catalysts

Review

Visible-Light-Driven α-C(sp^3)–H Bond Functionalization of Glycine Derivatives

Yao Tian [1], Xiubin Bu [1], Yuanrui Chen [1], Luohe Wang [1], Junnan E [1], Jing Zeng [1], Hao Xu [2,3,*], Aihong Han [1,*], Xiaobo Yang [1,2,*] and Zhen Zhao [1]

[1] Institute of Catalysis for Energy and Environment, College of Chemistry and Chemical Engineering, Shenyang Normal University, Shenyang 110034, China; 13840996737@163.com (Y.T.); buxb@synu.edu.cn (X.B.); yuanrui84116@163.com (Y.C.); wangluohe5413@163.com (L.W.); ejunnan0118@163.com (J.E.); 13840169428@163.com (J.Z.); zhenzhao@cup.edu.cn (Z.Z.)

[2] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China

[3] Institute of Functional Organic Molecular Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, China

* Correspondence: xuhao@henu.edu.cn (H.X.); hanhong@synu.edu.cn or hanhong@hotmail.com (A.H.); bxy1223@gmail.com or yangxb@synu.edu.cn (X.Y.)

Abstract: The glycine motif is widely prevalent in bioactive peptides. Thus, the direct and precise modification of glycine derivatives has attracted significant attention over the past few decades. Among various protocols for the modification of glycine derivatives, the visible-light-driven direct α-C(sp^3)–H bond functionalization of glycine derivatives has emerged as a powerful tool to achieve this objective, owing to its merits in atom economy, selectivity, reaction simplicity, and sustainability. This review summarizes the recent advancements in visible-light-driven direct α-C(sp^3)–H bond functionalization of glycine derivatives. The contents of this review are organized based on the photocatalysts employed and the various reaction modes in the functionalization process. The mechanism, the challenges encountered, and future trends are also discussed, enabling readers to understand the current developmental status in this field.

Keywords: visible-light-driven; α-C(sp^3)–H bond; C–H bond functionalization; glycine derivatives

Citation: Tian, Y.; Bu, X.; Chen, Y.; Wang, L.; E, J.; Zeng, J.; Xu, H.; Han, A.; Yang, X.; Zhao, Z. Visible-Light-Driven α-C(sp^3)–H Bond Functionalization of Glycine Derivatives. *Catalysts* **2023**, *13*, 1502. https://doi.org/10.3390/catal13121502

Academic Editor: Broggini Gianluigi

Received: 16 November 2023
Revised: 1 December 2023
Accepted: 5 December 2023
Published: 8 December 2023

1. Introduction

Visible light, a renewable energy resource, emerges as a prime reagent conducive to environmentally sustainable and green chemical synthesis. In recent decades, a noteworthy upswing in interest has been observed, regarding the utilization of visible light to expedite organic transformations [1–4]. The integration of visible light into the reaction system consistently facilitates high-energy consumption synthetic processes under remarkably mild reaction conditions. Notably, the abundance of wavelengths within the visible light spectrum, as manifested in the solar spectrum, underscores the potential of visible-light-driven organic reactions as a promising, clean, cost-effective, and sustainable alternative for synthesizing functional organic molecules.

As the simplest α-amino acid, glycine's direct derivatization and modification could consistently deliver diverse unnatural amino acids that are meaningful for constructing bioactive peptides and peptide drugs [5–7]. For this reason, the past decades have seen a booming interest in the direct derivatization and modification of glycine derivatives. Many pioneering works toward this target have been intensively reported. Among them, the direct α-C(sp^3)–H bond functionalization of glycine derivatives is privileged, owing to the inherent advantages of the atom economy, chemoselectivity, and reaction simplicity [8–14]. To date, according to the reaction modes, the strategies for accomplishing this process could be classified into four types: (1) Strong base-assisted functionalization of α-carbanions [15]; (2) Traditional radical precursors involved or UV light promoted direct radical coupling [16–20]; (3) Transition-metal catalyzed or thermal catalytic cross-dehydrogenative coupling (CDC) [21–36]; (4) Visible-light-driven α-C(sp^3)–H bond functionalization [37–42].

Among these strategies, visible-light-driven α-C(sp^3)–H bond functionalization has demonstrated a progressive trajectory, characterized by its propensity for mild reaction conditions, judicious utilization of solar energy, commendable reaction efficiency, and concomitant adherence to environmentally conscientious practices [37–42]. More importantly, benefiting from the very mild reaction conditions of this strategy, it might possess the following two superiorities: (1) The direct modification of glycine motif-containing polypeptides with undisturbed biological functions and spatial structures [43–45]; (2) The excellent reaction stereoselectivity assisted by the chiral ligands or additives [46,47]. Recently, the visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives has been successfully used for constructing the C–C bond and C–X bond, producing a variety of α-substituted glycine derivatives efficiently and selectively (Figure 1) [37–42]. The construction of C–C bonds mainly proceeded via the α-alkylation and α-arylation. The photocatalytic cycle always involved visible-light-driven single electron transfer (SET) and the following cascade transformations [48].

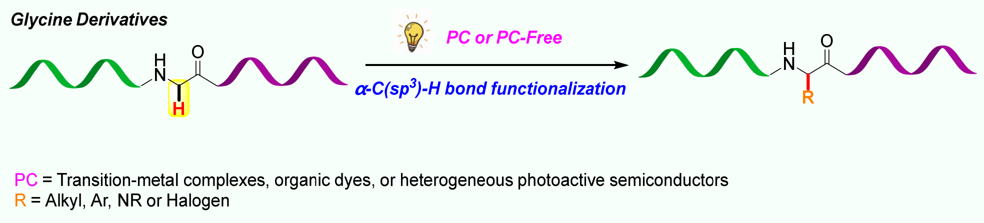


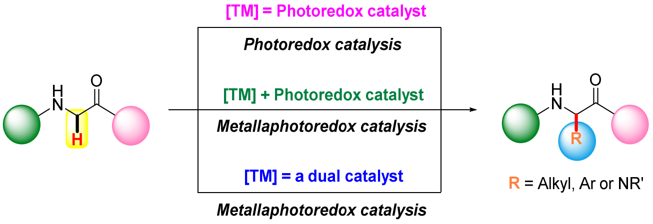
Figure 1. Visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives.

It is widely recognized that the short-conjugated system of many glycine derivatives hinders the direct absorption of visible light. Consequently, the augmentation of photocatalytic efficiency in such reactions commonly relies on the utilization of external photocatalysts, which include transition-metal complexes, organic dyes, and heterogeneous photoactive semiconductors. Nonetheless, noteworthy investigations have emerged wherein visible-light-driven α-C(sp^3)–H bond functionalization has been accomplished without the reliance on traditional photocatalysts. These findings suggest that electron donor-acceptor (EDA) complexes formed within the confines of these reaction systems possess the capacity to function as internal photocatalysts [49,50].

This comprehensive review summarizes the recent advancements in visible-light-driven C–H bond functionalization of glycine derivatives. The organization is based on the type of photocatalyst employed and the reaction modes utilized. Furthermore, the review discusses the reaction mechanisms and challenges associated with specific cases. This review aims to impart readers with an in-depth understanding of this promising field and inspire further development of this novel strategy for modifying molecules containing the glycine motif.

2. Visible-Light-Driven α-C(sp^3)–H Bond Functionalization of Glycine Derivatives with Transition-Metal Complexes

Transition-metal (TM) complexes have been extensively utilized in the visible-light-driven α-C(sp^3)–H bond functionalization glycine derivatives. The role of transition-metal complexes within this context can be categorized into three primary functions based on the reaction mechanism. Firstly, transition-metal complexes, such as Ru or Ir complexes, act solely as photocatalysts, absorbing visible light and initiating the photocatalytic cycle through energy transfer (ET) or single electron transfer (SET). Secondly, transition-metal salts work synergistically with the photocatalyst to facilitate the reaction, exclusively contributing to the transition-metal catalytic cycle. Lastly, the transition-metal complex serves as a dual catalyst in the reaction system by harnessing visible light and enabling the transition-metal catalytic cycle (Scheme 1).



Scheme 1. Different roles of [TM] in visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives.

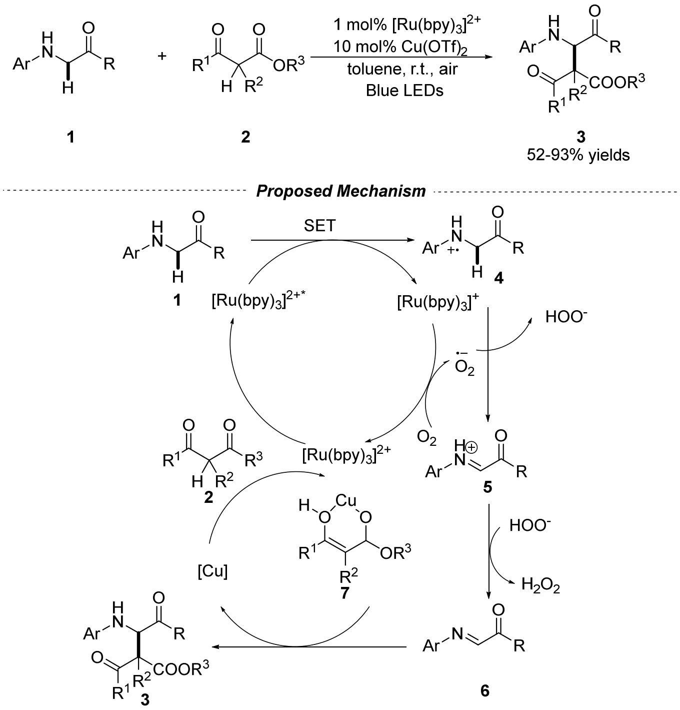
Over the past few decades, there have been significant advancements in the utilization of transition metal complexes to drive visible-light-induced reactions involving glycine derivatives. These developments have brought about noteworthy improvements in reaction selectivity, efficiency, and the range of applicable substrates. This section explores representative examples within this context, considering the specific reaction types and the pivotal role transition metal complexes play in the photocatalytic cycle.

2.1. α-C(sp^3)–C Bond Formation

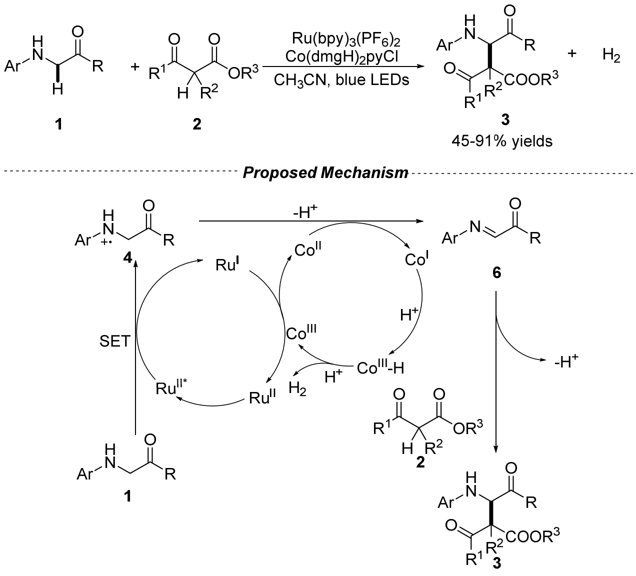
2.1.1. α-C(sp^3)–H Alkylation

The utilization of visible light to drive the α-C(sp^3)–H alkylation of glycine derivatives represents a versatile method to generate alkylated glycine derivatives or valuable heterocycles via subsequent cascade cyclization [51–59]. Various alkyl sources were constantly employed in this alkylation, including β-keto esters, alkyl boronic acids, alkanes, alkyl Katritzky salts, and NHPI esters. The accomplishment of this alkylation primarily relies on a radical cross-coupling or a transition metal-catalyzed nucleophilic process. In 2013, Wu et al. introduced a dual photocatalytic system for the α-C(sp^3)–H alkylation of glycine derivatives **1** using $Ru(bpy)_3Cl_2$ and $Cu(OTf)_2$ (Scheme 2) [60]. In this approach, with visible light exposure in the presence of air, the photocatalyst $Ru(bpy)_3Cl_2$ facilitates the initial oxidation of glycine derivatives **1** to iminium intermediates, which could be isolated without the alkylation partner under the standard reaction conditions. Concurrently, the nucleophilic alkyl source, β-keto esters **2**, coordinated with the copper catalyst to enhance the β-keto esters' nucleophilicity. Subsequently, the nucleophilic reaction of the copper complex with the iminium intermediate occurs efficiently, leading to the selective and efficient generation of a broad array of α-C(sp^3) alkylated products. This particular α-C(sp^3)–H alkylation strategy harmonizes photoredox and copper catalysis, with the Ru complex serving solely as the photocatalyst. In contrast to conventional transition-metal catalyzed thermal methods, this approach yields comparable productivity while operating under mild reaction conditions and obviates the need for stoichiometric external oxidants.

In 2015, the same research group reported an alternative protocol for the visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives with β-keto esters. This approach involved the utilization of $Ru(bpy)_3(PF_6)_2$ as a photocatalyst to instigate the visible-light-driven single electron transfer (SET) process for the oxidation of glycine derivatives. $Co(dmgH)_2pyCl$ (where dmgH signifies dimethylglyoximate) served as a metal catalyst, responsible for the interception of electrons and protons. Through the synergistic interplay of photoredox catalysis and cobalt catalysis, various alkylated glycine derivatives were efficiently synthesized under redox-neutral conditions. More importantly, due to using a cobalt catalyst, the reaction occurred sacrificial oxidant-free and external base-free. The sole byproduct, as substantiated through a series of deuterium experiments, is hydrogen gas. (Scheme 3) [61].

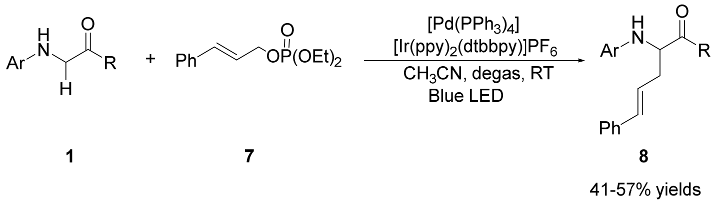


Scheme 2. A dual photocatalytic system for the α-C–H alkylation of glycine derivatives with β-keto esters.



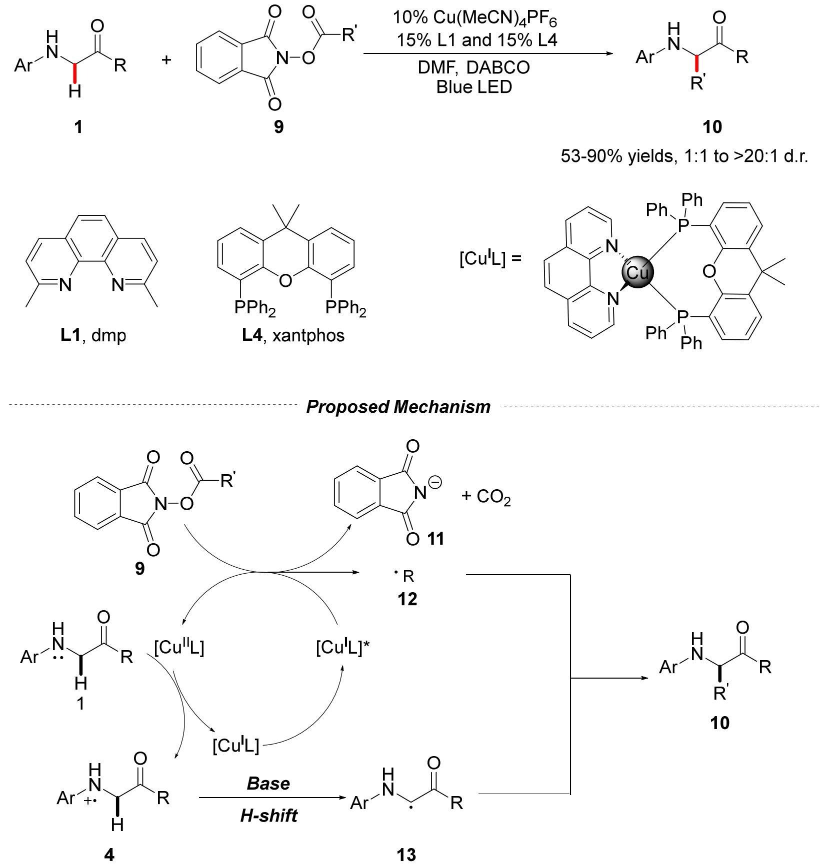
Scheme 3. A Ru/Co co-catalyzed visible-light-driven alkylation of glycine esters with β-keto es-ters.

As a powerful transition-metal catalyst in cross-coupling and C–H bond activation reactions, the Pd complex can also work with photocatalysts to trigger the visible-light-driven α-C–H alkylation of glycine derivatives [62]. In 2015, Xiao et al. disclosed a combination of palladium catalysis and visible light photoredox catalysis for the α-C–H allylation of glycine derivatives (Scheme 4) [63]. In this reaction, [Pd(PPh_3)$_4$] and [Ir(ppy)$_2$(dtbbpy)]PF_6 were used as co-catalysts, and cinnamyl diethyl phosphates **7** were selected to be the allyl source. The proposed reaction mechanism indicated that visible-light-excited Ir(III)* oxidized the glycine derivative to deliver the radical cation of the glycine derivative. Subsequently, the allyl radical was generated from the reduction of α-allylpalladium (II) complex by Ir(II). Then, the radical cross-coupling of the radical cation and the allyl radical produced the desired α-C–H allylation product.



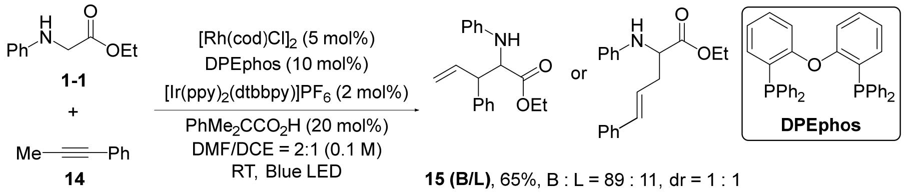
Scheme 4. Visible-light-driven α-C–H allylation of glycine derivatives with cinnamyl diethyl phos–phate.

In the past few decades, the alkyl NHPI ester, a well-known alkyl radical source, was widely employed in visible-light-driven alkylation reactions [64–68]. As such, Xu et al. reported a visible-light-induced Cu-catalyzed α-C(sp^3)–H decarboxylative alkylation of glycine derivatives and alkyl NHPI esters in 2018 (Scheme 5) [69]. This approach features excellent functional group tolerance, high efficiency, and mild reaction conditions. More importantly, the reaction is compatible with synthesizing diverse alkylated peptides, providing an optimistic application potential in developing peptide drugs. Control experiments revealed that the inclusion of the copper catalyst with the two ligands (L1 = dmp, L4 = xantpho) is imperative for achieving optimal reaction productivity. The copper complex might function exclusively as a photosensitizer. Upon the blue LED light irradiation, the excited copper complex [Cu^IL]* reduced the NHPI ester **9** to give the alkyl radical **12** via a single electron transfer (SET). Meanwhile, the formed [Cu^{II}L] species oxidized the glycine derivative **1** to generate the radical cation intermediate **4**. Intermediate **4** underwent deprotonation and subsequent 1,2-*H* shift process in the presence of a base, forming the stable α-carbon radical **13**. Finally, a radical–radical cross-coupling between alkyl radical **12** and α-carbon radical **13** occurred to deliver the alkylated product **10**.



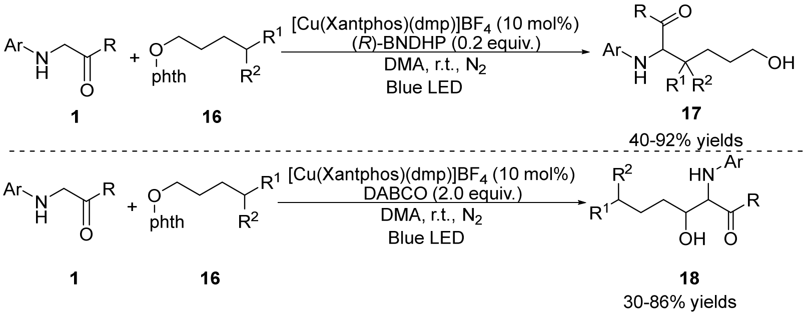
Scheme 5. Visible-light-driven Cu-catalyzed C(sp^3)–H alkylation of glycine derivatives.

Due to the high reactivity of radicals, it is well-known that the regioselectivity control of radical-involved visible-light-driven reactions usually faces challenges in many scenarios [70]. In this context, a rhodium/photoredox dual-catalyzed regiodivergent α-allylation of glycine derivatives was developed by Breit in 2019 (Scheme 6) [71]. In this protocol, 1-phenyl-1-propyne **14** was employed as the allyl source. With the cooperation of photoredox catalysis and Rh catalysis, the radical intermediate generated from the photoredox catalytic cycle reacted with the Rh-coordinated alkyne regioselectively, delivering the corresponding homoallylic glycine derivative (branched or linear, B/L) in 65% yield. This direct and regioselective synthetic strategy serves as a complementary approach to other transition-metal-catalyzed allylation protocols.



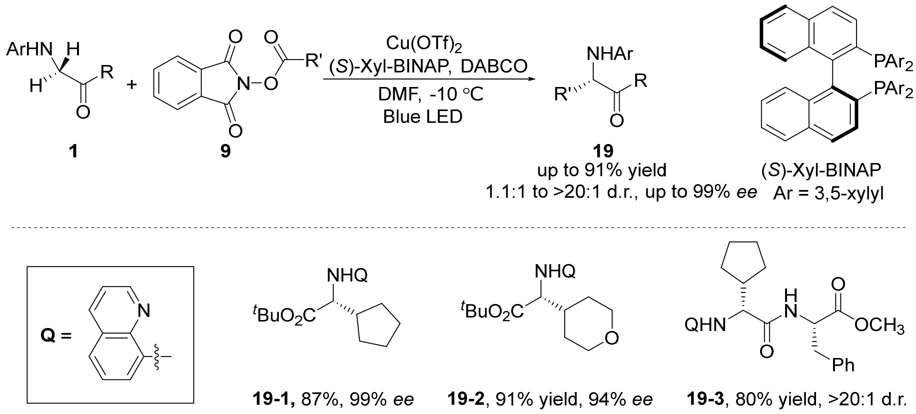
Scheme 6. A rhodium/photoredox catalyzed α-allylation of glycine derivatives.

Continuous focusing on the regioselectivity of visible-light-driven reactions, in the same year, Duan et al. presented a controllable regioselective visible-light-driven α-C(sp^3)−H alkylation reaction of glycine derivatives (Scheme 7) [72]. In this case, *N*-alkoxyphthalimides **16** were employed as the alkyl source, and a copper complex ([Cu (Xantphos)(dmp)]BF$_4$) was used as the photocatalyst. The different additives tuned the reaction site. The introduction of *R*-BNDHP, an acid, prompted the 1,5- hydrogen atom transfer (HAT), delivering the δ-C(sp^3)–H alkylated alcohols (28 examples, 40–92% yields). While DABCO, a base, provided the α-C(sp^3)–H alkylated alcohols (18 examples, 30–86% yields). Notably, certain glycine acids underwent alkylation under modified conditions, accompanied by concurrent decarboxylation, yielding decarboxylated products seamlessly. The scalability of this reaction was demonstrated effectively, operating seamlessly in larger quantities, thus indicating a promising avenue for late-stage functionalization of peptides.



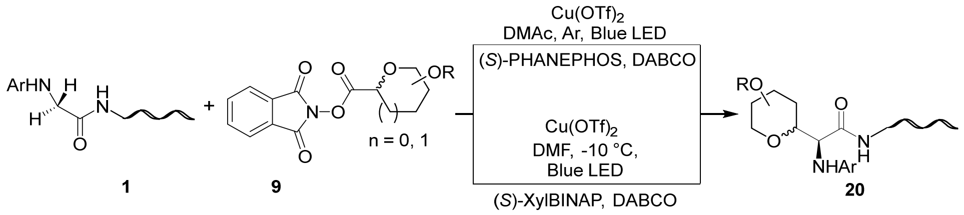
Scheme 7. A controllable regioselective visible-light-driven α-C(sp^3)–H alkylation reaction of glycine derivatives.

Apart from the regioselectivity control, the high reactivity of photogenerated radical ions or radicals also provides significant hurdles for controlling stereoselectivity in visible-light-driven catalytic organic processes. In 2021, Xu et al. reported a visible-light-induced Cu-catalyzed asymmetric C(sp^3)–H alkylation of glycine derivatives [73]. In this work, the NHPI ester was used as the alkyl radical source, and the copper complex generated from the copper salt and the organic chiral ligand was employed as a photocatalyst as well as a chiral catalyst (Scheme 8). The collaboration of chiral ligand (*S*)-BINAP and Cu(OTf)$_2$ elegantly controlled the stereoselectivity, giving the desired C(sp^3)−H alkylation product efficiently in high enantiomeric excess (*ee*) value (**19-1** to **19-3**). This reaction provides a new asymmetric approach for synthesizing essential molecules such as unnatural α-amino acids and bioactive peptides.



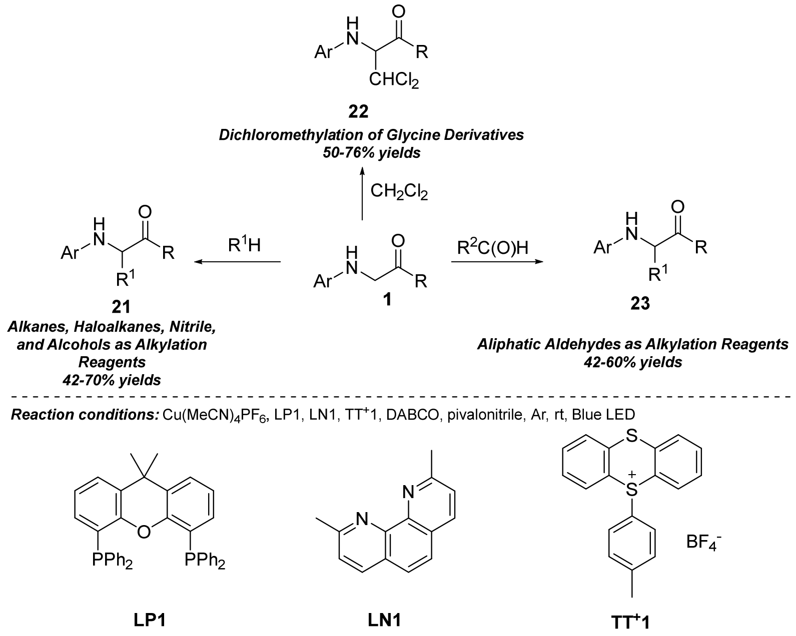
Scheme 8. A visible-light-induced Cu-catalyzed asymmetric C(sp^3)—H alkylation of glycine derivatives.

Recently, two indispensable works have successfully extended the above asymmetric photocatalytic synthesis. In these two works, using glycosyl NHPI esters as alternative alkylation sources delivered various glycopeptides stereoselectively under similar reaction conditions (Scheme 9) [74,75]. These two photocatalytic systems merged the photoredox and asymmetric catalysis, featuring a high efficiency and good functional group tolerance. More importantly, these two strategies might be suitable for the synthesis of carbohydrate moiety-containing peptides in an excellent stereoselective manner, which shows great application potential for the development of peptide drugs.



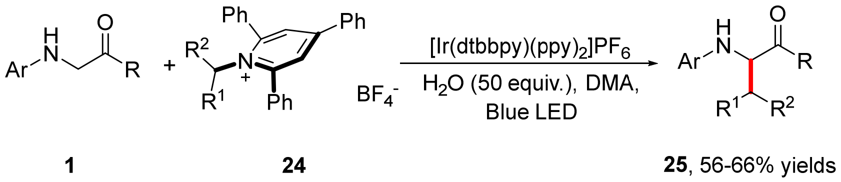
Scheme 9. Cu-catalyzed visible-light-driven stereoselective α-C(sp^3)–H glycosylation of glycine derivatives.

The photoactive copper complex possesses the inherent advantage over the Ru or Ir complex regarding availability and cost [76–79]. Therefore, it has become an effective photocatalyst in diverse visible-light-driven organic reactions [78]. In 2021, on their continuous interests in the modification of glycine derivatives [24–28,31,34], Huo et al. reported an efficient Cu-catalyzed visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives with diverse alkylation reagents (Scheme 10) [80]. Alkanes, haloalkanes, nitriles, alcohols, and even aliphatic aldehydes are all well-compatible with this alkylation reaction. In this photocatalytic cycle, with the aid of Cu photocatalyst and visible-light-irradiation, aryl radical, and α-amino radical formed via single electron transfer (SET), evidenced by the radical capture experiments. The C–H bond cleavage of the alkyl donor occurred via the hydrogen atom transfer (HAT) with the aryl radical, delivering the alkyl radical smoothly. The alkylation was finally accomplished by the direct radical coupling of the alkyl and the α-amino radical. In comparison to preceding methodologies, the current approach demonstrates advancements in accommodating a diverse range of alkylation sources, and notably, it operates without the requirement for external oxidants or reductants.



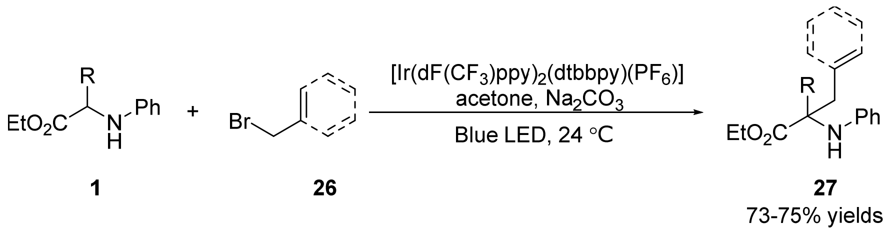
Scheme 10. An efficient Cu-catalyzed visible-light-driven C(sp^3)−H alkylation of glycine derivatives with diverse alkylation reagents.

Katritzky salts, assembled with 2,4,6-trimethylpyrylium tetrafluoroborate and alkylamines because of their low redox potential, have become popular alkyl radical precursors for visible-light-driven organic reactions [45,81]. In this regard, Lou et al. reported a visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives using Katritzky salts **24** as the alkyl source (Scheme 11) [82]. In this protocol, $[Ir(dtbbpy)(ppy)_2]PF_6$ was selected as the photocatalyst to reduce the Katritzky salts for the generation of alkyl radicals under blue LED irradiation. As a qualified alkyl radical donor, the Katritzky salts performed well and delivered diverse alkylated glycine derivatives precisely and efficiently. Due to the mild reaction conditions and high efficiency inherent in this approach, it can be effectively employed to modify drug molecules and bioactive peptides.



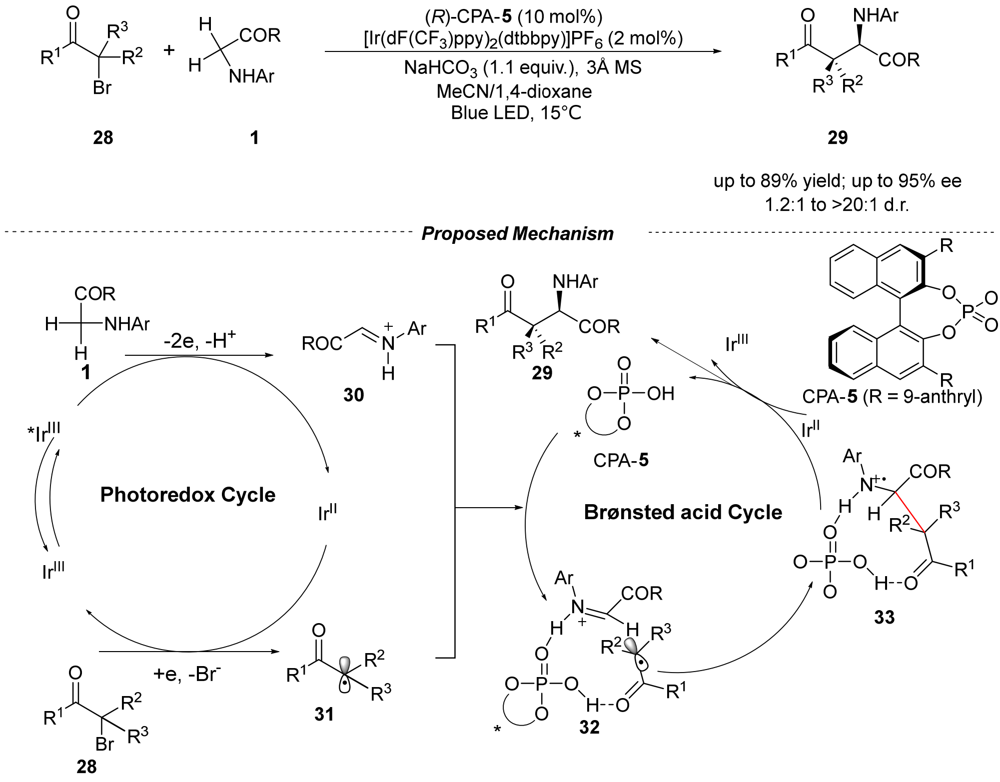
Scheme 11. Visible-light-driven α-C(sp^3)−H alkylation of glycine derivatives using Katritzky salts.

Alkyl bromides, as readily available alkyl sources, also can be applied to the visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives with a transition-metal complex. Accordingly, Ready et al. reported a visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives with alkyl bromides in 2019 (Scheme 12) [83]. In this visible-light-driven reaction, $[Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)]$ was chosen as the photocatalyst. Exploiting the appropriate photoredox potential of the Ir complex ($E_{1/2}^{ox}$ = 1.21 V vs. SCE, Ir^{+3*}/Ir^{2+}; $E_{1/2}^{red}$ = −1.37 vs. SCE, Ir^{2+}/Ir^{3+}), the photoexcited [Ir(III)]* complex facilitated the smooth oxidation of the glycine derivative into the α-amine radical. Simultaneously, the Ir(II) species exhibited the capability to reduce the alkyl bromide, yielding the corresponding alkyl radical. The cross-coupling of α-amine radical and alkyl radical produced the final alkylated glycine derivatives.



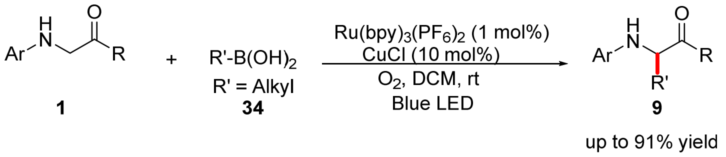
Scheme 12. A visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives with alkyl bromides.

Alkyl bromides also can be used as the effective alkyl donor in the visible-light-driven regioselective and enantioselective synthesis of alkylated glycine derivatives. In 2021, Wang et al. disclosed a merge of Brønsted acid/photoredox catalysis, enabling the synthesis of enantioenriched alkylated glycine derivatives with α-bromoketones as the alkylation reagents (Scheme 13) [84]. Depending on the combination of the Brønsted acid and the photoredox catalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, glycine esters **1** and racemic α-bromoketones **28** reacted smoothly, giving highly valuable alkylated glycine derivatives with two contiguous stereogenic centers. The photocatalytic cycle begins with the oxidation of the glycine ester **1** by the photoexcited $[Ir^{III}]^*$ through twice single electron transfer (SET) processes with the formation of $[Ir^{II}]$, leading to the iminium **30**. The $[Ir^{II}]$ species then reduces the α-bromoketone **28** into the carbon radical **31,** accompanied by the regeneration Ir photocatalyst. Subsequently, a stereoselective radical addition occurred with the help of chiral phosphoric acid (*R*)-CPA-**5**, giving the enantiomeric cationic radical **33**. Finally, **33** undergoes a reduction by the Ir^{II} species to produce the alkylation product **29** stereoselectively. In contrast to alternative methodologies, this approach holds a distinct advantage in achieving high diastereoselectivities and outstanding enantioselectivities. Consequently, it offers a straightforward pathway to accessing chiral amino acids.



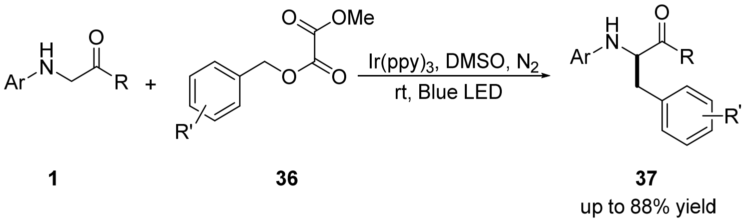
Scheme 13. A visible-light-driven regioselective and enantioselective synthesis of alkylated glycine derivatives with α-bromoketones.

Alkyl boronic acids, serving as the alkyl radical precursors, are also compatible with the visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives. In 2022, Huo et al. developed a visible-light-driven aerobic oxidative alkylation of glycine derivatives **1** with alkyl boronic acids **34** (Scheme 14) [85]. In this approach, the synergistic copper catalysis and photoredox catalysis fruitfully delivered a wide range of alkylated glycine derivatives under very mild reaction conditions. Notably, the photocatalytic cycle produced the alkyl radical in the presence of air.



Scheme 14. A visible-light-driven aerobic oxidative alkylation of glycine derivatives with alkyl boronic acids.

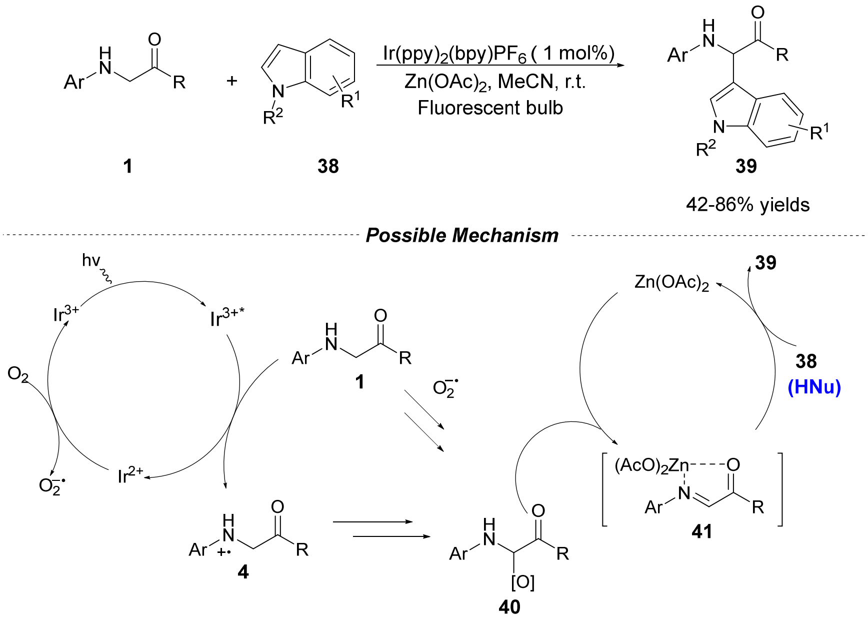
As an alternative alkyl donor of NHPI esters, oxalates can also be used in visible-light-driven C(sp^3)–H alkylation of glycine derivatives. Very recently, Cheng's group disclosed a novel method for synthesizing α-amino phenylpropanoids through α-C–H benzylation of *N*-phenyl glycine ester **1** with benzyl oxalates **36** under visible light irradiation (Scheme 15) [86]. In this reaction, Ir(ppy)$_3$ served as the most suitable photocatalyst to initiate the generation of the alkyl radical and α-amino radical, and the radical cross-coupling produced the desired product phenylpropanoids. This protocol represents a novel discovery in the realm of alkylation reagents, showcasing a unique capability for functionalizing natural molecules.



Scheme 15. A method for synthesizing α-amino phenylpropanoids through visible-light-driven α-C–H benzylation of *N*-phenyl glycine esters with benzyl oxalates.

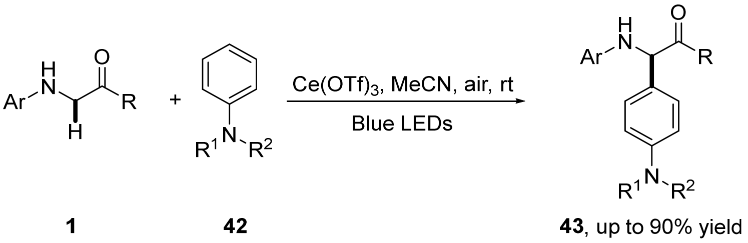
2.1.2. α-C(sp^3)–H Arylation

Visible-light-driven α-C(sp^3)–H arylation of glycine derivatives with transition metal complexes has also been a hot topic in the past decade. Various arylated unnatural amino acids and peptides could be synthesized successfully in a green and sustainable manner via this reaction. In contrast with the redox-neutral alkylation mentioned above, the arylation always proceeded via aerobic visible-light-driven oxidation and nucleophilic addition [87–92]. In 2012, Rueping et al. reported the first application of visible-light photo redox catalysis in the α-C(sp^3)–H arylation of glycine derivatives and peptides with indoles as the aryl source. In this work, the Ir complex, as the photocatalyst, worked with the Lewis acid catalyst Zn(OAc)$_2$ to trigger the photocatalytic cycle (Scheme 16) [93]. The visible-light-driven oxidation delivered the intermediate imine **40**. The desired product was obtained via a Lewis acid-catalyzed nucleophilic addition of imine with the indole as the nucleophilic reagent. The reaction site of the indole is the C3 position, which possesses the highest electron density. In the same year, Li et al. also reported a protocol for the photocatalytic α-C(sp^3)–H arylation of glycine derivatives and peptides with indoles. The most significant difference between these two works is the reaction conditions. In Li's work, the Ru(bpy)$_3$Cl$_2$ was employed as the photocatalyst, and the nucleophilic addition proceeded without the Lewis acid catalyst [94].



Scheme 16. Photocatalytic α-C(sp^3)–H arylation of glycine derivatives and peptides with indoles.

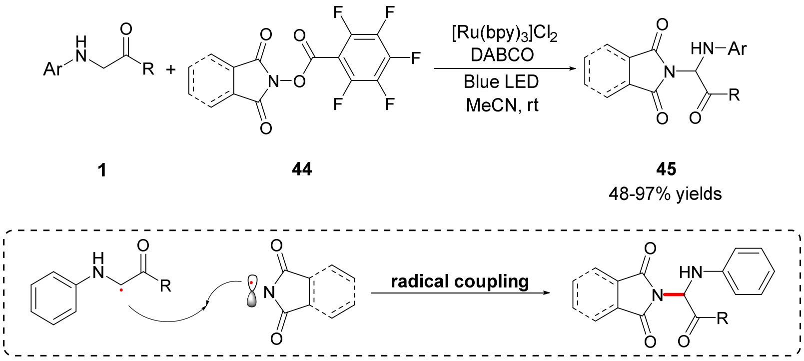
Similar to the C3 position of indoles, the *para* position of phenyl amines also possesses high electron density and could participate in nucleophilic reactions. Zhang's group recently created an efficient aerobic oxidative visible-light-driven dehydrogenative coupling reaction between glycine esters **1** and electron-rich phenyl amines **42** (Scheme 17) [95]. In this work, the Ce(OTf)$_3$ acted as the photocatalyst as well as the Lewis acid catalyst. The reaction tolerates various substituents and offers a rapid method for synthesizing α-aryl glycine derivatives efficiently.



Scheme 17. Photocatalytic α-C(sp^3)–H arylation of glycine derivatives with electron-rich phenyl amines.

2.2. α-C(sp^3)–N Formation

C–N bonds widely occur in drug candidates and natural bioactive compounds [96,97]. Pleasingly, the visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives with transition metal complexes can also be used to construct C–N bonds. In 2021, Jiang's group first reported a visible-light-driven C–H bond functionalization of glycine derivatives to form C–N bonds (Scheme 18) [98]. Possibly due to the installation of polyfluorophenyl, the polarity of the NHPI ester molecule completely reversed. Consequently, in contrast with previous works [64–68], the NHPI ester is not the carbon radical source. Conversely, it functioned as the source of nitrogen radicals, as substantiated by the formation of TEMPO-trapped adducts. In the presence of [Ru(bpy)$_3$]Cl$_2$, the photocatalytic cycle worked well and smoothly produced the α-amino carbon radical and the nitrogen radical. Their coupling provides a wide range of N-decorated glycine derivatives and peptides in good to excellent yields.



Scheme 18. A visible-light-driven C–H bond functionalization of glycine derivatives for forming C–N bonds.

3. Visible-Light-Driven α-C(sp^3)–H Bond Functionalization of Glycine Derivatives with Organic Dyes

Organic dyes offer a viable alternative to transition-metal (TM)-based photocatalysts when considering the visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives [99–101]. The utilization of organic dyes presents notable advantages in terms of cost-effectiveness, low toxicity, and ease of handling (Figure 2). However, organic dyes differ from multifunctional transition-metal complexes in that they exclusively facilitate the absorption of visible light and initiate the photoredox catalytic cycle. In specific scenarios, the organic dyes can synergistically cooperate with transition-metal catalysts to achieve metallaphotoredox catalysis. In this section, representative examples of the application of organic dyes in visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives will be discussed, emphasizing their role in the photocatalytic cycle.

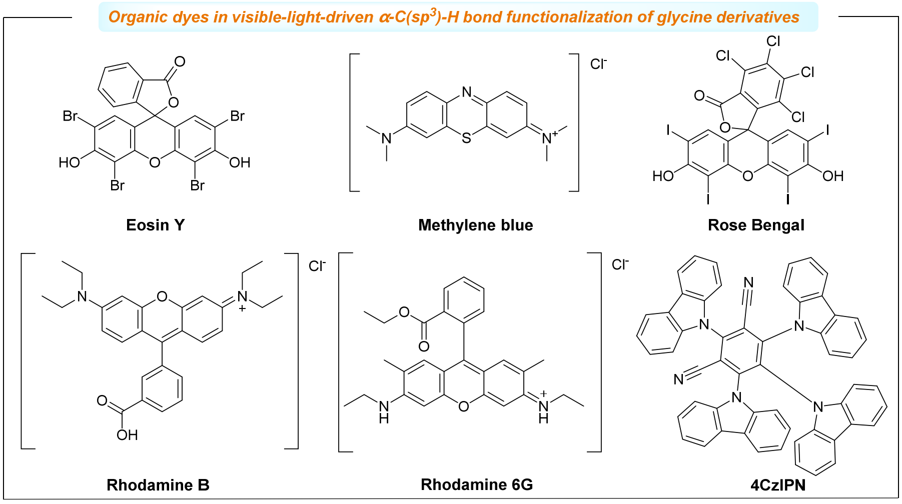


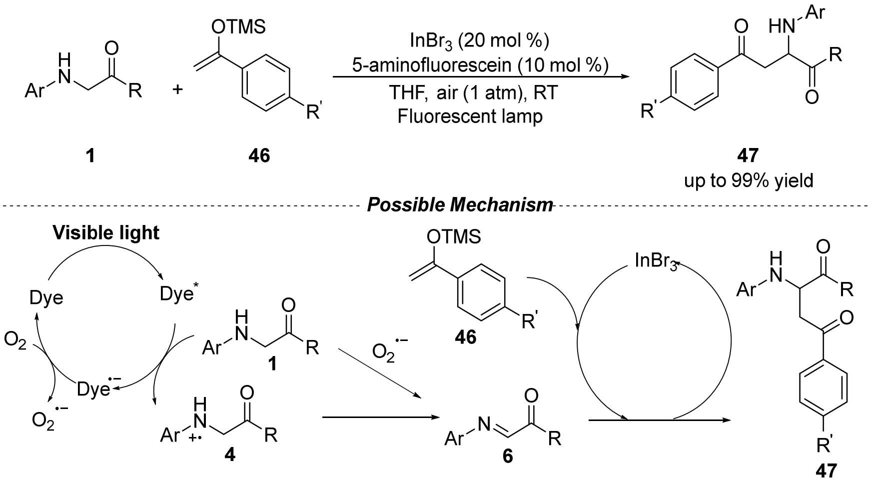
Figure 2. Commonly used-organic dyes in visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives.

3.1. *α-C(sp^3)–C Formation*

3.1.1. α-C(sp^3)–H Alkylation

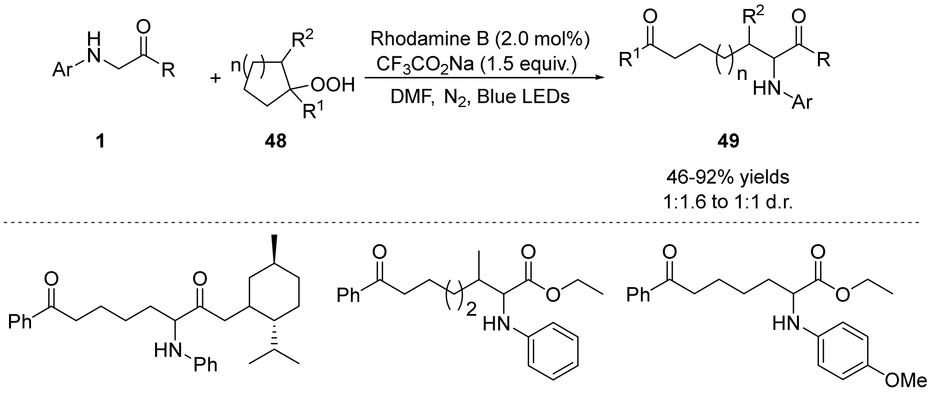
The introduction of organic dye as the photocatalyst could make the visible light α-C(sp^3)–H alkylation of glycine derivatives occur efficiently in a metal-free manner [102–108]. However, it can only be a photocatalyst; in some cases, it must work with other catalysts to maximize its catalytic power. In 2017, Sugiyama reported an organic dye-catalyzed visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives (Scheme 19) [109]. In this reaction, 5-aminofluorescein was used to accelerate the visible-light-driven oxidation of the glycine derivative **1**. The glycine derivative **1** was oxidized into the imine intermediate

6 via this process. Subsequently, with the help of the Lewis acid catalyst ($InBr_3$), 1-phenyl-1-trimethylsiloxyethylene **46,** as a nucleophile, reacted with the imine intermediate smoothly, delivering a variety of alkylated glycine derivatives in high yields. In contrast to preceding the transition-metal catalytic processes, this protocol eliminates the necessity for rigorous reaction conditions, such as *t*-BuOOH, DDQ, and elevated temperatures.



Scheme 19. An organic dye-catalyzed visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives with 1-phenyl-1-trimethylsiloxyethylenes.

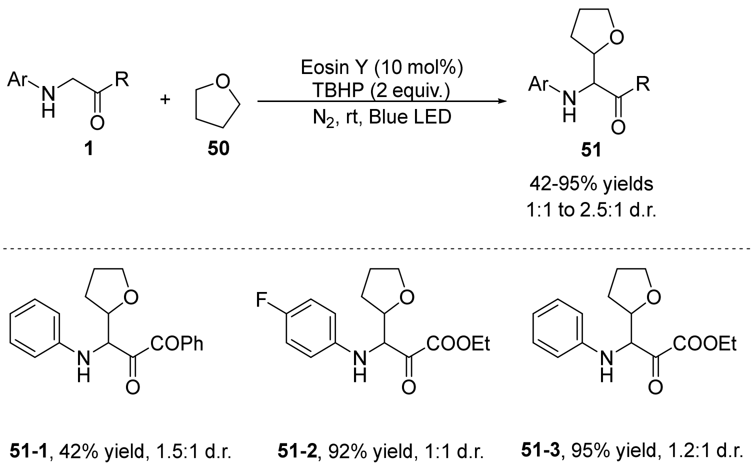
Peroxides are typically used as oxidants to fulfill oxidation reactions. In 2021, Guo presented a visible-light-induced α-C(sp^3)–H ketoalkylation of glycine derivatives using a cheap and non-toxic organic dye as the photocatalyst (Scheme 20) [110]. In this reaction, the cyclic peroxide was an effective alkylation reagent, not an oxidant. In the presence of rhodamine B, the *N*-phenylglycinate **1** was oxidized into an α-amine carbon radical under visible light irradiation, and the cyclopentyl hydroperoxide **48** was reduced into a carbon radical through an alkoxy radical-initiated C–C bond cleavage process. The ketoalkylation was accomplished by their radical cross-coupling. The above approach features transition metal-free and good functional group compatibility, providing an ideal tool to access distal keto-functionalized α-amino acid derivatives.



49-1, 52% yield, 1:1.6 d.r. **49-1**, 70% yield, 1:1 d.r. **49-3**, 92% yield

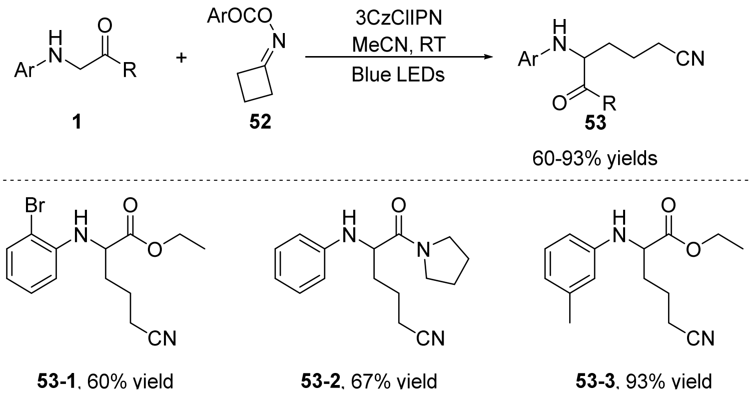
Scheme 20. A visible-light-driven C(sp^3)–H ketoalkylation of glycine derivatives.

Hydroperoxides always act as radical initiators in thermal cross-dehydrogenative reactions. The working temperature of them is typically above 100 °C [22]. Using them in visible-light-driven organic reactions could make them effective under very mild reaction conditions. In 2021, Yao et al. reported an Eosin-Y catalyzed visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives (Scheme 21) [111]. Additionally, hydrofurans were used as the alkyl radical precursors. In the presence of *tert*-butyl hydroperoxide (TBHP), the alkyl radial generation via the photocatalytic cycle proceeded well and efficiently, and a range of α-alkylated glycine derivatives were obtained in good to excellent yields. The procedure is operationally easy, providing an economical, metal-free, mild alternative for synthesizing the α-alkylated glycine derivatives.



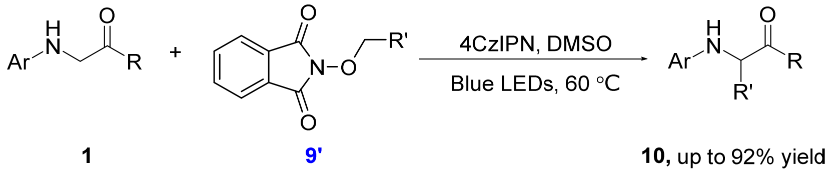
Scheme 21. A visible-light-induced oxidative α-alkylation of glycine derivatives.

In the past few years, cycloketone oxime esters were intensively explored as radical precursors in light-induced organic transformations [112]. In 2022, Li et al. reported a visible-light-induced α-C(sp^3)–H alkylation of glycine derivatives **1** with cycloketone oxime esters **52** as the radical source (Scheme 22) [113]. In this transformation, an organic dye named 3CzClIPN was chosen as the suitable photocatalyst. The reaction proceeded without any additives. Many glycine derivatives can be converted into corresponding products under mild reaction conditions in good to excellent yields (**53-2** to **53-3**). The catalytic cycle began with visible-light-induced oxidation to produce the iminyl radical from the glycine derivative and the generation of the alkyl radical from the cycloketone oxime ester via the single electron transfer and ring-opening. In the end, the radical coupling proceeded to provide the desired product. This reaction highlights the introduction of a novel alkylation reagent for the modification of glycine derivatives coupled with the utilization of an organic photocatalyst.



Scheme 22. A 3CzClIPN catalyzed visible-light-induced α-C(sp^3)–H alkylation of glycine deriva-tives with cycloketone oxime esters.

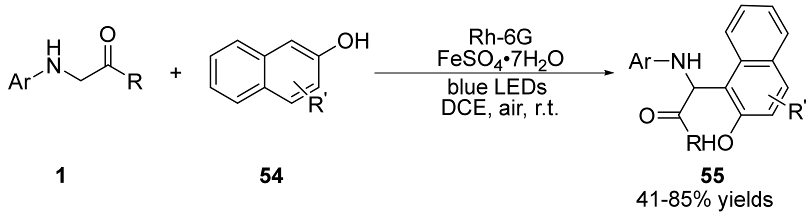
The fluorophore 4CzIPN, characterized by its inherent stability and conducive photoredox potential, has emerged as a compelling organic photocatalyst in recent investigations [114–117]. Within this context, Cai and colleagues documented a 4CzIPN-catalyzed visible-light-induced α-C(sp^3)–H alkylation of glycine derivatives using *N*-alkoxyphthalimides as the radical precursors (Scheme 23) [118]. As the NHPI ester analogs, *N*-alkoxyphthalimides were prepared from aliphatic alcohols rather than carboxylic acids. 4CzIPN exhibited a comparative advantage over transition metal-based photocatalysts, demonstrating pronounced photoactivity in generating iminyl and alkyl radicals. Diverse alkylated glycine derivatives were obtained with commendable yields. Using 4CzIPN in this protocol presents a facile alternative to alkylation strategies relying on transition metal-based photocatalysts.



Scheme 23. A 4CzIPN catalyzed visible-light-induced α-C(sp^3)–H alkylation of glycine derivatives.

3.1.2. α-C(sp^3)–H Arylation

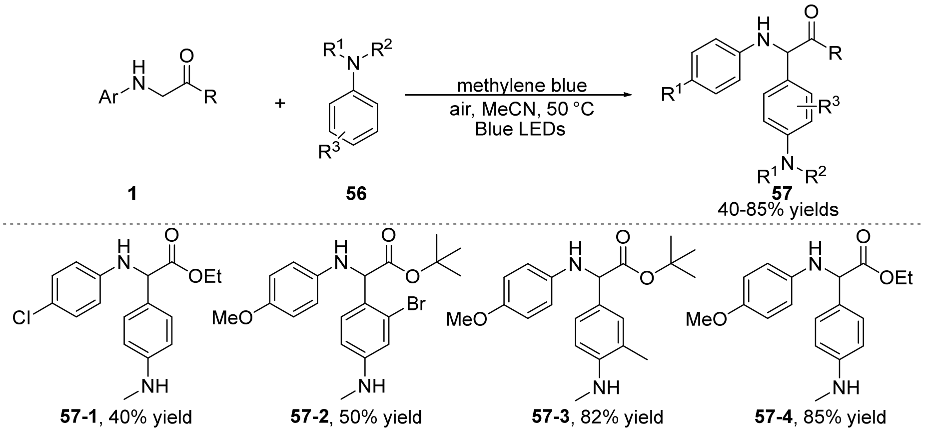
Besides alkylations, organic dyes are also capable of catalyzing the visible-light-driven α-C(sp^3)–H arylation of glycine derivatives. In most cases, the photocatalytic cycle includes two core steps: (1) The generation of iminyl radicals from glycine derivatives triggered by the photo-excited organic dyes. (2) The nucleophilic reaction of electron-rich aromatics with the iminyl radical. Better than the transition-metal complex involved visible-light-driven α-C(sp^3)–H arylation, organic dye always makes the approaches cheaper and greener [119–121]. In 2018, Li et al. reported a visible-light-driven α-C(sp^3)–H arylation of glycine derivatives with electron-rich β-naphthols (Scheme 24) [122]. In this reaction, the rhodamine 6G (Rh-6G) was the photocatalyst for the photo-oxidation to produce the iminyl radical. The veracity of this interaction was corroborated through a fluorescence quenching experiment. $FeSO_4 \cdot 7H_2O$ is a Lewis acid catalyst for the nucleophilic coupling of the iminyl radical with β-naphthol. The reaction site is the hydroxy group's *ortho*-position, which possesses the highest electron density.



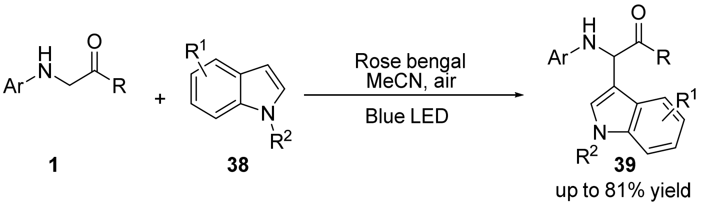
Scheme 24. A visible-light-driven α-C(sp^3)–H arylation of glycine derivatives with β-napthols.

In the same year, a photocatalytic α-C(sp^3)–H arylation of glycine derivatives with N-substituted anilines **56** was developed by Su's group (Scheme 25) [123]. This reaction proceeded smoothly using methylene blue as a photocatalyst under visible-light-irradiation. A paramount innovation in this work is the complete omission of any metal, oxidant, or additive in the entire approach. A range of α-aryl amino derivatives are synthesized in moderate to excellent yields (**57-1** to **57-4**). Analogous to the aforementioned arylation, the nucleophilic arylation took place at the *para* position of the amine group, characterized by its electron-rich nature.

In 2019, Lu et al. reported a visible-light-driven oxidative arylation of glycine derivatives **1** with indoles **38** in the presence of Rose Bengal (RB) (Scheme 26) [124]. Benefitting from using RB, the reaction could occur under transition-metal-free and mild reaction conditions. A bunch of indole-decorated glycine derivatives were obtained efficiently. Like other arylations, the electron-rich position, the C3 position of indole is still the reaction target site.



Scheme 25. A photocatalytic α-C(sp^3)–H arylation of glycine esters with N-substituted anilines.



Scheme 26. A rose bengal-catalyzed visible-light-driven α-C(sp^3)–H arylation of glycine derivatives with indoles.

4. Visible-Light-Driven α-C(sp^3)–H Bond Functionalization of Glycine Derivatives with Heterogeneous Photocatalysts

Exploiting the heterogeneous nature of photocatalysts, the incorporation of heterogeneous photocatalysts (HE-PC) in the visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives has consistently demonstrated remarkable capabilities in terms of photocatalyst reusability and recyclability. Thus far, various photoactive semiconductors, including quantum dots (QDs), metal-covalent organic frameworks (M-COFs), and covalent organic frameworks (COFs), have been effectively employed as viable options within this visible-light-driven reaction system [125–131]. These photocatalysts have demonstrated comparable reaction efficiencies to their homogeneous counterparts. Upon excitation of the heterogeneous photocatalyst by visible light, the photogenerated hole can oxidize the glycine derivative to form a radical cation. The radical cation could subsequently undergo direct coupling with another alkyl radical donor for alkylation or transform into an imine cation, enabling Lewis acid-catalyzed arylation (Figure 3).

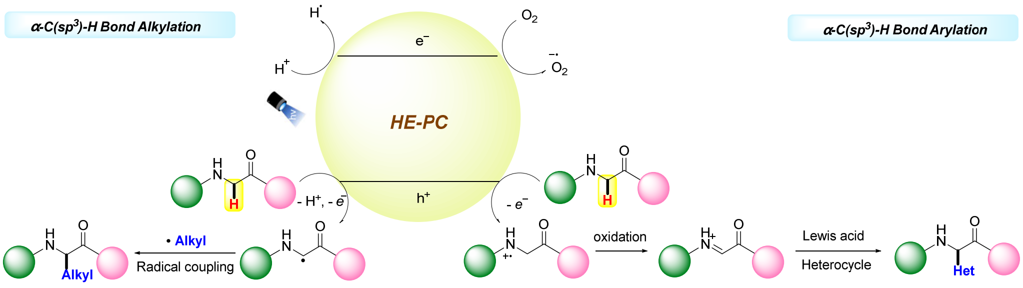
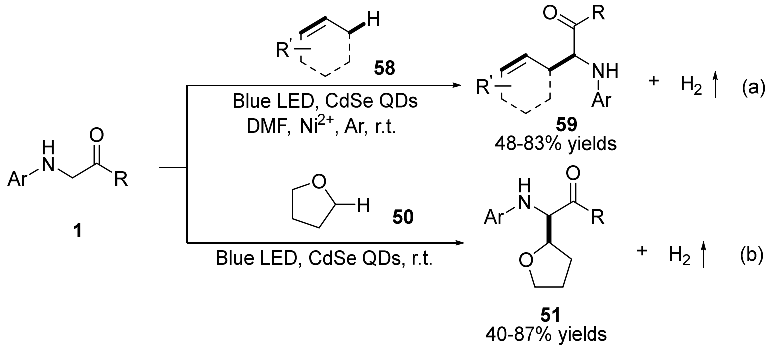


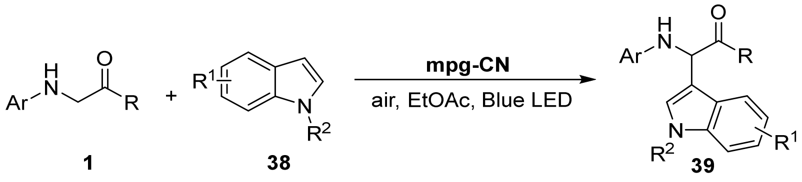
Figure 3. The role of HE-PC in heterogeneous visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives.

Quantum dots (QDs) represent semiconductor particles with dimensions on the order of nanometers. Because of the quantum mechanical effects, these entities manifest distinctive optical and electronic characteristics, including notable light absorption, modulated photoredox potential, large surface area, and good stability. These inherent features bestow upon quantum dots the potential for compelling applications as heterogeneous photocatalysts in visible-light-driven organic transformations [132]. In 2021, Wu et al. developed a QDs-catalyzed visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives with alkenes (Scheme 27a) [133]. In this work, benefitting from the fantastic power of photoexcited QDs, allylic C(sp^3)–H bonds and a-amino C–H bonds were both activated together to form the corresponding allylic radicals and α-amino alkyl radicals. Various alkylated glycine derivatives were precisely obtained via the radical cross-coupling in good yields. Notably, the generated proton from the C–H bond activation steps accepted electrons from QDs to form hydrogen radicals, and two of them combined to release one molecule of hydrogen to accomplish the catalytic cycle. In the same year, they disclosed another application of QDs in visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives (Scheme 27b) [134]. In this case, tetrahydrofuran (THF) was used as the alkylation reagent. The α-C–H bond of THF was directly activated to give the alkyl radical with QDs under visible-light-irradiation. The mechanistic investigation indicated that QD/THF conjugates formed and played a crucial role in the C–H bond activation of THF. Compared with previous works, the above two works highlight no need for oxidants or additives, and the only byproduct is hydrogen gas. The ease of catalyst recyclization exhibits a bright future for QDs in visible-light-driven organic transformations and green chemistry.



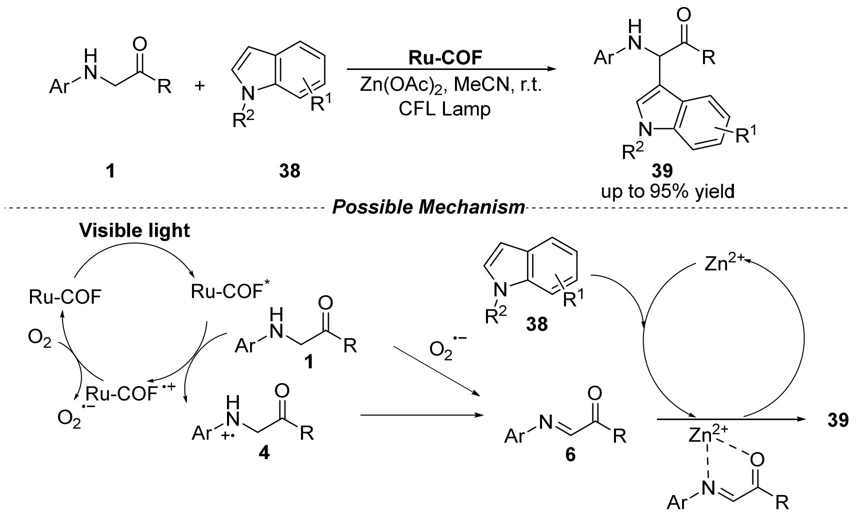
Scheme 27. QDs-catalyzed visible-light-driven α-C(sp^3)–H alkylation of glycine derivatives with (**a**) alkenes or (**b**) tetrahydrofuran.

Except for QDs, other heterogeneous photocatalysts (HE-PC) were also found to be effective in the visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives [135]. In 2022, Di Carmine's group applied mesoporous graphitic carbon nitride (mpg-CN) as a heterogeneous organocatalyst for the photocatalytic α-C(sp^3)–H arylation of glycine derivatives with indoles **38** to synthesize indole-functionalized unnatural NPAAs (Scheme 28) [136]. In this reaction, mpg-CN functioned as a heterogeneous photocatalyst, generating an iminyl radical that was identified through in situ EPR experiments. The iminyl radical underwent oxidation by molecular oxygen to yield the imine intermediate. Subsequently, facilitated by mpg-CN, the Friedel–Crafts arylation proceeded seamlessly to furnish the desired product. Notably, the heterogeneous nature and exceptional photoactivity of mpg-CN distinguish this approach from previous methods, ensuring the efficient accomplishment of reactions in a sustainable manner.



Scheme 28. Visible-light-driven α-C(sp^3)–H arylation of glycine derivatives catalyzed by mpg-CN.

Two-dimensional covalent organic frameworks (2D-COFs), as a rapidly emerging class of crystalline porous materials, due to their highly ordered structure, large surface area, good chemical stability, and excellent photoactivity, have been a kind of suitable photocatalysts for visible-light-driven organic transformations. In 2021, Neogi et al. designed and synthesized a Ru-immobilized COF (Ru-COF) and applied it as the photocatalyst for visible-light-driven α-C(sp^3)–H arylation of glycine derivatives with indoles. In this heterogeneous system, like homogeneous catalysts, Ru-COF worked for the photo-oxidation of glycine derivatives into the imine. $Zn(OAc)_2$ is responsible for the nucleophilic coupling with electron-rich indoles (Scheme 29) [137]. This work features the immense potential of a modified COF as a synergistic heterogeneous and recyclable photocatalyst for environmentally friendly visible-light-driven α-C(sp^3)–H arylation of glycine derivatives.



Scheme 29. The photocatalytic arylation of glycine derivatives with indoles catalyzed by Ru-COF.

5. External Photocatalyst-Free Visible-Light-Driven α-C(sp^3)–H Bond Functionalization of Glycine Derivatives

The direct absorption of visible light by glycine derivatives is limited. Typically, it is always a must to add external photocatalysts for achieving visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives. However, in some cases, electron donor-acceptor (EDA) complexes, formed from glycine derivatives, radical precursors, and additives, could harvest the visible light to trigger the catalytic cycle. Consequently, external photocatalysts are unnecessary for these reactions, offering a facile and sustainable alternative to accomplish this photocatalytic transformation [138–149]. In external-photocatalyst-free reactions, either glycine derivatives or additives can serve as electron donors, leading to the excitation of the EDA complex upon exposure to visible light. Subsequently, a radical intermediate is generated through single electron transfer (SET), and the ensuing radical coupling process culminates in the α-C(sp^3)–H bond functionalization (Figure 4).

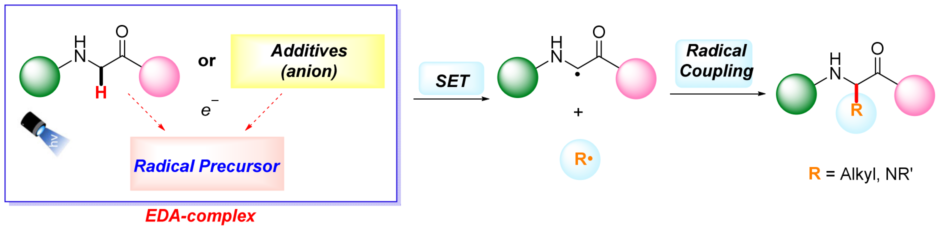
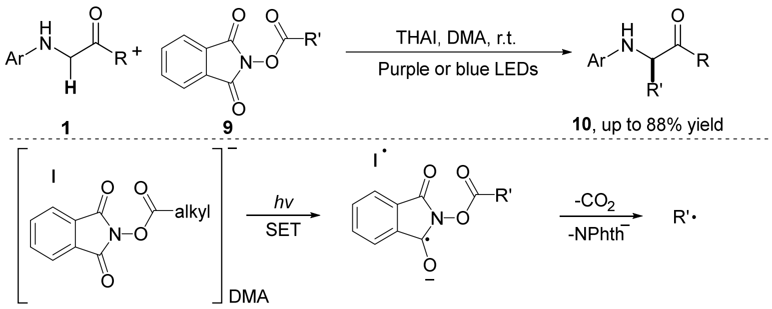


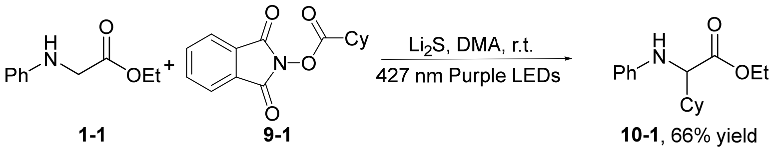
Figure 4. The role of EDA complex in visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives.

In 2019, Fu and Shang discovered that a combination of triphenylphosphine and sodium iodide, when exposed to blue LEDs, can trigger the decarboxylative alkylation with NHPI esters [150]. In this reaction, the EDA complex formed with triphenylphosphine, sodium iodide, and NHPI esters is the actual internal photocatalyst. As a continuous study of this work, in 2021, Shang disclosed that a catalytic amount of ammonium iodide salt could initiate the regioselective decarboxylative alkylation of glycine derivatives (Scheme 30) [151]. In this reaction, relying on the EDA complex formed with tetrahexylammonium iodide (THAI) and NHPI esters, a single electron transfer (SET) occurred smoothly under visible-light irradiation to produce the alkyl radical. Compared with their previous works, this present work advances the avoidance of triphenylphosphine. However, to ensure the stability of the EDA complex via a solvent cage, the use of dimethylacetamide (DMA) as the solvent is still necessary. The simplicity and practicality of this approach, along with its broad substrate scope, highlights the synthetic potential of photocatalysis mediated by the EDA complex.



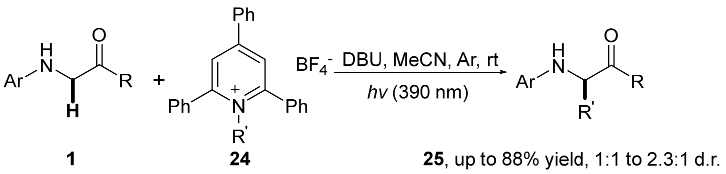
Scheme 30. Visible-light-driven alkylation of glycine derivatives with ammonium iodide salt.

In the same year, Wang et al. presented an alternative additive (Li_2S) for the generation of the EDA complex to drive the decarboxylative alkylation of glycine derivatives under visible-light irradiation (Scheme 31) [152]. The sulfide anion was employed to work with the NHPI esters to form the EDA complex. As with the above work, DMA as the solvent is also indispensable for reaction efficiency.



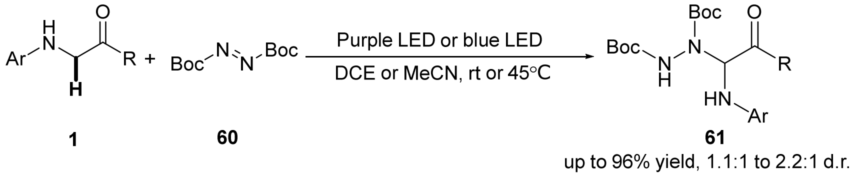
Scheme 31. Visible-light-driven alkylation of glycine derivatives with Li_2S.

Katritzky salts can also be used to form an EDA complex for light harvesting. In 2020, Xu et al. reported a photocatalyst-free visible-light-driven deaminative C(sp^3)−H alkylation of glycine derivatives and peptides (Scheme 32) [153]. In this process, a photoactive EDA complex is formed with the Katritzky salt and the glycine derivative. The alkyl radical is produced along with the single electron transfer occurring between them under light irradiation. A series of alkylated glycine derivatives and peptides were obtained via the radical cross-coupling. Notably, benefitting from the mild reaction conditions, this approach provides a facile path for the modification of peptides.



Scheme 32. Visible-light-driven deaminative C(sp^3)−H alkylation of glycine derivatives.

Not all external photocatalyst-free reactions rely on the EDA complex. In 2021, as a continuation of their interest in external photocatalyst-free reactions, Fu et al. developed a convenient and environmentally friendly method for the site-selective C(sp^3)–H hydrazination of glycine derivatives and peptides with azo compounds (Scheme 33) [154]. In this protocol, no external photocatalysts and additives are needed. Differing from the EDA complex-involved strategy, the azo compound in this photocatalytic cycle is the real reagent for light harvesting. It is not only the actual photocatalyst but also the hydrazination source. Consequently, the reaction features a high atomic efficiency and a low E factor (E = 0), which is ideal for synthesizing unnatural α-amino acids and short peptides.



Scheme 33. The site-selective visible-light-driven C(sp^3)–H hydrazination of glycine derivatives and peptides with azo compounds.

6. Summary and Outlook

The field of visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives has experienced significant advancements in recent years, unveiling a plethora of efficient methods for this transformative process. Through visible light irradiation, the normally inert α-C(sp^3)–H bonds in glycine derivatives can be selectively activated under mild reaction conditions, forming new C–C or C–X bonds. Mechanistic investigations have revealed that generating radical cations from glycine derivatives is pivotal in this process, achieved through photo-induced electron transfer with either external or internal photocatalysts. Subsequent radical coupling or nucleophilic reactions facilitate the formation of functionalized products, potentially offering a more sustainable and environmentally friendly approach for synthesizing unnatural amino acids and peptides.

Nevertheless, several challenges must be addressed to advance this transformation further. Firstly, relying on organic solvents for the current functionalization methods may pose limitations when modifying bioactive proteins, necessitating exploring alternative solvent systems. Secondly, while electron donor-acceptor (EDA) complexes hold promise as alternatives to external photocatalysts, their efficiency relies heavily on the structural features and visible light absorption properties of the substrates. Developing a designable heterogeneous photocatalyst or collaborating with the enzyme catalysis [155–158] may provide a more sustainable solution. Thirdly, the restricted availability of aryl sources for C–H bond arylation, primarily limited to nucleophilic heterocycles like indoles, calls for developing a universal aryl source to expand the scope of this transformation. Lastly, implementing visible-light-driven methodologies in scale-up and industrial contexts poses challenges. The constrained utilization rate of low light energy has restricted their practical application in fine-chemical production. Exploring potential solutions involves the development of technologies such as flow chemistry or enhancing photochemical processes, such as sunlight-driven organic reactions, to establish more robust and efficient methodologies for addressing this issue.

The authors anticipate that this comprehensive review will serve as a catalyst for organic chemists, inspiring them to conceive and implement innovative catalytic systems that effectively address crucial considerations encompassing substrate scope, product diversity, reaction efficiency, and green chemistry principles in the realm of visible-light-driven α-C(sp^3)–H bond functionalization of glycine derivatives. By advancing such methodologies, the synthesis of novel peptide drugs stands to gain substantial advancements and improvements.

Author Contributions: Y.T.: Writing the original draft; X.B.: writing, review, and editing; Y.T. and X.B. contributed equally; Y.C.: conceptualization; L.W.: editing; J.E.: editing; J.Z.: conceptualization; H.X.: conceptualization; A.H.: conceptualization; X.Y.: conceptualization, writing, review, and editing, funding acquisition, and supervision; Z.Z.: conceptualization. All authors have read and agreed to the published version of the manuscript.

Funding: This work was financially supported by the Basic Scientific Project of the Universities in Liaoning Province (LJKQZ2021052), Liaoning Revitalization Talents Program (XLYC2203110), Natural Science Foundation of Shenyang (23-503-6-10), Youth Cross-disciplinary Fund of Henan University, and the Engineering Technology Research Centre of Catalysis for Energy and Environment-Major Platform for Science and Technology of the Universities in Liaoning Province.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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