



Photochemical reactions as synthetic tool for pharmaceutical industries

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ABSTRACT

In the quest for new agrochemicals and pharmaceuticals, chemists seek access to reliable and mild synthetic techniques to allow for the systematic modification of chemical structures, exploration of unexplored chemical space, and facilitation of practical synthesis in their search for novel agrochemicals and pharmaceuticals. In this regard, photocatalytic reactions enabled the synthesis of intricate and more functionalized compounds. This review overviews the developed synthetic methodologies and their utility in the chemical synthesis of pharmaceuticals. This review also offers in-depth insights into contemporary photoredox reactions such as allylic additions, cyclization, reductive cross-coupling, C–H activation, ring opening, oxidative cross-coupling, dehydrogenation, desulphonation, and decarboxylation. It provides a positive outlook for the promising future of this field.

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1. Introduction

Chemists have been fascinated by the potential of visible light in organic synthesis since its early days [1–4]. It offers a renewable energy source, making photochemistry inherently connected to sustainability. The synthetic potential of photochemistry is equally alluring, unlocking unique reaction pathways not accessible through conventional ground-state reactivity [5–7]. However, until recently, photochemistry faced limitations due to specialized light apparatus and scattered absorption properties of organic molecules. The advent of photoredox catalysis in the past decade has revolutionized photochemical reactions, making them more widely applicable and efficient. These advancements in synthetic chemistry hold promise for industries like pharmaceuticals and agrochemicals, enabling expanded chemical space, improved route efficiency, and safer processes. Embracing novel technologies can simplify synthesis, unlock diverse chemical possibilities, and create novel biologically active compounds [8–14].

The demand for environmental protection and sustainable practices drives the pursuit of green and eco-friendly synthetic strategies for organic transformations. Visible light-promoted photoredox catalysis has emerged as an attractive approach, leveraging visible light as a mild and powerful tool for activating or-

ganic molecules through single-electron transfer (SET) processes [1,15–24]. With renowned researchers contributing seminal studies, visible-light photoredox catalysis continues attracting significant attention and driving innovations in organic chemistry [25–36].

In their excited states, molecular chromophores frequently display advantageous redox characteristics. A charge-separated electron–hole pair, known as an electrically excited state, is created when a photon promotes an electron from the HOMO to LUMO. This excited state can either donate its high-energy electron to a suitable acceptor or accept an electron from a suitable electron donor if it lasts long enough for future intermolecular reactions. As a result of possessing an electron–hole pair, an excited photocatalyst can participate in both oxidative and reductive chemistry, making it a more potent reductant and oxidant than its ground-state counterpart.

Developments in synthetic chemistry have profound implications for both the agrochemical and pharmaceutical industries. They offer the potential to expand the accessible chemical space, improvement in route effectiveness, and facilitate the adoption of cost-effective and safer methodologies [37,38]. While these industries tend to favor classical and powerful transformations, adopting new synthetic methodologies can be slow. Nonetheless, embracing new technologies can lead to more straightforward synthesis, broadening chemical space and enabling the synthesis of pharmaceuticals. The acceptance of such methods is generally guided by

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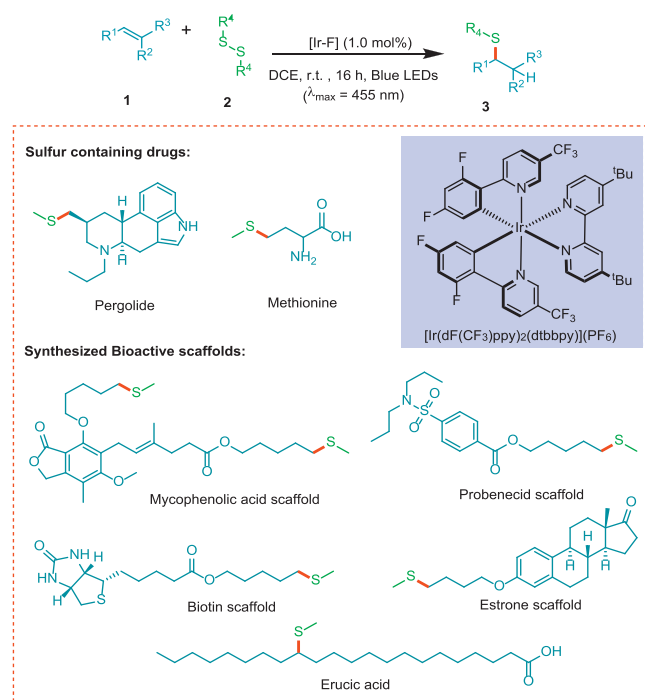
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various criteria, which include the availability of starting materials, catalysts, reagents, specialized equipment, and the overall practical feasibility of the approach [39].

At the heart of this progress is the utilization of light to access reactive intermediates, enabling the development of novel bond-forming protocols not easily achievable under thermal conditions. Photoredox catalysis stands out for its ability to operate under very mild reaction conditions, which making it suitable for late-stage functionalization and more functionalized compounds [40–45]. Moreover, photoredox catalysis grants chemists the opportunity to utilize safer, cost-effective, and environmentally friendly reagents while enabling novel disconnections that can lead to enhanced synthetic routes and the development of valuable intellectual property [46]. The categorization of photochemical reactions into allylic additions, cyclization, reductive cross-coupling, C–H activation, ring opening, oxidative cross-coupling, dehydrogenation, desulphonation, and decarboxylation represents a systematic and comprehensive approach to harness the energy of light-induced transformations for the synthesis of pharmaceutically relevant scaffolds and compounds. This categorization not only reflects the richness and diversity of photochemical methods but also underscores their utility in addressing the intricate challenges of synthesizing biologically active molecules. As a result, this systematic classification provides researchers with a broad and nuanced framework to navigate the complex landscape of photochemical synthesis for pharmaceutical applications. This review covers the five-year overview of the potential photoredox methodologies which have the potential for drug synthesis or late-stage functionalization.

2. Allylic additions reactions

Addition reaction finds its worth in its variety of approaches, e.g., Markovnikov-type radical addition using radical hydrogen [47], conjugate addition (1,2-, 1,4-, and 1,6-) controls stereo and regiochemistry of the product by introducing chiral center [48], cycloaddition (inter-, intra-) [49,50], allylic addition [51] and aldol addition reaction [52]. The addition reaction is one of the most important steps in polymerization, and recently it has been performed in the presence of light and photocatalyst $\text{Ru}(\text{bpy})_3\text{Cl}_2$ [53]. In 2018, Rossolini *et al.* synthesized α -amino- γ -lactam from a photocatalyzed addition reaction between imine and electrophilic olefin moiety [54]. In 2020, Wang *et al.* opted for a nanocage-confined approach to photocatalyzed synthesis of cyclobutane derivatives via cycloaddition reaction [55]. In 2022, Vijayakrishnan *et al.* synthesized ($\pm$)-rolipram drug in the presence of CTF-2 as a photocatalyst for decarboxylative conjugate addition [56]. The methylthioether scaffolds are involved in various metabolic processes and may be found in key pharmaceuticals such as methionine and pergolide because thiol-ene click reaction in the presence of a photocatalyst occurs under mild reaction conditions and is frequently employed in bioconjugate molecules, polymer chemistry, and drug manufacturing [51]. Lately, UV rays have been commonly utilized to generate thiyl radicals [57]. Though, the limited substrate scope, expensive UV irradiation setups, and the creation of massive waste have been limiting considerations [58]. Teders *et al.* proposed a chemoselective anti-Markovnikov hydroalkyl/aryl thiolation of alkenes and alkynes, opening the door for the hydromethylthiolation of disulfides *via* triplet–triplet EnT (Scheme 1) [51]. These are generally partitioned into three classes: alkenes that have been activated undergo *E/Z* isomerization [59], [2+2] photocycloadditions [60,61], and transition metal complex sensitization [62]. Alkenes can be hydromethylated with many functional groups, such as ketones, aldehydes, epoxides, alcohols, nitriles, sulfonamides, amides, heterocycles, and esters. This methodology yields products of 42% to 85%.



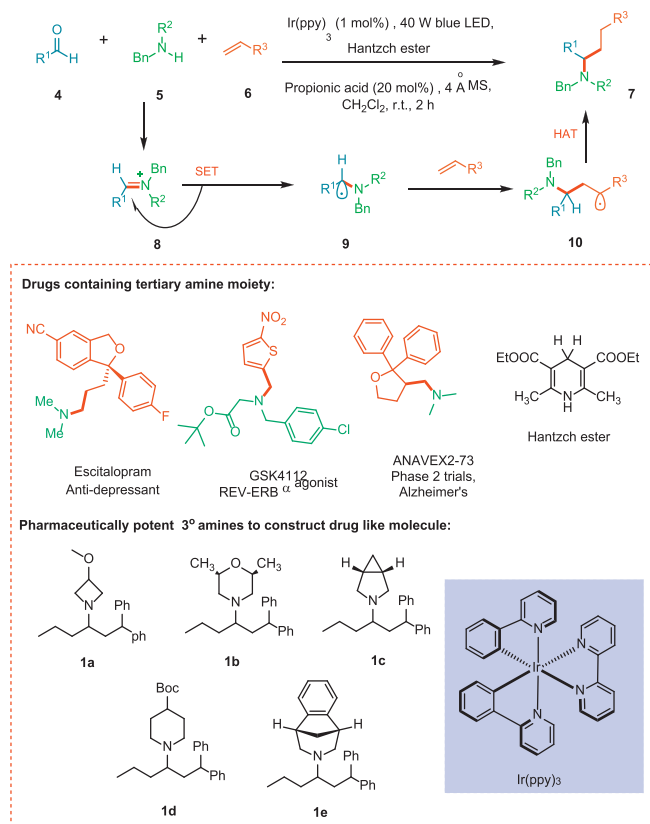
Scheme 1. The hydromethylthiolation of disulfides.

Tertiary aliphatic amines **7** are highly effective pharmaceutical agents due to their physiological properties and ability to disrupt natural neurotransmission pathways [63]. These applications cover various biological treatments, from neuroimpaired diseases [64] to metabolic issues [65]. The Buchwald–Hartwig amination [66] and olefin-hydroamination [67,68] methods have limitations in forming complex alkylamines in the novel transition-metal-catalyzed amine synthesis strategies [69,70]. Trowbridge *et al.* recommended that a photoexcited photocatalyst could simultaneously intervene in SET to synthesize alkylated iminium ion, giving rise to the required α -amino radical under mild conditions. The core of this approach lies in the regioselectivity of the newly synthesized α -amino radical. The iminium ion **8**, is formed by the combination of alkyl-substituted carbonyls **4** and secondary alkylamines **5**, undergoes SET resulting α -amino radical **9**, which reacts with an alkene **6**, forming sp^3 hybridized carbon-carbon bond **10** (Scheme 2) [45].

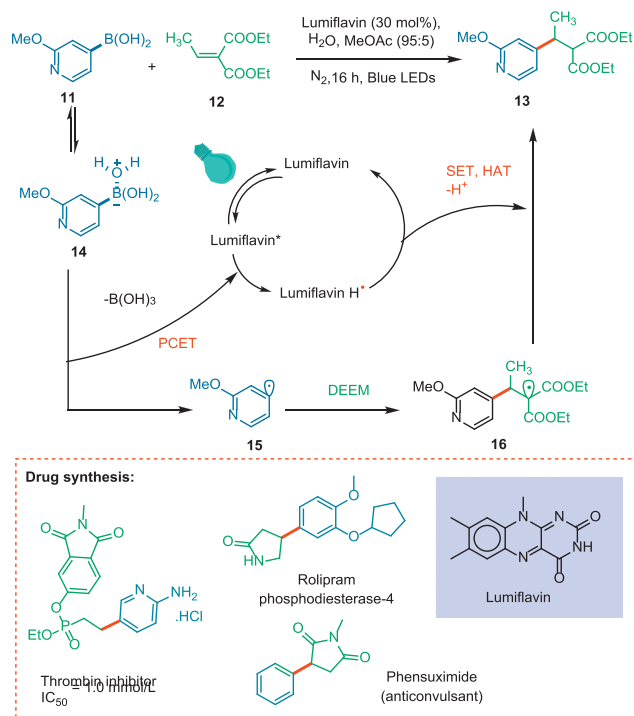
Chilamari *et al.* proposed an aqueous technique that uses a bioinspired flavin photocatalyst to convert a broad range of boronic acids to carbon radicals which are employed to deliver different kinds of alkylated pharmaceutical compounds. Water coordinates with the boronic acid **11**, which results in the aqua-boryl complex **14**. The excited PC lumiflavin removes a proton and an electron from **14**. The fragmentation of the intermediate **14** forms the heteroaryl radical **15**. The former is quickly captured by adding open-shell conjugates to diethyl ethylidene malonate **12** to produce the α -malonyl radical **16**, which is then reduced to produce the required alkylated product **13**, and the photocatalyst is regenerated (Scheme 3) [71].

The oxetane ring is found in several significant natural products and pharmaceuticals, such as taxol (paclitaxel), an antitumor agent [72]. Ravelli *et al.* used decatungstate photocatalysis to achieve $\text{C}(\text{sp}^3)\text{-H}$ activation in oxetanes **17** selectively at a second position under mild conditions. The resultant α -oxy radical **20** is attacked by electrophilic alkene **18** and produces 2-substituted oxetanes **19** (Scheme 4) [73].

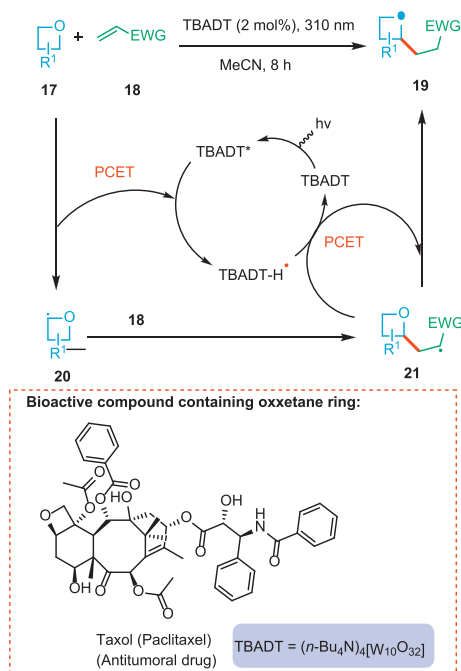
Oh *et al.* reported the photoredox catalysis of vicinal chlorotri-fluoromethylation of alkene. The SET from photoexcited PC



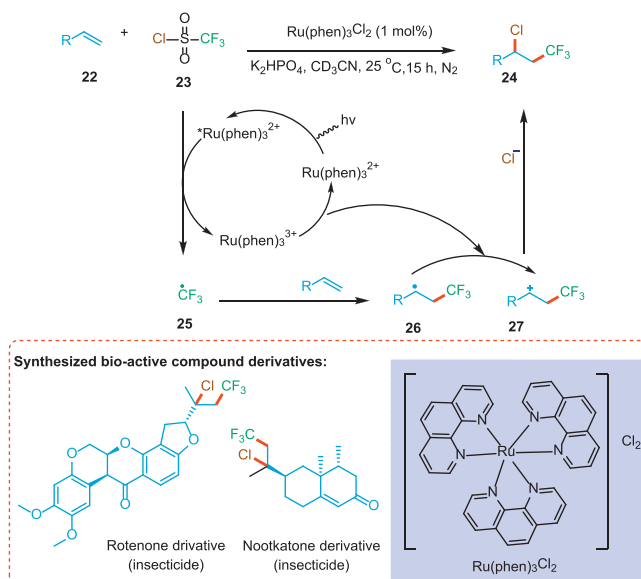
Scheme 2. Synthesis of tertiary aliphatic amines.



Scheme 3. A bioinspired flavin photocatalyst employed in boonic acid conversion to carbon radicals.



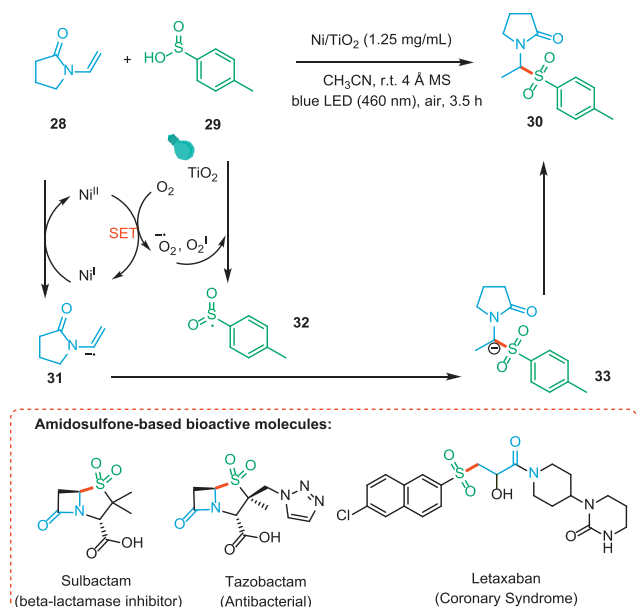
Scheme 4. Oxetane ring activation.



Scheme 5. The photoredox catalysis of vicinal chlorotrifluoromethylation of alkene.

* $\text{Ru(Phen)}_3\text{Cl}_2$ to $\text{CF}_3\text{SO}_2\text{Cl}$ (**23**) forms the CF_3 radical **25**, which reacts with an alkene to form the radical intermediate **26**. The SET from **26** to oxidized PC Ru(Phen)_3^{3+} regenerates ground state PC and creates cationic intermediate **27**, which was captured by Cl^- to form the product **24** (Scheme 5). Numerous terminal and internal alkenes underwent vicinal chlorotrifluoromethylation to produce their derivatives. In order to produce the desired results, biologically active chemicals were used under the conditions [74].

The increased interest in single-atom photocatalysis is evident as it is a significant method of organic transformation, with efficacy influenced by catalyst design. Yang *et al.* reported a visible light mediated approach that uses a single-atom photocatalyst (Ni/TiO_2) to sulfonate enamides producing amidosulfones and β -propionamidosulfones. The singlet oxygen $^1\text{O}_2$ oxidizes *p*-methylbenzenesulfonic acid **29**, generating the sulfone radical and



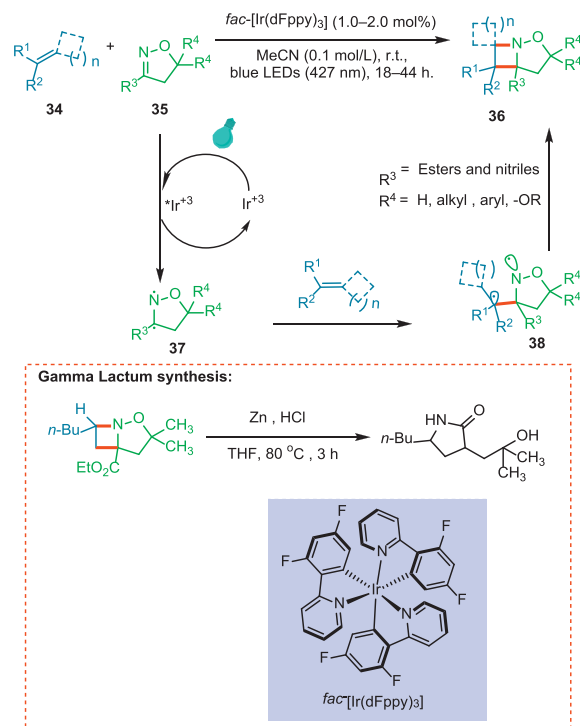
Scheme 6. The synthesis of amidosulfones and β -propionamidosulfones.

molecular oxygen is reduced by remaining photo-generated electrons forming O_2 radical and $^1O_2$. The remaining electrons will be transferred to Ni^{II} to produce Ni^I , which can then be further oxidized by enamide **28** to produce Ni^{II} and radical anion intermediate **31**, which is attacked by a sulfone radical **32** to produce carbanion intermediate **33**. The desired product, α -amidosulfones **30**, can be produced by protonating carbanion intermediate **33** (Scheme 6). This single-atom photocatalysis-based synthesis approach has excellent functional group tolerance, is easily scaled up, and is highly recyclable [75].

3. Cyclization reactions

In 2023, Lu *et al.* synthesized benzo[e]imidazo[1,5-c][1,2,3]oxathiazine 5,5-dioxide derivatives by cyclization reaction using the combination of heterogeneous semiconductor photocatalyst (WSe_2) and homogeneous redox catalyst (ferrocene) [76]. Ji *et al.* proposed a mild photo-induced approach to synthesize naphthoselenazol-2-amines at ambient temperature in the presence of air as an oxidant and water as solvent without employing an exogenous photosensitizer or additive [77].

Four-membered azetidine heterocycles are important scaffolds in drug development [78,79]. Maruoka and coworkers revealed that *N*-aryl sulfonyl imines successfully participate in the [2+2] photocycloaddition reaction, yielding protected azetidines [80]. Unfortunately, this technique is confined to aromatic imines and styrenes because the singlet-state between the reactants is required. Becker *et al.* discovered an intermolecular aza Patern-Büchi reaction initiated by visible light that makes the use of unusually high triplet state energy of oximes, which is easily accessible via photocatalyst of iridium complex, allowing cycloaddition with a wide variety of olefins. Visible light excites the photocatalyst, which transfers energy effectively to **35** to form triplet-state isoxazoline **37**, which undergoes stepwise cycloaddition with alkene **34** to give rise to major diastereomer product biradical intermediate **38**, in which there is a minimal steric hindrance between the alkene moiety and the oxazole moiety **35** backbone (Scheme 7). This method enables the formation of azetidines derivatives, which are highly functionalized, from easily accessible starting materials. It is distinguished by its operational simplicity, mild conditions, and broad substrate scope of olefins which could be formerly

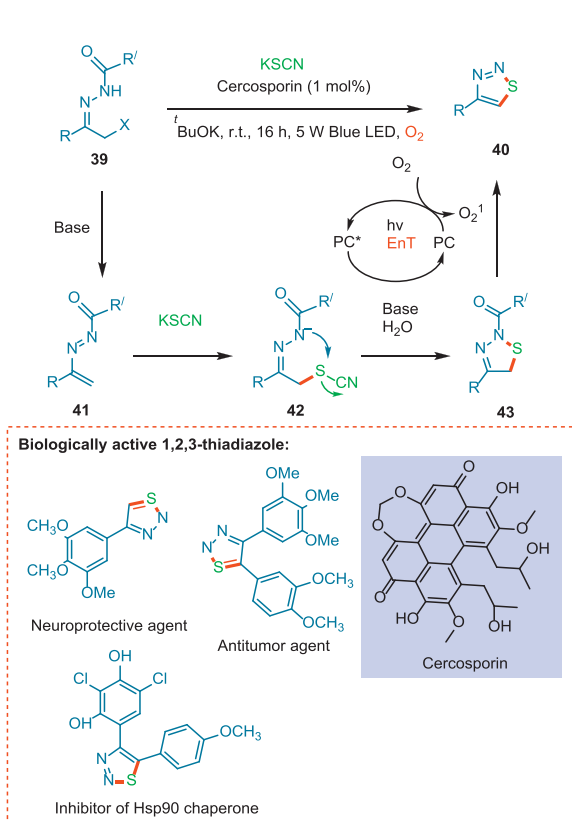


Scheme 7. The intermolecular aza Patern-Büchi reaction of oxime with olefins.

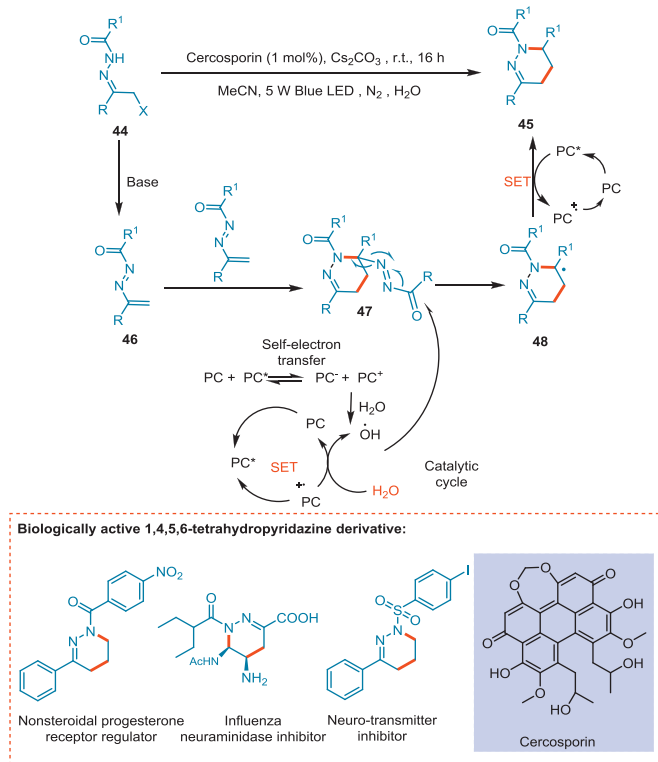
transformed via UV-light only. Additionally, the utilization of isoxazoline carboxylate is advantageous owing to the formation of unprotected azetidines, which used to be challenging to obtain [81].

Traditional organic synthesis methods mainly rely on thermal cycloaddition reactions; hence, novel methodologies for forming *N*-heterocycles under moderate conditions are needed. Zhang *et al.* devised a novel approach for constructing nitrogen-containing heterocycles under mild conditions by employing cercosporin, a perylenequinonoid derivative, as a metal-free, cost-effective, and green photocatalyst. The [4+1] annulation of azoalkenes in the presence of photocatalyst yields 1,2,3-thiadiazoles using thiocyanate salt while photocatalyzed [4+2] cyclodimerization of azoalkenes yields 1,4,5,6-tetrahydropyridazines. Base extracts hydrogen from α -halo hydrazones **39**, releasing the halo group and forming azoalkene **41**. The synthesis of 1,2,3-thiadiazoles starts when azoalkene **41** reacts with thiocyanate forming intermediate **42**, which transforms into *N*-acylated thiadiazole **43** and cyano moiety being hydrolyzed [82,83]. The former is aromatized [84] via $^1O_2$ [85], yielding 1,2,3-thiadiazole **40** (Scheme 8). While the formation of 1,4,5,6-tetrahydropyridazines is initiated when azoalkene **47** gives pyridazine **48** via a radical pathway. The OH radical, which is formed by PC self-electron transfer attacks at carbonyl carbon of **48**, yielding radical intermediate **49**, which via SET followed by protonation, forms the product (1,4,5,6-tetrahydropyridazine) (Scheme 9) [86].

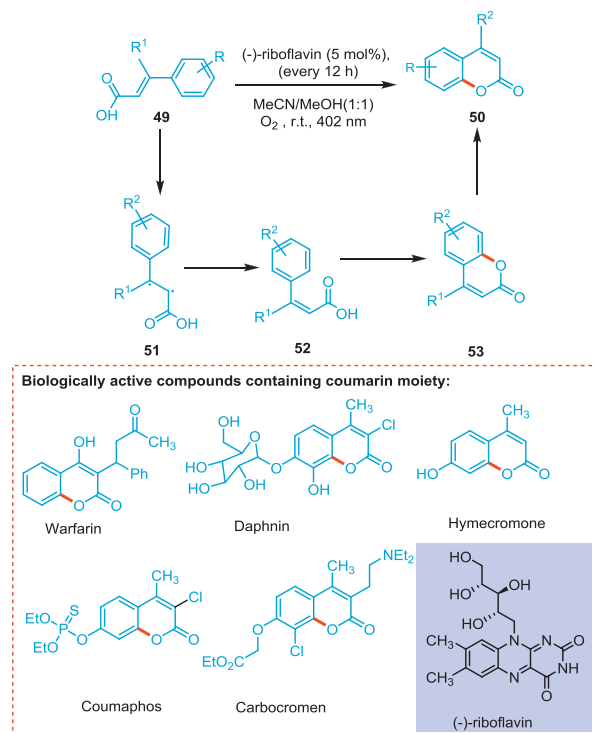
Metternich and Gilmour reported a direct coumarin synthesis from *E*-cinnamic acids. This biomimetic method does not need the aryl ring to be prefunctionalized before cyclization. It is possible to enable isomerization and cyclization consecutively via energy transfer (ET) and SET activation routes of (-)-riboflavin by leveraging the two separate photochemical activation mechanisms. The basic mechanistic idea, that blends ET followed by SET, integrates proven "one catalyst, two reactions" methods. A biradical intermediate **51** converts (*E*)-cinnamic acid **49** to (*Z*)-cinnamic acid **52**. This isomerization arises through photocatalysis. The SET process converts (*Z*)-cinnamic acid **52** to coumarin **50**, and reduced RFH2 is re-



Scheme 8. The cercosporin catalyzed [4+1] annulation of azoalkenes yielding 1,2,3-thiadiazoles.



Scheme 9. The cercosporin catalyzed [4+2] cyclodimerization of azoalkenes yields 1,4,5,6-tetrahydropyridazines.

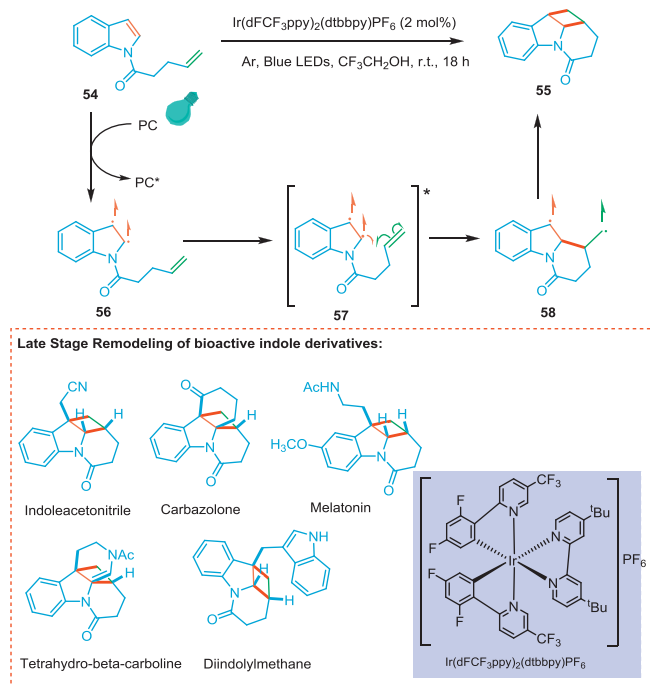
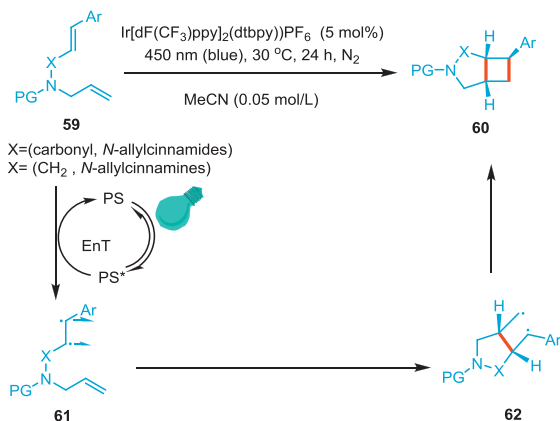


Scheme 10. A direct coumarin synthesis from *E*-cinnamic acids.

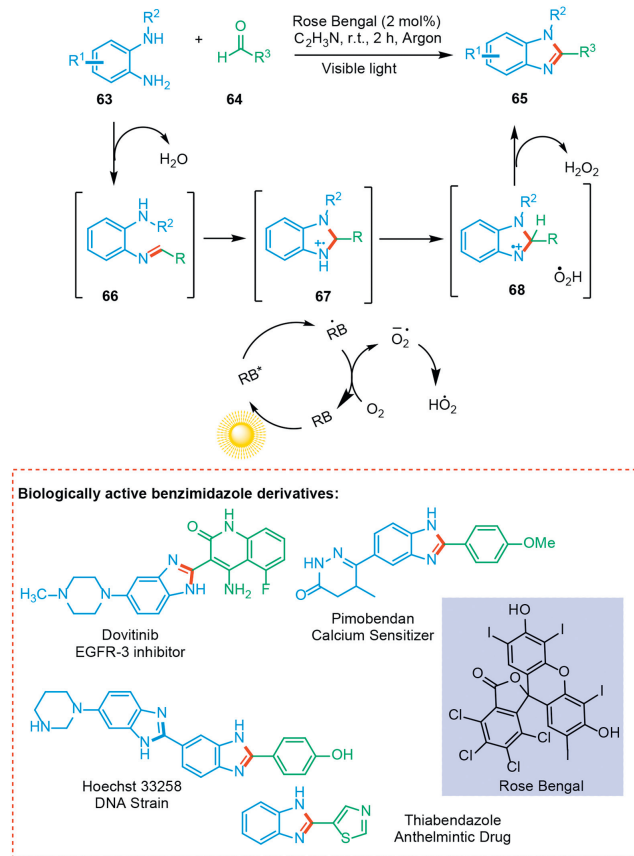
leased, which is oxidized to (-)-riboflavin, completing the catalytic cycle (Scheme 10) [87].

Numerous alkaloid-based natural products and pharmaceuticals contain polycyclic indoline scaffolds, and significant effort has been made in recent years to synthesize them [88,89]. High energies of the excited state favor photoinduced dearomative [2+2] cycloaddition of indole derivatives linked to alkene at the N1 position has been thought to be energetically impractical. Zhang *et al.* explained visible-light favored [2+2] cycloaddition with accompanied dearomatization of indole derivatives linked to olefins at N1 position yielding cyclobutane-fused indoline-based polycycles which have remarkable yields and diastereoselectivities (> 99:1). The indole derivative **54** in the presence of photocatalyst goes converted into biradical **56** via EnT followed by excited triplet state **57** which undergoes intramolecular cyclization between olefin moiety and C2, C3 positions of indole ring forming tricyclic biradical indole derivative **58** with new bridged bond at C2. Radicals combine to form a new bond, and the targeted product **55** is achieved (Scheme 11). The creation of hydrogen bonding between product and solvent decreases the reactant's triplet state energy and significantly increases productivity. Late-stage modification of bioactive indole derivatives serves as an example of the method's application [90].

Oderinde *et al.* put forward that by using photocatalyst (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆, the intramolecular [2+2] cycloaddition of *N*-allylcinnamamides and *N*-allylcinnamamides is possible. The former is converted into aryl-3-azabicyclo[3.2.0]heptanones while the later into aryl-3-azabicyclo[3.2.0]heptanes. The iridium photosensitizer under milder conditions is effective in stimulating this type of reaction owing to its high triplet EnT and diastereoselectivity. This reaction has broad substrate scope, proven to be tolerated in drug development. Energy transfer from PC to *N*-allylcinnamamides and *N*-allylcinnamamides **59** results in a bi-radical triplet state **61**, which undergoes triplet to singlet inversion to form **62** followed by ring-closing to yield corresponding products **60** (Scheme 12) [91].

**Scheme 11.** Synthesis of cyclobutane-fused indoline-based polycycles.**Scheme 12.** The intramolecular [2 + 2] cycloaddition of *N*-allylcinnamamines and *N*-allylcinnamamides.

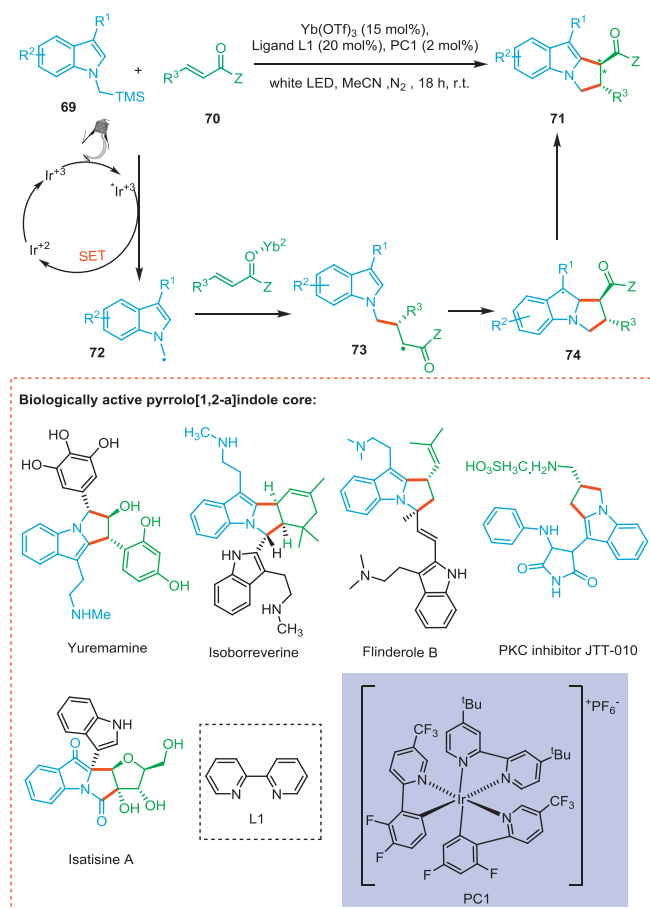
Benzimidazole derivatives exhibit diversified pharmaceutical properties such as antimicrobial [92], anticancer like dovitinib (renal cancer) [93], thiabendazole (anthelmintic activity) [94], pimobendan (vasodilator) [95] and Hoechst stain is used to stain DNA in fluorescence microscopy [96]. Metal-catalyzed condensations need high temperatures, and lingering metal contaminants in the product can result in toxicity in subsequent phases of drug development [97,98]. Kovvuri *et al.* devised a durable, operationally

**Scheme 13.** Synthesis of functionalized benzimidazoles.

easy, and highly generic approach for the photocatalytic condensation of *o*-phenylenediamines and aldehydes in metal-free conditions to produce functionalized benzimidazoles. This method was effective for combining less reactive heterocyclic aldehydes with *o*-phenylenediamines. Unreactive electron-rich aldehydes are useful in this technique. The rose Bengal can be collected and reused thrice during the catalytic process. The imine **66** is generated by the condensation of **63** and **64**. Under visible light irradiation, the excited state of RB can take one electron from imine via a SET. The photo-redox cycle of O₂ oxidizes the RB radical anion back to the ground-state RB. The imine radical cation **67** undergoes HAT resulting in **68**, and hydrogen abstraction by the hydroperoxyl radical results in the formation of product **65** (Scheme 13) [99].

Stephenson's group published the preparation of racemic pyrrolo[1,2-*a*]indoles using Ru(bpy)₃²⁺ as PC [100]. Li described the production of difluoroalkylated pyrrolo[1,2-*a*]indoles employing the *fac*-Ir(ppy)₃ as a PC [101]. All of these photocatalytic reactions produced a racemic mixture. Sánchez *et al.* achieved the asymmetric pyrrolo[1,2-*a*]indoles synthesis in stereoselective fashion through [3 + 2] cycloaddition between indole derivatives **69** and α,β -unsaturated derivatives **70** employing a dual catalytic combination as an Ir^{III} photocatalyst and lewis acid. The former **69** is used to form the α -amino radical **72**, which reacts with α,β -unsaturated derivative **70** to form a radical intermediate **73**. The homolytic breakage of the carbon-carbon pi bond is followed by a radical combination to form a tricyclic radical intermediate **74**, which undergoes HAT to form the targeted product **71** (Scheme 14). Pyrrolo[1,2-*a*]indole is an important scaffold in drug synthesis [102]. Among them, JTT-010 is an important protein kinase C (PKC) inhibitor [103].

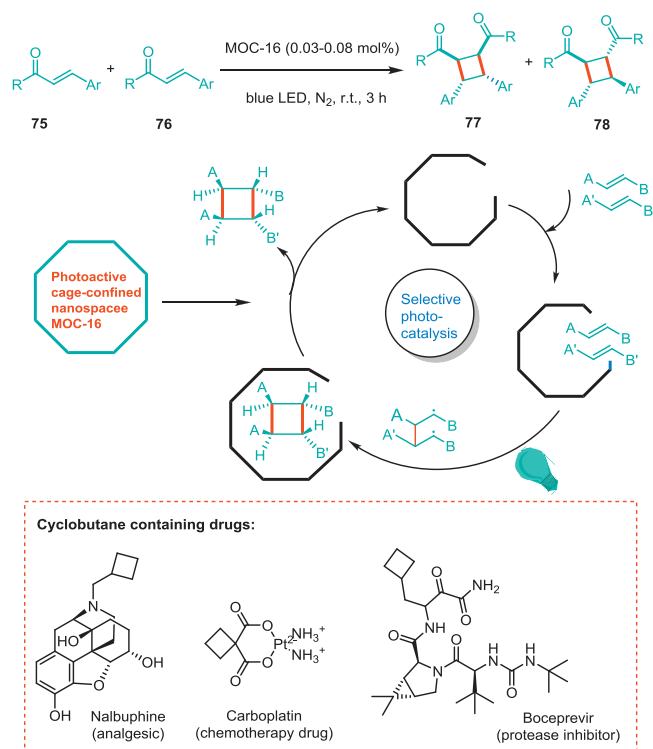
Natural products and bioactive molecules frequently contain cyclobutane scaffolds [104,105], dramatically sparking synthetic in-



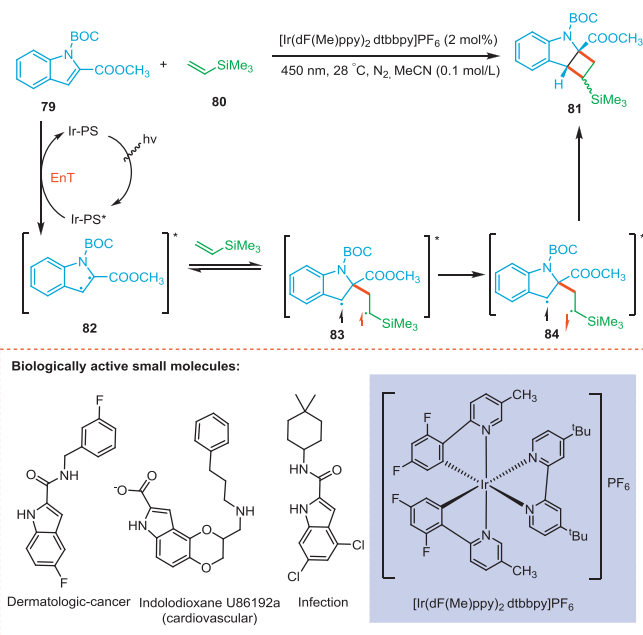
Scheme 14. The asymmetric pyrrolo[1,2-a]indoles synthesis.

terest in building four-membered carbocycles [106,107]. Considering photoinduced [2 + 2] cycloaddition of acyclic enones and cinnamates, Wang *et al.* devised a practical synthesis process with remarkable selectivity based on the correct design and photoactive cage nano space in a single MOC supramolecular reactor. The cage-confined catalysis makes the homo- and hetero-coupling photoreaction possible, yielding *syn*-HH cyclobutanes **77** (Scheme 15). A relatively low photocatalyst loading makes broad substrate scope possible. The supramolecular cage regulates selectivity, concentrates the reaction mixture, speeds up reaction time, encourages EnT, and recycles catalytic operation [55].

Indole and its bioisosteres are present in drugs approved by the FDA, such as azaindoles, indazole, benzofuran, and benzothio-phenone [108,109]. Ikeda and colleagues investigated the [2 + 2] cycloaddition between *N*-benzoylindole and alkenes using UV light [50]. Inevitably, the intermolecular cycloaddition was unsuccessful due to high-intensity UV light, the need for alkene in greater amounts, the limited substrate scope, and undesired homodimerization side-products. Oderinde *et al.* argued that by studying the relationship between structure and reactivity, *N*-protected indole-2-carboxyesters and carboxamides could discover those indole derivatives that may undergo [2 + 2] cycloaddition reaction with alkenes derivatives. Oderinde *et al.* developed a visible-light photocatalytic system for the formation of cyclobutane-fused frameworks through dearomatizing, intermolecular [2 + 2] cycloaddition of indoles and azaindoles with a variety of substituted alkenes, including unactivated alkenes. A triplet-triplet EnT via photocatalyst-photosensitizer (Ir-PS) to *N*-protected indole-2-carboxyesters **79** initiates the reaction, yielding biradical intermediate (**82**), which combines with **80** to yield triplet state biradical intermediate **83**.



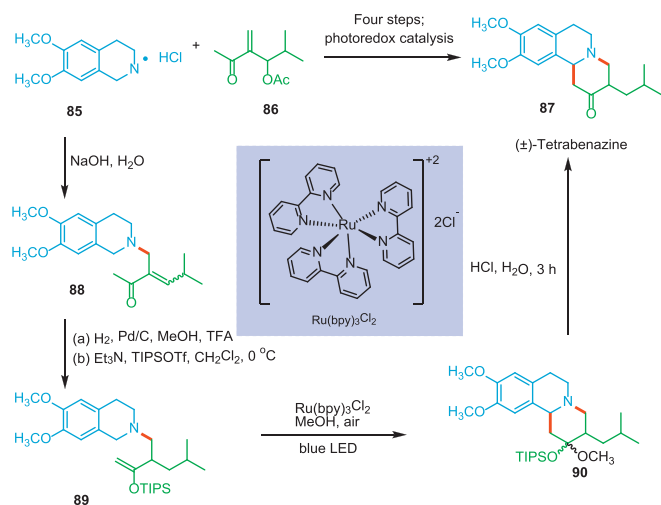
Scheme 15. The synthesis of cyclobutane scaffolds.



Scheme 16. Visible-light photocatalyzed formation of cyclobutane-fused frameworks.

The triplet to singlet inversion results in **84** which undergoes ring closure to obtain **81** (Scheme 16). This reaction approach has broad alkene scope giving a high yield. The conversion is highly regio- and diastereoselective [110].

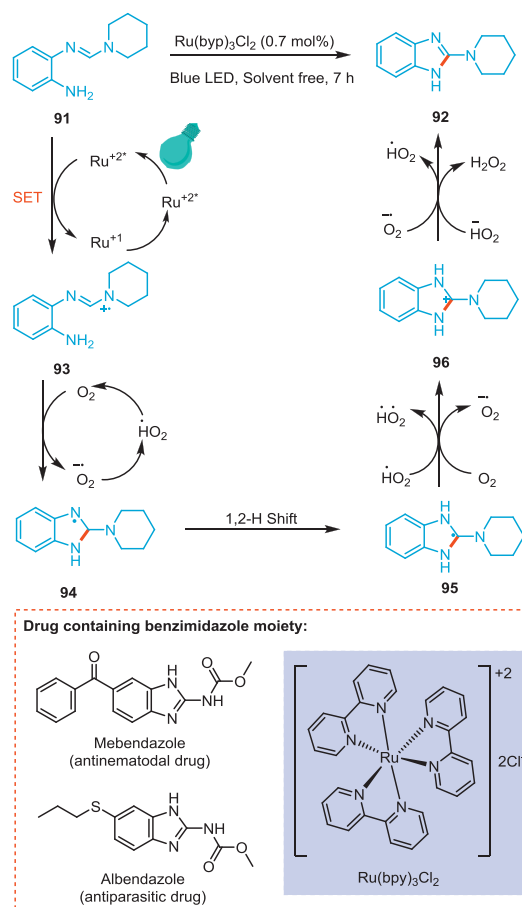
Orgren *et al.* synthesized ($\pm$)-tetrabenazine from readily accessible chemicals in six stages. The cyclization substrate was quickly built using Baylis-Hillman and aza-Michael processes. Photocatalysis results in new ring formation in the presence of visible light, with C-C bond-making via tertiary amine oxidation. The nature of the solvent is crucial in the photoredox cyclization; methanol



Scheme 17. Synthesis of (±)-tetrabenazine.

results in a mixed ketal, while acetonitrile/water results in direct and faster cyclization. When hydrolyzed with NaOH, tetrahydroisoquinoline salt **85** and methyl vinyl ketone **86** facilitate rapid conjugate addition, which is followed by rapid β -elimination of acetate, yielding enone **88**. The alkene in enone **88** was selectively reduced to get TIPS enol ether **89** followed by photoredox cyclization with a blue LED and $\text{Ru}(\text{bpy})_3\text{Cl}_2$ catalyst to obtain **90**, which was subsequently on acidic hydrolysis to yield (±)-tetrabenazine **87** (Scheme 17) [111]. Tetrabenazine has antipsychotic properties [112].

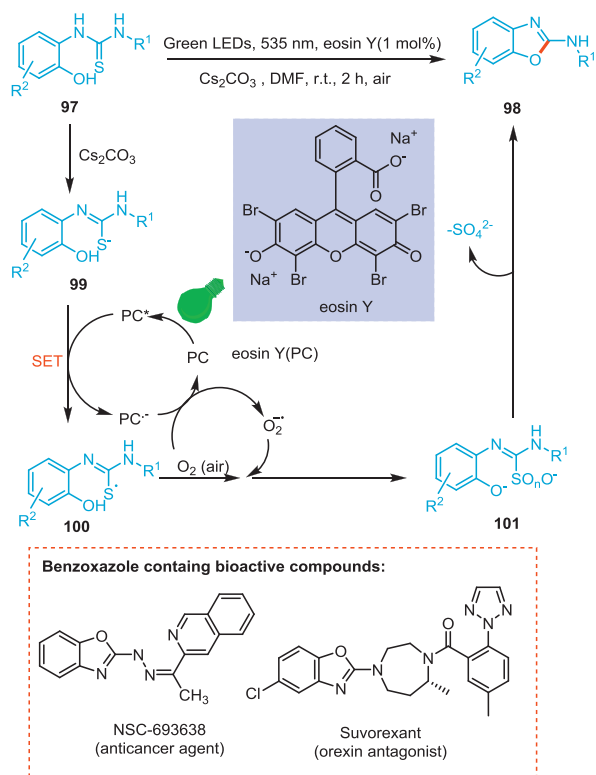
Photocatalytic reactions involve radical chemistry. Radical cyclization is a powerful tool to synthesize products under stereo- and regioselective control. This kind of reaction usually exhibits broad substrate scope and requires milder reaction conditions to build monocyclic and polycyclic complex structures. Cyclization is an intramolecular step involving the addition of radicals to the unsaturated system and trapping the resultant radical *via* SET [113]. In 2016, Liu *et al.* synthesized a ring by forming new carbon-carbon bonds in a strained ring system which was earlier difficult to construct. In this strategy, affordable TiO_2 was used as a photocatalyst, O_2 as an oxidant, and solar light as a light source [114]. In 2019, Li *et al.* developed a metal and oxidant-free strategy to synthesize cyclization product benzimidazole derivatives using organic dye as a photocatalyst, *e.g.*, fluorescein, and blue LED as a light source [115]. In 2021, Zhuang *et al.* synthesized γ -lactam derivatives *via* the HAT/SAT photocatalytic approach through the intramolecular radical cyclization pathway [116]. A key motif in medicinal chemistry, benzimidazole is found in many therapeutic agents [117], including albendazole (antiparasitic), mebendazole (antinematodal) [118] anticonvulsant [119], antimicrobial [120], anti-HIV [121], anti-inflammatory [122], and anticancer [123]. Siddiqui *et al.* reported a simple and effective strategy for synthesizing the benzimidazole amine hybrid. It involves the interaction of benzimidazole with amine, which can be either cyclic or acyclic, in the presence of photocatalyst $\text{Ru}(\text{bpy})_3\text{Cl}_2$ without using solvent. The oxidation of *o*-aniline amidines **91** *via* SET to excited PC ($^*\text{Ru}^{2+}$) results in a radical cation species **93**. The HAT from **93** to oxygen radical anion followed by intramolecular hetero-cyclization yields aminyl radical **94**. The 1,2-H shift of **94** forms radical intermediate **95**, which on oxidation produces the corresponding carbocation intermediate **96** and lastly aromatization *via* deprotonation forming product **92** (Scheme 18). Additionally, the acyclic amines react faster and give the desired product. This approach is an effective replacement for previously described methodologies due to its quick reaction times,

Scheme 18. Synthesis of γ -lactam derivatives.

outstanding yields, and, most significantly, natural energy source (visible light). This solvent-free approach is aligned with the aim of organic synthesis for generating greener organic reactions due to environmental and energy concerns [124].

The 2-aminobenzoxazoles are desirable synthetic scaffolds for pharmaceuticals treating inflammatory disorders, HIV, neurodegenerative diseases, insomnia, and cancer [125–127]. Yadav *et al.* reported an effective one-pot procedure for cyclodesulfurization of *o*-phenolic thioureas to produce 2-aminobenzoxazole derivatives in the presence of light. The base Cs_2CO_3 abstracts thiolic H from phenolic thioureas **97** to create a more oxidizable sulfur anion **99**. Eosin Y (PC) transitions to its excited state (PC^*) on absorbing light. The sulfur radical **100** and PC radical anion are produced through a SET between sulfur anion **99** and PC^* . The sulfur radical **100** and O_2 radical interact to generate an intermediate **101**. The targeted products **98** are produced by cyclizing **101** (Scheme 19). The methodology provides a better alternative to the current approaches for the cyclodesulfurization of phenolic thioureas and is carried out as light-mediated process using organo-photocatalyst eosin Y. This strategy makes use of visible light and greener oxidant (air), which is one of the critical characteristics of the current metal-free technique [128].

The 1,5-dihydro-2H-pyrrol-2-one is a significant moiety in unsaturated conjugated lactam derivatives present in various pharmaceuticals and drugs. Compounds containing 1,5-dihydro-2H-pyrrol-2-one show cytotoxic (antiradical) activity [129]. Ye *et al.* revealed an unusual photoinduced chain pathway for *N*-allylbromodifluoroacetamide cyclization/defluorination with cyclic secondary amines. Consequently, a diverse range of valuable 3-fluoro-1,5-dihydro-2H-pyrrol-2-ones were synthesized

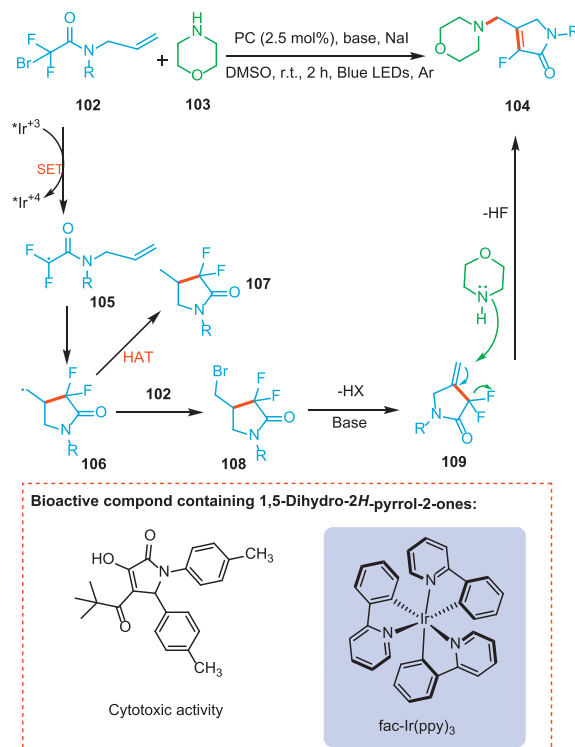


Scheme 19. Cyclodesulfurization of *o*-phenolic thioureas.

under mild conditions using easily accessible precursors. A SET from *N*-allylbromodifluoroacetamide **102** to PC* yields *N*-allylbromodifluoroacetamide radical **105**, which undergoes 5-*exo-trig* cyclization to generate **106**, which reacts with **102** and yields **109** after proton abstraction by a base. The addition of cyclic amine **103** followed by defluorination from **109** yields the targeted product **104** (Scheme 20) [130].

Zhou *et al.* reported the synthesis of C3/C5-substituted selenomorpholines and 1,4-selenazepanes under mild photocatalytic conditions from various aldehydes by using SLAP reagents containing selenium atoms (Scheme 21). Enantiomerically pure forms as 1,2-amino alcohol and α -amino acid of heterocycles were also prepared. This developed strategy has also modified biologically active molecules in the late stages. Chrysin having selenium embedded in the structure exhibits improved selectivity against cancerous cells compared to its derivatives having O or S. They also exhibit significantly increased anticancer action on nine distinct malignant cell lines. In another case, selenomorpholine derivatives of acenaphtho[1,2-*b*]pyrroles showed an improved antitumor effect [131].

According to Russo *et al.* 1,3,4-oxadiazole derivative can be synthesized by using a photocatalytic MCR approach utilizing *N*-alkyl-*N*-methylanilines, *N*-isocyanoimino triphenylphosphorane, and carboxylic acids in the presence of visible light. As further evidenced by the late-stage derivatization of pharmaceutical products, this reaction utilizes an extensive substrate range under milder reaction conditions. A two-step one-pot methodology is also published for producing non-symmetrical diacylhydrazines. The *N,N*-dimethylanilines **113** via an excited ruthenium photocatalyst is converted into the corresponding iminium ion **117**, which reacts with isocyanoimino triphenylphosphorane **114** to form a cationic intermediate **118** followed by the reaction with carboxylic acid **115** to form **119** that undergoes intramolecular cyclization resulting in **120**. The OPPh₃ leaves from 1,3,4-oxadiazole derivatives **116** (Scheme 22). It is worth noticing that the result of the reaction is

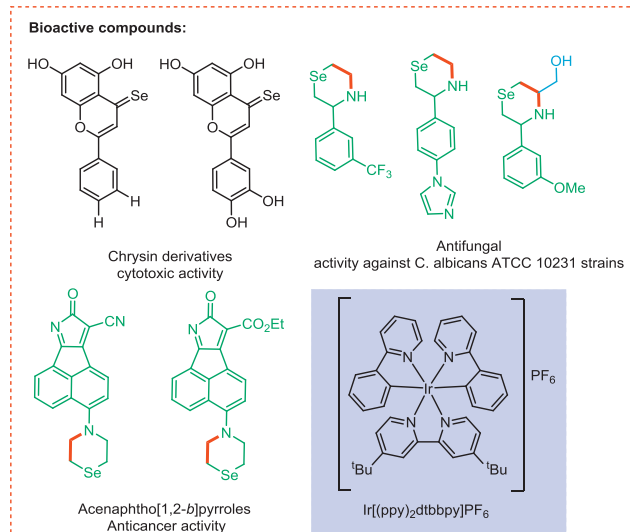
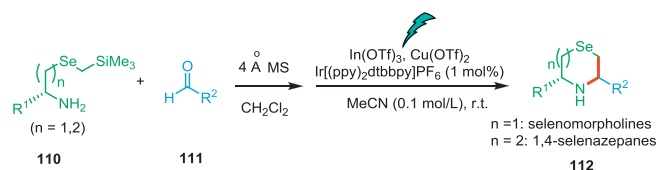


Scheme 20. *N*-Allylbromodifluoroacetamide cyclization/defluorination with cyclic secondary amines.

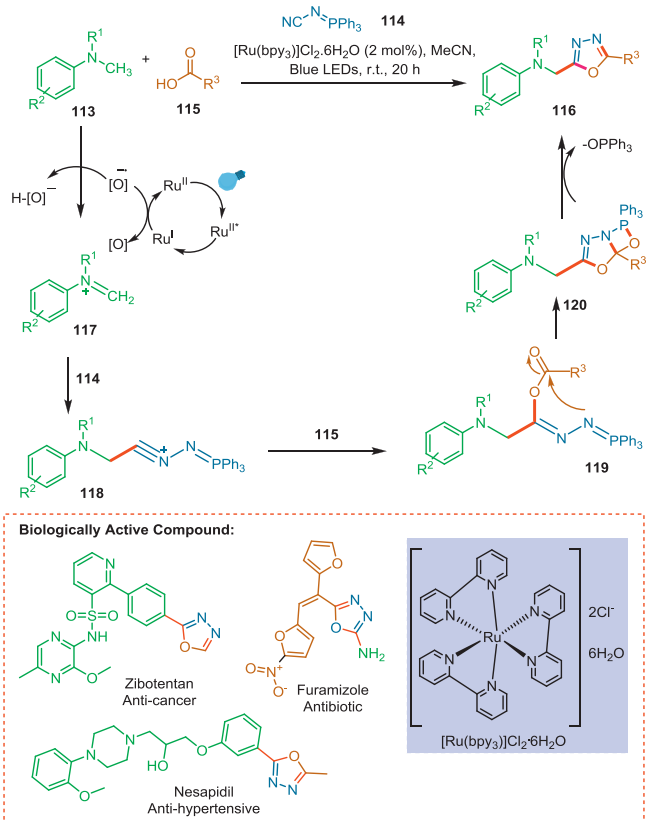
the formation of three new bonds that is carbon-carbon, carbon-oxygen, and carbon-nitrogen while only losing an equivalent hydrogen atom and one of P(OPh)₃, which shows a high atom economy [132]. This novel synthetic method demonstrates the fusion of multicomponent reactions with photoredox catalysis, effectively expanding the chemical space that can be accessed through efficient and cost-effective means [133].

Quinoline has been recognized as an exclusive scaffold due to its promising biological activities proven by approved drugs such as pitavastatin, cinchophen, camptothecin, and quinine [134]. Xu *et al.* reported the synthesis of quinolines by cyclizing secondary alcohol into 2-aminobenzyl alcohols at room temperature in the presence of light and an organic photocatalyst. This photochemical method eliminated the need for extreme thermal conditions and complex metal-based catalysts by using DMSO and easily accessible AQ as PC. The excited photocatalyst AQ* extracts an H-atom from **121** or **122** via HAT resulting **121a** or **122a** radicals, followed by another HAT to produce 2-aminobenzaldehyde **121b** or acetophenone **122b**. The DMSO oxidizes protonated AQ to AQ. Finally, **121b** and **122b** undergo condensation to form the targeted product **123** (Scheme 23) [135].

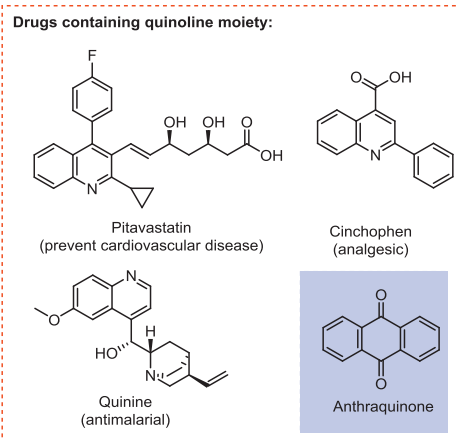
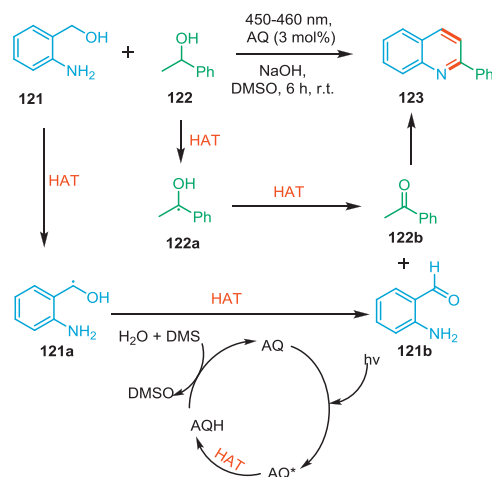
Ma *et al.* developed a regioselective intermolecular [2 + 2] photocycloaddition/ring expansion that makes use of indoles, Gd³⁺ photocatalyzed, and may allow divergent approach to both cyclopenta[*b*]indoles **127** and indolines **126**. The easily accessible Gd(OTf)₃ salt works best for this visible violet light-mediated transition. The bidentate coordination of **124** to photoexcited PC* forms an excited state **128**, which then undergoes [2 + 2] cycloaddition with alkene **125** forming biradical intermediate **129** followed by cyclobutane formation **130** and cyclobutane-expansion cascade [136]. The former **130** expands to a cyclopentane **131**. Now, the reaction pathway splits into two. The 1,3-H transfer from **131** and pyrazole elimination from (**132**) provide the targeted product **127** via route I. The indole substrate **133** is converted into the product **126** via pyrazole migration (route II) (Scheme 24) [24].



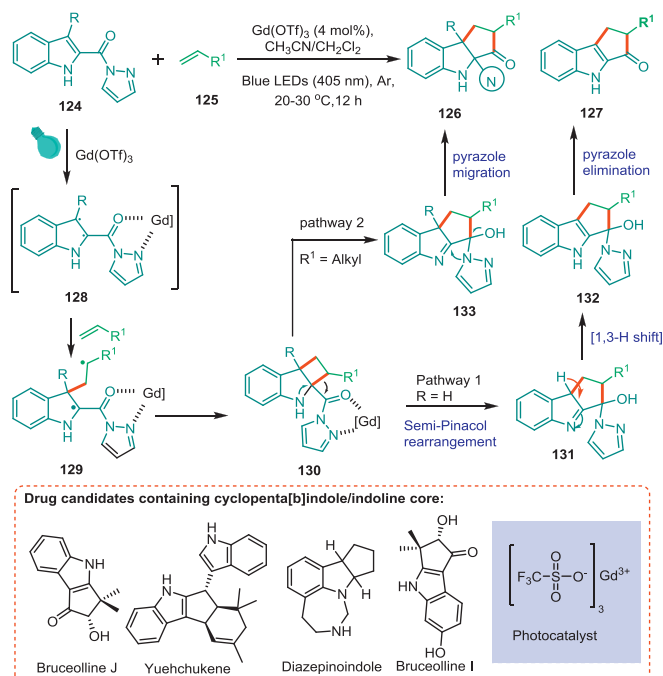
Scheme 21. The synthesis of C3/C5-substituted selenomorpholines and 1,4-selenazepanes.



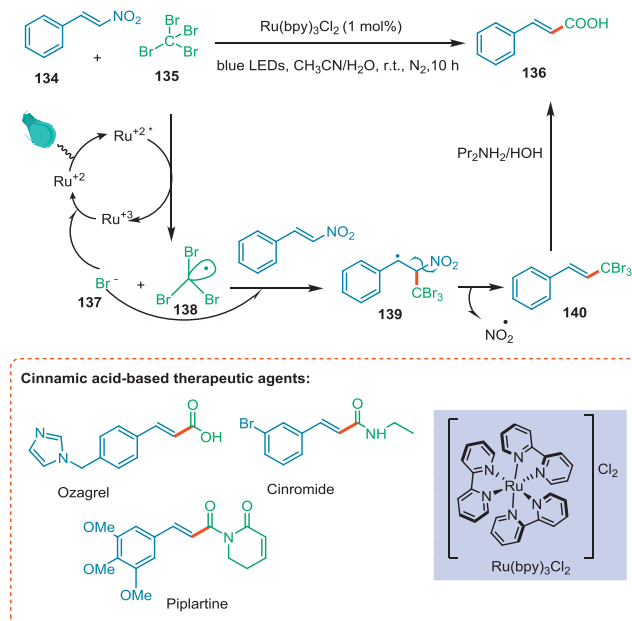
Scheme 22. Synthesis of 1,3,4-oxadiazole derivative by photocatalytic MCR approach.



Scheme 23. Synthesis of quinolines.



Scheme 24. A regioselective intermolecular [2 + 2] photocycloaddition/ring expansion.



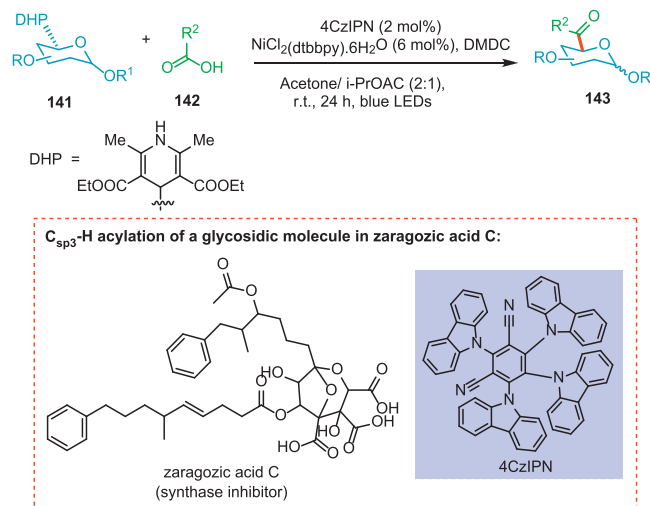
Scheme 25. Ru(bpy)₃Cl₂ catalyzed stereoselective synthesis of (*E*)-cinnamic acids.

4. Reductive cross-coupling

Reductive cross-coupling is simply a new bond formation between two electrophilic centers selectively carbon-carbon bond is formed. That is why also known as electrophile coupling. Metals typically employed are Ni, Pd, Fe, Co, *etc.*, while reductants are Mn, Zn, Mg, *etc.* [137]. Selectivity in reductive cross-coupling is more challenging than the orthodox cross-coupling method, which utilizes the reactivity aptitude between nucleophiles and electrophiles. Reactivity is favored via a radical pathway [138]. In 2019, Xia *et al.* used a photocatalytic reductive coupling approach following the radicals combination to form a new C–C bond and synthesize difluorinated 3-pyrazolidinone [139]. In 2022, Tian *et al.* performed photocatalytic water splitting to use it as an electron donor for reductive coupling in green organic synthesis [140].

Although cinnamic acids have been synthesized using several techniques, each has its complexities, such as reduced efficiency, extended reaction times, decreased catalytic capacity, lower yield, and limited substrate scope. Tripathi and Yadav used visible light photoredox catalysis to create a new, highly stereoselective synthesis of (*E*)-cinnamic acids **136** from β -nitrostyrene **134** and CBr₄ (**135**). Photoexcited photocatalyst converts **135** into CBr₃ radicals **138** and **137**. The former **138** is trapped by **134** and generates a stable radical **139**, which undergoes denitration forming **140** accompanied by hydrolysis yields **136** (Scheme 25). The (*E*)- β -nitrostyrenes have broad substrate scope and yield good products, especially when installed in electron-releasing groups. This approach is not favorable for aliphatic nitroalkanes. No product is formed by employing CCl₄. Tripathi and Yadav conducted the reaction with eosin Y, but it was not proved as efficient as Ru(bpy)₃Cl₂ [141].

Various strategies have been developed to put acyl groups at the anomeric carbon in glycosides, but those methods use severe conditions and reactive organometallic chemicals. Natural products with glycosidic attachment have improved biological tissue solubility, membrane transport, and specificity [142]. These compounds are abundant and contribute as essential structures to a wide range of anticancer, antibiotic, and type-II antidiabetic drugs [143]. C-Acyl glycosides have been shown to suppress reactive oxygen species, play an essential function in cell signaling, and cause glutamate-



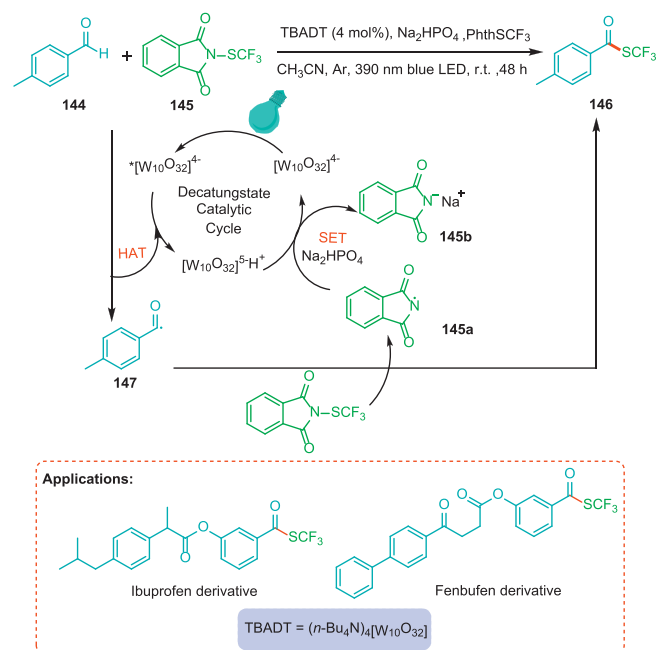
Scheme 26. Ni/photoredox dual catalysis to create non-anomeric C-acyl glycosides.

induced cell death [144,145]. The photochemical C(sp³)-H acylation of a glycosidic molecule is used to manufacture zaragozic acid C (synthase inhibitor) [19]. Badir *et al.* used Ni/photoredox dual catalysis to create non-anomeric C acyl glycosides (Scheme 26). The retention of anomeric carbon as a tool for subsequent late-stage functionalization is critical for transition. This process has a wide range of functional group tolerance and is simple to operate. The synthesis of zaragozic acid C is founded on a photochemical C(sp³)-H acylation approach of a glycosidic moiety [146]. A variety of glycosyl-based radicals are produced by an organic photocatalyst and cross-coupled with activated carboxylic acids to produce molecules with potential therapeutic use [147].

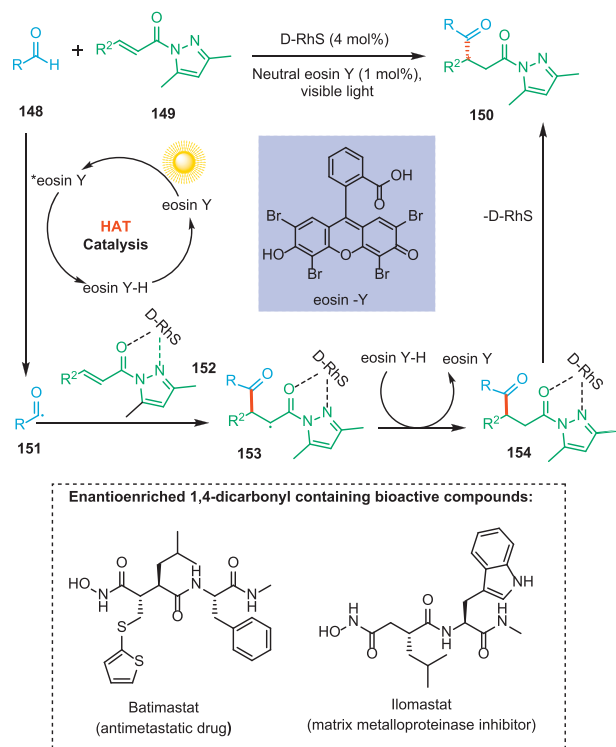
Wang *et al.* reported trifluoromethylthiolation of aldehydes under redox-neutral conditions using a decatungstate HAT photocatalyst. The procedure is highly selective, easy to perform, and has good functional group tolerance. The TBADT is used as a HAT photocatalyst in this approach to effectively synthesize trifluoromethylthioesters via direct functionalization processes of aldehydic C(O)-H bonds. The HAT occurs from **144** to photoexcited photocatalyst, forming reduced PC and nucleophilic formyl radical **147**, which rapidly reacts with the electrophilic reactant **145** to yield the targeted product **146** upon the removal of a Phth-radical **145a**, which is reduced to **145b** by employing base (Na₂HPO₄) and reduced PC with concurrent regeneration of ground state PC (Scheme 27). It is useful for late-stage derivitization of pharmaceutical scaffolds, making this a valuable approach in drug synthesis [148].

Enantioenriched 1,4-dicarbonyl compounds are structural motifs in ilomastat, batimastat, and (-)-burshehem and are useful building blocks in pharmaceutical drug production [149]. Kuang *et al.* developed a moderate approach that uses a combination of chiral rhodium catalyst and neutral eosin Y (HAT photocatalyst) to produce 1,4-dicarbonyl compounds straight from aldehydes efficiently. The photoexcited photocatalyst takes up hydrogen atom from aldehyde **148**, forming reduced PC–H and radical of aldehyde **151**, which reacts with rhodium-activated 1,4-dicarbonyl derivative **152** creating radical intermediate **153**. The HAT from reduced PC–H to **153** results in the formation of rhodium coordinated compound **154** followed by the removal of the rhodium catalyst yielding the targeted product **150** (Scheme 28). This process stands out for its ease of operation, atom economy, high yields (up to 99%), as well as the enantioselectivity (up to 99% ee) of the produced products [150].

Li *et al.* proposed that at ambient temperature, a photocatalyzed multicomponent triple defluorinative functionalization of

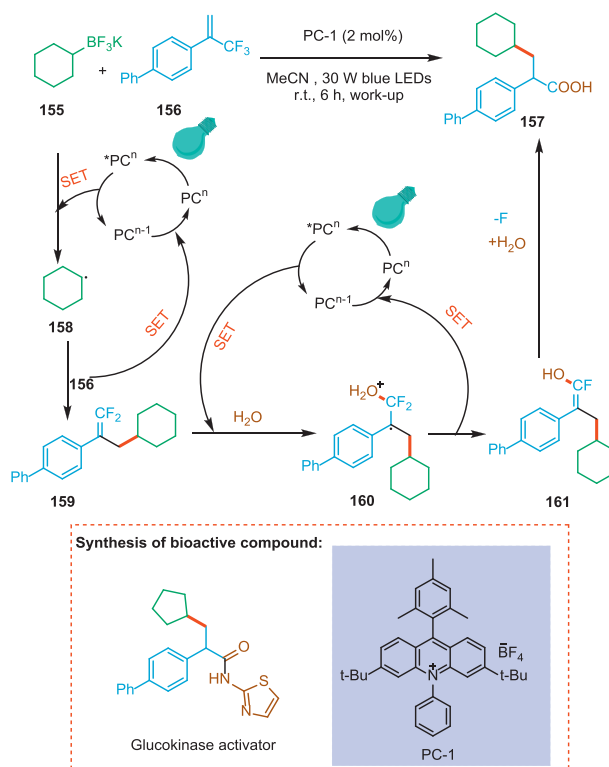


Scheme 27. Decatungstate catalyzed trifluoromethylthiolation of aldehydes under redox-neutral conditions.



Scheme 28. Dual catalysis approach synthesizing 1,4-dicarbonyl compounds straight from aldehydes.

α -trifluoromethyl alkenes yields an array of α -arylated carboxylic acids, primary, secondary, and tertiary amides [151]. The photoexcited photocatalyst $^*\text{PC}^n$ undergoes SET with **155** producing radical intermediate **158** and PC^{n-1} [152,153]. The former **158** combines with radical species **156** to form benzylic radical **160**. The first catalytic cycle completed by SET from PC^{n-1} to **160**, yields *gem*-difluoroalkenes **161** (Scheme 29) [154]. The third C-F bond is cleaved by the second β -fluoride elimination and acyl substitution



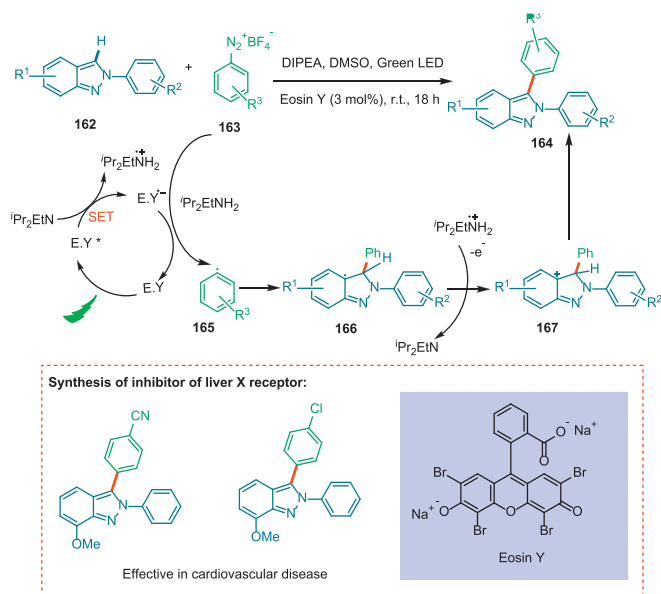
Scheme 29. Photocatalyzed multicomponent triple defluorinative functionalization of α -trifluoromethyl alkenes.

with oxygen nucleophile [151]. The PC-1 and H_2O were needed to carry out this reaction, and the yield was lowered as the work-up was not done. The reaction involves three separate C-F bond cleavages, allowing the conversion of methyltrifluorides into synthetically useful functional groups. The trifluoromethyl alkenes are coupled with alkyltrifluoroborates, water, and amines to produce α -arylated carboxylic acids and amides. As a result, these key motifs can now be constructed from basic and readily available starting materials [151].

5. C-H activation

LSF has its mark in drug and natural product synthesis exploring new drug analogues. In late-stage functionalization (LSF), both participating reactants' radicals combine forming new bonds like carbon-carbon, carbon-nitrogen, carbon-oxygen, etc. One moiety having a C-H bond undergoes homolytic cleavage via SET/HAT generating carbon radical [155]. Sustainability [156], high step-economy [157], no need for prefunctionalization, and new disconnection approach [157] make C-H functionalization even more significant. In 2019, Vidyacharan *et al.* synthesized a liver X-receptor inhibitor drug by C-H functionalizing indazoles with an aryl group at C-2, employing eosin Y as a photocatalyst [159]. In 2021, Hou *et al.* formulated a metal and oxidant-free photocatalytic approach to acylate pyridine *N*-oxide at C-2 and applied this strategy to acrivastine synthesis, an important drug intermediate [160]. In 2023, external photocatalyst-free C-H activation has been reported [161,162].

In the pharmaceutical industry, indazoles offer a broad spectrum of bioactivity [163], including antimicrobial [164], anti-inflammatory [165], HIV protease inhibition [166], and anticancer agents [167]. Indazole is a basic scaffold in commercially relevant medicinal products such as MK-4827 and pazopanib [168]. Most of the cases of Negishi cross-coupling [169] and arylation by aryl

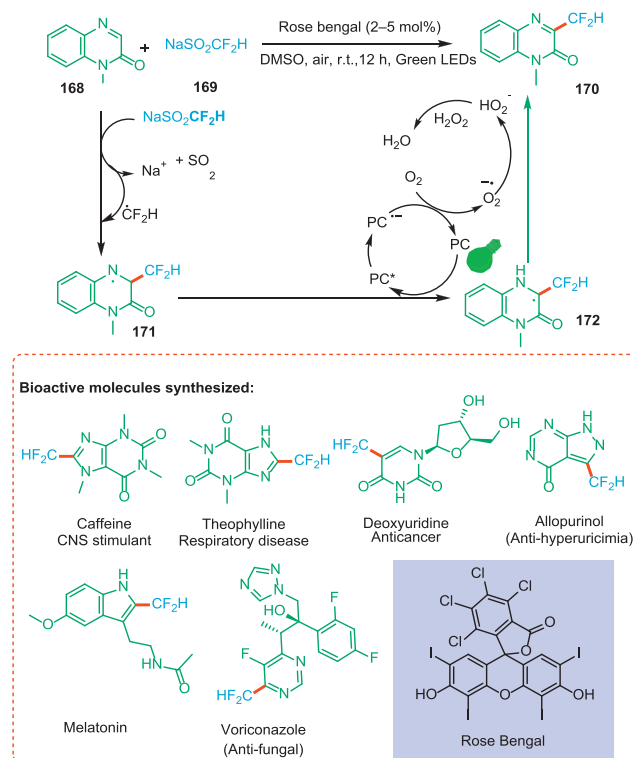


Scheme 30. Organo-photoredox catalyzed direct C-3 arylation of 2H-indazoles.

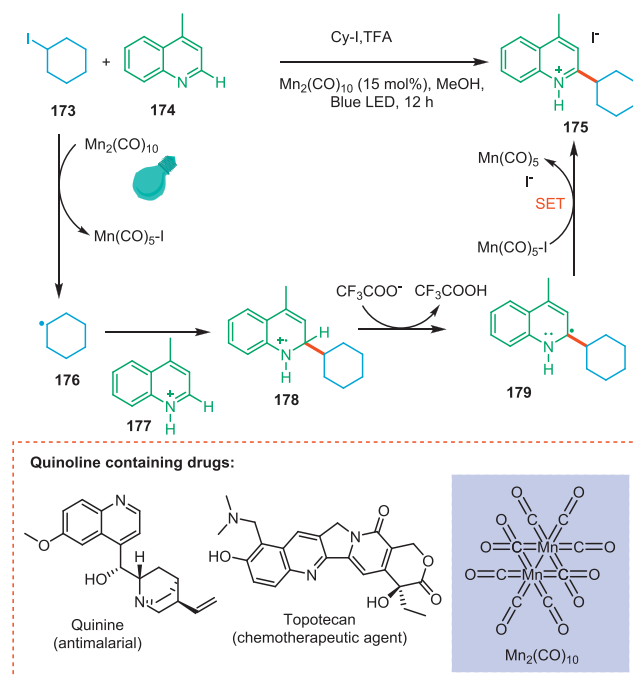
halides [170,171], which needed Cu/Pd as catalysts, costly ligands, and use of base and oxidant as additives having prolonged reaction times. So, less work is reported for direct arylation of 2H-indazoles at the C-3 position. Vidyacharan *et al.* proposed a simple eco-friendly methodology for direct C-3 arylation of 2H-indazoles with aryldiazonium salts using organo-photoredox catalysis with green light under milder conditions and synthesized inhibitor drugs of liver X-receptor without converting DIPEA into its radical cation. The SET from reduced PC completes the catalytic cycle forming aryl radical **165** and recovering the photocatalyst too. The resultant radical moiety **165** reacts with heteroarene **162**, giving radical intermediate **166**, which is changed to carbocation intermediate **167** by supplying electrons to the DIPEA. The deprotonation aromatizes the system and yields the targeted product **164** (Scheme 30) [159]. The phenyl moiety with electron-donating groups resulted in high yields, whereas bromosubstitution yielded extremely low yields. Unfortunately, N-2 substituents of 2H-indazoles did not give targeted products due to decreased aromatic nature of the parent ring [172].

Zhang *et al.* devised a light-driven direct C–H difluoromethylation of heterocycles by employing $\text{NaSO}_2\text{CF}_2\text{H}$ as a source of CF_2H radicals. The green oxidizing agent O_2 is used in this process with no metal additives and mild conditions. The difluoromethylation of carbon-hydrogen bond transforms nitrogen-containing heterocyclic molecules **168** into N-radical species **171**. The C-radical species **172** is the product of intramolecular radical transfer. The N–H homolytic cleavage produces the desired product **170** (Scheme 31). Furthermore, certain nitrogen-containing bioactive compounds can be directly difluoromethylated via this technique. Additionally, the difluoromethylation approach might help drug discovery because 2'-deoxy-5-difluoromethyluridine (F_2TDR) has potential action against various cancer cell lines [173].

Nuhant *et al.* established a photoredox Minisci reaction with unactivated iodoalkanes in the presence of Mn complex, $\text{Mn}_2(\text{CO})_{10}$ as a catalyst. This mild reaction is light-mediated and has good functional group tolerance. Photocatalyst converts iodoalkane **173** to alkyl radical **176**. The protonated 4-methylquinoline **177** reacts with **176** to yield a cation radical intermediate **178** followed by HAT, resulting in 2-cyclohexyl-4-methyl-1,2-dihydroquinoline **179**. The SET results in **175** (Scheme 32).



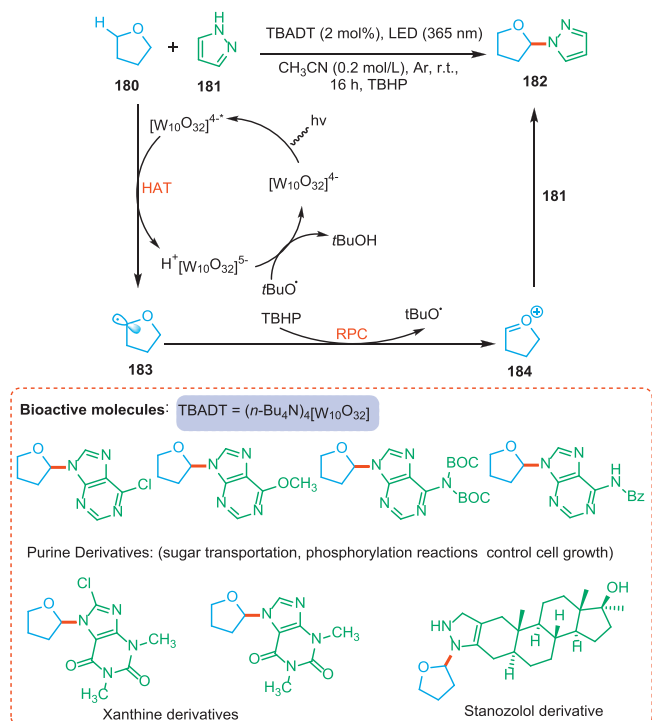
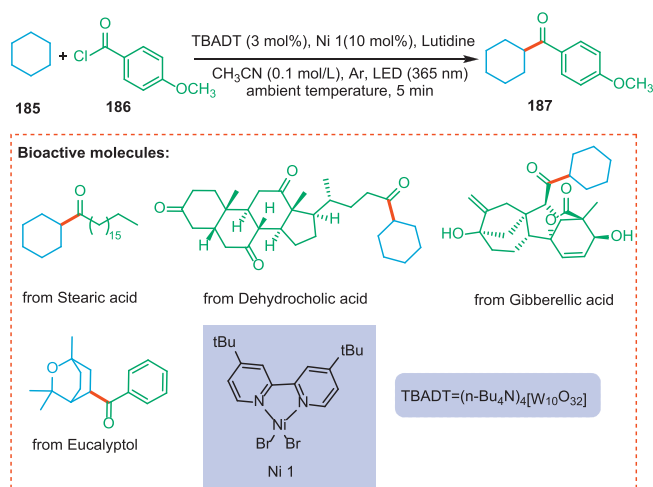
Scheme 31. Light-driven direct C–H difluoromethylation of heterocycles.



Scheme 32. Photoredox Minisci reaction with unactivated iodoalkanes.

Nuhant *et al.* showed this approach with remarkable success for late-stage functionalization of complicated medicines [174].

Photocatalytic HAT is a highly effective strategy for $\text{C}(\text{sp}^3)$ -H functionalization of organic compounds. Wan *et al.* established decatungstate HAT photocatalysis for $\text{C}(\text{sp}^3)$ -H oxidative heteroarylation using the radical polar cross-over (RPC) approach. The current strategy is scalable and has broad substrate scope. There is no need for prefunctionalization [175]. The breaking of the C–H bond in α -position regarding heteroatom **180** by PC^* gives a carbon-

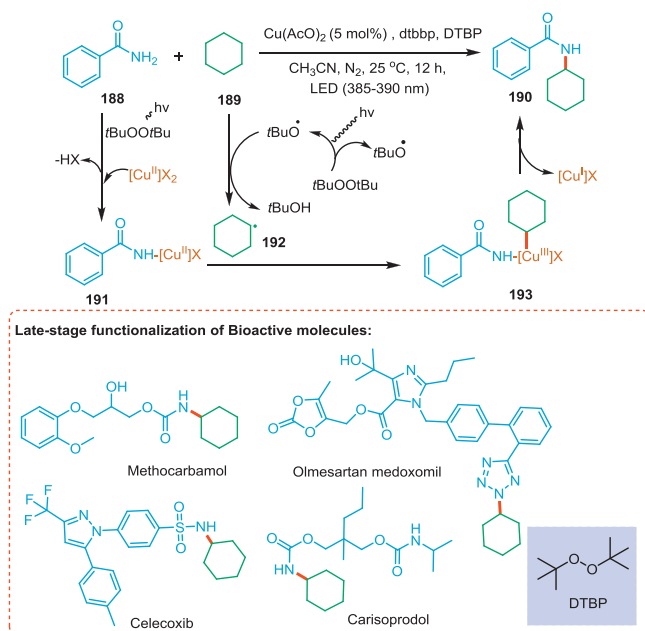
Scheme 33. Decatungstate catalyzed C(sp³)-H oxidative heteroarylation.

Scheme 34. Acylation/arylation of unfunctionalized alkyl derivatives.

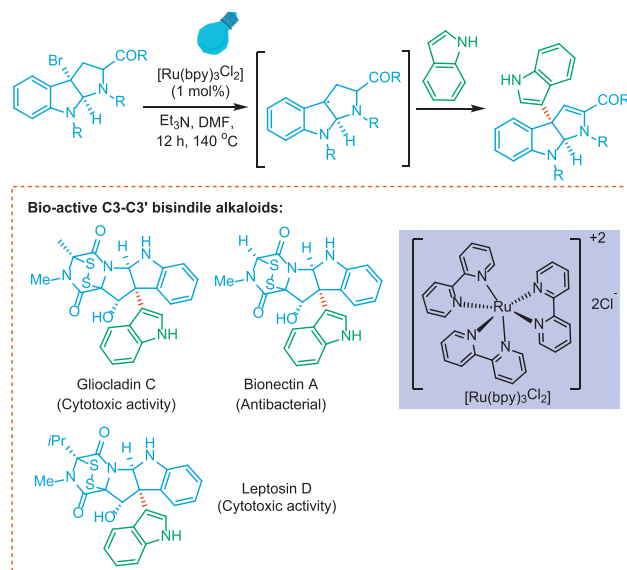
centered radical **183**, which gets oxidized by TBHP, yielding a stable electrophilic oxocarbenium ion **184** (Scheme 33). The $[\text{W}_{10}\text{O}_{32}]_4^-$, which is HAT photocatalyst has selectivity, robustness, and is easy to synthesize [176]. This methodology can be applied for the late-stage modification of bioactive products, that is stanozolol, (-)-ambroxide, podophyllotoxin, and dideoxyribose [175].

Mazzarella *et al.* described a photocatalytic process for the acylation/arylation of unfunctionalized alkyl derivatives. The $[\text{W}_{10}\text{O}_{32}]_4^-$ creates carbon-centered nucleophilic radicals. The Ni catalyst captures these radicals and eventually forms C(sp³)-C(sp²) bonds (Scheme 34). Mazzarella *et al.* also functionalized complicated organic or natural scaffolds at a late stage [177].

Zheng *et al.* established a light-mediated copper^{II}-peroxide method for alkylating amides and nitrogen nucleophiles with unactivated alkanes. This strategy can be employed for the late-stage N-alkylation of bioactive compounds. Under the action of peroxide



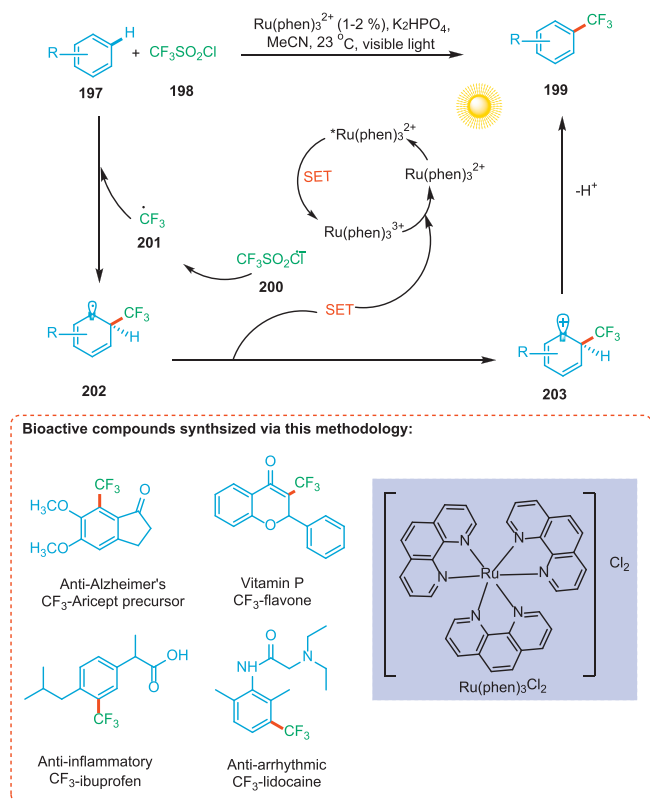
Scheme 35. Alkylation of amides and nitrogen nucleophiles with unactivated alkanes.



Scheme 36. Synthesis of gliocladin C.

and light, the $[\text{Cu}^{\text{II}}]$ -amide complex **191** is produced from a copper source and the amide **188**. The photolysis of DTBP forms the *t*BuO radical. The HAT from cyclohexane **189** to *t*BuO radical creates cyclohexyl radical **192**, which gets coordinated with the $[\text{Cu}^{\text{II}}]$ -amide complex **191**, resulting in the formation of the $[\text{Cu}^{\text{III}}]$ complex **193**. The coupling product **190** is formed via reductive elimination from **193**. The $[\text{Cu}^{\text{II}}]$ -phth complex is a crucial component (Scheme 35) [178].

The C3-C3' indole, including the 3*a*-(3-indolyl)-hexahydropyrrolo-[2,3-*b*]indole skeleton that is drugs like gliocladin C [179], leptosin D [180], and bionectins [181], which are antibacterial and cytotoxic, respectively. Furst *et al.* prepared 30% of gliocladin C in 10 stages using Boc-D-tryptophan methyl ester that was easily accessible in the market (Scheme 36). This study emphasizes photoredox catalysis as an effective technique

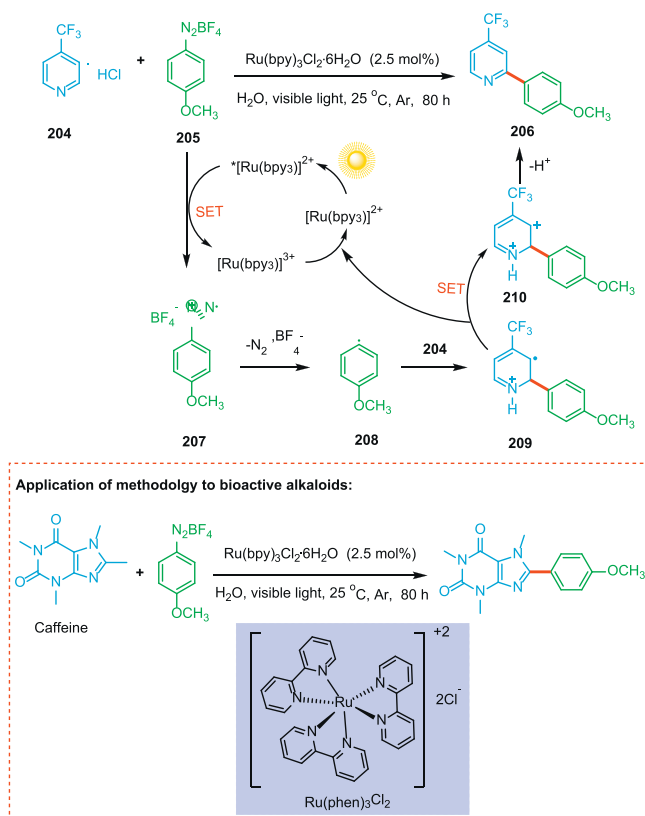


Scheme 37. Trifluoromethylation of aromatic and heteroaromatic compounds.

for this specific synthesis and a reliable way to obtain a range of complicated compounds [182].

Nagib and MacMillan's photoredox-based method is free from prefunctionalization and allows trifluoromethylation of aromatic and heteroaromatic materials. The significance of this conversion has been emphasized by the trifluoromethylation of bioactive compounds using affordable PC and an ordinary light source. The SET from photoexcited $\text{PC}^* \text{Ru(phen)}_3^{2+}$ to triflyl chloride **198** creates CF_3 radical **201** and Ru(phen)_3^{3+} . The CF_3 radical **201** is formed by splitting the $\text{CF}_3\text{SO}_2\text{Cl}$ radical anion **200**. The SET from cyclohexadienyl radical **202**, formed by the addition of the CF_3 radical **201** to benzene **197**, to oxidized PC (Ru^{III}) forming a cationic intermediate **203**, and PC is regenerated. In the end, the arene prefunctionalization is not required because the cyclohexadienyl cation **203** may be deprotonated with a base to produce the required trifluoromethyl arene **199** (Scheme 37) [183].

Baran proposed a "radical-type" arylation of *N*-heterocycles using boronic acids [184]. On the other hand, the Gomberg-Bachmann reaction is the coupling of arene compounds with diazonium salts using base-forming biaryls. This reaction has a broad substrate scope yet low efficiency due to the numerous side reactions [185]. Xue *et al.* proposed "radical type" coupling of *N*-heteroarenes with aryldiazonium ions in the presence of light and water as solvent. The SET from photoexcited $[\text{Ru(bpy)}_3]^{2+}$ to the aryldiazonium salt **205** creates phenyl radical **208** and the oxidized $[\text{Ru(bpy)}_3]^{3+}$. The phenyl radical **208** is added to the pyridine hydrochloride **204** to create radical **209**, which is then converted to cationic intermediate **210** followed by deprotonation to form coupling adduct **206** (Scheme 38). This reaction has a broad substrate scope of pyridine, and only monosubstituted products with varying regioselectivities are produced. Various xanthenes, thiazole, pyrazine, and pyridazine are appropriate in this approach when aqueous formic acid is used as the solvent. This process is a feasible and environmentally acceptable due to water as a solvent,



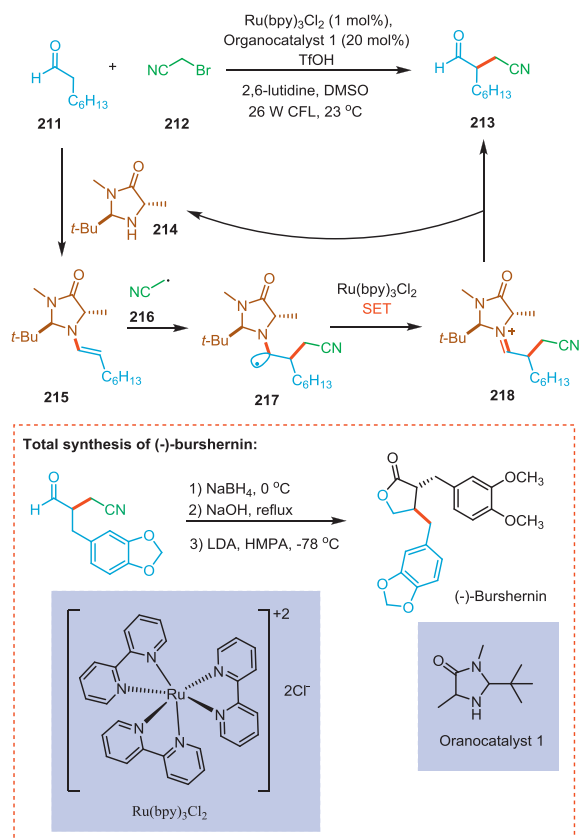
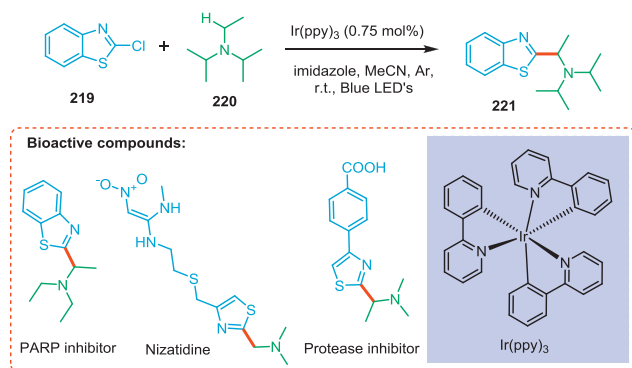
Scheme 38. The "radical type" coupling of *N*-heteroarenes with aryldiazonium ions.

broad substrate scope, and mild reaction conditions to prepare the compounds bearing aryl-heteroaryl motifs [186].

Welin *et al.* reported that by combining photoredox and enamine catalysis, preparation of enantioselective α -cyanoalkylation of aldehydes is possible. This synergistic catalysis method enables the diversification of oxonitrile products into various drug derivatives and heterocycles. The bromonitrile species **212** is reduced by the highly reducing Ru(bpy)_3^+ ion via SET yielding cyanoalkyl radical **216**. Concurrently, an amine catalyst **214** condenses with an aldehyde **211**, forming an enamine having chirality **215**, which couples with an electron-deficient radical **216** to create an amino radical **217**. The organocatalytic cycle is completed when photoexcitation of Ru(bpy)_3^{2+} causes SET to produce α -amino ion **218**, which upon hydrolysis produces the α -cyanoalkylated aldehyde **213** simultaneously recovering amine **214** (Scheme 39). This approach has also accomplished the natural lignan product (-)-burshehennin's complete synthesis [187].

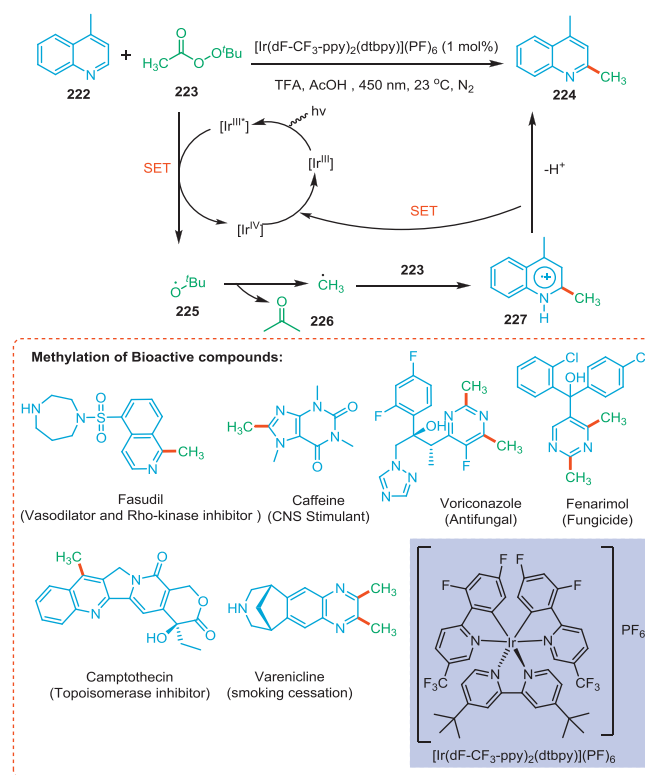
Singh *et al.* explained the conditions for tertiary aliphatic amines' C-H functionalization following their coupling with various 2-chloroazole derivatives. The photocatalyst tris-*fac*- Ir(ppy)_3 is aided by blue light irradiation and proceeds in a mild and practical environment (Scheme 40). The majority of couplings occur with great regioselectivity. The procedure permits quick access to *R*-azole carbinamines, frequently present in post-translationally modified peptides, and has excellent functional group tolerance [188].

Previous approaches require powerful oxidants and high temperatures to form the required radical species, so small alkyl groups are not inserted in complex formation. DiRocco *et al.* proposed that by employing a photocatalyst and light-mediated approach, stable peroxides are formed, which are used in the alkylation of an array of heterocycles present in bioactive compounds. The *t*BPA **223** via PCET yields *t*BuO radical **225**, which is converted into methyl radical **226** via the β -scission. The addition of methyl

**Scheme 39.** Synthesis of enantioselective α -cyanoalkylation of aldehydes.**Scheme 40.** C-H functionalization of tertiary aliphatic amines.

radical **226** to the protonated heterocycle **222** yields radical cation intermediate **227** followed by HAT to the oxidized PC $[\text{Ir}^{\text{IV}}]$, resulting in the targeted product **224** (Scheme 41). This approach is a significant tool for drug discovery due to its straightforward methodology, mild response conditions, and unusual tolerability [189].

Without prefunctionalization, hydroalkylation of alkene mediated by HAT provides a simple way to produce $\text{C}(\text{sp}^3)$ -rich compounds. In contrast, Giese-type hydroalkylation of unactivated olefins is still tricky due to a lack of ideas for dealing with the associated polarity mismatch. Lei *et al.* used dual HAT catalysis to accomplish this objective in the presence of light, using catalytic quantities of an amine-borane and thiol as H-atom abstractor and donor, respectively. A substrate with electrophilic C-H bonds **228** undergoes HAT via borane catalysis to yield radical specie **231**, which is alkylated with an unactivated alkene **229** to form free radical species **232**. The resultant radical intermediate abstracts hy-

**Scheme 41.** Photocatalyzed alkylation of heterocycles.

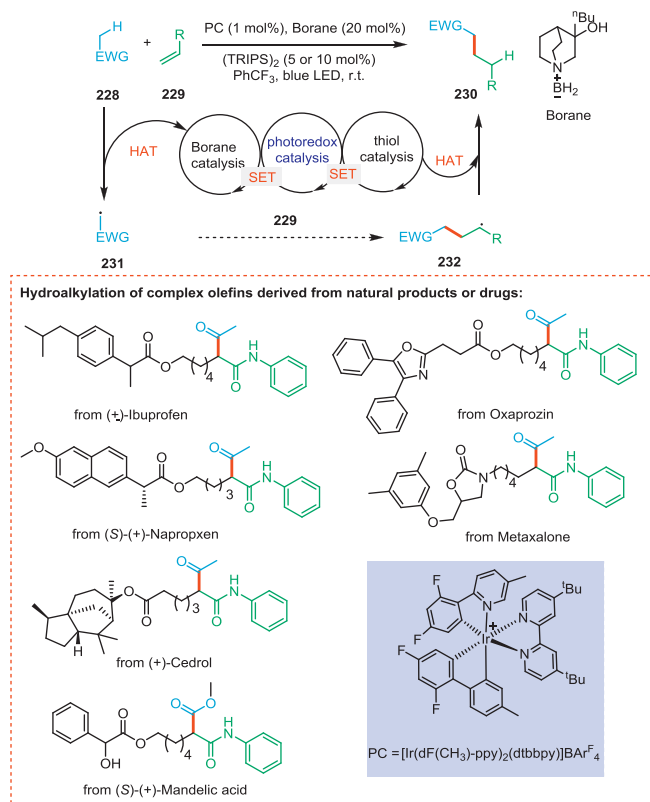
drogen resulting in the product **230** via thiol catalysis (Scheme 42). The reaction has a high atom economy and good substrate scope [190].

The HAT is a fundamental stage in free-radical processes [191,192]. Advancements in photocatalyzed reaction revolutionized [193,194] light-mediated HAT as an efficient technique for creating molecular complexity from easily accessible starting materials without requiring prefunctionalization [191]. The polarity-matching effect makes compound functionalization via HAT restricted to substrates having hydridic RH ($\text{R} = \text{C}, \text{Si}, \text{B}, \text{etc.}$) bonds [195]. The nucleus-loving radicals formed via HAT reagents must exist to render electrophilic carbon-hydrogen bonds suitable to remove hydrogen atoms.

Direct and selective $\text{C}(\text{sp}^3)$ -H functionalization is an emerging approach due to the inexpensive starting materials and excellent atom economy. Cao *et al.* devised a three-component ($\text{C}(\text{sp}^3)$ -H precursor, SO_2 substitute, and α,β -unsaturated carbonyl molecule) asymmetric sulfonylation reaction enabling direct functionalization under mild conditions to yield an array of medically relevant α -C chiral sulfones. The cycloalkane **233** is converted into cycloalkane radical **237** via the photocatalytic cycle **240**, which gets trapped by SO_2 **234** to generate the stabilized sulfonyl radical **238**. The compound **235** interacts with the metal-coordinated Michael acceptor **239** due to electronic and steric phenomena. Finally, the ligand exchange results in the chiral sulfone product **236** (Scheme 43). This approach is suitable for the late-stage functionalization of bioactive compounds opening a novel route to enantioenriched drugs derived from hydrocarbon compounds [196].

6. Ring opening

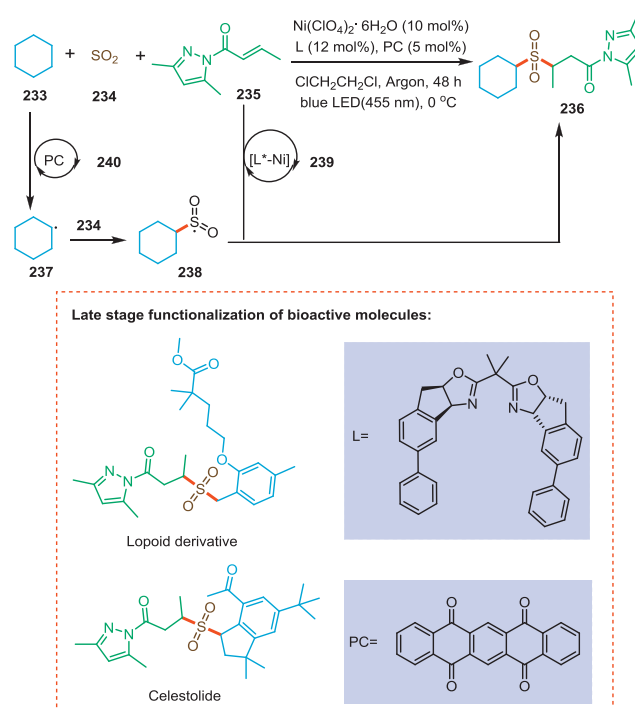
Ring-opening is a stability dependant process. Strained rings tend to open more easily like a five-membered ring undergoes ring opening rapidly compared to a six-membered ring. The smaller the ring size, the more strained it will be and the more easily it will



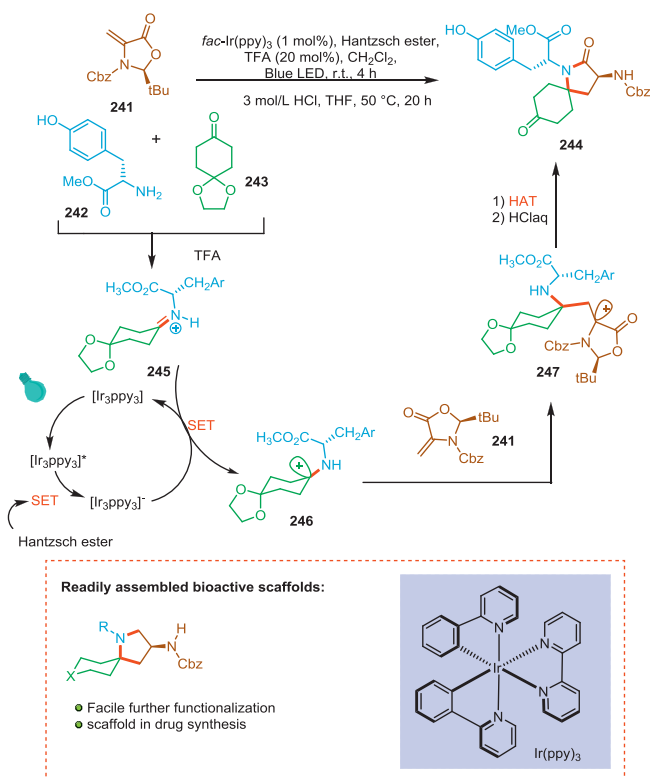
undergo ring opening reactions [197]. In 2019, Zhang *et al.* reported oxidant-free ring opening of cyclobutanone oxime esters in visible light and PC to synthesize alkylnitrile derivatives of various heterocycles [198]. In 2022, Zhu *et al.* reported ring opening of sulfonium salts by using hetero-arene moieties in the presence of light and photocatalyst Cu-complex [199].

Reich *et al.* described a multicomponent photocatalytic hydroaminoalkylation method for producing the azaspirocycle with amino substitution on the ring, which is present in (-)-FR901483 and (+)-TAN1251C. This approach is key to synthesize spiro lactam moiety *via* a novel synthesis strategy. This technology finds use in natural products since starting materials are readily available and it is simple to operate. Spiro lactam was synthesized by the photocatalytic olefin hydroaminoalkylation, followed by further three steps to produce the TAN125C equivalent, resulting in a high yield (Scheme 44). The FR901483 has an immunosuppressive effect that is extraordinarily potent (more than 100 times stronger than cyclosporine) [45].

Ou *et al.* designed a fast production of 3-formyloxindoles by double C–H functionalization of *N*-arylacrylamides and 1,3-dioxolane in a metal-free and light-mediated manner employing a heterogeneous photocatalyst [200]. The photoexcited PC* undergoes SET to TBHP and yields a *tert*-butoxy radical. The regioselectivity of *tert*-butoxy radical then abstracts a proton from C-2 of 1,3-dioxolane **248** to create radical specie **251** [201], which adds to acrylamide **249** to form radical specie **252** undergoing intramolecular cyclization to yield radical intermediate **253**. The dioxolane acetal intermediate **254** is produced by oxidizing radical intermediate **253** with the PC⁺, subsequently regaining aromaticity. Ultimately, the acidic hydrolysis yields the required product **250** (Scheme 45). This study illustrates the tremendous promise of employing CMPs, as light-triggered photocatalysts with stability, reusability, and metal-free characteristics that offer sustainable

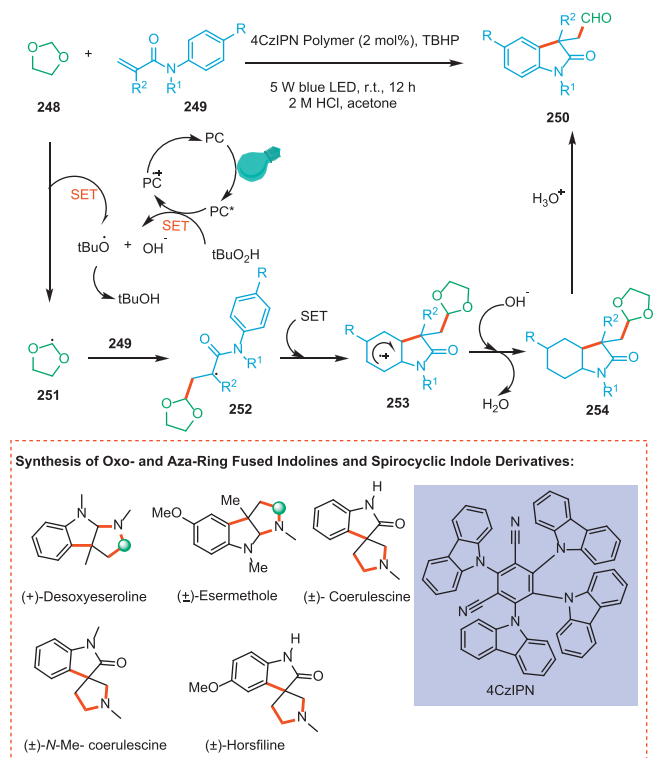


Scheme 43. Asymmetric sulfonylation reaction enabling direct functionalization.



Scheme 44. Hydroaminoalkylation method for producing the azaspirocycle with amino substitution on the ring.

production of bioactive heterocycles and medicinal molecules. The obtained 3-formyloxindoles act as an essential component for the quick generation of an array of pharmaceutically essential products such as (±)-desoxyseroline, (±)-esermethole, and (±)-*N*-Me-coerulescine, in better amounts in comparison to multistep reactions [200].

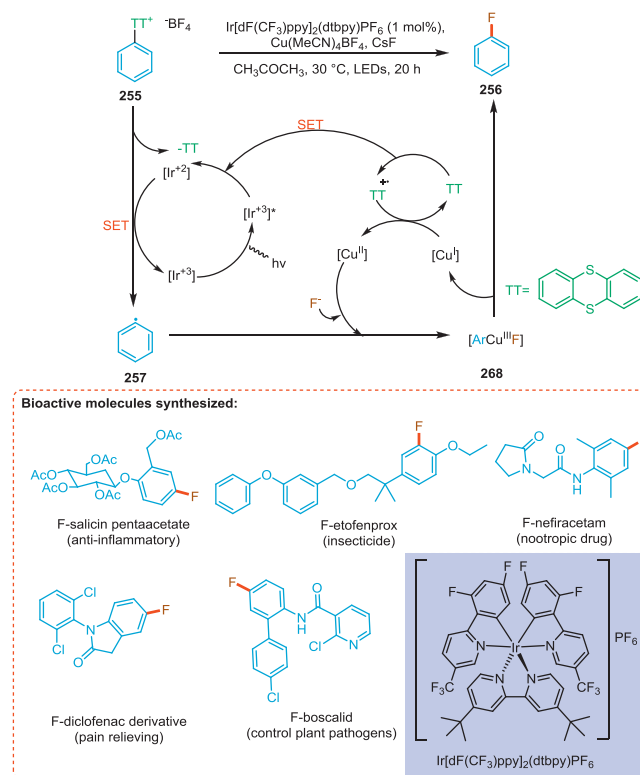


Scheme 45. Synthesis of 3-formyloxindoles by double C–H functionalization of *N*-arylacrylamides and 1,3-dioxolane.

7. Oxidative cross-coupling

In synthetic chemistry, selective C–C bond or C–heteroatom bond formation is tricky. In this regard, cross-coupling reactions contribute significantly. Heck, Suzuki, and Negishi won the Nobel Prize in 2010 for palladium-catalyzed cross-coupling reaction. Conventional cross-coupling reaction operates between nucleophilic and electrophilic reactants and has some limitations as lack of sustainability, requiring prefunctionalization and side products (low step economy). Oxidative coupling involves the release of two electrons from both nucleophilic reactants with the use of various oxidants and catalysts. Oxidative coupling resolves the above limitations of conventional cross-coupling reaction as its nucleophilic center reactants have hydrogen atoms attached to carbon or heteroatoms. Thus, prefunctionalization and oxidants are unnecessary too [202]. Song *et al.* proposed the metal-free, semi-heterogeneous $g\text{-C}_3\text{N}_4$ /iodide salt dual catalysis potent for forming oxidative bonds [203].

According to Li *et al.*, photoredox catalysis helps make bonds that are difficult to form in conventional redox catalysis, particularly when transition metals are used as PC. The ArTT^+ salt **255** via SET from reduced iridium PC goes converted into aryl radical **257**, which coordinates with Cu redox catalyst to form a copper-aryl coordinated intermediate **258**. The Cu is removed in reduced form, yielding a fluorinated aryl compound **256** (Scheme 46). The leaving groups useful in traditional cross-coupling catalysis, like bromide, are being utilized effectively in metalphotoredox catalysis for arene functionalization. However, most aryl bromides are not reduced by usual photoredox catalysts, making it difficult to produce synthetically valuable aryl radicals directly. So, the redox potential of leaving group and photocatalyst should match for better reactivity and selectivity. That is complicated coupling reactions by using arylcopper-III complexes. Li *et al.* demonstrated the prospec-



Scheme 46. Fluorination of aryl thianthrenium salts.

tive significance of aryl thianthrenium salts and the application of this photoredox metal PC in late-stage aromatic fluorination [204].

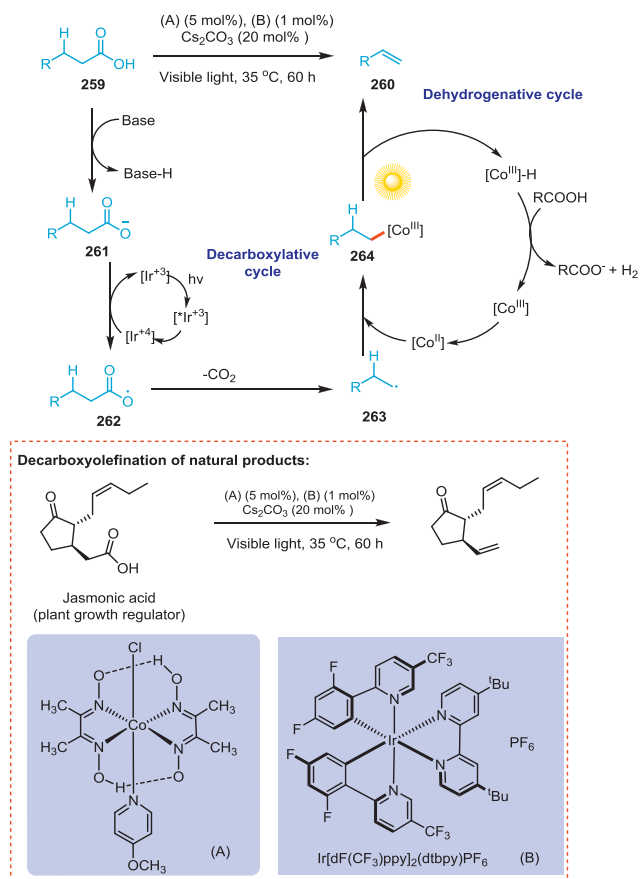
8. Dehydrogenation

Sun *et al.* described a decarboxyolefination method that does not require stoichiometric additions, paving the way for developing an approach for the green synthesis of α -olefins from renewable carboxylic acids. The carboxylic acid **259** is converted by base into carboxylate anion **261**, which then undergoes a decarboxylative cycle with the aid of a PC to create alkyl radical **263**, which then undergoes a dehydrogenative cycle to yield **260** (Scheme 47). This approach can be applied in the late-stage functionalization of natural products and even in drug discovery [205].

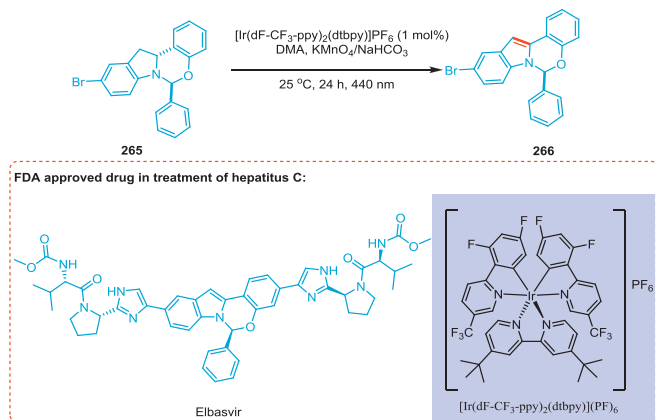
A potent NS5A antagonist used to treat chronic hepatitis C is elbasvir. Yayla *et al.* reported the identification and investigation of indoline dehydrogenation for the photoredox-mediated synthesis of elbasvir. The $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ and the ecologically safe oxidant *tert*-butyl peroxybenzoate have been proven as good photoredox catalyst and oxidant combination yielding the targeted product with excellent yields without disturbing optical purity through multi-parallel experiments (Scheme 48). A pharmaceutical intermediate is produced for the first time using photoredox catalysis [206].

9. Desulphonation

Douglas *et al.* proposed a radical Smiles rearrangement in the presence of visible light to develop *gem*-difluoro group found in an opioid receptor-like (ORL-1) antagonist, which is used to treat depression and obesity. The effective amalgamation of the difluoroethanol moiety with aryl and heteroaryl systems is achieved by this strategy. Thus, an array of new molecules can be synthesized. The single electron reduction of thiophene **267** produces the required difluoromethyl radical **269** recovering photocatalyst. The



Scheme 47. A decarboxyolefination method synthesizing alpha-olefins.



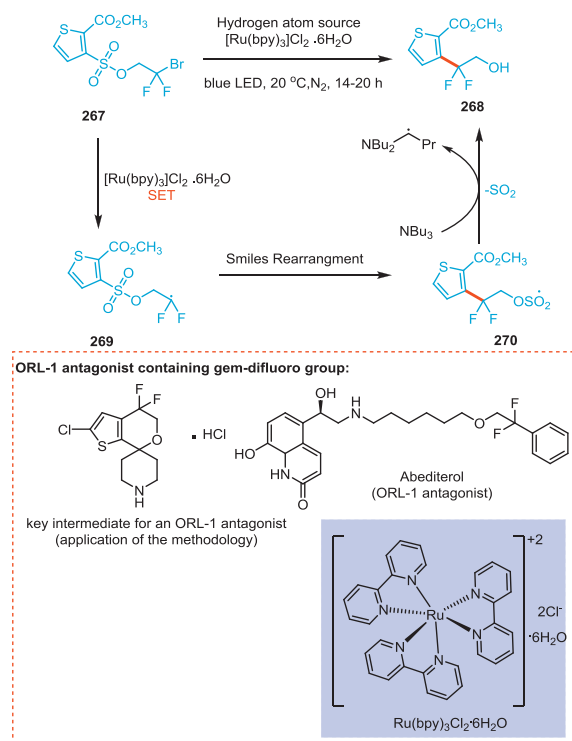
Scheme 48. Photoredox-mediated synthesis of elbasvir.

radical **269** undergoes Smiles rearrangement with the sulfonate group to yield **270**, followed by H atom abstraction and polar SO₂ extrusion to yield **268** (Scheme 49) [207].

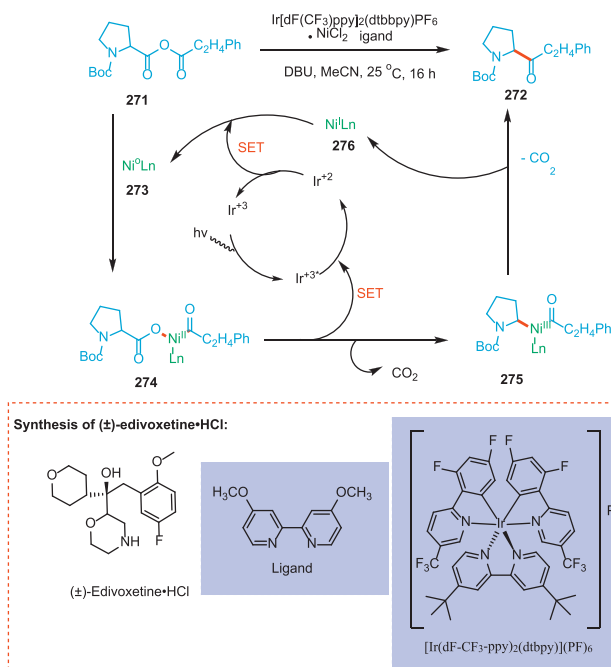
10. Decarboxylation

Over the past few decades, the cleavage of bonds, particularly carbon-carbon bonds, has challenged the traditional model, which has led to changes in synthetic approaches [208].

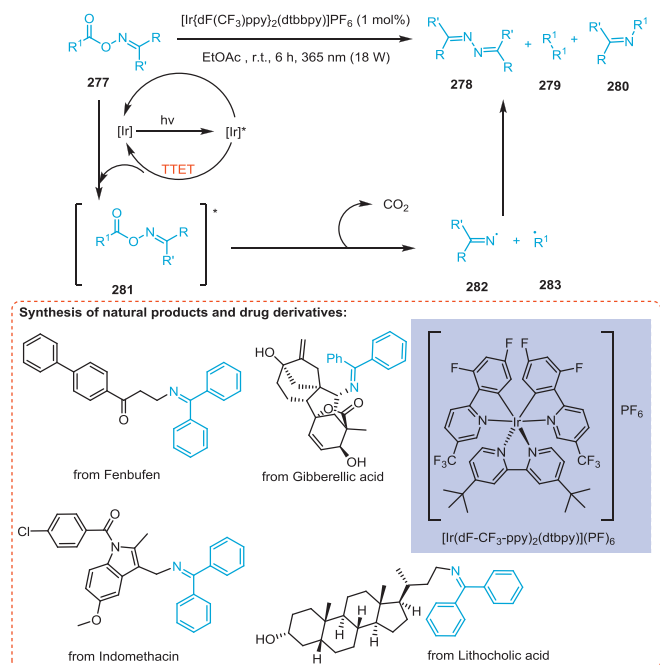
Le *et al.* found that, when subjected to metallaphotoredox catalysis, molecular fragments that can be easily coupled, may engage in metal insertion, decarboxylation, and recombination to make Csp²-Csp³ bonds. The acid anhydride **271** undergoes the oxidative insertion of the Ni⁰ complex **273** to create the equivalent acyl-



Scheme 49. Photocatalyzed radical Smiles rearrangement to develop gem-difluoro group.

Scheme 50. Metallaphotoredox catalysis to synthesize Csp²-Csp³ bonds.

carboxylate-Ni^{II} complex **274**. The PC Ir^{III} undergoes photoexcitation resulting in the corresponding *Ir^{III} complex. The decarboxylation and SET from **274** form alkyl acyl Ni^{II} complex **275** and Ir^{II}, respectively. The reductive elimination of embedded nickel complex results in the formation of ketone products **272**. Lastly, the Ir^{II} complex and Ni^I species **276** would engage in a SET to simultaneously complete both catalytic cycles and restore the ground state photocatalyst Ir^{III} and Ni⁰ catalyst **273** to their ground states (Scheme 50). This innovative decarboxylation-recombination ap-



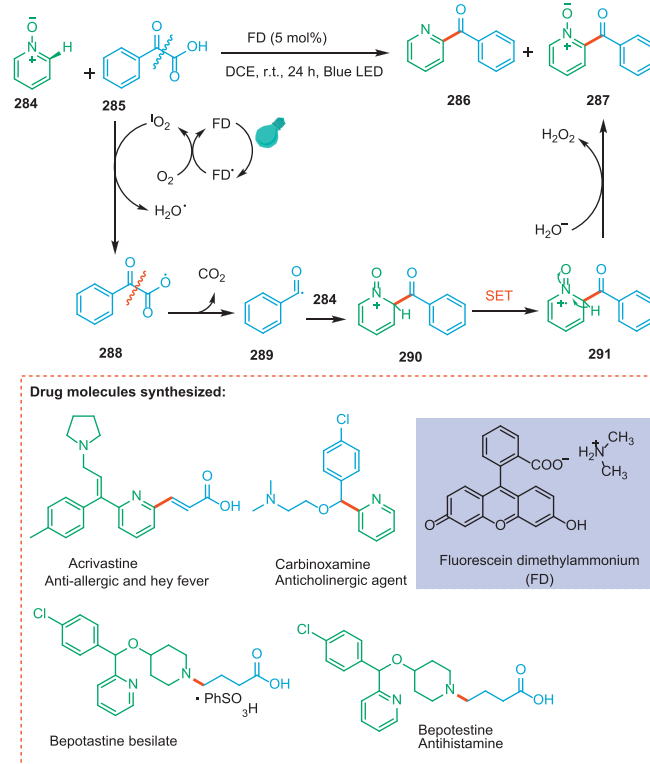
Scheme 51. EnT technique couples difficult radical-radical C(sp³)-N.

proach also outlines a three-step production of the drug edivoxetine [209].

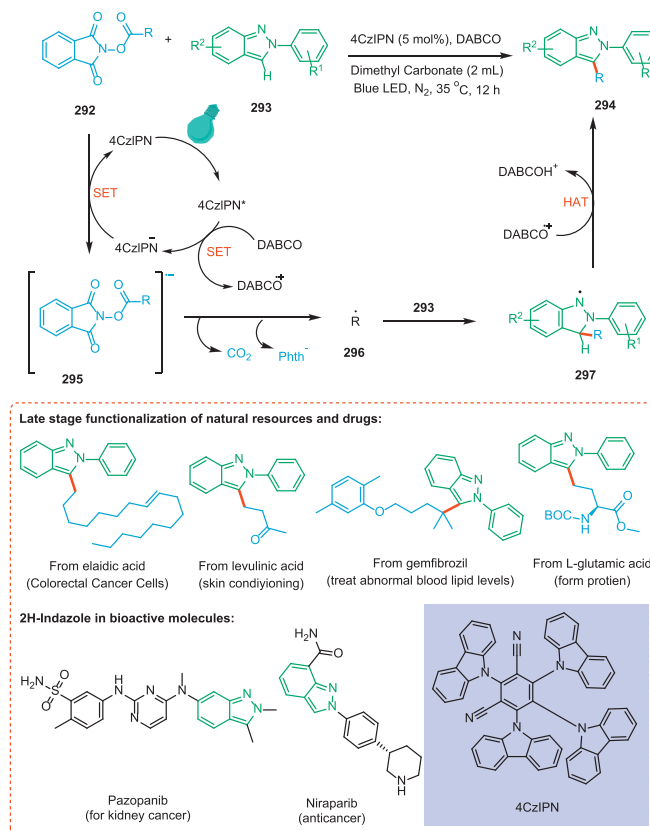
The cleavage of a reductive N-O bond generates nitrogen and oxygen radicals to make coupling products. This photocatalyzed approach is not much successful regardless of its major advancement due to the low atom economy. In this scenario, homolytic breaking of the N-O bond *via* the EnT route gives two essential radicals which is extremely helpful for circumventing the restrictions of using a single fragment. Soni *et al.* disclosed a novel EnT technique that couples difficult radical-radical C(sp³)-N *via* catalytic system reactivity modification. In the presence of photocatalyst and light, the oxime esters break homolytically, yielding oxygen radicals *e.g.*, acyloxy radical, and nitrogen radical species *e.g.*, iminyl radicals, which undergo decarboxylation yielding imines. The triplet state excited photocatalyst reacts with oxime ester **277** forming excited oxime ester **281**, which undergoes decarboxylation by breaking nitrogen-oxygen bond homolytically to give C **283** and N **282** radicals. These radicals couple to yield the targeted imine product **280** (Scheme 51). The solvent's nature and reaction content concentration was crucial in this cross-coupling procedure for obtaining selectivity and reactivity [210].

Hou *et al.* used fluorescein dimethylammonium, which is an organic dye, as a novel form of photocatalyst to carry out the decarboxylative acylation of pyridine *N*-oxides with α -oxocarboxylic acids. The α -oxocarboxylic acids **285** in the presence of PC goes converted into α -oxocarboxylic acids radical **288** which on decarboxylation yields benzyl radical **289**. The pyridine *N*-oxides **284** react with benzyl radical **289** to give rise to intermediate **291**, which undergoes SET resulting in cation radical intermediate **291** followed by hydrogen abstraction to yield targeted products **286** and **287** (Scheme 52). The new technique was effectively employed for synthesizing acrivastine, a vital drug intermediate [160].

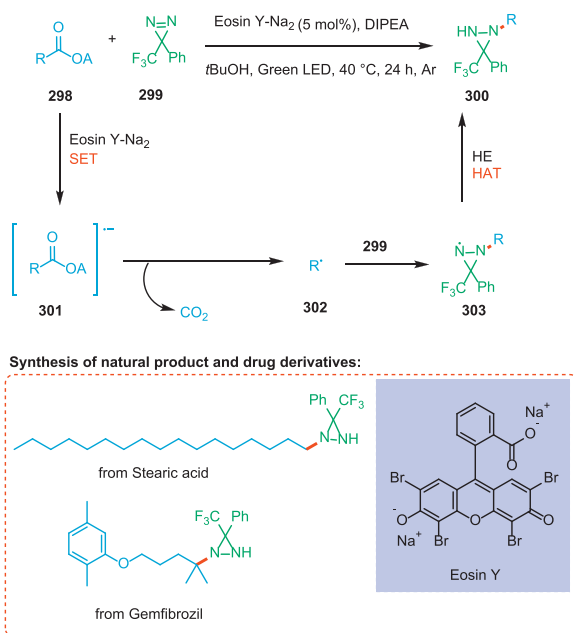
The 4CzIPN and alkyl *N*-hydroxyphthalimide esters **292**, as the alkylating reagents, were employed by Ma *et al.* for alkylating 2*H*-indazoles without using metal. The decarboxylation and the removal of phthalimide anion convert **292** to the alkyl radical **296**, which is added to the C-3 position of radical **293**, forming a dearomatized radical **297**. Finally, the C-3 alkylated product **294** and DABCO-H⁺ are produced *via* HAT from **297** to DABCO⁺ (Scheme 53). The good functional-group compatibility makes this



Scheme 52. Decarboxylative acylation of pyridine *N*-oxides with α -oxocarboxylic acids.



Scheme 53. Alkylation of 2*H*-indazoles without using metal.



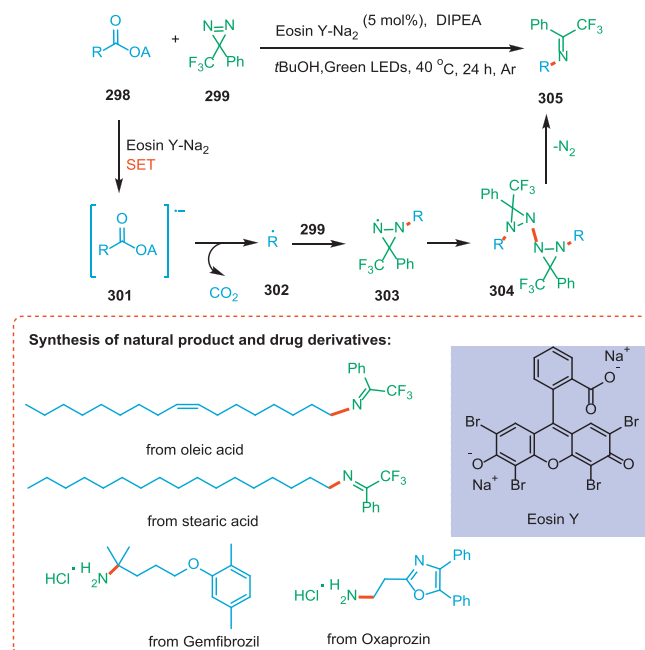
Scheme 54. Decarboxylative amination reaction of alkyl carboxylic acid-derived redox-active esters to synthesize diaziridines.

procedure effective to modify medicinal molecules and create new, synthetic amino acids [211].

Shu *et al.* reported a novel divergent decarboxylative amination reaction of alkyl carboxylic acid-derived redox-active esters, allowing accessibility of amine and hydrazine from TPD [212]. The photoexcited eosin Y- Na_2 (PC) is reductively quenched by DIPEA or Hantzsch ester (HE) *via* SET [213]. The radical anion of photocatalyst thus produces and converts ester **298** into its radical anion **301** *via* SET resulting in C–C bond splitting and decarboxylation forming alkyl radical **302** [214] which adds to TPD **299** to form radical species **303**. These radical species take hydrogen from HE *via* double nitrogen transfer to yield the diaziridine products **300** (Scheme 54). Suitable hydrogen atom donors assist in hydrogen atom transfer, resulting in more diaziridine molecules. The key radical intermediate **303** can dimerize to yield the tetrazolone intermediate **304** [215,216], which then undergoes N_2 extrusion to yield two molecules of the required imines **305** (Scheme 55). This approach has broad substrate scope and has applications in drug chemistry. As a result, a wide range of imines, diaziridines, masked amines, and hydrazines are synthesized in more significant structural variations with efficacy [212].

11. Conclusion

The field of synthetic chemistry is embracing photochemical catalytic processes, offering novel opportunities for academia and industry. This review explores the advancements in photoredox reactions having the potential for the synthesis or modification of natural products and pharmaceuticals. Dual-catalyst systems have been successfully employed to enhance photocatalysis. Despite challenges, visible light-mediated reactions continue to grow, driven by academic curiosity and the potential for discovery within the industry and successful scaling up of photoredox reactions. Collaboration between academia and industry is crucial for addressing challenges and maximizing opportunities in photocatalysis. As the field evolves, advancements in visible light catalysis offer exciting prospects for efficient and sustainable synthetic chemistry.



Scheme 55. Decarboxylative amination reaction of alkyl carboxylic acid-derived redox-active esters to synthesize imines.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

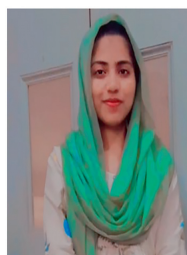
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References

- [1] C.K. Prier, D.A. Rankic, D.W. MacMillan, *Chem. Rev.* 113 (2013) 5322–5363.
- [2] K. Kalyanasundaram, *Coord. Chem. Rev.* 46 (1982) 159–244.
- [3] A. Juris, V. Balzani, F. Barigelli, et al., *Coord. Chem. Rev.* 84 (1988) 85–277.
- [4] K.L. Wang, H.T. Ji, L.J. Ou, W.M. He, *Eur. J. Org. Chem.* 26 (2023) e202300752.
- [5] G. Ciamician, P. Silber, *Chem. Lichtwirkungen, Ber. Dtsch. Chem. Ges.* 41 (1908) 1071–1080.
- [6] A. Albini, M. Fagnoni, *Green Chem.* 6 (2004) 1–6.
- [7] M.H. Shaw, J. Twilton, D.W. MacMillan, *J. Org. Chem.* 81 (2016) 6898–6926.
- [8] V. Srivastava, P.K. Singh, S. Tivari, P.P. Singh, *Org. Chem. Front.* 9 (2022) 1485–1507.
- [9] B. Dam, A.K. Sahoo, B.K. Patel, *Green Chem.* 24 (2022) 7122–7130.
- [10] Y. Zhou, Y. Qin, Q. Wang, Z. Zhang, G. Zhu, *Angew. Chem.* 134 (2022) e202110864.
- [11] P.P. Singh, P.K. Singh, V. Srivastava, *Org. Chem. Front.* 10 (2023) 216–236.
- [12] M.P. Wiesenfeldt, J.A. Rossi-Ashton, I.B. Perry, et al., *Nature* 618 (2023) 513–518.
- [13] D. Yang, Q. Yan, E. Zhu, J. Lv, W.M. He, *Chin. Chem. Lett.* 33 (2022) 1798–1816.
- [14] L. Wang, P. Bao, W. Liu, et al., *Chin. J. Org. Chem.* 38 (2018) 3189.
- [15] L. Zheng, X. Zhuo, Y. Wang, et al., *Org. Chem. Front.* 9 (2022) 3012–3021.
- [16] W.B. He, L.Q. Gao, X.J. Chen, *Chin. Chem. Lett.* 31 (2020) 1895–1898.
- [17] Z. Guo, X. Liu, R. Bai, et al., *Inorg. Chem.* 60 (2021) 8672–8681.
- [18] K. Sun, G. Li, Y. Li, et al., *Adv. Synth. Catal.* 362 (2020) 1947–1954.
- [19] M.T. Pirnot, D.A. Rankic, D.B. Martin, D.W. MacMillan, *Science* 339 (2013) 1593–1596.
- [20] M. González-Esguevillas, J. Miró, J.L. Jeffrey, D.W. MacMillan, *Tetrahedron* 141 (2023) 133494.
- [21] J.H. Shen, M. Shi, Y. Wei, *Chem. Eur. J.* 29 (2023) e202301157.
- [22] P. Chuentragool, D. Yadagiri, T. Morita, et al., *Angew. Chem.* 131 (2019) 1808–1812.
- [23] N. Kvasovs, V. Gevorgyan, *Chem. Soc. Rev.* 50 (2021) 2244–2259.
- [24] M. Rivas, V. Palchykov, X. Jia, V. Gevorgyan, *Nat. Rev. Chem.* 6 (2022) 544–561.

- [25] D.A. Nicewicz, D.W. MacMillan, *Science* 322 (2008) 77–80.
- [26] L. Shi, W. Xia, *Chem. Soc. Rev.* 41 (2012) 7687–7697.
- [27] J.M. Narayanam, C.R. Stephenson, *Chem. Soc. Rev.* 40 (2011) 102–113.
- [28] T.P. Yoon, M.A. Ischay, J. Du, *Nat. Chem.* 2 (2010) 527–532.
- [29] D.M. Schultz, T.P. Yoon, *Science* 343 (2014) 1239176.
- [30] M.W. Johnson, K.I. Hannoun, Y. Tan, G.C. Fu, J.C. Peters, *Chem. Sci.* 7 (2016) 4091–4100.
- [31] P. Marquetand, *Chem. Rev.* 122 (2022) 15996–15997.
- [32] Y.M. Tian, X.N. Guo, H. Braunschweig, U. Radius, T.B. Marder, *Chem. Rev.* 121 (2021) 3561–3597.
- [33] M. Fagnoni, D. Dondi, D. Ravelli, *Chem. Rev.* 107 (2007) 2725–2756.
- [34] M.J. Genzink, J.B. Kidd, W.B. Swords, T.P. Yoon, *Chem. Rev.* 122 (2021) 1654–1716.
- [35] K.L. Skubi, T.R. Blum, T.P. Yoon, *Chem. Rev.* 116 (2016) 10035–10074.
- [36] T. Nevesely, M. Wienhold, J.J. Molloy, R. Gilmour, *Chem. Rev.* 122 (2021) 2650–2694.
- [37] D.C. Blakemore, L. Castro, I. Churcher, et al., *Nat. Chem.* 10 (2018) 383–394.
- [38] K.R. Campos, P.J. Coleman, J.C. Alvarez, et al., *Science* 363 (2019) eaat0805.
- [39] K.D.C. Lisa Candish, G.C. Cook, J.J. Douglas, et al., *Chem. Rev.* 122 (2022) 2907–2980.
- [40] T. Cernak, K.D. Dykstra, S. Tyagarajan, P. Vachal, S.W. Krska, *Chem. Soc. Rev.* 45 (2016) 546–576.
- [41] M. Moir, J.J. Danon, T.A. Reekie, M. Kassiou, *Expert Opin. Drug Discov.* 14 (2019) 1137–1149.
- [42] L. Capaldo, L.L. Quadri, D. Ravelli, *Green Chem.* 22 (2020) 3376–3396.
- [43] R. Cannalire, S. Pelliccia, L. Sancineto, et al., *Chem. Soc. Rev.* 50 (2021) 766–897.
- [44] P. Bellotti, H.M. Huang, T. Faber, F. Glorius, *Chem. Rev.* 123 (2023) 4237–4352.
- [45] A. Trowbridge, D. Reich, M.J. Gaunt, *Nature* 561 (2018) 522–527.
- [46] M.D. Eastgate, M.A. Schmidt, K.R. Fandrick, *Nat. Rev. Chem.* 1 (2017) 0016.
- [47] R.W. Hoffmann, *Chem. Soc. Rev.* 45 (2016) 577–583.
- [48] A.G. Csáky, G. de la Herrán, M.C. Murcia, *Chem. Soc. Rev.* 39 (2010) 4080–4102.
- [49] J. Zhao, J.L. Brosmer, Q. Tang, et al., *J. Am. Chem. Soc.* 139 (2017) 9807–9810.
- [50] M. Ikeda, K. Ohno, S.I. Mohri, M. Takahashi, Y. Tamura, *J. Chem. Soc., Perkin Trans. 1* (1984) 405–412.
- [51] M. Teders, C. Henkel, L. Anhäuser, et al., *Nat. Chem.* 10 (2018) 981–988.
- [52] C. Palomo, M. Oiarbide, J.M. García, *Chem. Soc. Rev.* 33 (2004) 65–75.
- [53] J. Xu, C. Boyer, *Macromolecules* 48 (2015) 520–529.
- [54] T. Rossolini, J.A. Leitch, R. Grainger, D.J. Dixon, *Org. Lett.* 20 (2018) 6794–6798.
- [55] J.S. Wang, K. Wu, C. Yin, et al., *Nat. Commun.* 11 (2020) 4675.
- [56] S. Vijayakrishnan, J.W. Ward, A.I. Cooper, *ACS Catal.* 12 (2022) 10057–10064.
- [57] F. Denes, M. Pichowicz, G. Povie, P. Renaud, *Chem. Rev.* 114 (2014) 2587–2693.
- [58] G. Ciamician, *Science* 36 (1912) 385–394.
- [59] J. Metternich, R. Gilmour, *Synlett* 27 (2016) 2541–2552.
- [60] Z. Lu, T.P. Yoon, *Angew. Chem.* 124 (2012) 10475–10478.
- [61] T.R. Blum, Z.D. Miller, D.M. Bates, I.A. Guzei, T.P. Yoon, *Science* 354 (2016) 1391–1395.
- [62] E.R. Welin, C. Le, D.M. Arias-Rotondo, J.K. McCusker, D.W. MacMillan, *Science* 355 (2017) 380–385.
- [63] J. Mayol-Llinas, A. Nelson, W. Farnaby, A. Ayscough, *Drug Discov. Today* 22 (2017) 965–969.
- [64] V. Lahmy, R. Long, D. Morin, V. Villard, T. Maurice, *Front. Cell. Neurosci.* 8 (2015) 463.
- [65] D.P. Marciano, M.R. Chang, C.A. Corzo, et al., *Cell Metab.* 19 (2014) 193–208.
- [66] P. Ruiz-Castillo, S.L. Buchwald, *Chem. Rev.* 116 (2016) 12564–12649.
- [67] S.B. Herzon, J.F. Hartwig, *J. Am. Chem. Soc.* 130 (2008) 14940–14941.
- [68] L. Huang, M. Arndt, K.T. Gooßen, H. Heydt, L.J. Goossen, *Chem. Rev.* 115 (2015) 2596–2697.
- [69] P. Kalck, M. Urrutigoity, *Chem. Rev.* 118 (2018) 3833–3861.
- [70] F. Perez, S. Oda, L.M. Geary, M.J. Krische, *Top. Curr. Chem.* 374 (2016) 365–387.
- [71] M. Chilamari, J.R. Immel, S. Bloom, *ACS Catal.* 10 (2020) 12727–12737.
- [72] G. Wuitschik, E.M. Carreira, B.r. Wagner, et al., *J. Med. Chem.* 53 (2010) 3227–3246.
- [73] D. Ravelli, M. Zoccolillo, M. Mella, M. Fagnoni, *Adv. Synth. Catal.* 356 (2014) 2781–2786.
- [74] S.H. Oh, Y.R. Malpani, N. Ha, Y.S. Jung, S.B. Han, *Org. Lett.* 16 (2014) 1310–1313.
- [75] J. Yang, Z. Sun, K. Yan, et al., *Green Chem.* 23 (2021) 2756–2762.
- [76] Y.H. Lu, C. Wu, J.C. Hou, et al., *ACS Catal.* 13 (2023) 13071–13076.
- [77] H.T. Ji, K.L. Wang, W.T. Ouyang, et al., *Green Chem.* 25 (2023) 7983–7987.
- [78] P.V. Fish, A.D. Brown, E. Evrard, L.R. Roberts, *Bioorg. Med. Chem. Lett.* 19 (2009) 1871–1875.
- [79] A. Brown, T.B. Brown, A. Calabrese, et al., *Bioorg. Med. Chem. Lett.* 20 (2010) 516–520.
- [80] M. Maetani, J. Zoller, B. Melillo, et al., *J. Am. Chem. Soc.* 139 (2017) 11300–11306.
- [81] M.R. Becker, E.R. Wearing, C.S. Schindler, *Nat. Chem.* 12 (2020) 898–905.
- [82] F. Wang, C. Chen, G. Deng, C. Xi, *J. Org. Chem.* 77 (2012) 4148–4151.
- [83] F. Ke, Y. Qu, Z. Jiang, et al., *Org. Lett.* 13 (2011) 454–457.
- [84] Z. Chen, Q. Yan, Z. Liu, Y. Zhang, *Chem. Eur. J.* 20 (2014) 17635–17639.
- [85] M.E. Daub, M. Ehrenschaft, *Annu. Rev. Phytopathol.* 38 (2000) 461–490.
- [86] Y. Zhang, Y. Cao, L. Lu, et al., *J. Org. Chem.* 84 (2019) 7711–7721.
- [87] J.B. Metternich, R. Gilmour, *J. Org. Chem.* 138 (2016) 1040–1045.
- [88] G.K. Jana, S. Paul, S. Sinha, *Org. Prep. Proc. Int.* 43 (2011) 541–573.
- [89] X.Y. Liu, Y. Qin, *Acc. Chem. Res.* 52 (2019) 1877–1891.
- [90] Z. Zhang, D. Yi, M. Zhang, et al., *ACS Catal.* 10 (2020) 10149–10156.
- [91] M.S. Oderinde, J. Kempson, D. Smith, et al., *Eur. J. Org. Chem.* 2020 (2020) 41–46.
- [92] Y. Bansal, O.J.B. Silakari, *Bioorg. Med. Chem.* 20 (2012) 6208–6236.
- [93] P.A. Renhowe, S. Pecchi, C.M. Shafer, et al., *J. Med. Chem.* 52 (2009) 278–292.
- [94] C. Zhang, B. Zhong, S. Yang, et al., *Bioorg. Med. Chem.* 23 (2015) 3774–3780.
- [95] P.D. Verdouw, J.M. Hartog, D.J. Duncker, W. Roth, P.R. Saxena, *Eur. J. Pharmacol.* 126 (1986) 21–30.
- [96] R. Mocharla, H. Mocharla, M.E. Hodes, *Nucleic Acids Res.* 15 (1987) 10589.
- [97] Y. Kim, M.R. Kumar, N. Park, Y. Heo, S. Lee, *J. Org. Chem.* 76 (2011) 9577–9583.
- [98] K. Bahrami, M.M. Khodaei, F. Naali, *J. Org. Chem.* 73 (2008) 6835–6837.
- [99] J. Kovvuri, B. Nagaraju, A. Kamal, A.K. Srivastava, *ACS Comb. Sci.* 18 (2016) 644–650.
- [100] J.W. Tucker, J.M. Narayanam, S.W. Krabbe, C.R. Stephenson, *Org. Lett.* 12 (2010) 368–371.
- [101] H. Huang, M. Yu, X. Su, et al., *J. Org. Chem.* 83 (2018) 2425–2437.
- [102] P.D. Bass, D.A. Gubler, T.C. Judd, R.M. Williams, *Chem. Rev.* 113 (2013) 6816–6863.
- [103] T. Sasase, H. Morinaga, T. Abe, et al., *Diabet. Obes. Metab.* 11 (2009) 1084–1087.
- [104] V.M. Dembitsky, *J. Nat. Med.* 62 (2008) 1–33.
- [105] S. Ren, F. Pan, W. Zhang, G.W. Rao, *Curr. Med. Chem.* 29 (2022) 4113–4135.
- [106] E. Lee-Ruff, G. Mladenova, *Chem. Rev.* 103 (2003) 1449–1484.
- [107] Y. Xu, M.L. Conner, M.K. Brown, *Angew. Chem. Int. Ed.* 54 (2015) 11918–11928.
- [108] T. Sravanthi, S. Manju, *Eur. J. Pharm. Sci.* 91 (2016) 1–10.
- [109] N. Chadha, O. Silakari, *Eur. J. Med. Chem.* 134 (2017) 159–184.
- [110] M.S. Oderinde, A. Ramirez, T.M. Dhar, et al., *J. Org. Chem.* 86 (2020) 1730–1747.
- [111] L.R. Orgren, E.E. Maverick, C.C. Marvin, *J. Org. Chem.* 80 (2015) 12635–12640.
- [112] A. Bossi, L. Chopard-dit-Jean, O. Schnider, *Helv. Chim. Acta* 41 (1958) 1793–1806.
- [113] B. Giese, B. Kopping, T. Göbel, et al., *Org. React.* 48 (2004) 301–856.
- [114] Y. Liu, M. Zhang, C.H. Tung, Y. Wang, *ACS Catal.* 6 (2016) 8389–8394.
- [115] Z. Li, H. Song, R. Guo, et al., *Green Chem.* 21 (2019) 3602–3605.
- [116] X. Zhuang, X. Shi, R. Zhu, et al., *Org. Chem. Front.* 8 (2021) 736–742.
- [117] S. Özden, D. Atabey, S. Yıldız, H. Göker, *Bioorg. Med. Chem.* 13 (2005) 1587–1597.
- [118] J.Y. Chai, B.K. Jung, S.J. Hong, *Korean J. Parasitol.* 59 (2021) 189.
- [119] S.M. Sondhi, S. Rajvanshi, M. Johar, et al., *Eur. J. Med. Chem.* 37 (2002) 835–843.
- [120] X.Z. Guo, L. Shi, R. Wang, et al., *Bioorg. Med. Chem.* 16 (2008) 10301–10310.
- [121] A. Chimirri, A. De Sarro, G. De Sarro, R. Gitto, M. Zappala, *Farmaco* 56 (2001) 821–826.
- [122] A. Lee-Dutra, K.L. Arienti, D.J. Buzard, et al., *Bioorg. Med. Chem. Lett.* 16 (2006) 6043–6048.
- [123] M.J. O’Neil, M. Smith, P. Heckelman, *The Merck Index*, 13th Edition, Merck and Co, Inc NJ, 2001, p. 1785.
- [124] I. Siddiqui, F. Ibad, A. Ibad, M.A. Waseem, G. Watal, *Tetrahedron Lett.* 57 (2016) 5–10.
- [125] A. Armstrong, J.C. Collins, *Angew. Chem. Int. Ed.* 49 (2010) 2282–2285.
- [126] A. Gauld, *STEPS: suvorexant (Belsomra) for insomnia*, *Am. Fam. Phys.* 93 (2016) 1016.
- [127] V.S. Patil, D.V. Patil, S.S. Potdar, *Org. Commun.* 15 (2022) 71–80.
- [128] V.K. Yadav, V.P. Srivastava, L.D.S. Yadav, *Tetrahedron Lett.* 57 (2016) 155–158.
- [129] S. Zykova, S. Shurov, V. Talismanov, et al., *J. Pharm. Sci. Res.* 10 (2018) 947–949.
- [130] Z.P. Ye, Y.Z. Hu, J.P. Guan, et al., *Org. Lett.* 23 (2021) 4754–4758.
- [131] G. Zhou, X. Deng, C. Pan, et al., *Chem. Comm.* 56 (2020) 12546–12549.
- [132] C. Russo, R. Cannalire, P. Luciano, et al., *Synthesis* 53 (2021) 4419–4427.
- [133] G.E. Crisenza, P. Melchiorre, *Nat. Commun.* 11 (2020) 1–4.
- [134] V.R. Solomon, H. Lee, *Curr. Med. Chem.* 18 (2011) 1488–1508.
- [135] J.X. Xu, N.L. Pan, J.X. Chen, J.W. Zhao, *J. Org. Chem.* 86 (2021) 10747–10754.
- [136] J. Ma, F. Schäfers, C. Daniliuc, et al., *Angew. Chem.* 132 (2020) 9726–9732.
- [137] C.E. Knappe, S. Grupe, D. Gärtner, et al., *Chem. Eur. J.* 20 (2014) 6828–6842.
- [138] D.A. Everson, D.J. Weix, *J. Org. Chem.* 79 (2014) 4793–4798.
- [139] P.J. Xia, Z.P. Ye, D. Song, et al., *Chem. Comm.* 55 (2019) 2712–2715.
- [140] X. Tian, Y. Guo, W. An, et al., *Nat. Commun.* 13 (2022) 6186.
- [141] S. Tripathi, L.D.S. Yadav, *New J. Chem.* 42 (2018) 3765–3769.
- [142] R.W. Gantt, P. Peltier-Pain, J.S. Thorson, *Nat. Prod. Rep.* 28 (2011) 1811–1853.
- [143] Y. Yang, B. Yu, *Chem. Rev.* 117 (2017) 12281–12356.
- [144] Q. Wu, J.G. Cho, D.S. Lee, et al., *Carbohydr. Res.* 372 (2013) 9–14.
- [145] W. Disadee, C. Mahidol, P. Sahakitpichan, et al., *Phytochemistry* 74 (2012) 115–122.
- [146] T. Kawamata, M. Nagatomo, M. Inoue, *J. Am. Chem. Soc.* 139 (2017) 1814–1817.
- [147] S.O. Badir, A. Dumoulin, J.K. Matsui, G.A. Molander, *Angew. Chem. Int. Ed.* 57 (2018) 6610–6613.
- [148] X. Wang, J. Dong, Y. Liu, H. Song, Q. Wang, *Chin. Chem. Lett.* 32 (2021) 3027–3030.
- [149] M.P. DeMartino, K. Chen, P.S. Baran, *J. Am. Chem. Soc.* 130 (2008) 11546–11560.
- [150] Y. Kuang, K. Wang, X. Shi, et al., *Angew. Chem.* 131 (2019) 17015–17019.
- [151] S. Li, P.W. Davies, W. Shu, *Chem. Sci.* 13 (2022) 6636–6641.
- [152] N.A. Romero, K.A. Margrey, N.E. Tay, D.A. Nicewicz, *Science* 349 (2015) 1326–1330.

- [153] J.K. Matsui, D.N. Primer, G.A. Molander, *Chem. Sci.* 8 (2017) 3512–3522.
- [154] H. Liu, L. Ge, D.X. Wang, N. Chen, C. Feng, *Angew. Chem.* 131 (2019) 3958–3962.
- [155] M.A. Miranda, M.L. Marin, *Curr. Opin. Green Sustain. Chem.* 6 (2017) 139–149.
- [156] L. Guillemard, N. Kaplaneris, L. Ackermann, M.J. Johansson, *Nat. Rev. Chem.* 5 (2021) 522–545.
- [157] B. Liu, L. Yang, P. Li, F. Wang, X. Li, *Org. Chem. Front.* 8 (2021) 1085–1101.
- [158] K.J. Jiao, Y.K. Xing, Q.L. Yang, H. Qiu, T.S. Mei, *Acc. Chem. Res.* 53 (2020) 300–310.
- [159] S. Vidyacharan, B.T. Ramanjaneyulu, S. Jang, D.P. Kim, *ChemSusChem* 12 (2019) 2581–2586.
- [160] C. Hou, S. Sun, Z. Liu, et al., *Adv. Synth. Catal.* 363 (2021) 2806–2812.
- [161] H.Y. Song, F. Xiao, J. Jiang, et al., *Chin. Chem. Lett.* (2023) 108509.
- [162] H. Xu, X. Li, J. Ma, et al., *Chin. Chem. Lett.* (2023) 108403.
- [163] H. Cerecetto, A. Gerpe, M. Gonzalez, V.J. Aran, C.O. de Ocariz, *Mini-Rev. Med. Chem.* 5 (2005) 869–878.
- [164] X. Li, S. Chu, V.A. Feher, et al., *J. Med. Chem.* 46 (2003) 5663–5673.
- [165] G. Picciola, F. Ravenna, G. Carenini, P. Gentili, M. Riva, *Il Farmaco, Edizione Sci.* 36 (1981) 1037–1056.
- [166] W. Han, J.C. Pelletier, C.N. Hodge, *Bioorg. Med. Chem. Lett.* 8 (1998) 3615–3620.
- [167] J. Liu, C. Qian, Y. Zhu, et al., *Bioorg. Med. Chem.* 26 (2018) 747–757.
- [168] S.V. Keisner, S.R. Shah, *Drugs* 71 (2011) 443–454.
- [169] A. Unsinn, P. Knochel, *Chem. Comm.* 48 (2012) 2680–2682.
- [170] S.A. Ohnmacht, A.J. Culshaw, M.F. Greaney, *Org. Lett.* 12 (2010) 224–226.
- [171] X. Ding, J. Bai, H. Wang, et al., *Tetrahedron* 73 (2017) 172–178.
- [172] G. Bogonda, H.Y. Kim, K. Oh, *Org. Lett.* 20 (2018) 2711–2715.
- [173] W. Zhang, X.X. Xiang, J. Chen, et al., *Nat. Commun.* 11 (2020) 1–10.
- [174] P. Nuhant, M.S. Oderinde, J. Genovino, et al., *Angew. Chem. Int. Ed.* 56 (2017) 15309–15313.
- [175] Q.Q. Han, D.M. Chen, Z.L. Wang, et al., *Chin. Chem. Lett.* 32 (2021) 2559–2561.
- [176] M.D. Tzirakis, I.N. Lykakis, M. Orfanopoulos, *Chem. Soc. Rev.* 38 (2009) 2609–2621.
- [177] D. Mazzarella, A. Pulcinella, L. Bovy, R. Broersma, T. Noël, *Angew. Chem. Int. Ed.* 60 (2021) 21277–21282.
- [178] Y.W. Zheng, R. Narobe, K. Donabauer, S. Yakubov, B. König, *ACS Catal.* 10 (2020) 8582–8589.
- [179] J.Y. Dong, H.P. He, Y.M. Shen, K.Q. Zhang, *J. Nat. Prod.* 68 (2005) 1510–1513.
- [180] C. Takahashi, A. Numata, E. Matsumura, et al., *J. Antibiot.* 47 (1994) 1242–1249.
- [181] C.J. Zheng, C.J. Kim, K.S. Bae, Y.H. Kim, W.G. Kim, *J. Nat. Prod.* 69 (2006) 1816–1819.
- [182] L. Furst, J.M. Narayanam, C.R. Stephenson, *Angew. Chem. Int. Ed.* 50 (2011) 9655.
- [183] D.A. Nagib, D.W. MacMillan, *Nature* 480 (2011) 224–228.
- [184] I.B. Seiple, S. Su, R.A. Rodriguez, et al., *J. Am. Chem. Soc.* 132 (2010) 13194–13196.
- [185] R. Pschorr, *Ber. Dtsch. Chem. Ges.* 29 (1896) 496–501.
- [186] D. Xue, Z.H. Jia, C.J. Zhao, et al., *Chem. Eur. J.* 20 (2014) 2960–2965.
- [187] E.R. Welin, A.A. Warkentin, J.C. Conrad, D.W. MacMillan, *Angew. Chem. Int. Ed.* 54 (2015) 9668–9672.
- [188] A. Singh, A. Arora, J.D. Weaver, *Org. Lett.* 15 (2013) 5390–5393.
- [189] D.A. DiRocco, K. Dykstra, S. Kraska, et al., *Angew. Chem. Int. Ed.* 53 (2014) 4802–4806.
- [190] G. Lei, M. Xu, R. Chang, I. Funes-Ardoiz, J. Ye, *J. Am. Chem. Soc.* 143 (2021) 11251–11261.
- [191] J.M. Mayer, *Acc. Chem. Res.* 44 (2011) 36–46.
- [192] M. Costas, M. Bietti, *Acc. Chem. Res.* 51 (2018) 2601–2602.
- [193] C.R. Stephenson, T.P. Yoon, D.W. MacMillan, *Visible Light Photocatalysis In Organic Chemistry*, John Wiley & Sons, 2018.
- [194] D. Staveness, I. Bosque, C.R. Stephenson, *Acc. Chem. Res.* 49 (2016) 2295–2306.
- [195] B.P. Roberts, *Chem. Soc. Rev.* 28 (1999) 25–35.
- [196] S. Cao, W. Hong, Z. Ye, L. Gong, *Nat. Commun.* 12 (2021) 2377.
- [197] H. Du, C. Fairbridge, H. Yang, Z. Ring, *Appl. Catal. A: Gen.* 294 (2005) 1–21.
- [198] W. Zhang, Y.L. Pan, C. Yang, X. Li, B. Wang, *Org. Chem. Front.* 6 (2019) 2765–2770.
- [199] X. Zhu, X. Song, X. Li, et al., *Adv. Synth. Catal.* 364 (2022) 4384–4391.
- [200] W. Ou, G. Zhang, J. Wu, C. Su, *ACS Catal.* 9 (2019) 5178–5183.
- [201] X.Z. Fan, J.W. Rong, H.L. Wu, et al., *Angew. Chem.* 130 (2018) 8650–8654.
- [202] I. Funes-Ardoiz, F. Maseras, *ACS Catal.* 8 (2018) 1161–1172.
- [203] H.Y. Song, J. Jiang, C. Wu, et al., *Green Chem.* 25 (2023) 3292–3296.
- [204] J. Li, J. Chen, R. Sang, et al., *Nat. Chem.* 12 (2020) 56–62.
- [205] X. Sun, J. Chen, T. Ritter, *Nat. Chem.* 10 (2018) 1229–1233.
- [206] H.G. Yayla, F. Peng, I.K. Mangion, et al., *Chem. Sci.* 7 (2016) 2066–2073.
- [207] J.J. Douglas, H. Albright, M.J. Sevrin, K.P. Cole, C.R. Stephenson, *Angew. Chem. Int. Ed.* 54 (2015) 14898–14902.
- [208] Y.F. Liang, M. Bilal, L.Y. Tang, et al., *Chem. Rev.* 123 (2023) 12313–12370.
- [209] C.C. Le, D.W. MacMillan, *J. Am. Chem. Soc.* 137 (2015) 11938–11941.
- [210] V.K. Soni, S. Lee, J. Kang, et al., *ACS Catal.* 9 (2019) 10454–10463.
- [211] C. Ma, Z. Feng, J. Li, et al., *Org. Chem. Front.* 8 (2021) 3286–3291.
- [212] X. Shu, R. Xu, S. Liao, *Sci. China Chem.* 64 (2021) 1756–1762.
- [213] R. Xu, T. Xu, M. Yang, T. Cao, S. Liao, *Nat. Commun.* 10 (2019) 3752.
- [214] K. Okada, K. Okamoto, M. Oda, *J. Am. Chem. Soc.* 110 (1988) 8736–8738.
- [215] D.M. Gale, W.J. Middleton, C.G. Krespan, *J. Am. Chem. Soc.* 88 (1966) 3617–3623.
- [216] D.H. Barton, J.C. Jaszberenyi, E.A. Theodorakis, J. Reibenspies, *J. Am. Chem. Soc.* 115 (1993) 8050–8059.



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