterosubstituted-Carbon Radicals.** Carbon radicals adjacent to nitrogen can be generated in several ways using visible-light photoredox catalysis and play prominent roles in total syntheses of numerous alkaloids. In one approach, α-amino acids are employed as convenient precursors of α-amino radicals. This tactic is illustrated in a short synthesis of the pyrrolidine alkaloid norruspoline (**147**) (Scheme 28), which exploits MacMillan's method to form *α*-amino radicals by catalytic oxidative decarboxylation of carbamate derivatives of *α*-amino acids.[95] To achieve high stereoselection in the β-fragmentation of the coupled intermediate **148**, the authors found that the use of milder photooxidants such as $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**1**) or $Ir(ppy)_2(dtbbpy)PF_6$ (**3**) were preferred.

**Scheme 28.**



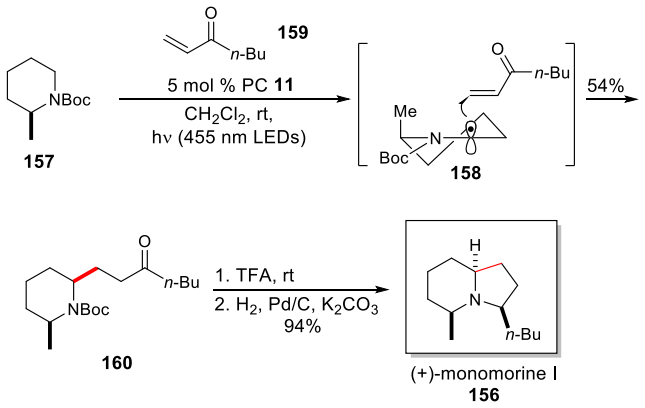
The second-generation synthesis of the structurally elaborate lycopodium alkaloid (+)-fastigiatine (**149**) accomplished by Rychnovsky and co-workers provides a second example of using an α-aminoacid-derived α-amino radical in a coupling reaction (Scheme 29A).[96] The synthesis begins with Diels–Alder adduct **150**, which was advanced in five steps to cis-bicyclic enone **151**. The final carbon and nitrogen atoms of fastigiatine are added using the Ir photoredox catalyzed 1,4-addition of the α-carbamyl radical generated from *N*-Boc-sarcosine to give **152** and its C-4/C-10 *trans* diastereomer in a 5.2:1 ratio and high yield. In earlier model studies, these authors found that this method to append an aminomethyl fragment to an enone was superior to an alternative process employing a cuprate reagent. Stereoisomer **152** was advanced to **153**, which when exposed to camphorsulfonic acid at high temperature promoted the retro-aldolization and transannular aza-Prins cyclization of intermediate **154** to give (+)-fastigiatine (**149**) in a remarkable 90% yield. A similar Giese coupling of an α-amino radical was employed a year later in the Rychnovsky group's synthesis of the structurally more elaborate alkaloid (–)-himeradine A (**155**, Scheme 29B).[97]

**Scheme 29.**



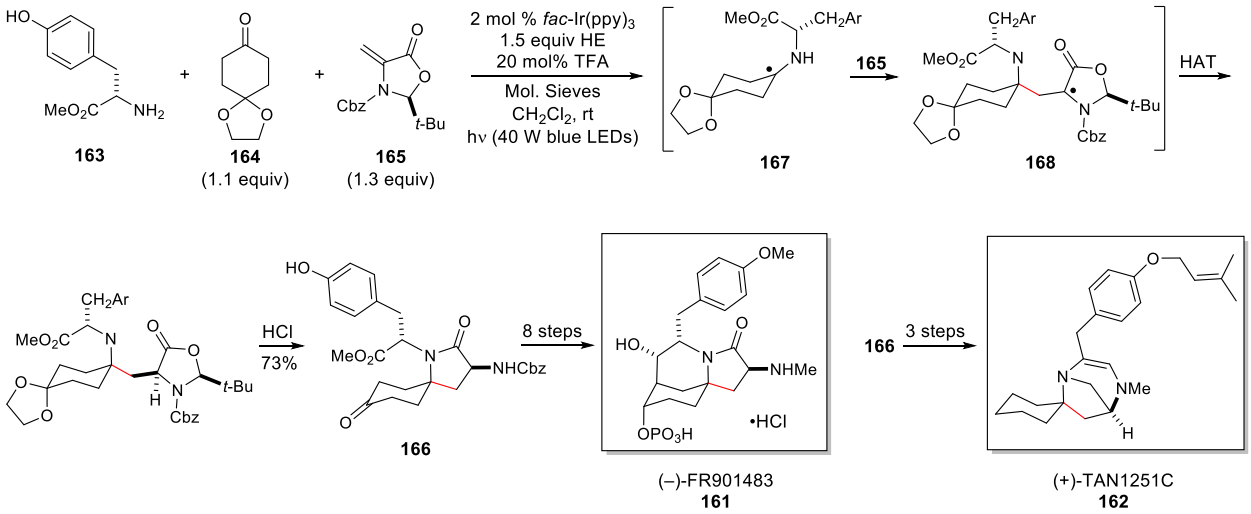

In 2008, Nicewicz and co-workers reported that α-carbamyl radicals could be generated from carbamate precursors by C–H activation using acridinium PC **11**. In this initial report, a short synthesis of the indolizidine alkaloid (+)-monomorine I (**156**) from the Boc derivative of (*S*)-2-methylpyrrolidine (**157**) was described (Scheme 30).[98] Proton loss from the photocatalytically-generated carbamyl radical cation takes place at the less-substituted α-carbon to form α-amino radical **158**. Giese coupling of this radical with enone **159** occurs from the pseudoaxial face of its more-stable conformer **158** to form **160** in 54% yield.

**Scheme 30.**




A third method to generate α-aminoradical intermediates using visible light photoredox catalysis was disclosed by Gaunt and co-workers in 2018 and used subsequently in their total syntheses of the tyrosine-derived alkaloids (–)-FR901483 (**161**) and (+)-TAN1252C (**162**) (Scheme 31).[99] The key step in these syntheses is the stereoselective multi-component combination of methyl tyrosine (**163**), the mono ketal of 1,4-cyclohexandione (**164**) and dehydroalanine derivative **165** to form spirobicyclic product **166** in 73% yield over two steps. In this reaction, the iminium cation produced by acid-promoted dehydrative condensation of **163** and **164**, undergoes SET reduction by highly reducing $[Ir^{II}(ppy)_3]^-$ to form α-amino radical **167**. This intermediate adds to the radical acceptor **165** from its less-hindered equatorial face to give the coupled intermediate **168**, which undergoes HAT from the HE radical cation from its least hindered face to ultimately form **166** after acid-promoted lactamization. These incisive steps construct the challenging spirocyclic stereocenter and introduces all the heavy atoms of the natural product targets (–)-FR901483 (**161**) and (+)-TAN1252C (**162**).

**Scheme 31.**

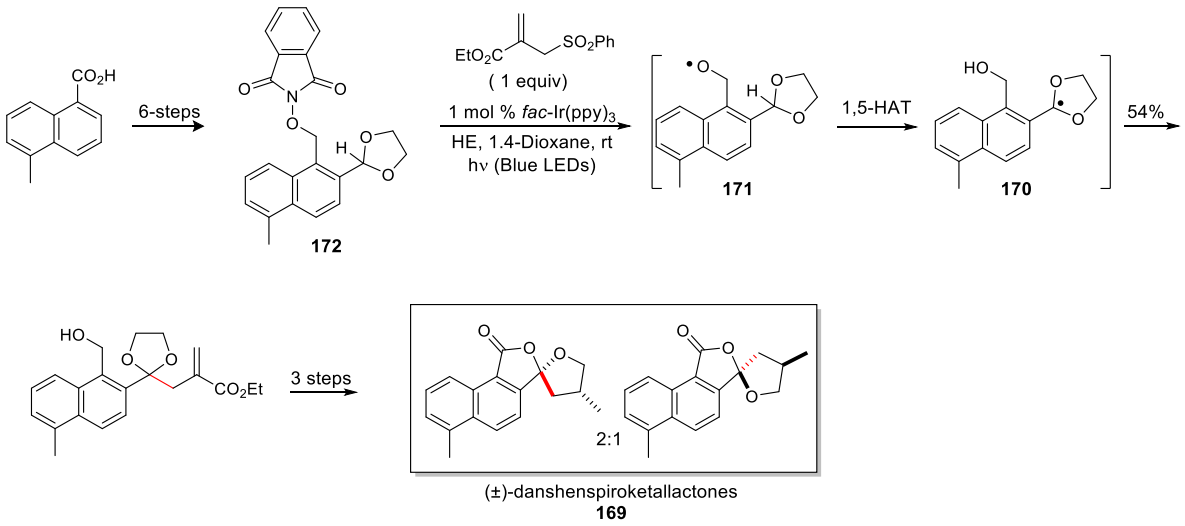



The translocation of radical intermediates by 1,5-hydrogen atom transfer is a well-established process in the chemistry of free radicals. A Giese radical coupling step in a recent total synthesis of the (±)-danshenspiroketallactones (**169**) by Smith and co-workers exploited rapid 1,5-hydrogen atom transfer to generate the 2-dioxalanyl radical intermediate **170** (Scheme 32).[100] In this case, alkoxy radical **171** was formed from benzylic *N*-hydroxyphthalimide ether **172** using the Ir-photocatalyzed method first reported by Chen and co-workers.[101]

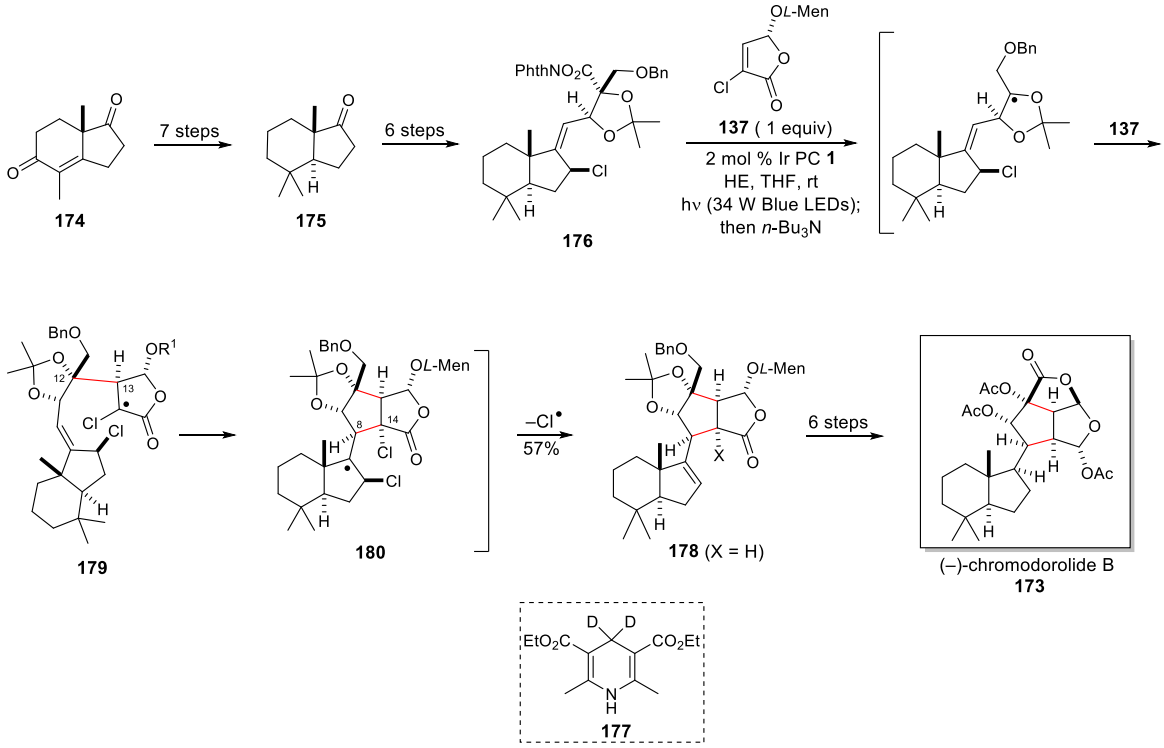
Late-stage coupling of an acetonide radical with a butenolide was the early step in a pivotal cascade reaction of the enantioselective total synthesis of (–)-chromodorolide B (**173**) reported by Overman and co-workers.[102,103] Five of the 10 contiguous stereocenters and the bond linking the two chiral fragments are harbored in the cyclopentane ring of the tricyclic lactone fragment of (–)-chromodorolide B. The synthesis begins with commercially available (*S*)-enedione **174**, which was advanced in seven steps to *trans*-hydrindanone **175** and further elaborated to acetonide NHPI ester **176**. In the optimized second-generation synthesis, **176** was coupled with 1 equiv of (*S*)-chlorobutenolide **137** upon irradiation in THF with blue LEDs in the presence of 2 mol % of Ir PC **1** and an excess of 4,4-dideuterio-HE **177** to give a mixture of **178** having X = H or Cl. Complete dechlorination of this intermediate was achieved by the addition of *n*-$Bu_3N$ and further irradiation, giving **178** in 57% yield as the sole pentacyclic product. Although the union of **176** and **137** to form **178** can be realized also using $[Ru(bpy)_3](PF_6)_2$, the final dechlorination step was slow using this less reducing PC. The dideuterio-HE **177** was used in the fragment coupling to minimize premature quenching of coupled intermediate **179** by hydrogen atom transfer, allowing for the formation of cyclized intermediate **180**.

The cascade reaction in the synthesis of (–)-chromodorolide B builds the fully substituted cyclopentane ring and stereoselectively forms four of its five contiguous stereocenters. In the fragment coupling step, butenolide **137** reacts as expected from the face opposite the alkoxy substituent and the trisubstituted acetonide radical predominantly from the face proximal to the alkylidenehydrindane side chain to generate intermediate **179**. At first glance the latter stereoselectivity is counter intuitive, but had some precedent and was recently studied in detail by both experiment and computation.[104] The chlorine substituent likely improves the efficiency of the fragment coupling step, but its essential role was to position the two C–Cl dipoles apart during the 5-*exo* cyclization of radical intermediate **179** to form exclusively the required C-8 stereocenter of **178**. Low stereoselection was realized at C-8 in related coupling reactions of the butenolide lacking the chlorine substituent.

**Scheme 32.**



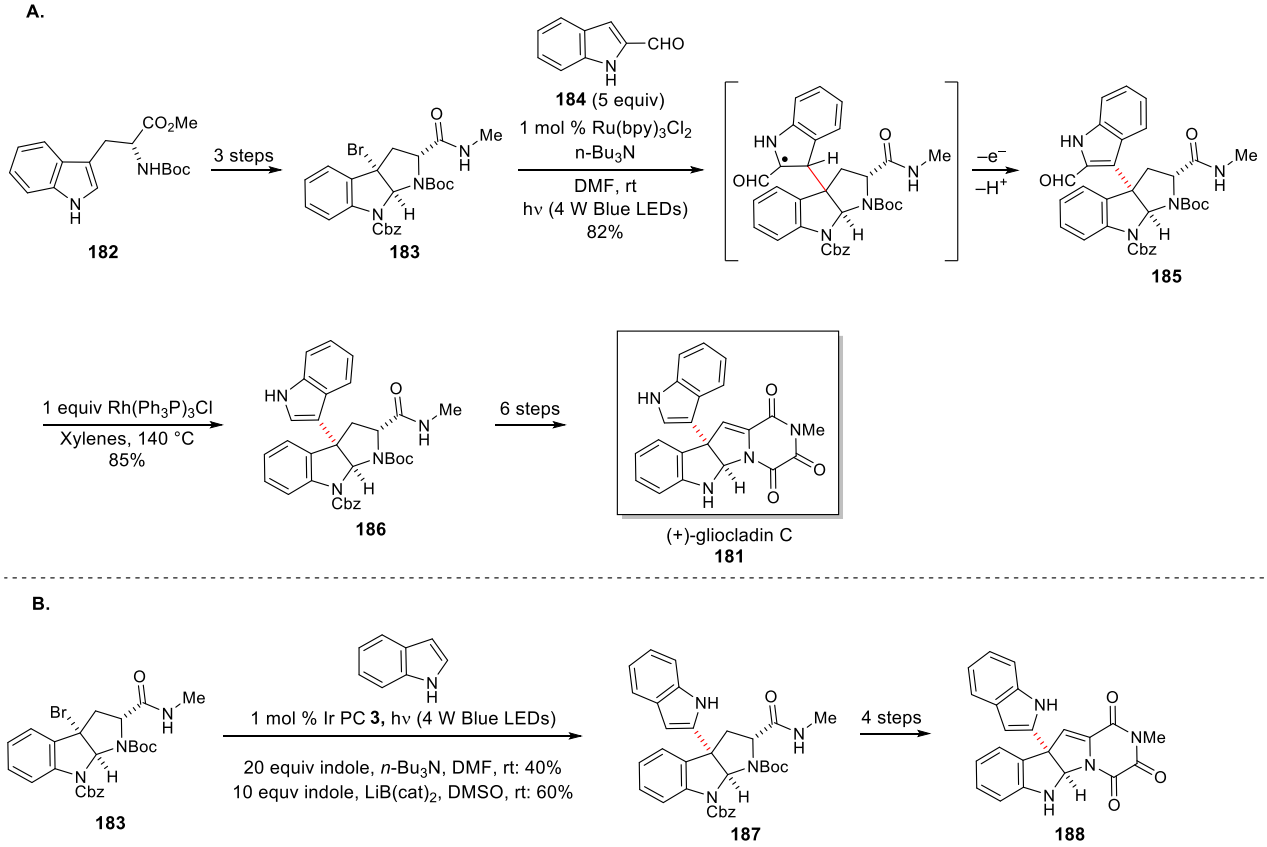

**Scheme 33.**




## 2.3. Carbon-Centered Radical Arene Coupling

**2.3.1. Alkyl carbon radical-aryl or heteroaryl coupling.** Homolytic substitution reactions of aromatic and heteroaromatic rings upon reaction with carbon-centered radicals in the presence of one-electron oxidizing agents have been known for over a century.[105] Photoredox-catalyzed variants of these substitution reactions were first described in the 1980s and have been developed rapidly in recent years.[106] Indoles feature predominantly in the use of photoredox-catalyzed homolytic substitution reactions in the synthesis of natural products. In an early influential report, Stephenson and coworkers reported in 2011 the concise total synthesis of (+)-gliocladin C (**181**) using visible-light photoredox catalysis (Scheme 34A).[107] Starting with (*R*)-Boc-tryptophan methyl ester (**182**), bromopyrrolidinoindoline **183** was prepared in three steps. Using *n*-$Bu_3N$ as the reductive quencher and $Ru(bpy)_3Cl_2$ as the PC, irradiation of bromide **183** and 5 equiv of 2-formylindole (**184**) with blue LEDs provided substitution product **185** in 82% yield. The formyl group, which was needed to block substitution at C-2 of the indole ring, was subsequently removed by Rh-promoted deformylation to give **186**. Advancement of this intermediate along established lines completed a ten-step enantioselective total synthesis of (+)-gliocladin C (**181**).

**Scheme 34.**

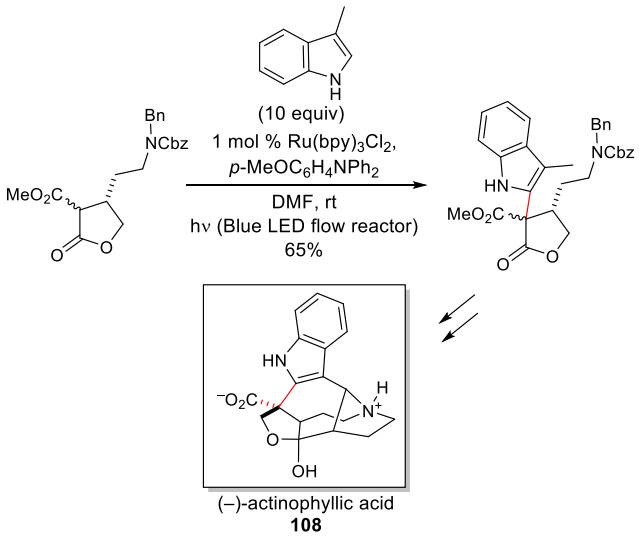



Competitive reduction of the carbon radical is a common side reaction in the reaction of carbon radicals with alkenes and arenes when the radical is generated from a halide (or related precursor) using a photocatalytic cycle involving an amine as the reductive quencher. One solution to this problem is the use an amine lacking α-hydrogens such as 4-methoxy-*N*,*N*-diphenylaniline so the *N*-centered radical cation produced upon reductive quenching cannot act as a hydrogen-atom donor. In a recent report, Stephenson and co-workers introduced the use of lithium bis-catechol borate ($LiB(cat)_2$) as an effective and inexpensive reductive quencher that minimizes the reduction of carbon radical intermediates. One illustration is provided in the coupling of tertiary bromide **183** with indole to form 2-substituted indole **187**, an intermediate in the synthesis of gliocladin C analogue **188** (Scheme 34B).[108]

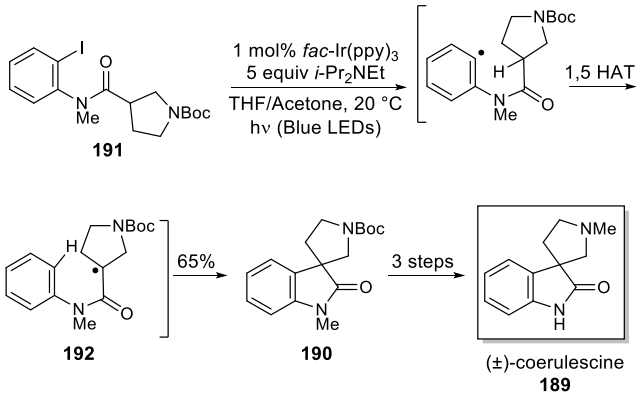
A related example of photoredox-catalyzed coupling of an indole with a tertiary radical, in this case an electron-deficient tertiary radical, is found in a second early step in Qin's synthesis of (–)-actinophyllic acid (**108**) (Scheme 35).[80]

Intramolecular arylations of halide-derived carbon radicals play central roles in several recently described syntheses of polycyclic indole alkaloids. One example is found in formal total syntheses of (±)-physovenine and (±)-coerulescine (**189**) reported by Xu and co-workers (Scheme 36).[109] The tricyclic spiro[pyrrolidin-3,3′-oxindole] ring system of **189** is found also in several structurally more elaborate oxindole alkaloids. In the synthesis of (±)-coerulescine (**189**), tricyclic precursor **190** was formed in good yield from *ortho*-iodoanilide **191** upon irradiation with blue LEDs in the presence of 1 mol % *fac*-$Ir(ppy)_3$ and *i*-$Pr_2NEt$. In this case, the tertiary radical intermediate **192** was generated by 1,5-hydrogen shift of the initially formed *ortho*-aryl radical.

**Scheme 35.**



**Scheme 36.**

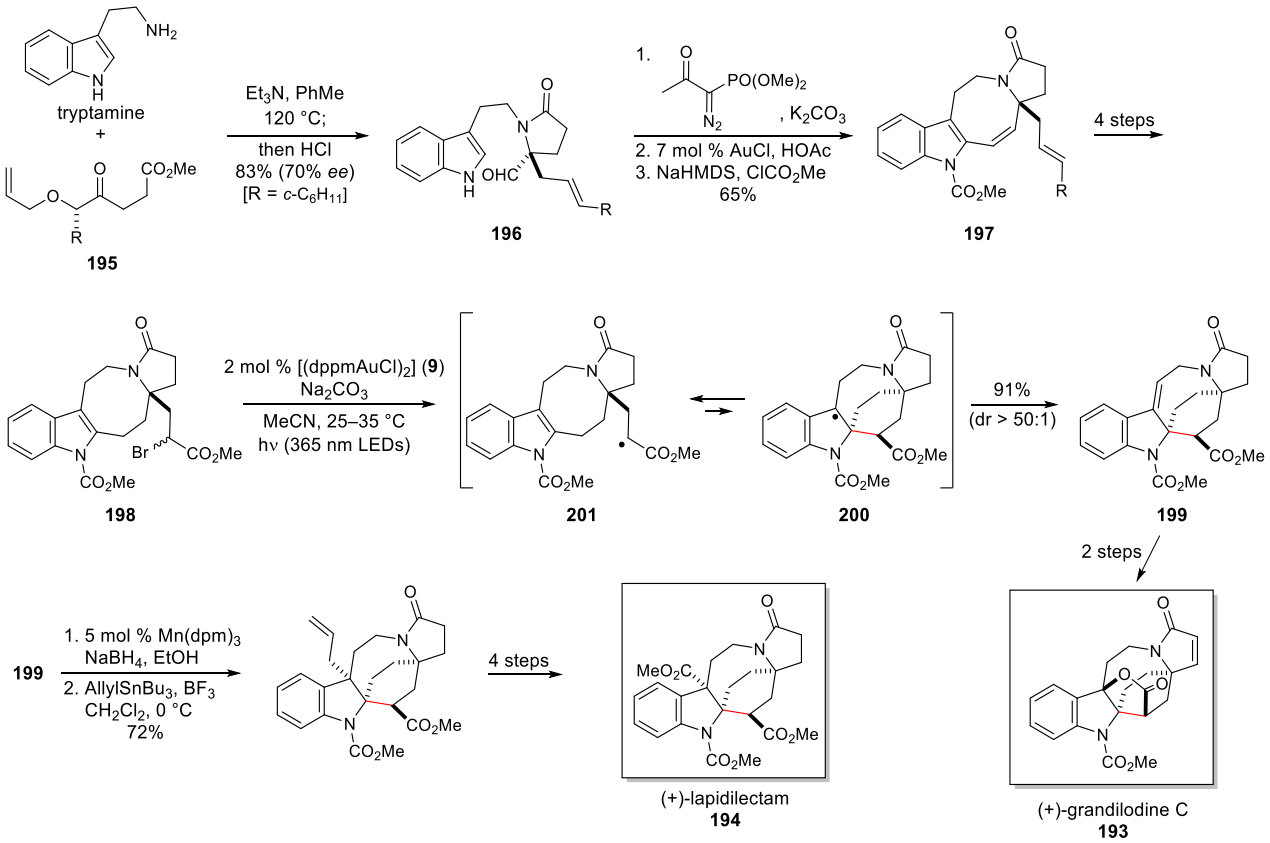



Echavarren and co-workers exploited Au-catalyzed hydroarylation chemistry pioneered in their laboratory to accomplish incisive total syntheses of many pyrroloazocine indole alkaloids isolated from plants of the *Kopsia* genus.[110] Their most recent total syntheses of members of the lapidilectine and grandiloline families also featured intramolecular photoredox catalyzed arylations of halide-derived secondary carbon radicals, as exemplified in total syntheses of (+)-grandilodine C (**193**) and (+)-lapidilectam (**194**) (Scheme 37).[111] Using a condensation/lactamization/enantioselective Claisen rearrangement cascade developed during their earlier studies, tryptamine and γ-ketoester **195** gave rise to lactam **196** in 83% yield and 70% *ee*. Ohiro-Bestmann elaboration of the aldehyde of **196** to an alkyne, and Au-catalyzed hydroarylation formed the eight-membered ring of intermediate **197**, which was subsequently advanced to α-bromoester **198**. Initial studies to accomplish spirocyclization of **198** to form the rigid bicyclo[4.2.2]decane ring system employing $Ru(bpy)_3Cl_2$ catalyzed photocatalysis successfully provided pentacyclic product **199**, however, the reaction did not proceed to completion because of catalyst decomposition. In contrast, the digold PC **9** utilized by Barriault and co-workers[17] was remarkably successful, providing **199** in 91% yield upon 365 nm LED irradiation. Diastereoselection is suggested to result from the carbomethoxy group adopting an equatorial position in a twist-boat-like transition structure. Computational studies found that **200** was less stable than cyclized radical intermediate **201**, suggesting that it is oxidation of **200** that drives formation of the cyclized product. In a short number of steps, intermediate **199** was transformed into seven pyrroloazocine indole alkaloids, exemplified by the formation of (+)-grandilodine C (**193**) and (+)-lapidilectam (**194**).

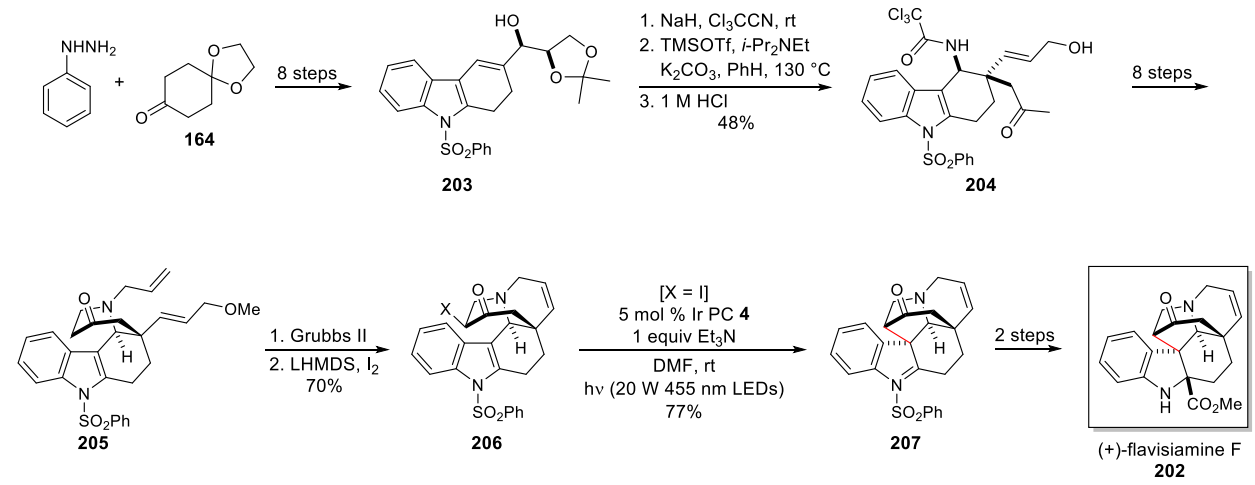
Another example of the utility of carbon radical indole coupling is found in the enantioselective total synthesis of (+)-flavisiamine F (**202**) reported by Xia and co-workers.[112] The synthesis begins with Fischer indolization of phenyl hydrazine and cyclohexanone **164** to give the corresponding tetrahydrocarboline, which was elaborated to dihydrocarboline allylic alcohol **203**. The first of two quaternary carbon stereocenters of flavisiamine F was formed by sequential Overman[113] and silicon-promoted ketal Claisen[114] rearrangements to provide **204**, with the second [3,3]-sigmatropic rearrangement proceeding with apparent high diastereoselectivity from the face of the trichloroacetamide substituent. Formation of the piperidine ring by a Mannich cyclization and further elaboration gave intermediate **205**. Formation of the tetrahydropyridine ring by ring-closing metathesis and regioselective iodination provided intermediate **206**. Attempts to perform the radical cyclization/sulfonyl radical elimination of **206** in classical fashion using either *n*-$Bu_3SnH$ or $(TMS)_3SiH$ resulted only in deiodination to form **206** (X= H). In contrast, under aerobic photoredox catalysis conditions using either $[Ru(bpy)_3](PF_6)_2$ or various Ir complexes as the PC, deiodination was avoided and the spiro quaternary carbon stereocenter was successfully forged. Nevertheless, under these photocatalytic conditions alcohol byproduct **206** (X= OH) was produced also. By using $[Ir(dF(CF_3)ppy)_2(d(CF_3)bpy]PF_6$ (**4**) and DMF as the solvent, formation of the alcohol byproduct was minimized and advanced intermediate **207** was formed in 77% yield.

The plicamine family of amayllidaceae alkaloids, exemplified by zephycarinatine D (**208**), are structurally distinguished by harboring a central spiro[5.5]undecane fragment (Scheme 39). The major challenge in stereocontrolled syntheses of these alkaloids is construction of this spirocyclic ring system and its quaternary carbon stereocenter. Most syntheses of these alkaloids employed biomimetic aryl-aryl couplings to form bond **a** of these alkaloids (Scheme 39). Last year, Ohno and co-workers reported total syntheses of (+)-zephycarinatines C and D (**208**) in which bond **b** is formed using a photoredox-catalyzed cyclization.[115] These syntheses begin with selective amide formation between carboxylic acid **209**, which was available in two steps from piperonylic acid, and the less-hindered *cis* epimer of the (*S*)-serine-derived oxazolidine **210** to give amide **211**. The α-amino radical generated by Ir-catalyzed oxidative decarboxylation of **211** cyclized onto the *ortho* phenyl substituent generating spirodienyl radical intermediate **212** and ultimately spirocyclic 1,4-diene product **213**. This intermediate was elaborated to 1,4-diene **214** and subsequently oxidized to generate the corresponding spirocyclic dienone intermediate. Trapping of this intermediate by the pendant amide side chain provided **215** in 70% yield. This key step desymmetrizes the prochiral quaternary carbon of the dienone intermediate to establish the quaternary carbon stereocenter of the spiro[5.5]undecane fragment. In five additional steps, **215** was advanced to (+)-zephycarinatine D (**208**).

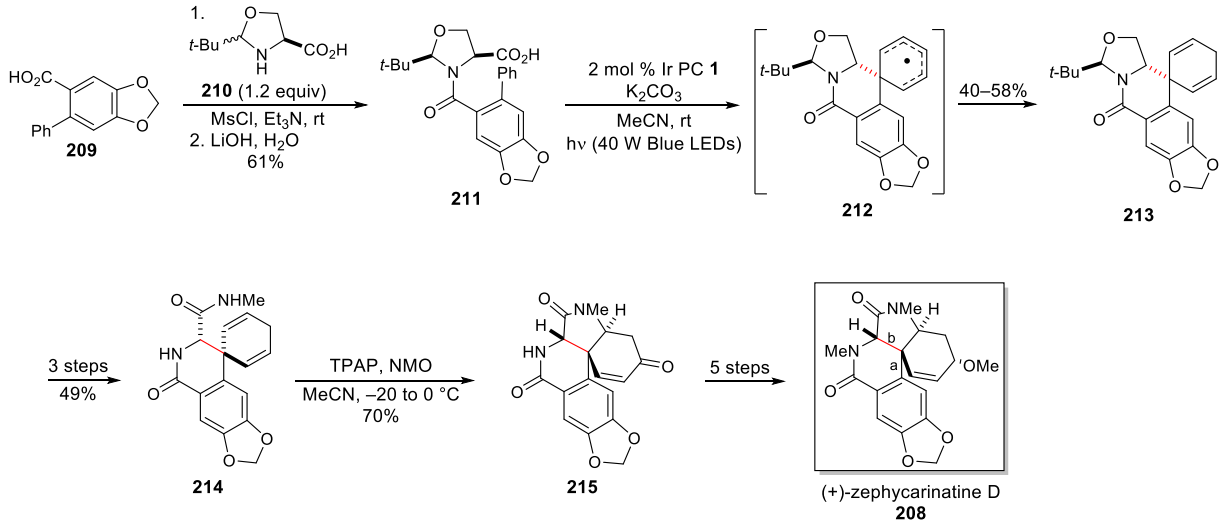
**Scheme 37.**




**Scheme 38.**

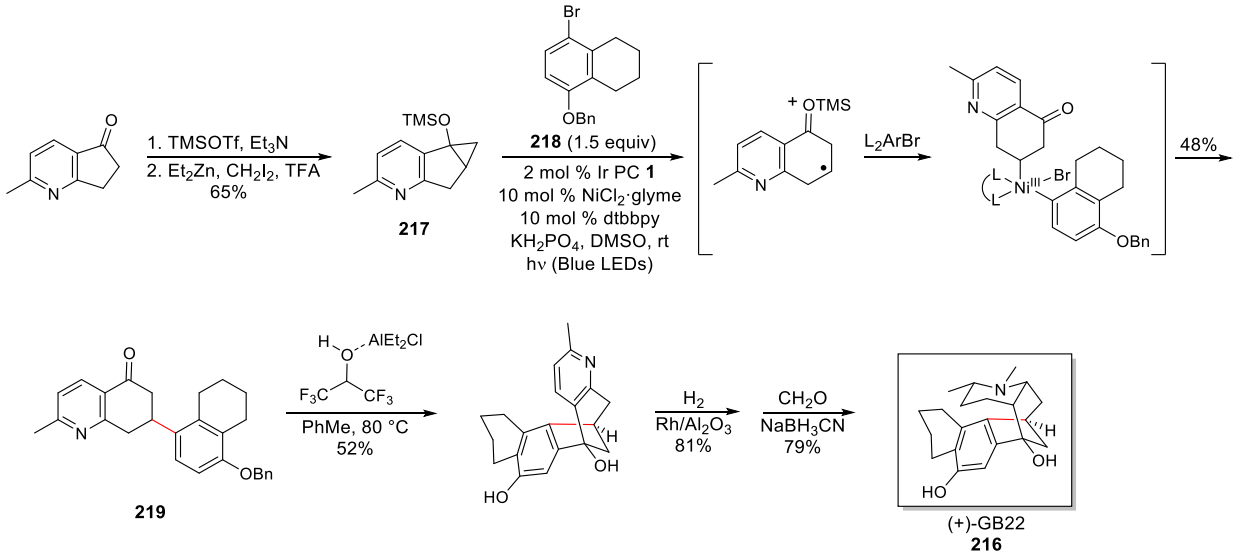


**Scheme 39.**



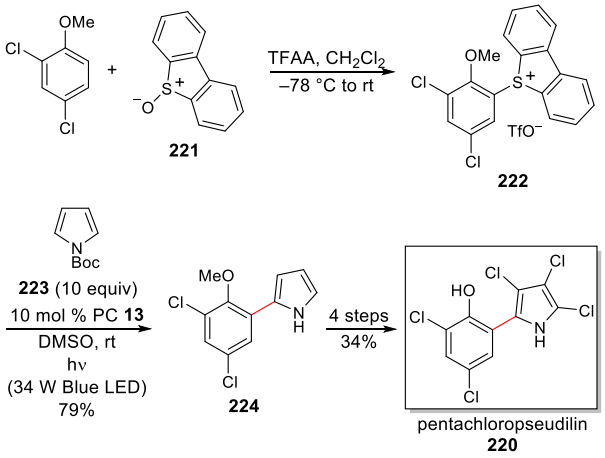

A photoredox catalyzed ketone β-arylation was a key step in the total synthesis by Shenvi and co-workers of (+)-GB22 (**216**), a recently isolated galbuliminia alkaloid (Scheme 40).[116] This synthesis exploited recent developments in dual nickel and photoredox catalysis.[117] In this case, irradiation with blue LEDs of a mixture of siloxycyclopropanol **217** and 1.5 equiv of arylbromide **218** in the presence of 2 mol % $Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**1**) and 10 mol % of $NiCl_2(MeOCH_2CH_2OMe)$ gave β-aryl ketone **219** in 48% yield. It merits note that **219** would not have been available from 1,4-addition of the tetrahydronapthalene fragment to an enone, as the enone in this case would exist as the phenol tautomer. In addition, alternative activation of siloxycyclopropanol **217** by palladium catalysis would have been expected to cleave the alternative bond of the cyclopropane to form a primary palladium alkyl intermediate. The pentacyclic ring system of (+)-GB22 (**216**) was generated in the next step of this concise synthesis by activating the carbonyl group of **219** for intramolecular Friedel-Crafts cyclization with $Et_2AlCl$ in the presence of hexafluoroisopropanol, conditions that also cleave the arylbenzyl ether.

**Scheme 40.**



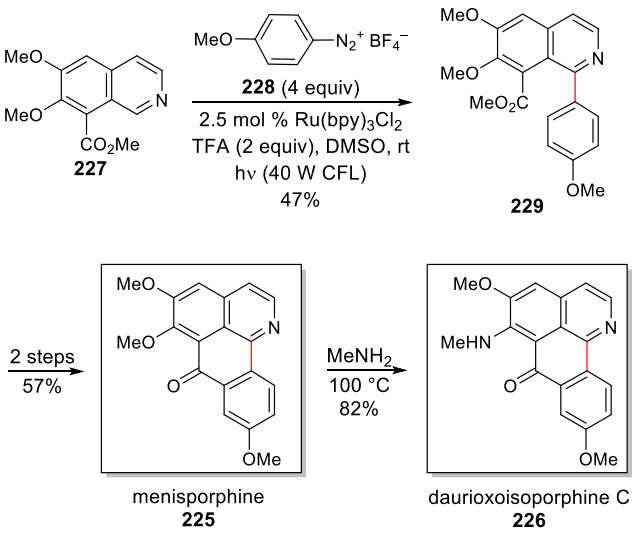
**2.3.2. Aryl carbon radical-heteroaryl coupling.** There are several recent total syntheses that link two aromatic fragments using visible-light photoredox catalysis. The bimolecular coupling of an aryl radical with pyrrole was the central step in the synthesis of pentachloropseudilin (**220**) reported last year by Proctor and co-workers (Scheme 41).[118] The synthesis exploits this group's preparation of triarylsulfonium salts from the reaction of arenes with commercially available dibenzothiophene *S*-oxide (**221**) and triflic anhydride. In optimization studies using furan as the coupling partner, the cross coupling of sulfonium salt **222** was realized in low yield using *fac*-Ir(ppy)$_3$ or Ru(bpy)$_3$Cl$_2$ as the PC and optimally using the organic PC 10-phenylphenothiazine (**13**). When carried out with *N*-Boc-pyrrole (**223**), the coupling with sulfonium salt **222** produced 2-arylpyrrole **224** in 79% yield.

**Scheme 41.**




Building on earlier disclosures of direct photocatalytic arylation of heteroarenes with aryl diazonium salts from the Konig and the Martin and Carrillo groups,[119,120] a bimolecular aryl radical isoquinoline coupling was the key step in total syntheses of the isoquinoline alkaloids menisporphine (**225**) and daurioxoisoporphine C (**226**) reported by Lei and coworkers (Scheme 42).[121] In early studies of the reaction of isoquinoline **227** with aryl diazonium salt **228**, the authors found that the yield of arylated product **229** was higher using Ru(bpy)$_3$Cl$_2$ than *fac*-Ir(ppy)$_3$ or Eosin Y as the PC, and higher than conventional coupling reactions using low-valent salts of Ag, Co, Cu, Fe and Mn.

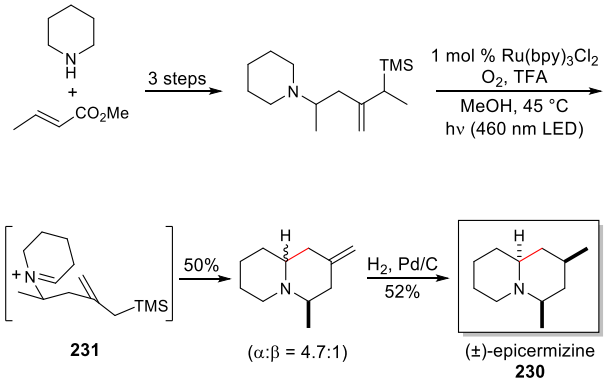
**Scheme 42.**




## 2.4 Other C–C Bond-Forming Cyclization Reactions

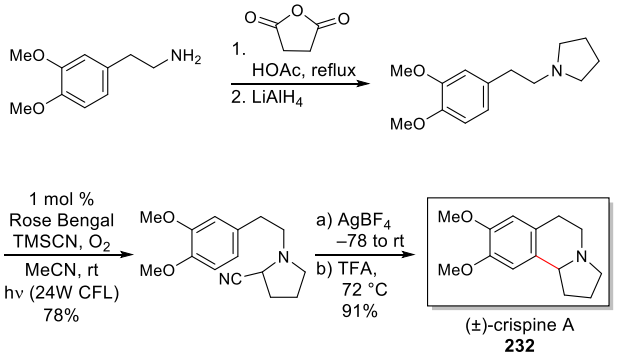
**2.4.1. Aza-Prins Cyclizations.** Intramolecular reactions of iminium or *N*-acyliminium cations with alkene or aromatic π-nucleophiles are often employed for the synthesis of azacyclic molecules. In addition, the generation of iminium cations by photoredox-catalyzed oxidation of trialkyl amines has been known for over 50 years,[122] with the use of oxygen as a stoichiometric oxidant for this conversion being common.[123] This method of generating an iminium cation was utilized by Marvin and co-workers in total syntheses of the quinolizidine alkaloids (±)-epimyrtine and (±)-5-epicermizine (**230**) (Scheme 43).[124] A prerequisite for a successful aza-Prins cyclization is the ability to co-generate the iminium cation and the trapping nucleophile. The stability of the highly reactive allylsilane nucleophile to the Ru(bpy)$_3$Cl$_2$-catalyzed generation of iminium ion intermediate **231** is a notable feature of this total synthesis.

**Scheme 43.**




Iminium electrophiles are often formed by ionization of amines harboring leaving groups at the α-carbon. α-Aminonitriles are among the most stable of these iminium ion precursors and have been used regularly in azacyclization reactions. The efficient synthesis of α-aminonitriles by photocyanation of tertiary amines was reported by Opatz and coworkers.[125] The activation of a pyrrolidine fragment for intramolecular cyclization with an electron-rich arene is illustrated in this group's total synthesis of the indolizidine alkaloid (±)-crispine A (**232**) (Scheme 44).

**Scheme 44.**




In a series of reports beginning in the late 1990s, Demuth and coworkers described the use of UV-promoted electron transfer to initiate radical polyene cyclization reactions.[126,127] More recently, Luo and coworkers reported the use of visible-light photoredox catalysis to accomplish polyene cyclizations that take place in the 6-*exo* cyclization fashion typically seen in biomimetic-cationic processes.[128] The utility of this method was illustrated in a total synthesis of the meroterpenoid (±)-hongoquercin A (**233**) (Scheme 45).[129] In the key step of this synthesis, cyclization precursor **234**, which was available in two steps from farnesol (**235**), was irradiated with green LEDs in the presence of 1 mol % of Eosin Y to give tetracyclic product **236** in good yield. In four additional steps and 36% overall yield, this cyclization product was elaborated to (±)-hongoquercin A (**233**). The cyclization step is presumed to take place by way of a radical cation intermediate, although details of this process and the origin of the hydrogen substituent at C-3 of product **236** are unclear.

## 3. CARBON-NITROGEN BOND FORMATION

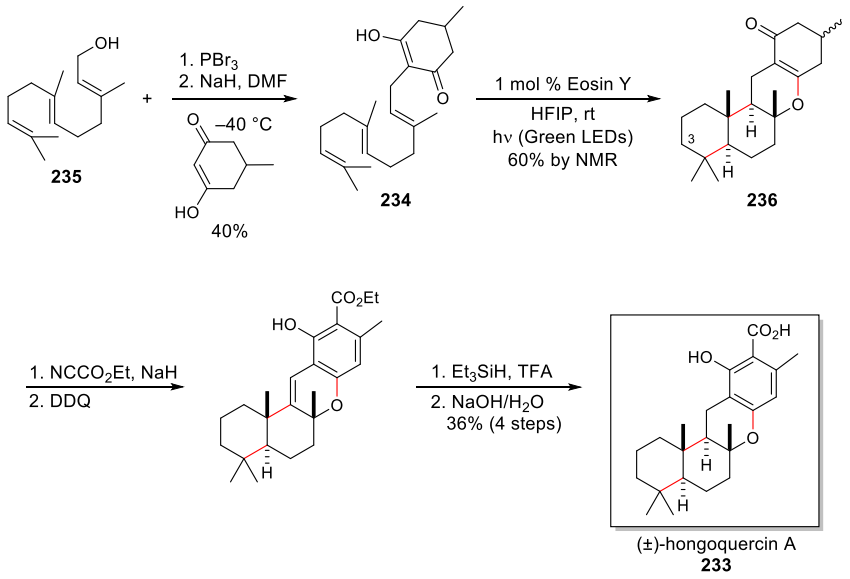
### 3.1 Cyclizations of Nitrogen-Centered Radicals

Cyclizations of nitrogen-centered radicals have long played a role in the synthesis of alkaloids and other nitrogenous natural products.[130-132] The generation of nitrogen-centered radicals under mild conditions using visible-light photoredox catalysis is opening new avenues in the synthesis of nitrogen-containing molecules, including natural products.[133-137] Fragmentation of a *N*–heteroatom bond is a common method to form nitrogen-centered amide and sulfonamide radicals. The direct formation of such radicals from N–H bonds, however, would avoid the need to pre-activate the nitrogen atom. In 2016, Nguyen and Knowles reported the use of $Ir(dF(CF_3)ppy)_2(bpy)PF_6$ (**1**) and a phosphate base to generate amidyl radicals from secondary amides by proton-coupled electron transfer (PCET), and their subsequent participation in 5-*exo* radical cyclizations.[138] A year later, Qin and co-workers reported that aryl sulfonamides could be oxidized efficiently in a related fashion upon irradiation in acetonitrile with blue LEDs in the presence of 1 mol % of $Ir(dtbppy)_2(bpy)PF_6$ (**5**) and $KHCO_3$.[139]

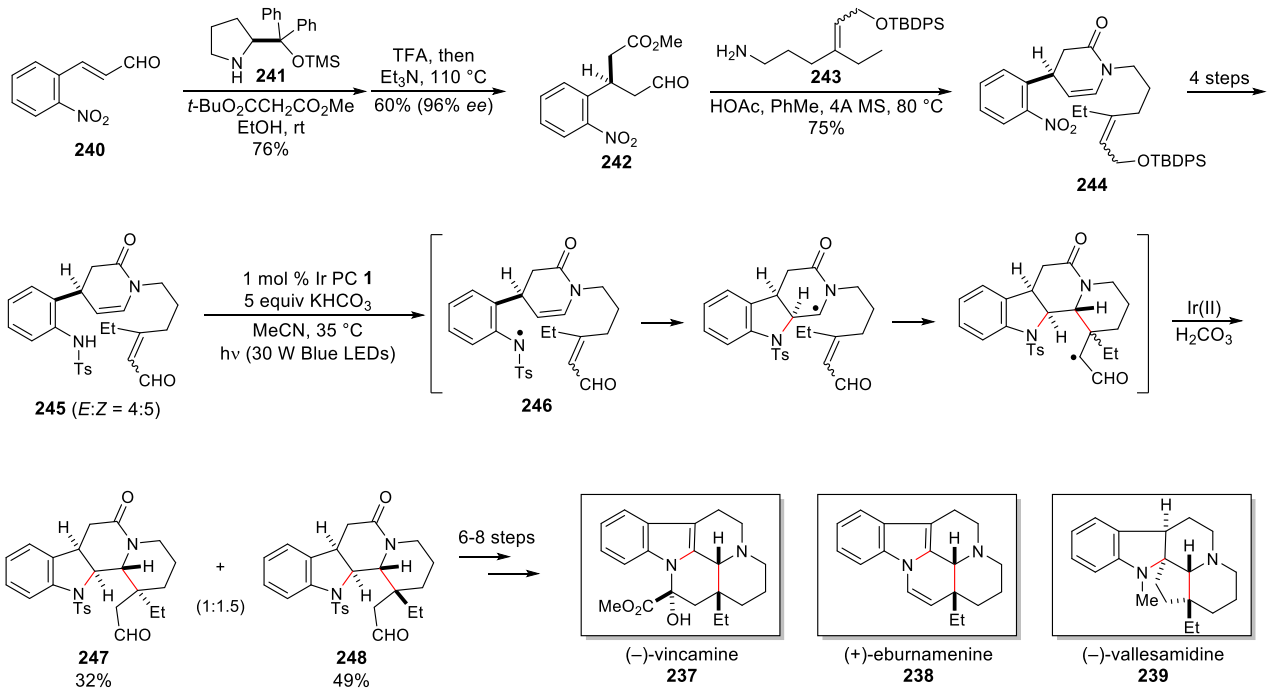
Extensive recent studies from the Qin group exploit sulfonamidyl radicals formed in this way to initiate a range of cascade radical cyclization and cyclization/coupling reactions, and their use in the total synthesis of a diverse array of indole alkaloids.[140] The common feature of these cascades is the initial formation of a *cis*-tetrahydro-β-carboline by 5-*exo* cyclization of an arylsulfonamidyl radical. One variant of this cascade approach forms two rings of alkaloids of the eburnamine-vincamine family, as exemplified in total synthesis of (–)-vincamine (**237**), (+)-eburnamenine (**238**) and (–)-vallesamisine (**239**) (Scheme 46).[139] Starting with the enantioselective Michael addition of *tert*-butyl methyl malonate to enal **240** catalyzed by proline analogue **241**, *o*-nitroaryl oxoester **242** was formed in high enantiomeric purity and 46% yield. Condensation of **242** with primary amine **243**, which is available in 11 steps from butyrolactone, gave dihydropyridone **244**, which in four additional steps was transformed to **245**. Photocatalytic generation of sulfonamidyl radical **246**, followed by successive 5-*exo* and 6-*exo* alkene cyclizations afforded ultimately a mixture of epimeric tetracyclic products **247** and **248** in 81% yield. The major stereoisomeric product **248** was elaborated subsequently to complete enantioselective total syntheses of seven alkaloids of the eburnamine-vincamine class, three of which are depicted in Scheme 46.[139] A similar cascade was used by Qin and co-workers to prepare five additional oxo-functionalized eburnane alkaloids.[141]

A cascade sequence featuring the bimolecular coupling of the *cis*-tetrahydro-β-carboline radical generated from the initial cyclization of a sulfonamidyl radical was employed by Qin and coworkers to synthesize the akuammiline alkaloids (–)-rhazinoline (**249**) and (–)-strictamine (**250**, Scheme 47).[142] In this case, irradiating of arylsulfonamide **251** in the presence of 0.5 mol % $Ir(dtbppy)_2(bpy)PF_6$ (**5**), $KHCO_3$ and 1.2 equiv of acrolein generated tetrahydro-β-carboline **252**. Since THF was the solvent for the photocatalytic step, subsequent addition of vinylmagnesium bromide and sodium naphthalenide gave rise to **253** in 47% overall yield. This intermediate was advanced subsequently to (–)-rhazinoline (**249**) and (–)-strictamine (**250**).

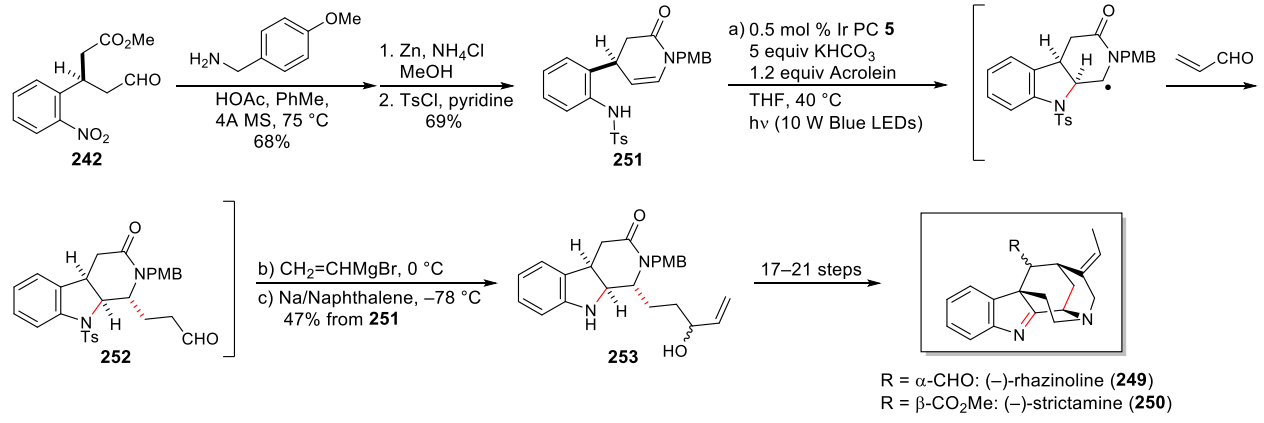
**Scheme 45.**




**Scheme 46.**




**Scheme 47.**



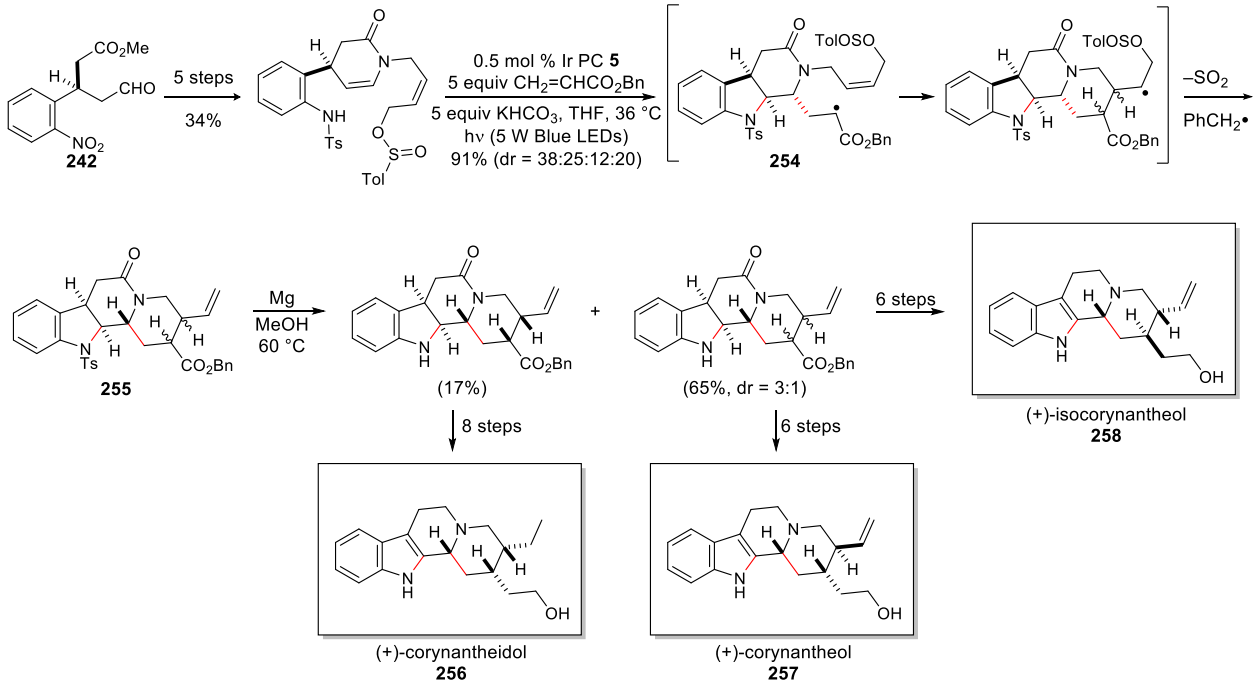
A third cascade sequence in which a bimolecular carbon radical coupling step was sequenced between two intramolecular radical cyclizations was introduced by the Qin group to synthesize members of the corynanthe, yohimbine, heteroyohimbine, strychnos and cinchona alkaloids.[139,143] One variant of this approach is summarized in Scheme 48 for the synthesis of corynanthe alkaloids. Although *cis*-tetrahydro-β-carboline intermediate **254** was generated stereoselectively during the cascade, the 6-*exo* cyclization step provided a mixture of three of the four possible stereoisomers of tetracyclic product **255**. In subsequent steps, single stereoisomers were obtained allowing several corynanthe alkaloids to be prepared as exemplified in total syntheses of (+)-corynantheidol (**256**), (+)-corantheol (**257**), and (+)-iosocorynantheidol (**258**).

The use of a related strategy to synthesize the enantiomer of natural strychnine (**259**) is summarized in Scheme 49.[144] In this case, an alkyne was tethered to the nitrogen of the dihydropyridone cyclization precursor so the final C–C bond-forming step of this notably efficient photoredox cascade gave **260** in 80% while installing the trisubstituted double bond of strychnine. After advancing **260** to **261**, intermediate **262** harboring the pentacyclic core of *Strychnos* alkaloids is generated by biomimetically inspired oxidative rearrangement of tetracyclic precursor **261**.[145]

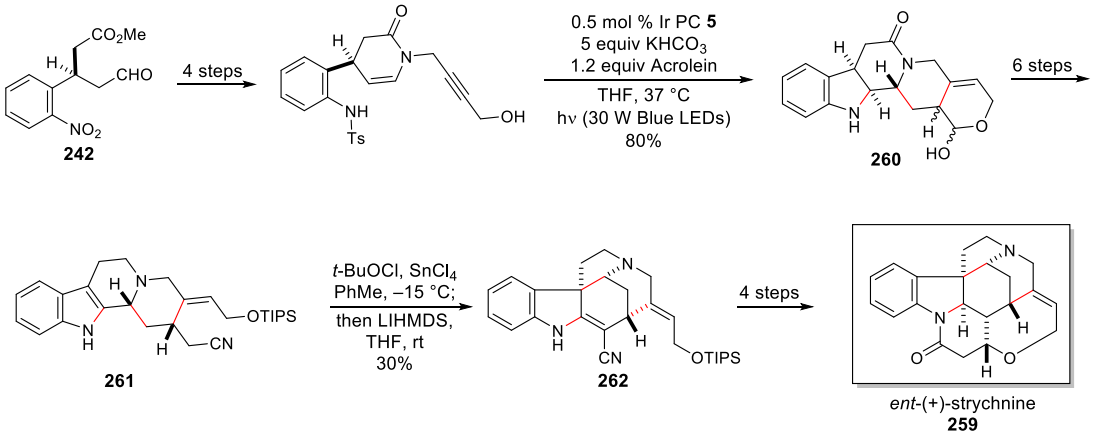
A radical cascade initiated by a benzamidyl radical was developed by Rao and co-workers for the synthesis of benzoindolizidines such as (–)-tylophorine (**263**) (Scheme 50).[146] Of the conditions surveyed, the use of $Ir[(dF(CF_3)ppy)_2(dF(CF_3)bpy)]PF_6$ (**4**) as the PC and a phosphate base were optimal for generation of a benzamidyl radical (e.g., **264**) by PCET. Various stoichiometric oxidants could be employed in the final oxidation of intermediate **265**. Using dilauroyl peroxide, the yield of unsubstituted benzoindolizidine **266**, the direct precursor of (±)-tylophorine (**263**), was only 5%. That the problem resides in the sensitivity of the benzylic methylene hydrogens and hydrogens adjacent to nitrogen to oxidation, is suggested by the high yield realized in the formation of the tylophorine analogue precursor **267**.

The hexahydropyrrolo[2,3-*b*]indole (cyclotryptamine) ring system is found in a variety of biologically active alkaloids. Wang and co-workers employed photoredox catalysis to construct cyclotryptamines by the cyclization of indole-3-acetic acid-derived amidyl radicals.[147,148] In their syntheses of the simple cyclotryptamine alkaloids (±)-flustramide B (**268**) and (±)-flustraminol B (**269**), the amidyl radical was generated by fragmentation of an electron-deficient aryloxy amide as reported by Leonori.[149] When the cyclization of *N*-aryloxyamide **270** was carried out under aerobic conditions by irradiation with 530 nm LEDs in the presence of 2 mol % of Eosin Y the cyclized radical intermediate was trapped by oxygen giving ultimately alcohol **271** in 79% yield. To install a carbon substituent at the benzylic quaternary carbon, similar irradiation in the presence of 3 equiv of allylic sulfone **272** delivered product **273** in 78% yield.

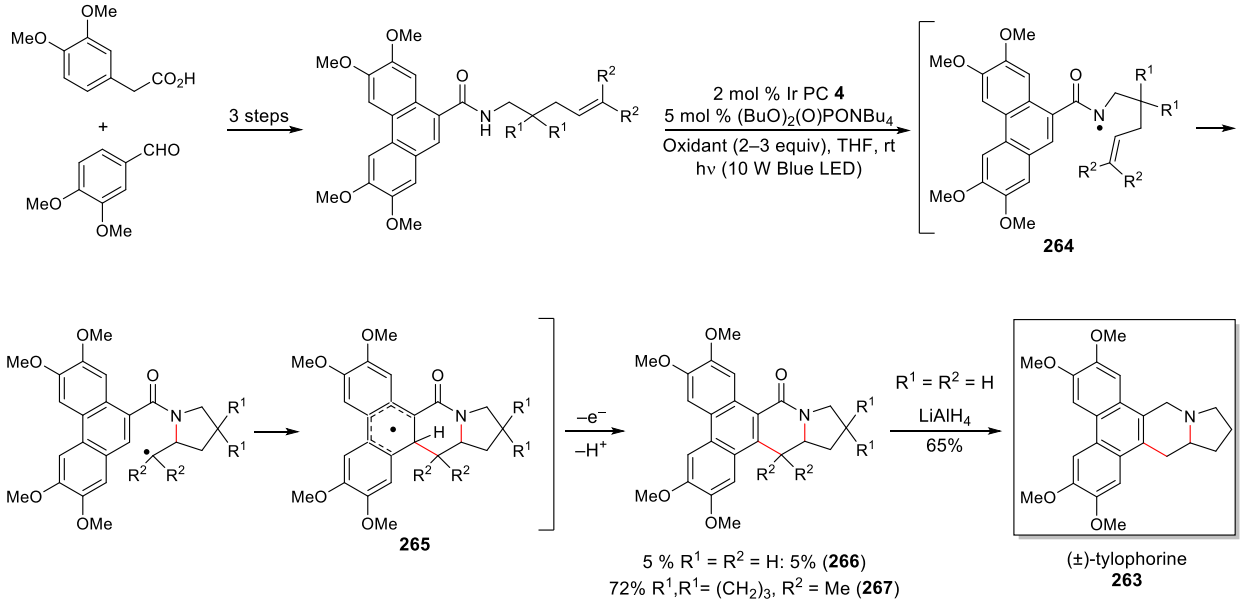
**Scheme 48.**



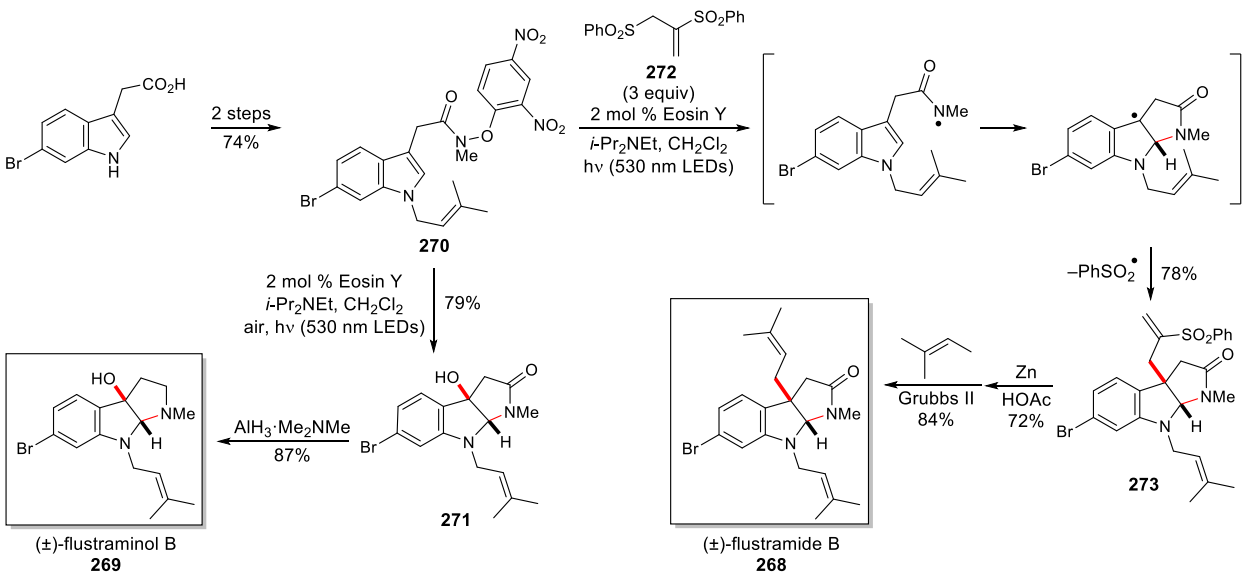

**Scheme 49.**




**Scheme 50.**

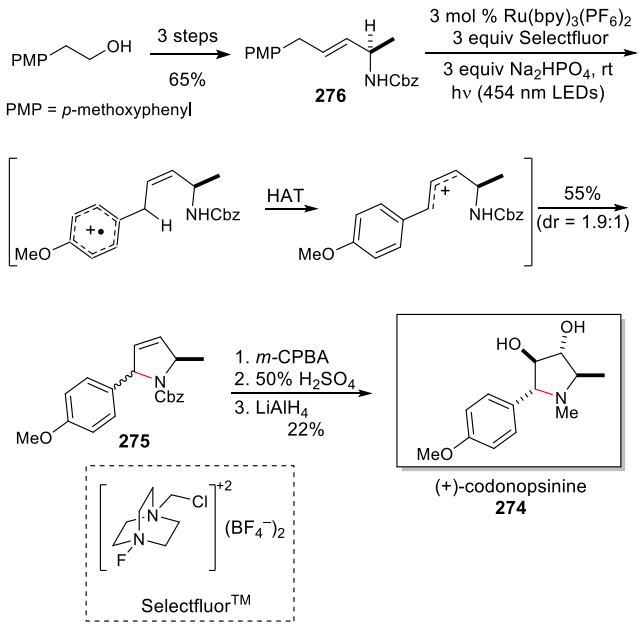


**Scheme 51.**




**3.2 Cyclizations of Nitrogen Nucleophiles with Carbonium Ion Intermediates.** Since Loffler's synthesis of nicotine in 1909, piperidines having an aromatic substituent at C-2 have often been constructed from acyclic amine precursors by C–H activation of a benzylic methylene group. Pandey and co-workers recently reported that 5- and 6-membered oxygen and nitrogen heterocycles harboring a *p*-methoxyphenyl substituent adjacent to the heteroatom can be formed from acyclic precursors using oxidative photoredox catalysis. The synthesis of (–)-condonopsinine (**274**) illustrates this method (Scheme 52). Using 3 mol % $Ru(bpy)_3(PF_6)_2$ as the PC, excess Selectfluor™ as the oxidative quencher, and irradiation with blue LEDs, dihydropyrrole **275** was isolated as a mixture of stereoisomers in 55% yield from allylic carbamate precursor **276**. In three subsequent steps, (–)-condonopsinine (**274**) was obtained from this isomer mixture.

**Scheme 52.**

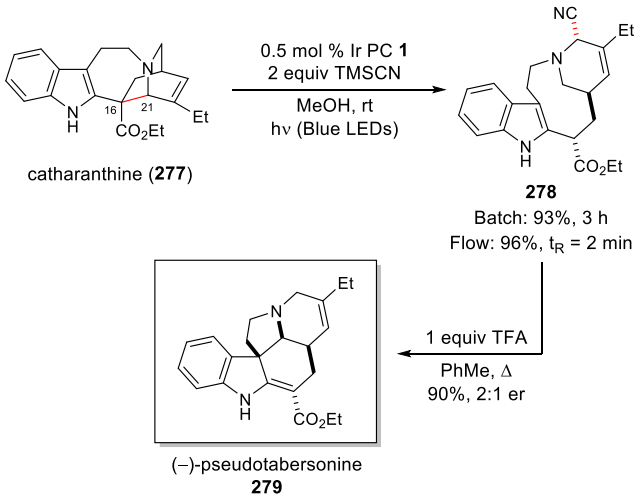



## 4. CARBON-CARBON BOND FRAGMENTATION

In 2014, Stephenson and co-workers used a photoredox-catalyzed C–C bond fragmentation approach in the semi-synthesis of indole alkaloids.[150,151] In this approach, the authors identified the readily available alkaloid (+)-catharanthine (**277**) as an ideal entry point for the synthesis of aspidosperma-type alkaloids by way of a common α-aminonitrile intermediate **278**. The utility of this method is summarized in Scheme 53 in the synthesis of (−)-pseudotabersonine (**279**). Visible-light irradiation of catharanthine (**277**) in the presence of polyfluorinated catalyst $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**1**) resulted in single-electron oxidation of **277** followed by fragmentation of C16–

C21 bond to give a radical cation intermediate that could be quenched by TMSCN, giving α-aminonitrile **278** in 93% yield after 3 h. Furthermore, this approach was amenable to flow conditions, where the fragmentation reaction was complete with a residence time of only 2 min with a yield of 96%. Refluxing **278** in toluene in the presence of TFA furnished (−)-pseudotabersonine (**279**) in 90% yield in 2:1 er and 86% overall yield from **277**. Furthermore, α-aminonitrile **278** could be further elaborated to (−)-pseudovincadifformine and (+)-coronaridine in 55% and 46% overall yield from (+)-catharanthine (**277**), respectively.

**Scheme 53.**




Another recent example of applying a photoredox-catalyzed C–C bond fragmentation approach was disclosed by Ohno and co-workers in their synthesis of (−)- and (+)-polyoxamic acid (**280**) starting from glucose (Scheme 54).[152] The fragmentation reaction took inspiration from photocatalytic ring-opening reaction previously established by the Knowles group[153], which proceeds through the generation of an alkoxy radical followed by β-scission to homolyze the C–C bond. Starting from known glucose derivative **281** derived from methyl-α-D-glucopyranoside **282**[154,155], a *N*-hydroxyphthalomido group, which have been previously shown to form alkoxy radicals under photoredox conditions[156], was inserted under Mitsunobu conditions. Removal of the TBS group then furnished substrate **283**. Subjecting *N*-alkoxyphthalamide precursor **283** to 5 mol % *fac*-Ir(ppy)$_3$ under blue LED irradiation led to β-scission followed by 1,5-HAT and oxidation of the benzyl radical to form benzyl cation **284**, which was subsequently trapped by the hydroxyl group to yield benzylidene acetal **285** in 63% yield. By switching to flow conditions, the catalyst loading was dropped to 2 mol % without any reduction in yield. Benzylidene acetal **285** was elaborated over a series of steps to complete the synthesis of (−)-polyoxamic acid **280**. Using the same approach, the authors also synthesized (+)-polyoxamic acid starting from L-glucose.

## 5. MISCELLANEOUS

### 5.1 Reductive dehalogenation

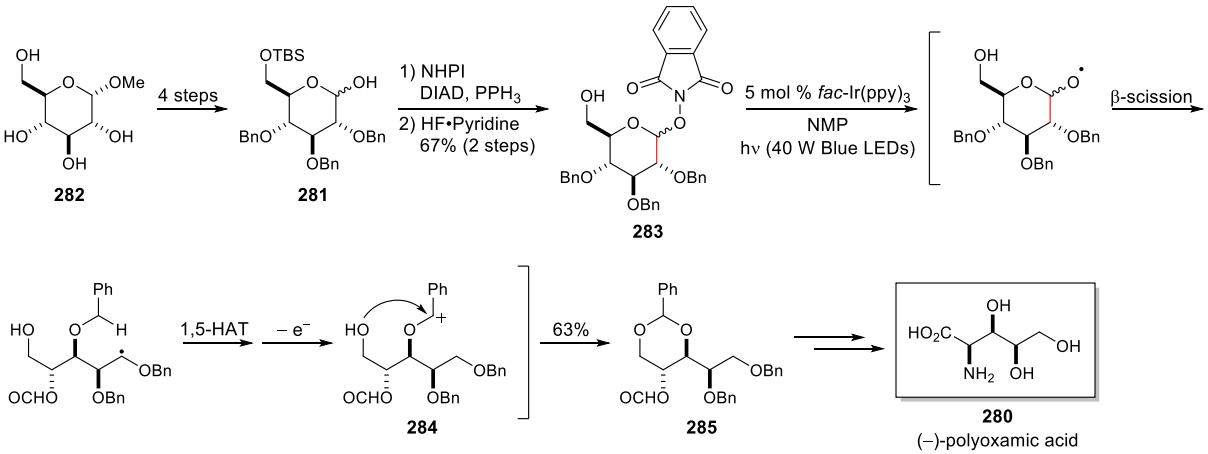
The homolytic cleavage of an alkyl halide has long been one of the most popular methods for carbon radical generation in organic synthesis. Much progress has been made in the replacement of toxic tin reagents in dehalogenation reactions by the implementation of visible-light photoredox catalysis, and has been the subject of several prior reviews.[5,9,157] In a recent synthesis and determination of absolute configuration of albucidin (**286**), an oxetane nucleoside phytotoxin, Yang and coworkers utilized visible-light photoredox catalysis for a late state deiodination.[158] As described in Scheme 55, the authors began with cheap and readily available D-xylose which they advanced over a series of steps to known intermediate epinoroxetanocin (**287**). Using a strategy similar to that previously reported by Takita[159], **287** was elaborated to secondary alkyl iodide intermediate **288**. After benzyl deprotection, treatment of **289** with *i*-Pr$_2$NEt and *p*-toluenethiol as the hydrogen atom

source in the presence of 1.5 mol % of *fac*-Ir(mppy)$_3$ under 1 W blue LED irradiation yielded (1*R*,3*S*)-albucidin (**286**) in 82% yield. Furthermore, the authors were able to synthesize the opposite enantiomer using an almost identical sequence starting from L-xylose, allowing them to assign the absolute configuration of natural albucidine as (1*R*,3*S*).

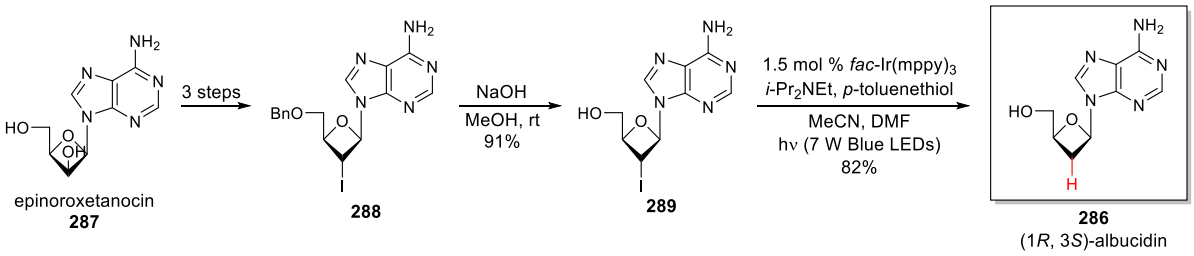
### 5.2 Mesolytic cleavage

Many contributions to methods for the generation of free radical intermediates via PCET reactions have been reported by the Knowles group.[160] In an extension of this work, the authors developed an approach where the enantioselectivity in the reactions of indole radical cations generated by oxidative PCET could be controlled by asymmetric induction from a chiral phosphoric acid, as exemplified in the short synthesis of the dimeric pyrroloindoline natural product (−)-calycanthidine (**290**, Scheme 56).[161] Irradiation of protected tryptamine **291** in the presence of 0.5 mol % of *fac*-Ir(ppy)$_3$ and 3 mol % of chiral H8-TRIP BINOL phosphate **292** and 2 equiv of TEMPO• by blue LEDs furnished the TEMPO-functionalized intermediate **293** in 91% and 93% *ee*. Furthermore, the reaction could be adapted to 10 mmol scale in flow with only a slight reduction in yield (81%) and no deleterious effects on the *ee*. The reaction is proposed to proceed through an oxidative PCET furnishing an ionic hydrogen-bonded complex between the tryptamine radical cation and the chiral phosphate base **292**, which is captured in asymmetric fashion by the persistent free radical TEMPO•. To complete the synthesis of (−)-calycanthidine (**290**), methylation of **293** in the presence of NaHMDS and MeI furnished **294** in 93% yield. Subjecting **294** to [Ir(dCF$_3$, mppy)$_2$(dtbbpy)]PF$_6$ (**6**) under blue LED irradiation led to single-electron oxidation of **294**, inducing mesolytic cleavage to generate TEMPO• and a configurationally biased tertiary pyrroloindoline carbocation. This cation is then intercepted by N-Me-N'-Cbz tryptamine **295** in a Friedal–Crafts process to form the unsymmetrical dimer **296** in 71% yield and 13:1 dr. Reduction of the two benzyl carbamate groups by Red-Al (80%) furnished (−)-calycanthidine (**290**) in four steps from tryptamine **291** and 24% overall yield. The authors also successfully utilized this approach in the synthesis of other dimeric pyrroloindoline natural products, namely (−)-chimonanthine and (−)-psychotriasine.

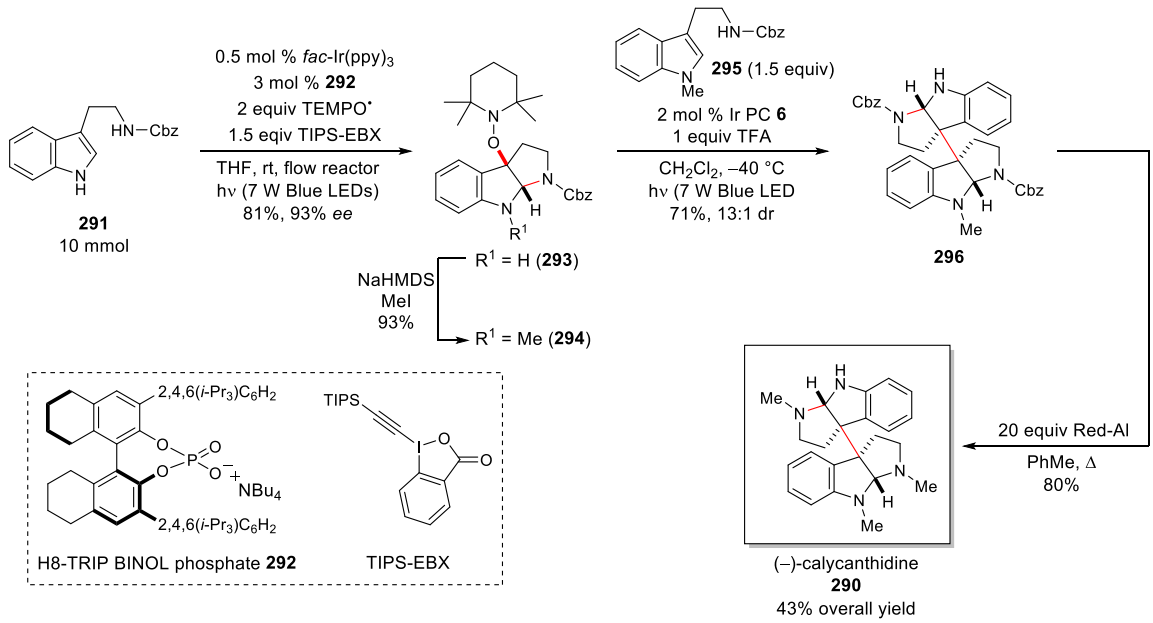
**Scheme 54.**




**Scheme 55.**



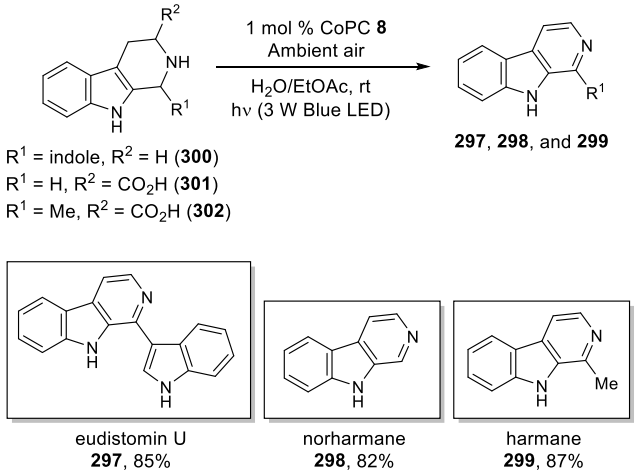

**Scheme 56.**




## 5.3 Oxidative dehydrogenation

Recently, Baskar and coworkers demonstrated the utility of their photoredox-catalyzed oxidative dehydrogenation method in the synthesis of β-carboline natural products such as eudistomin U (**297**), norharmane (**298**) and harmane (**299**).[162] In the case of eudistomin U (**297**), treating tetrahydro-β-carboline **300** with Co phthalocyanine catalyst **8** using ambient air as the oxidant under blue LED irradiation led to selective dehydrogenation, giving the natural product in 85% isolated yield. Analogous treatment of **301** and **302** bearing a carboxylic acid group at the $R^2$ position under their optimized conditions led to decarboxylative dehydrogenation, forming norharmane (**298**) and harmane (**299**) in 82% and 87% yield, respectively.

**Scheme 57.**




## 6. CONCLUDING REMARKS

The efficient synthesis of structurally elaborate organic molecules requires both an effective strategy and the use of powerful bond-forming reactions. Effective strategies reduce the step-count of a synthesis by minimizing steps that do not form bonds of the target structure, and, where possible, constructing several bonds of the target molecule in a single step. The total synthesis of natural products provides an ideal arena to evaluate the practical utility of new chemical transformations as well as their impact in enabling concise synthetic strategies. Apparent in the investigations summarized in this

review is the rapidly expanding impact of photocatalytic reactions on the synthesis of structurally complex natural products. Conclusions we can draw from the developments in this area to date are summarized in the following paragraphs.

The construction of C–C and C–N σ-bonds by free radical reactions has the important advantage that common polar functional groups such as alcohols, thiols, carboxylic acids, and primary and secondary amines, which are often not compatible with bond constructions that employ basic reagents, are typically tolerated in free-radical reactions.[54,55,58,60] Recent advances in visible-light photocatalysis have led to new ways to generate carbon- and nitrogen-centered radicals, both from new and well-established precursors.[59,134] Using visible-light photocatalysis it is now possible to generate carbon radicals directly from common functional groups, avoiding extra steps to introduce "radical-generating" derivatives. Exemplified in total syntheses we have discussed is the direct generation of tertiary-carbon radicals form tertiary alcohols,[87,88] α-amino radicals from α-aminoacids,[95,115] ketones,[99] and tertiary carbamates,[98] as well as nitrogen-centered radicals from secondary aryl sulfonamides[140] and benzamides.[146] In this review, numerous examples are seen of C–C bond formations being achieved, or yields being enhanced, in photocatalytic reactions of carbon radicals compared with the same conversion using conventional conditions for radical generation.[45,46,66,72,85,112,121] Even when yields were comparable, the photocatalytic reactions often avoided the formation of stoichiometric byproducts (e.g., tin residues) and gave reaction mixtures that were easy to purify.[68,71]

Although cyclization reactions of carbon radicals have long played a prominent role in the synthesis of natural products,[55,57,163] bimolecular reactions have not. The realization that structurally elaborate fragments can be united by photoredox-catalyzed bimolecular coupling reactions of carbon radicals is a key feature of many syntheses summarized in this review. Of particular importance for step-efficient convergent synthesis strategies is the ability to unite fragments using equal[87,90,93] or nearly equal[83,99] equivalents of the coupling partners. Also notable is the coupling of sterically bulky tertiary radicals with alkenes (sec 2.2.3) or aromatic heterocycles to generate synthetically challenging quaternary carbon centers.[83,85,87,88,90,92,93,107,161] The experimental ease with which radicals can be generated slowly by light-promoted photocatalysis is likely one reason for these advances.[85] In addition, many of the more complex total syntheses we have reviewed illustrate that fragment-coupling reactions of chiral carbon-based radicals reliably take place from the less-hindered face of the carbon radical, which in some cases can differ from related bond-constructions using organometallic intermediates.[83]

In the arena of cycloadditions, the ability of photocatalysts to promote [2+2]-cycloadditions by either energy transfer, photoxidation, or photoreduction pathways expands significantly the types of substrates that can participate in this foundational method for constructing cyclobutane rings. Synthetic studies reviewed here show that visible-light photocatalysis can promote [2+2]-cycloadditions that fail when high-energy UV light is employed,[26] and allows for various functional groups that would be photoactive under UV irradiation to be present. In addition, the scope of Diels–Alder bond constructions is also broadened, allowing [4+2] cycloadditions that are not successful thermally to be achieved photcatalytically[36] or the unfavored regioisomer of a bimolecular thermal Diels–Alder reaction to be generated in high yield.[34]

It seems assured that the impact of visible-light photocatalysis on the synthesis of structurally elaborate molecules will only increase in the future. Uniting photocatalysis with other diverse catalytic cycles holds enormous potential,[13] beyond the merged organocatalysis[77,78,80] and Ni-catalysis[116] sequences that are exemplified in syntheses reviewed here. Further progress in addressing the long-standing challenge in radical-based bond constructions—controlling enantioselectivity—will certainly continue to emerge.[164-166] One promising approach for controlling enantioselectivity in photoredox reactions involves the use of asymmetric photosensitizers, which has been demonstrated in methods by the Meggers group with bis-cyclometalated rhodium(III) complexes,[167] and recently by Yoon and coworkers with a chiral iridium photosensitizer.[168]

We expect that the development of new carbon-radical precursors[59] and new ways to generate radicals from more prevalent sources[169] will continue to evolve, which will allow for new disconnection approaches in total syntheses involving photocatalyzed reactions. We also anticipate an increased focus on the use of less-expensive earth-abundant transition metal photocatalysts[170] or organic photocatalysts[9,171] in lieu of precious-metal Ru and Ir complexes, in future syntheses, as well as an increased emphasis on performing photochemistry in continuous-flow reactors to improve the scalability of these photoreactions.[172]

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### Notes

The authors declare no competing financial interest.

### Biographies

Spencer P. Pitre obtained his B.Sc. with Honours from the University of Prince Edward Island in 2012, where he performed research under the tutelage of Brian Wagner. In 2012, Spencer joined the group of Juan (Tito) Scaiano at the University of Ottawa as a Ph.D. student. During his doctoral studies, he received a NSERC GGS-D scholarship, and spent time in the lab of Tehshik Yoon at the University of Wisconsin-Madison in 2015 as part of the NSERC Michael Smith Foreign Study program. After graduating in 2017, Spencer joined the lab of Larry Overman at the University of California, Irvine as a NSERC Postdoctoral Fellow. In 2019, Spencer began his independent career at Oklahoma State University in Stillwater, OK in the Department of Chemistry. His research group's interests focus on catalytic EDA photochemistry, cobalt photocatalysis, and the development of catalytic bifunctional materials.

Larry Overman was born in Chicago, Illinois, in 1943 and raised in Hammond, Indiana. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral dissertation in 1969 with Professor Howard W. Whitlock, Jr. at the

University of Wisconsin. After a NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine, in 1971, where he is now Distinguished Professor of Chemistry. Professor Overman's research centers on the invention of new reactions and strategies in organic synthesis, total synthesis of natural products, and medicinal chemistry.

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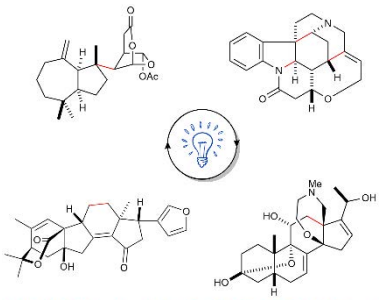

*Visible-Light Photoredox Catalysis Enables Natural Product Synthesis*