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Focus Review

Photoredox Couplings

Visible-Light Photoredox Decarboxylative Couplings

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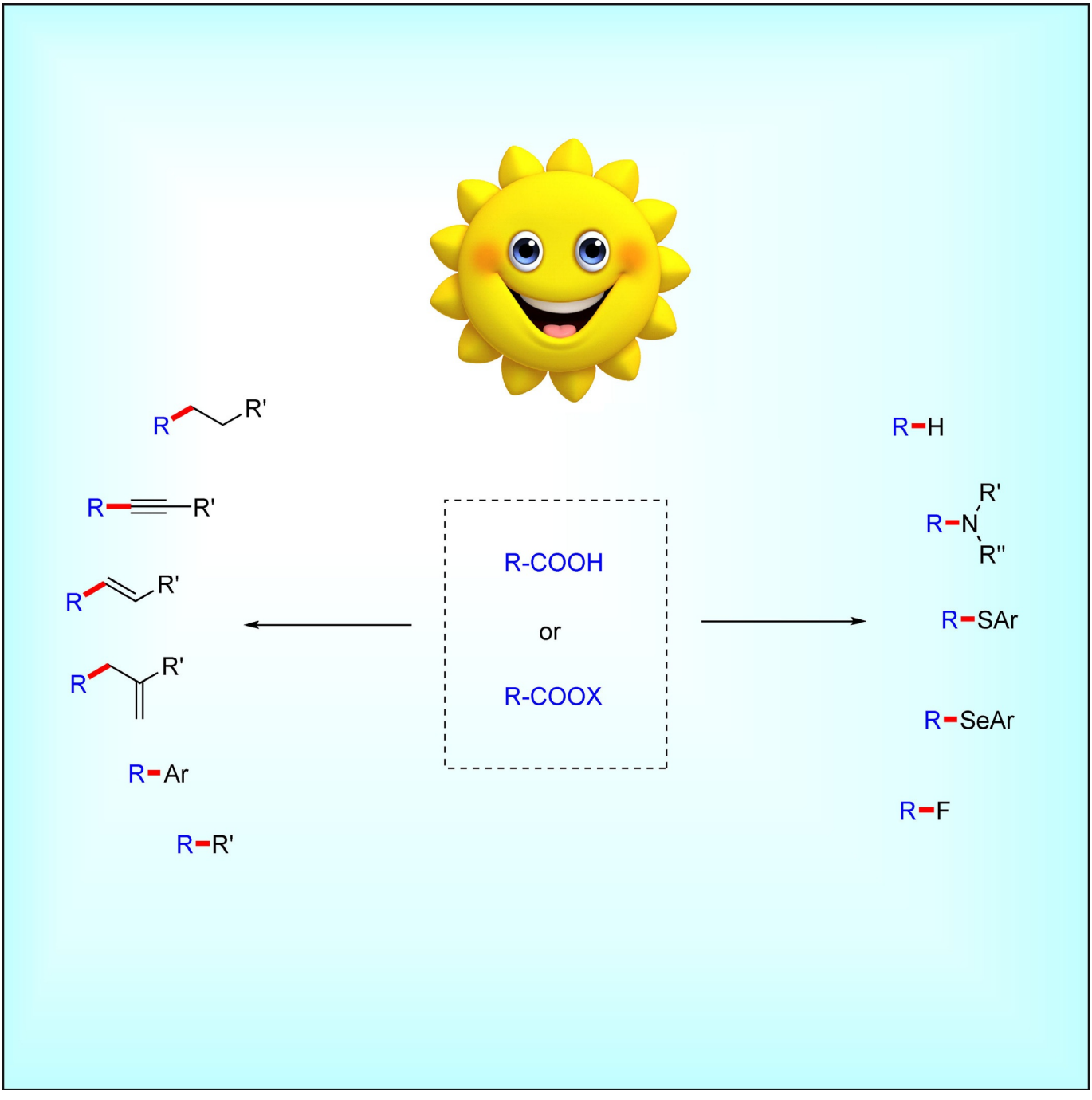


Abstract: Carboxylic acids and their derivatives are abundant and inexpensive organic and biomass-derived platform molecules, and their conversion into high-value products represents an important goal. Recently, visible-light photoredox decarboxylative coupling reactions have become an important chemical transformation because of their wide substrate scope, mild reaction conditions, high efficiency, and practicability. This review summarizes recent advances in visible-light photoredox decarboxylative coupling strategies, which include the formation of C–C and C–Y (Y = heteroatom) bonds.

1. Introduction

Carboxylic acids and their derivatives are common structures that are widely found in organic molecules and natural products,[1] and their decarboxylative coupling reactions have attracted much attention. Some classical reactions have been developed[2] such as Heck-type reactions,[3] allylations,[4] redox-neutral cross-coupling reactions,[5] and oxidative arylation reactions.[6] Although great success has been achieved in transition-metal-catalyzed decarboxylative coupling reactions, it is highly desirable to develop more convenient and efficient methods that take place under mild conditions.

In 1984, Barton and co-workers first reported the decarboxylative coupling reactions of thiohydroxamate esters by using disulfides, diselenides, and ditellurides under the irradiation of visible light.[7] In 1989, Okada and co-workers described their pioneering research on the decarboxylative coupling of *N*-(acyloxy)-
phthalimides under the irradiation of UV light.[8] Unfortunately, visible-light photoredox decarboxylative coupling reactions have not been studied for a while. Although this is the case, visible-light photoredox decarboxylative couplings of carboxylic acids and their derivatives as radical precursors have recently attracted much attention, and some important results have been obtained.[9] This review is intended to provide an overview of recent advances in visible-light photoredox decarboxylative coupling reactions, which include details regarding the formation of C–C and C–Y (Y = heteroatom) bonds.

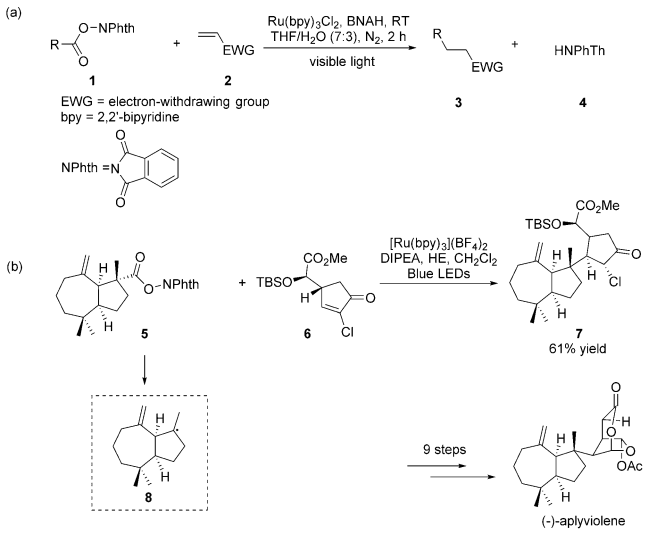
2. Formation of C–C Bonds

The formation of carbon-carbon bonds is a fundamental and important chemical transformation in organic synthesis. However, it still is a great challenge to develop convenient and efficient methods for the formation of these bonds under mild conditions with readily available starting materials. Herein, we discuss the formation of C–C bonds by using visible-light photoredox decarboxylative strategies that include decarboxylative addition, alkynylation, alkenylation, allylation, arylation, and alkylation reactions.

2.1. Addition Reactions

In 1991, Okada, Oda, and co-workers established a method for a visible-light photoredox decarboxylative Michael addition of *N*-(acyloxy)phthalimides **1** (Scheme 1a). The protocol used electron-deficient olefins **2** as the radical acceptor, $Ru(bpy)_3Cl_2$ as the photocatalyst, and 1-benzyl-1,4-dihydronicotinamide (BNAH) as the reductant, and the reaction proceeded smoothly in a mixture of tetrahydrofuran (THF) and water (7:3) under nitrogen to provide the target product **3**.[10] In 2012, Overman and co-workers applied this visible-light decarboxylative method towards the total synthesis of (−)-aplyviolene.[11] In this study, compound **7** was considered a key intermediate and was prepared by a visible-light photoredox decarboxylative Michael addition of *N*-(acyloxy)phthalimide **5** to alkene **6** in the presence of *N*,*N*-diisopropylethylamine (DIPEA) and the Hantzsch ester (HE) as the reductant. In addition, tertiary carbon radical **8** was formed from the decarboxylation of **5** (Scheme 1b).

In 2013, Reiser and co-workers established a radical cyclization strategy to prepare spirobutenolide and its furan deriva-



Scheme 1. Visible-light photoredox decarboxylative Michael addition of *N*-(acyloxy)phthalimides (LED = light-emitting diode).

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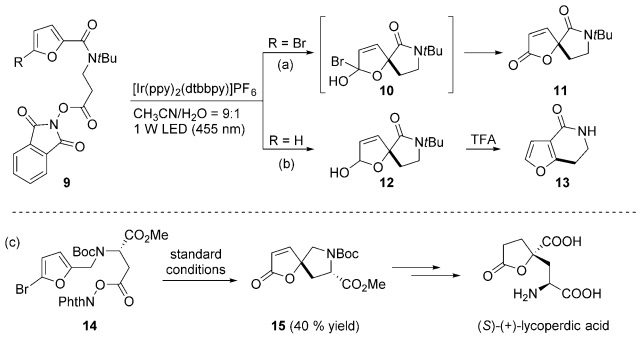
tives by visible-light photocatalysis[12] using $Ir(ppy)_2(dtbbpy)PF_6$ (ppy = 2-phenylpyridine, dtbbpy = 4,4′-di-tertbutyl-2,2′-dipyridyl) as the photocatalyst in a mixed solvent of acetonitrile and water (9:1) under irradiation with a 1 W LED (455 nm). For substrate **9**, in which R = Br, the intramolecular coupling reaction provided intermediate **10** and then released HBr to give spirobutenolide derivative **11** (Scheme 2a). For substrate **9**, in

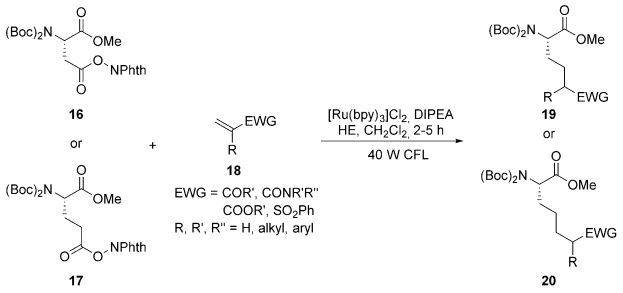


Scheme 2. Visible-light photoredox decarboxylative synthesis of spirobutenolides and its furan derivatives (TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl).

which R = H, a similar cyclization afforded **12**, and then dehydration in the presence of acid led to furan derivative **13** (Scheme 2b). Furthermore, the useful target compound (*S*)-(+)-lycoperdic acid was successfully prepared by the visible-light photoredox decarboxylative strategy using **14** as the starting material (Scheme 2c).

Unnatural chiral α-amino acids are important building blocks in the synthesis of biological and pharmaceutical peptides, peptidomimetics, and complex molecules, and the synthesis of these compounds has received tremendous attention.[13] Very recently, our group developed the visible-light photoredox synthesis of unnatural chiral amino acids by using the derivatives [i.e., *N*-bis(Boc)-Asp(ONPhth)-OMe and *N*-bis(Boc)-Glu(ONPhth)-OMe] of two genetically coded proteinogenic amino acids, L-aspartic acid and glutamic acid, as the radical precursors, and olefins including α,β-unsaturated ketones, amides, esters, and sulfones as the radical acceptors (Scheme 3).[14] The experimental results showed that the optimal conditions for the decarboxylative coupling involved 1 mol% of $[Ru(bpy)_3]Cl_2$ as the photocatalyst and dichloromethane as the solvent in the presence of DIPEA and HE under the irradiation of visible light at room temperature. The visible-light photoredox decarboxylative method provided high yields and demonstrated excellent tolerance for a variety of functional groups.

A possible mechanism for this transformation is shown in Scheme 4, and the decarboxylative coupling of *N*-bis(Boc)-Asp(ONPhth)-OMe (**16**) is used as an example. The irradiation of $Ru(bpy)_3^{2+}$ with visible light gives the excited state $[Ru(bpy)_3^{2+}]^*$, which is reduced by HE or DIPEA to afford $Ru(bpy)_3^{+}$ and convert HE or DIPEA into radical cation **A** or **B**. The treatment of **16** with $Ru(bpy)_3^{+}$ gives radical anion **C** and



Scheme 3. Visible-light photoredox synthesis of unnatural chiral amino acids (CFL = compact fluorescent light).

regenerates the $Ru(bpy)_3^{2+}$ catalyst. Elimination of phthalimide anion **D** and CO_2 from **C** provides radical **E**, which then undergoes an addition to olefin **18** to lead to radical **F**. Finally, the reaction of **F** with **A** affords product **19** and releases cation **G**.

In addition to Ru and Ir complexes, organic photosensitizers are also important photocatalysts. For example, König and coworkers recently developed a mild, environmentally friendly method for the visible-light decarboxylative coupling of *N*-(acyloxy)phthalimides **21** with electron-deficient alkenes **22** (Scheme 5).[15] The reaction was catalyzed by the organic dye eosin Y in the presence of green light (535 nm). The method employed a wide scope of substrates including abundant derivatives of amino acids, α-oxy acids, and fatty acids, which are available from renewable resources. The eosin Y catalyzed mechanism is similar to that shown in Scheme 4.

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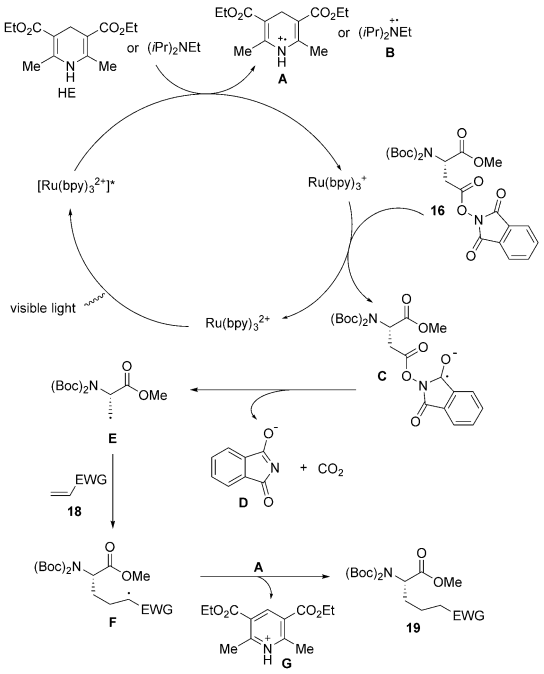
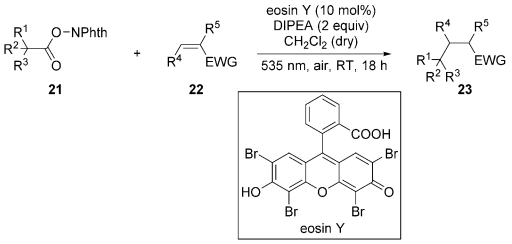
Hua Fu received his B.S. in Chemistry from Wuhan University (China) in 1989. In 1998, he obtained his Ph.D. in the Department of Chemistry at Tsinghua University (China) with Prof. Yufen Zhao. During 2000–2002, he performed his postdoctoral studies in the Department of Chemistry at The Ohio State University with Prof. Dehua Pei. He then began his independent career in the Department of Chemistry at Tsinghua University (China). He is a full professor in this department now. His research interests include transition-metal-catalyzed organic reactions: the development of biologically active molecules.

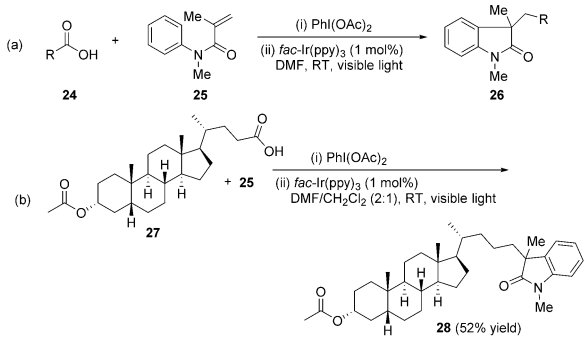


Scheme 4. Possible mechanism for visible-light photoredox synthesis of unnatural chiral amino acids.



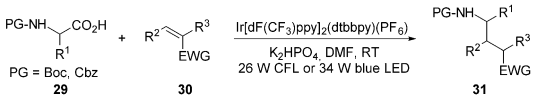
Scheme 5. Eosin Y catalyzed visible-light photoredox decarboxylative Michael addition.

Compared with the *N*-(acyloxy)phthalimide derivatives, free carboxylic acids are more readily available and inexpensive, and, thus, it is highly desirable to develop direct visible-light photoredox decarboxylative coupling reactions of free carboxylic acids. In 2013, Zhu and co-workers developed a tandem protocol for the formation of quaternary oxindoles under visible-light photoredox catalysis (Scheme 6 a).[16] The protocol used readily available primary, secondary, and tertiary aliphatic carboxylic acids **24** as the radical precursors, *N*-methyl-*N*-arylmethacrylamides **25** as the radical acceptors, and *fac*-Ir(ppy)$_3$ as the photocatalyst under the irradiation of a 35 W fluorescent light bulb. The reaction was successful, and investigations into the mechanism show that the reaction underwent a sequential exchange of phenyliodine(III) diacetate with **24**, an intermolecular coupling, and an intramolecular arylation reaction. Interestingly, this method was effectively applied to the conjugation of lithocholic acid derivative **27** with **25** to yield **28** (Scheme 6 b).



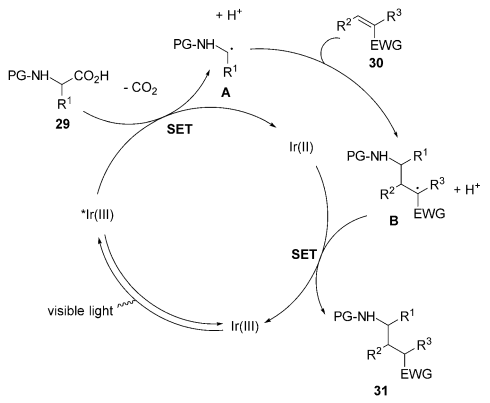
Scheme 6. Visible-light photoredox decarboxylative synthesis of oxindoles (DMF = *N*,*N*-dimethylformamide).

In 2014, MacMillan and co-workers reported a visible-light photoredox decarboxylative coupling reaction of carboxylic acids, especially *N*-protected amino acids, with Michael acceptors and iridium complexes as the catalyst. The method demonstrated a tolerance of various functional groups and a broad scope of both carboxylic acids and Michael acceptors (Scheme 7).[17] Compared with Zhu's work,[16] a larger scope of



Scheme 7. Visible-light photoredox decarboxylative coupling of *N*-protected amino acids with Michael acceptors (Cbz = benzyloxycarbonyl, PG = protecting group, dF = difluoro).

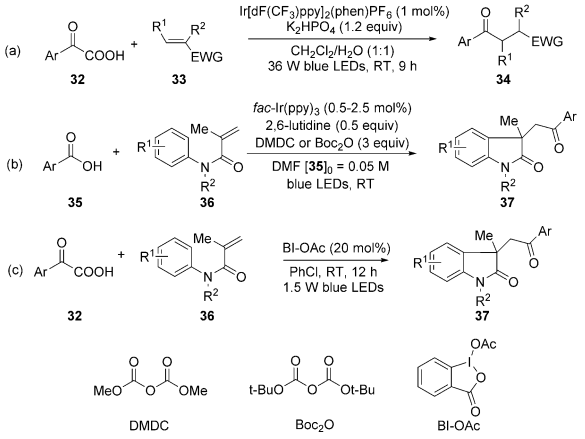
carboxylic acids including α-amino acids and α-*O*-acids could be employed, and no additional oxidant was needed. The corresponding mechanism is shown in Scheme 8. The Ir^{III} photocatalyst is transformed into its photoexcited *Ir^{III} state under the irradiation of visible light. A single-electron transfer (SET) from the carboxyl group of **29** to *Ir^{III} gives Ir^{II} and α-amino radical **A** along with the release of CO_2 and a proton. The addition of



Scheme 8. Proposed mechanism for visible-light photoredox decarboxylative coupling of *N*-protected amino acids with Michael acceptors.

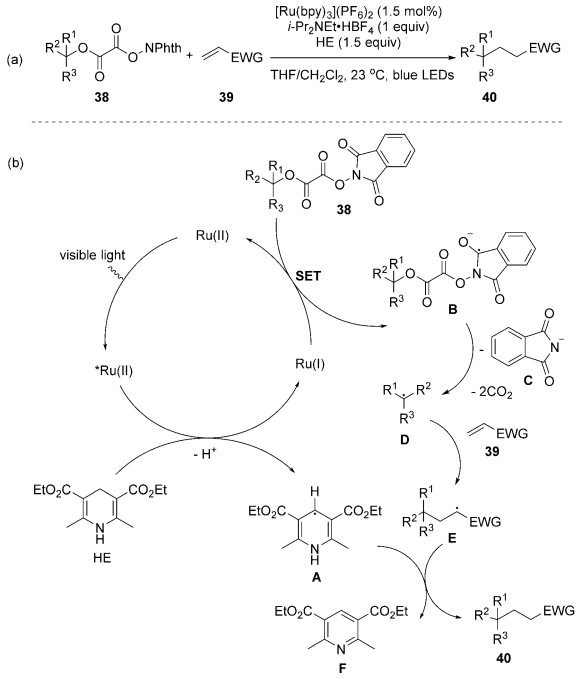
A to Michael acceptor **30** then provides carbon radical **B**. Finally, **B** receives an electron from Ir^{II} followed by capture of a proton to afford the target product **31**.

In 2015, Shang and Fu developed the decarboxylative 1,4-addition of α-keto acids **32** to Michael acceptors **33** under the photoredox catalysis of $Ir[dF(CF_3)ppy]_2(phen)PF_6$ (phen = 1,10-phenanthroline) at room temperature with the irradiation of 36 W blue LEDs (Scheme 9a).[18] The Michael acceptors included α,β-unsaturated esters, ketones, amides, aldehydes, nitriles, and sulfones. The method showed a good tolerance of various functional groups. In the same year, Wallentin and co-workers reported a convenient tandem acylarylation reaction sequence that involved olefins under visible-light photocatalysis (Scheme 9b).[19] Initially, they employed available aromatic carboxylic acids **35** in the photoredox decarboxylation to generate acyl radicals and also found that different types of olefins could be coupled with the generated acyl radicals. The additives, dimethyl dicarbonate (DMDC) or di-*tert*-butyl dicarbonate, were suggested to be key for the activation of the aromatic carboxylic acids. Very recently, Wang's group developed the hypervalent iodine(III) reagent 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (BI-OAc) to catalyze the carbonylarylation of acrylamides **36** with α-keto acids **32** under the radiation of a blue LED (450–455 nm) in the absence of a photoredox catalyst (Scheme 9c).[20] The reactions were conducted at room temperature and provided the corresponding oxindoles in good yields.



Scheme 9. Visible light photoredox decarboxylative addition of acyl radicals with Michael acceptors.

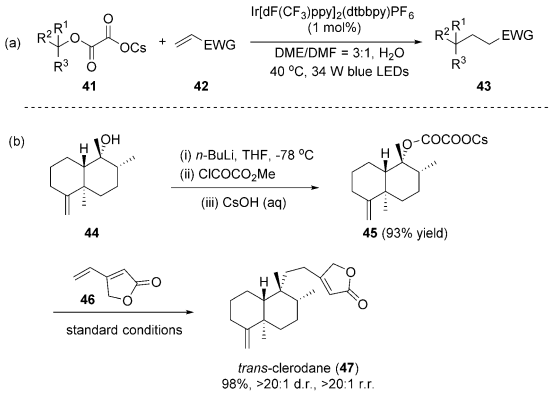
Besides carboxylic acids and their derivatives as radical precursors, in 2013, Overman and co-workers developed an elegant method to construct quaternary carbons by starting from tertiary alcohols and using a photomediated decarboxylative coupling reaction (Scheme 10a).[21a] Tertiary alcohols were first converted into tertiary alkyl *N*-phthalimidoyl oxalate intermediates **38**, and then the visible-light photoredox decarboxylative coupling of **38** with electron-deficient alkenes **39** provided the target products **40** that contained the quaternary carbon



Scheme 10. Visible light photoredox decarboxylative coupling of tertiary alkyl *N*-phthalimidoyl oxalates.

atoms. Among the reactions, the couplings of three chiral oxalates exhibited high diastereoselectivity (>20:1). During the optimization of the reaction conditions, the authors discovered that $iPr_2NEt{\cdot}HBF_4$ was key to the efficiency of reaction, as BF_4^- could undergo an anion exchange with that of the catalyst $[Ru(bpy)_3](PF_6)_2$ to result in the more soluble $[Ru(bpy)_3](BF_4)_2$ complex. In 2015, Overman and co-workers provided the mechanism shown in Scheme 10b.[21b] Irradiation of Ru^{II} with visible light gives the excited state $^*Ru^{II}$, which can be reduced by HE to afford Ru^I and radical **A**. A single-electron transfer from Ru^I to **38** yields radical anion **B**, and the loss of anion **C** and two molecules of CO_2 from **B** provides tertiary carbon radical **D**. The Michael addition of **D** to **39** in the presence of **A** affords the target product **40**.

Although the method in Scheme 10 has a wide substrate scope, it required a stoichiometric amount of the reductant and released a stoichiometric amount of the phthalimide byproduct during the visible-light photoredox coupling of *N*-phthalimidoyl oxalate derivatives of tertiary alcohols with Michael acceptors. In addition, *N*-phthalimidoyl oxalates are not stable to aqueous workup or flash chromatography, which can be an inconvenience during the experiment. In the same year, Overman and MacMillan cooperatively developed simple, stable, and easily handled oxalate salts of tertiary alcohols (i.e., **41**) as radical precursors, which underwent high-yielding photocatalytic coupling reactions with electron-deficient alkenes **42** in the presence of the $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ photocatalyst and visible light (Scheme 11).[22] The method was successfully applied to the synthesis of the natural product *trans*-clerodane (**47**). The acylation of tertiary alcohol **44** with methyl chlorooxoacetate followed by hydrolysis with aqueous CsOH

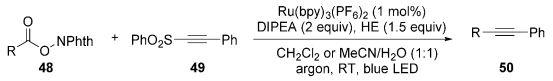


Scheme 11. Visible light decarboxylative couplings of alkyl oxalates and Michael acceptors (DME = 1,2-dimethoxyethane, dr = diastereomeric ratio, rr = regioisomeric ratio).

provided cesium oxalate **45** in 93% yield without the use of chromatography. The visible-light photoredox decarboxylative coupling of **45** with commercially available 4-vinylfuran-2-one (**46**) gave *trans*-clerodane (**47**) in 98% yield with high diastereo- and regioselectivity.

2.2. Alkynylation

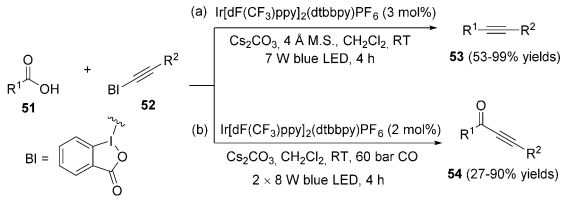
Alkynes are important chemical structures and synthetic intermediates, and the construction of alkyl-substituted alkynes is highly desirable. In 2015, Chen and co-workers reported a visible-light-induced reductive decarboxylative C_{sp^3}–C_{sp} bond coupling reaction to construct aryl-, alkyl-, and silyl-substituted alkynes by carrying out the reaction of *N*-(acyloxy)phthalimides **48** with alkynyl sulfones **49** at room temperature in an organic solvent or a neutral aqueous solution (Scheme 12).[23] The chemoselective alkynylation was then applied to the conjugation of biomolecules.



Scheme 12. Visible light photoredox decarboxylative coupling of *N*-(acyloxy)phthalimides and alkynyl sulfones.

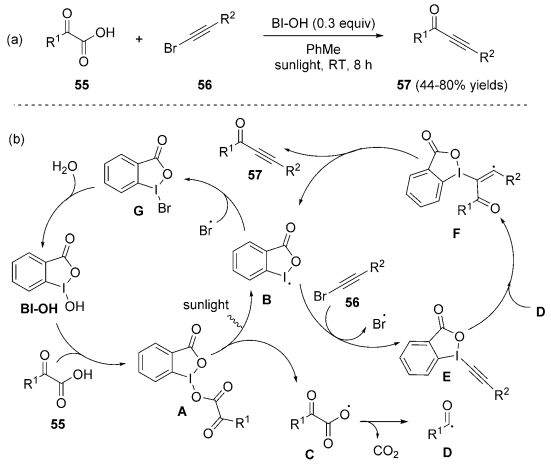
In the same year, Xiao, Liu, and co-workers developed a visible-light photoredox decarboxylative alkynylation by the reaction of carboxylic acids **51** with benziodoxolone (BI)-alkynes **52**.[24a] More interestingly, when the reaction was performed under 60 bar of carbon monoxide, a decarboxylative carbonylative alkynylation reaction occurred and afforded ynones **54** in good yields (Scheme 13). This method directly used carboxylic acids as radical precursors instead of the approach above that used *N*-(acyloxy)phthalimides.[23] In this year, Waser and co-workers also reported a similar reaction for the decarboxylative alkynylation of carboxylic acids.[24b]

As shown in Scheme 9, α-keto acids are also useful radical precursors. In 2015, Wang, Li, and co-workers reported a visi-



Scheme 13. Visible light photoredox decarboxylative alkynylation and carbonylative alkynylation (M.S. = molecular sieves).

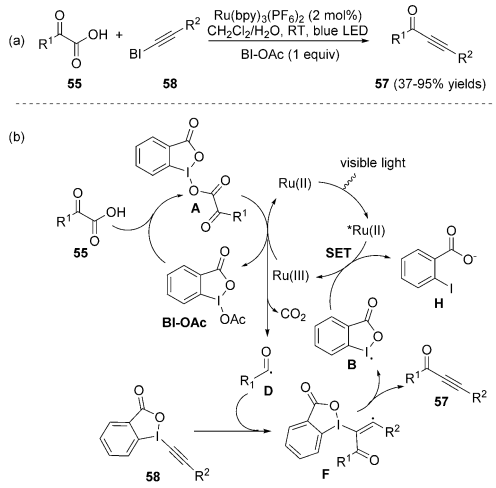
ble-light photoredox decarboxylative alkynylation of α-keto acids under the irradiation of sunlight or blue LED light (Scheme 14).[25] The reaction used bromoacetylenes **56** as the



Scheme 14. BI-OH catalyzed cross-coupling of α-keto acids with bromoacetylene derivatives under the irradiation of sunlight.

alkynyl precursors and 30 mol% of BI-OH as the hypervalent iodine catalyst to give ynones **57** in good yields at room temperature. A proposed mechanism has been provided. The coupling of BI-OH with α-keto acid **55** gives intermediate **A**, which is transformed under sunlight irradiation into two radicals, that is, iodine radical **B** and radical **C**. The decarboxylation of **C** yields acyl radical **D**. The treatment of **56** with **B** provides intermediate **E** along with Br•, and the addition of **D** to **E** provides vinyl radical **F**. Finally, **F** can undergo an elimination reaction to arrive at the target product **57** and release **B**. The combination of **B** with Br• forms hypervalent iodine(III) reagent **G**, and the hydrolysis of **G** regenerates the BI-OH catalyst.

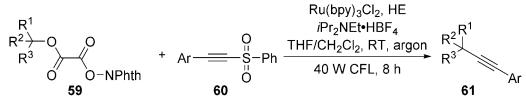
Almost at the same time, Chen and co-workers developed a similar decarboxylative ynonylation by using a hypervalent iodine(III) reagent/photoredox dual catalytic system (Scheme 15).[26] The ynonylation protocol used $[Ru(bpy)_3](PF_6)_2$ as the photocatalyst, α-keto acids **55** as the radical precursors, BI-alkyne **58** as the radical acceptor, and BI-OAc as the additive to provide ynones, ynamides, and ynoates at room temperature. The method employed a broad scope of substrates, and the reaction demonstrated excellent chemoselectivity. The mechanism of this Ru-catalyzed photoredox decarboxylation is



Scheme 15. Visible-light photoredox decarboxylative ynonylation reaction.

shown in Scheme 15. Similar to the above process, intermediate **A** is also generated during the reaction and can decompose to give acyl radical **D** and CO_2 after a single-electron transfer with the Ru^{III} complex. The combination of substrate **58** and **D** yields vinyl radical **F**, which is continuously converted into the final product **57** and iodine radical **B**. Another SET can occur between **B** and the Ru^{II}* complex to complete the catalytic cycle and generate anion **H**.

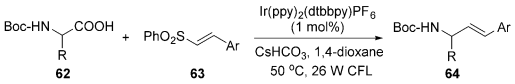
Recently, our group developed an efficient method for the visible-light photoredox synthesis of internal alkynes **61** that contain quaternary carbon atoms (Scheme 16).[27] This protocol used readily available *N*-phthalimidoyl oxalates of tertiary alcohols (i.e., **59**) and 1-[2-(arylsulfonyl)ethynyl]benzenes **60** as the starting materials, and the reaction proceeded smoothly at room temperature and demonstrated good functional group tolerance.



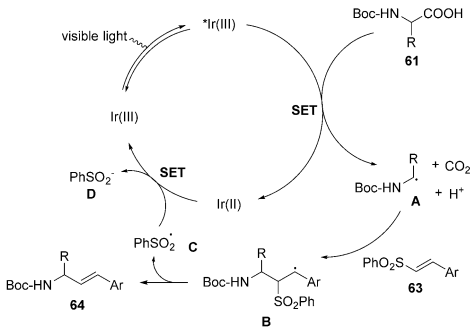
Scheme 16. Visible-light photoredox decarboxylative coupling of tertiary alkyl *N*-phthalimidoyl oxalates with alkynyl sulfones.

2.3. Alkenylation

Alkenes are another type of key building blocks, and their functionalization can transform them into diverse molecules. Recently, great progress in visible-light photoredox decarboxylative alkenylation has been achieved. In 2014, MacMillan and co-workers developed the photoredox decarboxylative α-vinylation reaction of *N*-Boc-α-amino acids **62** with vinyl sulfones **63** (Scheme 17).[28] This protocol employed $Ir(ppy)_2(dtbbpy)PF_6$ as the photocatalyst and $CsHCO_3$ as the base with 1,4-dioxane as the solvent, and the reaction was successfully carried out at 50 °C to provide a broad diversity of allylic amines in high yields with excellent geometric control of the olefin. The approach has been successfully applied to the syntheses of several natural products and a number of established pharmacophores. The proposed mechanism for this visible-light photoredox decarboxylative alkenylation reaction is shown in Scheme 18. First, the Ir^{III} photocatalyst is irradiated with a 26 W



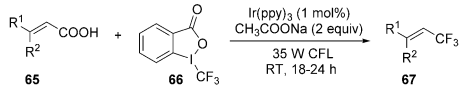
Scheme 17. Visible-light photoredox decarboxylative alkenylation of *N*-Boc-α-amino acids.



Scheme 18. The proposed mechanism for visible-light photoredox decarboxylative alkenylation.

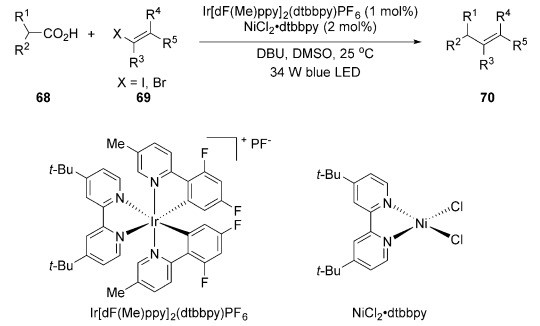
CFL to give the excited state $*Ir^{III}$, and a SET from **61** to $*Ir^{III}$ leads to α-amino radical **A**, which releases Ir^{II}, CO_2, and a proton. The addition of **A** to **63** provides carbon radical **B**, which releases sulfinyl radical **C** to afford the target product **64**. Finally, the SET from Ir^{II} to **C** affords sulfinyl anion **D**.

In the same year, Zhu and co-workers developed the visible-light-induced decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids **65** in the presence of the Togni reagent (**66**) as the CF_3 source (Scheme 19).[29] This method provided trifluoromethylated alkenes **67** in moderate to high yields with excellent functional group tolerance at ambient temperature.

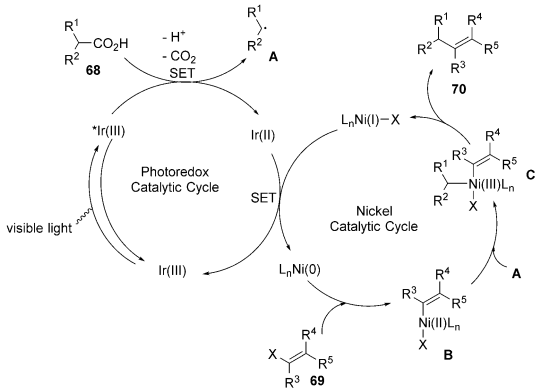


Scheme 19. Visible-light photoredox decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids.

In 2015, MacMillan and co-workers described the decarboxylative cross-coupling reaction of alkyl carboxylic acids **68** with vinyl halides **69** that was promoted by the synergistic merger of photoredox and nickel catalysis (Scheme 20).[30] The employed acids include α-oxy and α-amino acids as well as simple hydrocarbon-substituted acids, and their coupling reactions with vinyl iodides and bromides provided vinylation products **70** in high efficiency under mild conditions. The pro-



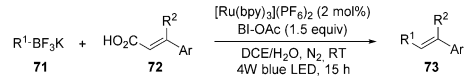
Scheme 20. Visible-light photoredox decarboxylative cross-coupling reaction of alkyl carboxylic acids with vinyl halides promoted by the synergistic merger of photoredox and nickel catalysis (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethyl sulfoxide).



Scheme 21. Proposed mechanism for the visible-light photoredox decarboxylative cross-coupling reaction of alkyl carboxylic acids with vinyl halides.

posed mechanism for this olefination is shown in Scheme 21. Photoexcitation of the iridium(III) photocatalyst Ir[dF(Me)ppy]$_2$(dtbbpy)PF$_6$ gives the long-lived excited state *Ir^{III} species. This photoexcited complex is a strong oxidant and undergoes a thermodynamically favorable single-electron transfer with the carboxylate that is formed by deprotonation of carboxylic acid **68** to lead to the formation of a carboxyl radical. The rapid CO_2 extrusion of the carboxyl radical provides radical **A** along with reduced Ir^{II} species. Meanwhile, the Ni catalytic cycle initiates the oxidative addition of the L_nNi^0 species to vinyl halide **69** to generate vinyl Ni^{II} intermediate **B**. The reaction of radical **A** with **B** gives organometallic Ni^{III} adduct **C**, and the reductive elimination of **C** affords the target product **70** and the Ni^{I} species. The two catalytic cycles are then completed by the reduction of the Ni^{I} species by the reduced state (i.e., Ir^{II}) of the photocatalyst, which regenerates the photocatalyst Ir^{III} and the Ni^0 catalyst.

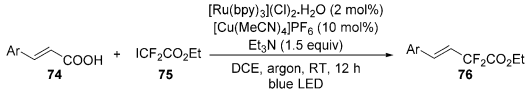
In the same year, Chen and co-workers developed a visible-light-induced deboronative/decarboxylative alkenylation reaction (Scheme 22).[31] The protocol used [Ru(bpy)$_3$](PF$_6$)$_2$ as the photocatalyst, alkyl trifluoroborates **71** as the radical source, and vinyl carboxylic acids **72** as the radical acceptors. The reac-



Scheme 22. Visible-light-mediated deboronative/decarboxylative alkenylation with BI-OAc as the oxidant.

tion proceed smoothly in the presence of acetoxybenziodoxolone (BI-OAc) under blue LED irradiation (λ_{max} = 443–493 nm).

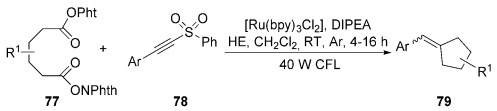
Recently, Liu and co-workers reported the photoredox/copper catalyzed decarboxylative difluoroacetylation reaction of α,β-unsaturated carboxylic acids (Scheme 23).[32] The dual



Scheme 23. Visible-light photoredox/copper catalyzed decarboxylative difluoroacetylation of α,β-unsaturated carboxylic acids.

catalyzed decarboxylative difluoroalkylation reaction used readily available α,β-unsaturated carboxylic acids **74** and ethyl iododifluoroacetate (**75**) as the starting materials and could tolerate a wide range of substituted cinnamic acids. With the introduction of the difluoroalkyl groups into the acid derivatives, the corresponding products **76** were obtained in moderate to high yields.

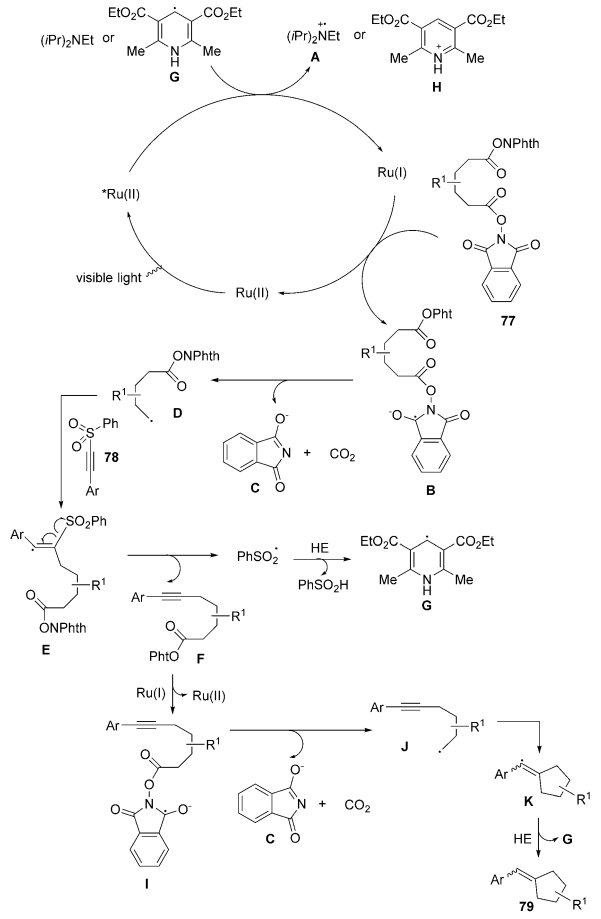
Very recently, our group developed efficient consecutive visible-light photoredox decarboxylative coupling reactions of substituted adipic acid active esters **77** [i.e., bis(1,3-dioxoisoindolin-2-yl)-substituted hexanedioates] with 1-(2-arylethynylsulfonyl)benzenes **78** under the assistance of the [Ru(bpy)$_3$]Cl$_2$ photocatalyst and visible light (Scheme 24).[33] The successive



Scheme 24. Consecutive visible-light photoredox decarboxylative coupling reactions.

photoredox decarboxylative C–C bond formations at room temperature had some function group tolerance and afforded the corresponding cyclic compounds **79** in good yields. This discovery provided a practical strategy for synthesis of cyclic molecules.

The proposed mechanism for the consecutive visible-light photoredox decarboxylative coupling reactions is shown in Scheme 25. The irradiation of Ru^{II} with visible light gives the oxidized excited state *Ru^{II}, and a SET from DIPEA to the photoexcited catalyst provides Ru^{I}. The transfer of one electron from Ru^{I} to the phthalimide of **77** yields radical anion **B** and regenerates the Ru^{II} catalyst. The subsequent release of phthalimide anion **C** and CO_2 affords carbon radical **D**, and the addi-

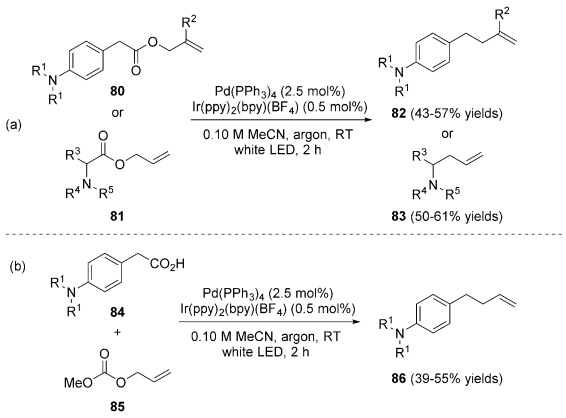


Scheme 25. Proposed mechanism for consecutive visible-light photoredox decarboxylative coupling reactions.

tion of **D** to alkyne sulfone **78** forms vinyl radical **E**. Subsequent homolytic cleavage of the C–S bond of **E** affords intermediate **F** and releases $PhSO_2^{\bullet}$, which upon treatment with HE affords $PhSO_2H$ and radical **G**. The SET from **G** to $*Ru^{II}$ gives Ru^{I} and cation **H**. Similarly, the treatment of **F** with Ru^{I} provides another radical anion **I** and regenerates the Ru^{II} catalyst. The elimination of **C** and CO_2 from **I** leads to radical **J**, and the intramolecular cyclization of **J** produces alkenyl radical **K**. Finally, the treatment of **K** with HE yields the desired target product **79** and releases another radical **G**.

2.4. Allylation

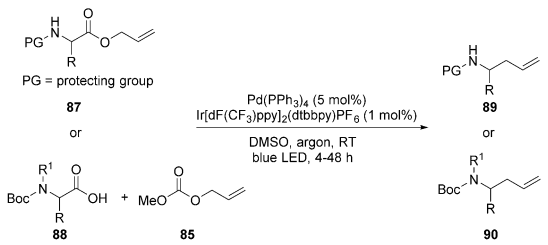
Allylation is an important chemical transformation in organic synthesis, but it is a challenge to conduct a room temperature decarboxylative allylation reaction. In 2014, Tunge and co-workers developed a combined photoredox and palladium catalyzed system to facilitate the room temperature decarboxylative allylation of amino alkanoic acids and esters (Scheme 26).[34] They achieved the intramolecular decarboxylative allylations of phenylacetic and α-amino allyl esters **80** and **81**, respectively, by the dual catalysis of $Pd(PPh_3)_4$ and $Ir(ppy)_2(bpy)BF_4$ (Scheme 26a). Under similar reaction conditions, the intermolecular allylation of *para*-amino-substituted phenyl



Scheme 26. Decarboxylative allylation of amino alkanoic esters and acids by dual catalysis.

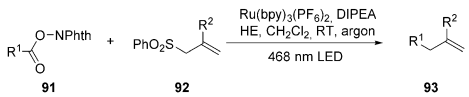
acetic acid **84** with allyl methyl carbonate (**85**) also generated the desired allylation products **86** in comparable yields to those obtained from the intramolecular process (Scheme 26b). A radical dual catalysis mechanism has been proposed in Tunge's research.

In 2015, the same group reported the decarboxylative allylation reactions of *N*-protected α-amino acid allyl esters **87** (intramolecular process) and *N*-protected α-amino acids **88** with allyl methyl carbonate (**85**) (intramolecular process) by using the dual catalyzed system of $Pd(PPh_3)_4$ and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (Scheme 27).[35]



Scheme 27. Decarboxylative allylation of *N*-protected α-amino esters and acids by dual catalysis.

Also in 2015, Chen and co-workers designed an effective method for photoredox carboxylative allylation reactions (Scheme 28),[36] which could be applied to diverse carboxylic acid derivatives including primary, secondary, tertiary, benzyl, and α-heteroatom-substituted carboxylic acids. Importantly, the decarboxylative allylation reaction is completed within mi-

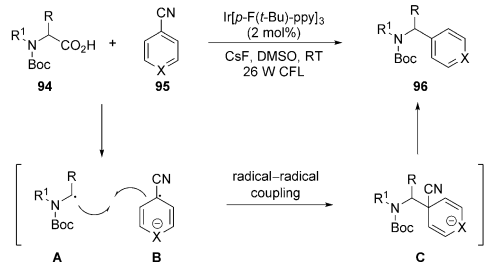


Scheme 28. Chemoselective decarboxylative allylation method for diverse carboxylic acids.

nutes with good chemoselectivity in both organic solvents and neutral aqueous solutions.

2.5. Arylation

In past decades, great progress has been made in transition-metal-catalyzed coupling reactions between aryl and olefinic (sp^2-hybridized) carbons in a selective and predictable manner with high functional group tolerance. However, coupling reactions that involving alkyl (sp^3-hybridized) carbons have proven more challenging.[37] In 2014, MacMillan and co-workers developed the direct decarboxylative arylation of *N*-protected α-amino acids **94** with arylnitriles **95** that contain electron-withdrawing groups by using visible-light-mediated photoredox catalysis (Scheme 29).[38] The method provided rapid entry to

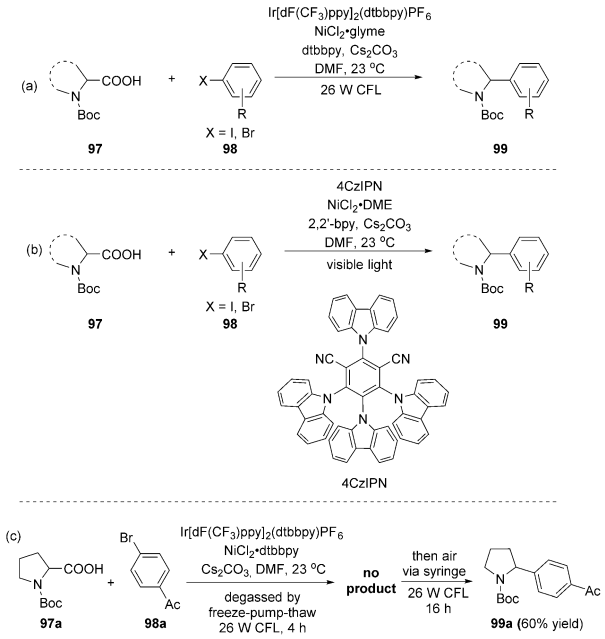


Scheme 29. Visible-light photoredox decarboxylative arylation of *N*-protected α-amino acids with arylnitriles.

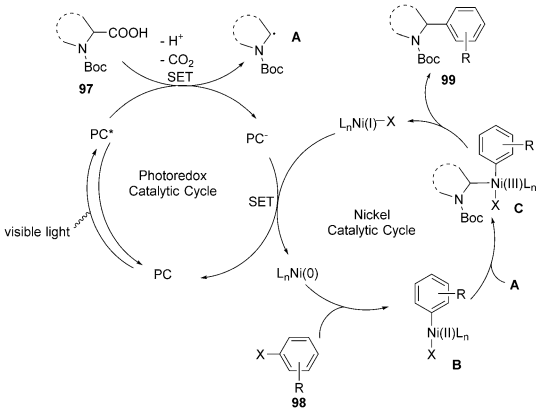
prevalent benzylic amine architectures from readily available α-amino acid precursors. The reaction initially underwent a visible-light-mediated photoredox reaction to form the two radicals **A** and **B**, the composite structure of which is **C**. The release of the CN^- anion from **C** then yields the target product **96**.

In the same year, Doyle and MacMillan cooperatively reported the direct decarboxylative C_{sp^3}–C_{sp^2} cross-coupling reactions of amino acids **97**, as well as α-*O*- or phenyl-substituted carboxylic acids, with aryl halides **98** by merging photoredox with nickel catalysis (Scheme 30a).[37a] This method significantly enlarged the scope of arylation reagents and also allowed for the preparation of products that contained electron-donating groups on the aromatic ring. Very recently, Zhang and co-workers performed a similar reaction with 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) as the photocatalyst (Scheme 30b).[37b] In addition, Oderinde, Johannes, and co-workers reported a similar method (Scheme 30c) and found that oxygen serves an important role in the dual-catalyzed decarboxylative coupling.[39] The mechanism, which is shown in Scheme 31, undergoes a similar pathway to that depicted in Scheme 21.

On the basis of the investigation above, MacMillan and Fu have cooperatively developed an enantioselective decarboxylative arylation of α-amino acids by the combination of photoredox and nickel catalysis (Scheme 32).[40] This method has some advantages including its mild and operationally simple reaction



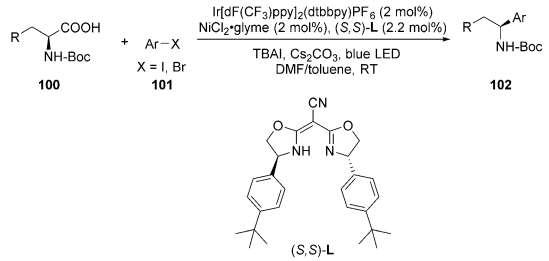
Scheme 30. Visible-light photoredox decarboxylative cross-coupling reaction of amino acids with aryl halides by merging photoredox with nickel catalysis.



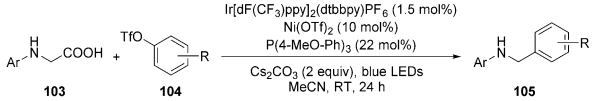
Scheme 31. Proposed mechanism for visible-light photoredox decarboxylative cross-coupling of amino acids with aryl halides (PC = photocatalyst).

conditions, its use of a wide variety of naturally abundant α-amino acids **100** and readily available aryl halides **101**, and its ability to provide valuable chiral benzylic amines **102** with high enantiomeric excess.

In the decarboxylative arylation above, aryl halides are used as the arylating agents. However, aryl triflates and tosylates can also be employed. Recently, Rueping and co-workers developed a visible-light photoredox decarboxylative arylation that involved the reaction of *N*-arylglycines **103** with aryl triflates **104** by using a combined photoredox and nickel catalytic system (Scheme 33).[41] A wide range of aryl triflates, mesylates, and tosylates as well as alkenyl triflates afforded the corresponding products in good to excellent yields.

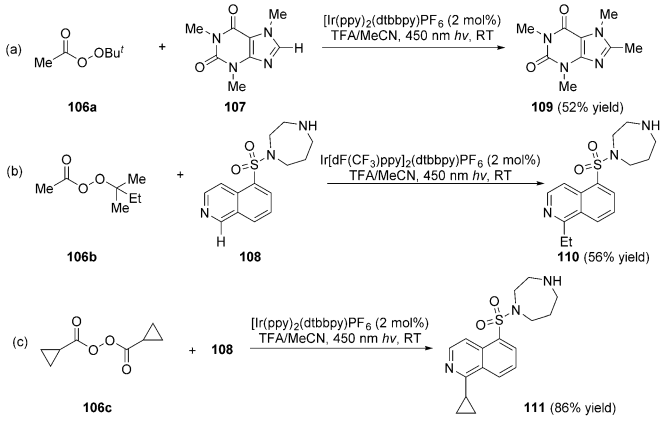


Scheme 32. Visible-light photoredox enantioselective decarboxylative arylation of amino acids by merging photoredox with nickel catalysis (TBAI = tetra-*n*-butylammonium iodide).



Scheme 33. Visible-light photoredox decarboxylative arylation of *N*-arylglycines by merging photoredox with nickel catalysis (TfO = trifluoromethanesulfonate).

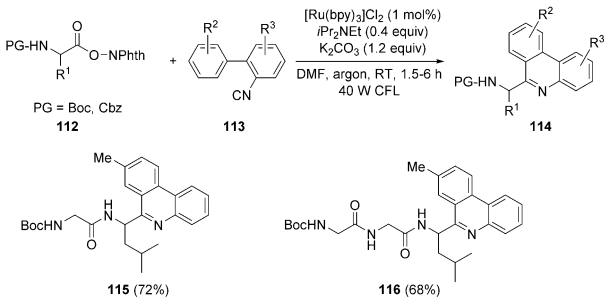
The late-stage modification of useful synthetic intermediates and drug candidates has emerged as an important strategy in contemporary drug discovery.[42] In 2014, DiRocco and co-workers developed a late-stage functionalization of biologically active heterocycles by employing a visible-light photoredox catalyzed reaction (Scheme 34).[43] They used stable organic



Scheme 34. Visible-light photoredox late-stage functionalization of biologically active heterocycles.

peroxides **106a**–**106c** to achieve the direct methyl-, ethyl-, and cyclopropylation reactions of a variety of biologically active heterocycles (such as **107** and **108**) under visible-light photoredox catalyzed conditions. The simple protocol, mild reaction conditions, and unique tolerability of this method make it an important tool for drug discovery.

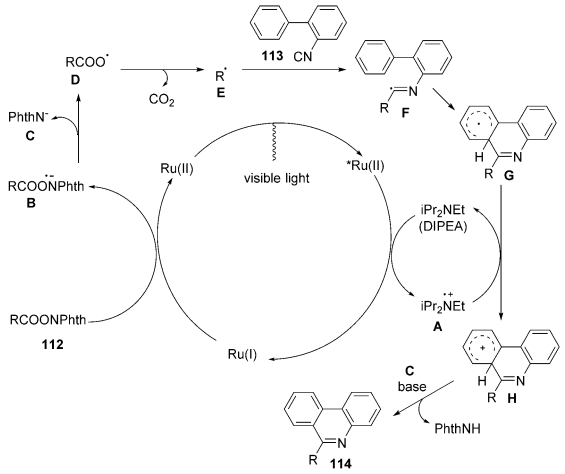
Recently, our group developed the visible-light photoredox coupling reaction of *N*-protected amino acids **112** with substituted 2-isocyanobiphenyls **113** at room temperature with the assistance of the $[Ru(bpy)_3]Cl_2$ photocatalyst (Scheme 35).[44]



Scheme 35. Visible-light photoredox decarboxylative coupling of *N*-protected amino acids and peptides with substituted 2-isocyanobiphenyls (Cbz = benzyloxycarbonyl).

The method provided the biologically and pharmaceutically active phenanthridine derivatives **114** in good yields and was successfully applied to the conjugation of phenanthridines with peptides (such as **115** and **116**). Importantly, the obtained products have amino acid and peptide fragments, and upon their deprotection, further modifications can provide diverse molecules . Therefore, this finding paves the way for the future synthesis of biological and pharmaceutical molecules that contain amino acid and peptide fragments.

We proposed a possible mechanism for the coupling of *N*-protected amino acids **112** with substituted 2-isocyanobiphenyls **113** (Scheme 36). The irradiation of Ru^{II} with visible light

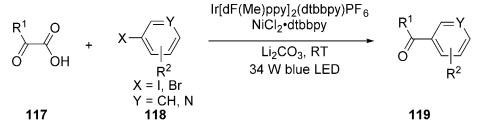


Scheme 36. Proposed mechanism for visible-light photoredox decarboxylative coupling of *N*-protected amino acids with substituted 2-isocyanobiphenyls.

gives the excited state $*Ru^{II}$, and the photoexcited catalyst is then reduced by DIPEA to yield Ru^{I} and radical cation **A**. The treatment of **112** with Ru^{I} produces radical anion **B** and regenerates the Ru^{II} catalyst, and subsequent elimination of the phthalimide anion (**C**) provides carboxyl radical **D**. The following release of CO_2 from **D** yields α-amino radical **E**, which undergoes an addition to substituted 2-isocyanobiphenyl (**113**) to afford imidoyl radical **F**. The intramolecular homolytic aromatic

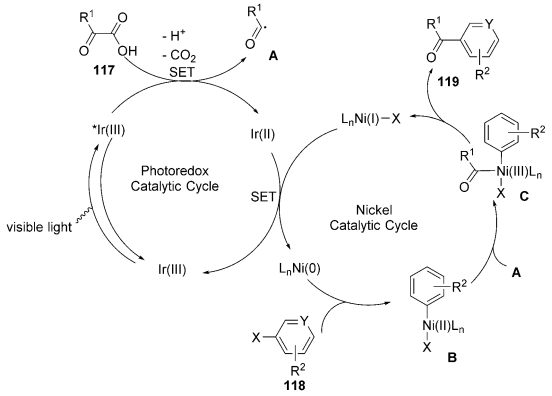
substitution of **F** provides radical intermediate **G**, which can undergo an oxidation in the presence of **A** to yield cation **H** and regenerate DIPEA. Finally, deprotonation of **H** in the presence of base and **C** leads to the target product **114**.

Besides the visible-light photoredox decarboxylative arylation of carboxylic acids, the decarboxylative arylation of α-keto acids has also been investigated by several groups. In 2015, MacMillan and co-workers reported the visible-light-mediated decarboxylative arylation of α-keto acids **117** with aryl halides **118** by using a photoredox and nickel dual catalytic system (Scheme 37).[45] The method provided an efficient route to the



Scheme 37. Visible-light photoredox decarboxylative arylation of α-keto acids with aryl halides by merging photoredox with nickel catalysis.

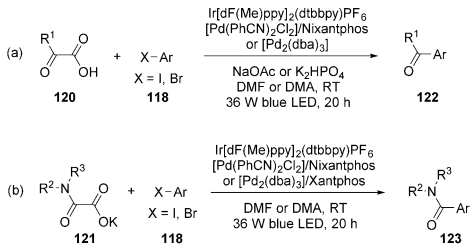
synthesis of aryl and alkyl ketones from simple α-keto acid precursors and had a wide substrate scope and functional group tolerance. The mechanism (Scheme 38) shows that the reaction undergoes a similar pathway to that depicted in Scheme 21.



Scheme 38. Proposed mechanism for visible-light photoredox decarboxylative arylation of α-keto acids with aryl halides.

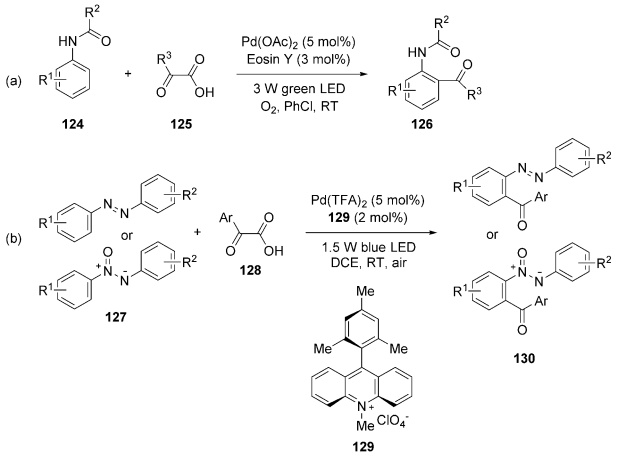
In the same year, Shang and Fu developed the decarboxylative arylation of α-keto carboxylates **120** and **121** with aryl halides **118** at room temperature by using a merged photoredox and palladium catalytic system. A variety of aromatic and heteroaromatic ketones **122** and amides **123** were prepared in good yields with excellent functional group compatibility (Scheme 39). The mechanistic investigations show evidence of a photoredox cycle for an iridium-catalyzed radical decarboxylation reaction combined with a Pd^0-Pd^{II}-Pd^{III} catalytic cycle, in which the Pd^{III} intermediate oxidizes Ir^{II} to link the two cycles.[46]

Meanwhile, Wang and Li reported on the decarboxylative *ortho*-acylation of acetanilides **124** with α-keto carboxylic acids



Scheme 39. Visible-light photoredox decarboxylative arylation of α-keto carboxylates with aryl halides by merging photoredox with palladium catalysis (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, dba = dibenzylideneacetone, DMA = *N*,*N*-dimethylacetamide).

125 at room temperature by using an eosin Y and Pd dual catalytic system (Scheme 40 a).[47a] The method exhibited a broad substrate scope and good functional group tolerance, and an array of *ortho*-substituted acylacetanilides were prepared in high yields under mild conditions. Subsequently, the same

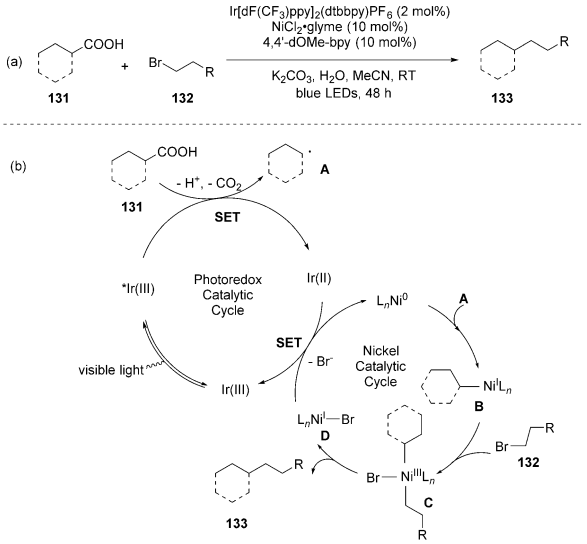


Scheme 40. Visible-light photoredox decarboxylative *ortho*-acylation of acetanilides as well as azo- and azoxybenzenes.

group described another decarboxylative *ortho*-acylation of azo- and azoxybenzenes **127** by using a combination of palladium catalysis and visible-light photoredox catalysis in the presence of organic catalyst **129** at room temperature under 1.5 W of blue LED irradiation (Scheme 40 b).[47b]

2.6. Alkylation

In comparison to related procedures that involve sp^2-hybridized carbon species, the development of transition-metal-catalyzed methods for C_{sp^3}–C_{sp^3} bond formation has been hindered historically by deleterious side reactions, such as β-hydride elimination with palladium catalysis and the reluctance of alkyl halides to undergo oxidative addition reactions.[48,49] Recently, MacMillan and co-workers described the visible-light-mediated decarboxylative alkylation of carboxylic acid **131** with alkyl halides **132** by using a photoredox and nickel dual catalytic



Scheme 41. Visible-light photoredox decarboxylative alkylation of carboxylic acids.

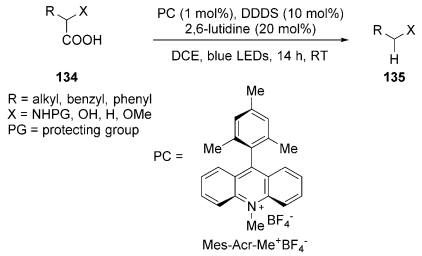
system (Scheme 41 a).[49] The metallaphotoredox method is suitable for many primary and secondary carboxylic acids. The mechanism, which is shown in Scheme 41 b, shows that the reaction undergoes a similar pathway to that depicted in Scheme 21.

3. Formation of C–Y (Y = Heteroatom) Bonds

The visible-light photoredox decarboxylative formation of C–Y (Y = heteroatom) bonds is described and includes the formation of C–H, C–N, C–S, C–Se, and C–F bonds.

3.1. Formation of C–H bonds

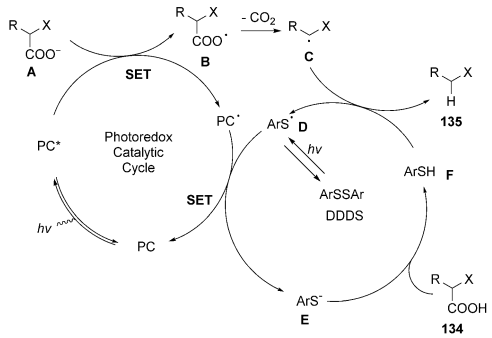
Although recently there have been great advances in visible-light decarboxylative coupling methods, the hydrodecarboxylation of carboxylic acids has been omitted. In 2014, Wallentin and co-workers reported a decarboxylative reduction of carboxylic acids **134** by using an acridinium (Acr) photoredox catalyst (PC = Mes-Acr-Me$^+$BF$_4^-$, Mes = 2,4,6-trimethylphenyl) in combination with bis(4-chlorophenyl)disulfide (DDDS) under visible-light irradiation (Scheme 42).[50] The method provided



Scheme 42. Visible-light photoredox decarboxylative reduction of carboxylic acids.

direct and easy access to hydrocarbons that contain alcohol or ether functional groups as well as biologically relevant enantioenriched amines.

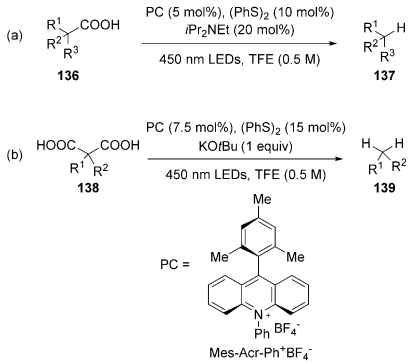
The authors proposed a possible mechanism for the visible-light photoredox decarboxylative reduction of carboxylic acids (Scheme 43). The deprotonation of carboxylic acid **134** gives



Scheme 43. Proposed mechanism of visible-light photoredox decarboxylative reduction of carboxylic acids.

the carboxylate of **A**. The photoexcitation of the catalyst (PC = Mes-Acr-Me$^+$BF$_4^-$) affords PC*, and then the single-electron oxidation of **A** by PC* results in the formation of an acyloxyl radical **B** and PC$^\bullet$, which rapidly rearranges to form carbon dioxide and carbon-centered radical **C**. Meanwhile, a photoinduced S–S bond homolysis forms arylthiyl radical **D**, and the SET from Mes-Acr-Me$^\bullet$ to **D** gives ArS$^-$ and regenerates the Mes-Acr-Me photocatalyst. A proton transfer from carboxylic acid **134** to ArS$^-$ forms thiophenol **F**, and treatment of ArSH with **C** provides the target product **135**.

In 2015, Nicewicz and co-workers developed the direct catalytic hydrodecarboxylation of primary, secondary, and tertiary carboxylic acids **136** by using an organic photoredox catalytic process (Scheme 44 a).[51] The catalytic system consisted of a Fukuzumi acridinium (PC = Mes-Arc-Ph$^+$BF$_4^-$) photooxidant in the presence of phenyldisulfide as a redox-active cocatalyst. The use of trifluoroethanol (TFE) as the solvent allowed for significant improvements in substrate compatibilities. The method

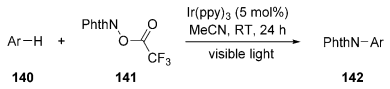


Scheme 44. Visible-light photoredox decarboxylative reduction of carboxylic acids and malonic acids.

was also applied to the direct double decarboxylation of malonic acids **138** (Scheme 44 b).

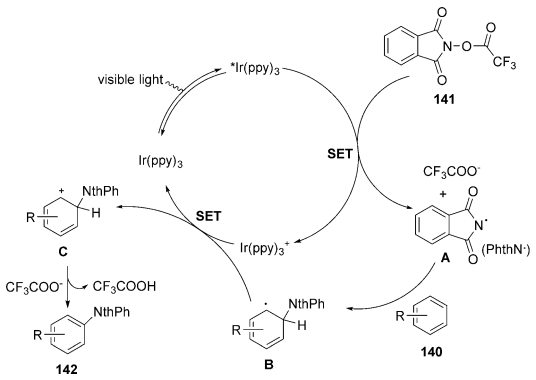
3.2. Formation of C–N Bonds

Nitrogen-containing compounds are widely found in natural products and biologically active molecules, so it is highly desirable to develop efficient methods for the formation of C–N bonds under mild reaction conditions. In 2014, Sanford and co-workers reported a mild photocatalytic method for the decarboxylative C–H amination of arene and heteroarene substrates **140** (Scheme 45). In this work, trifluoromethylacyloxyphthalimide (**141**) was used as the precursor to the nitrogen-based radical intermediates that are formed in these transformations.[52] In general, arenes that contained electron-withdrawing substituents afforded lower yields than those with electron-donating groups, and the reaction displayed high reactivity and selectivity for the aminiation of an arene C–H bond.



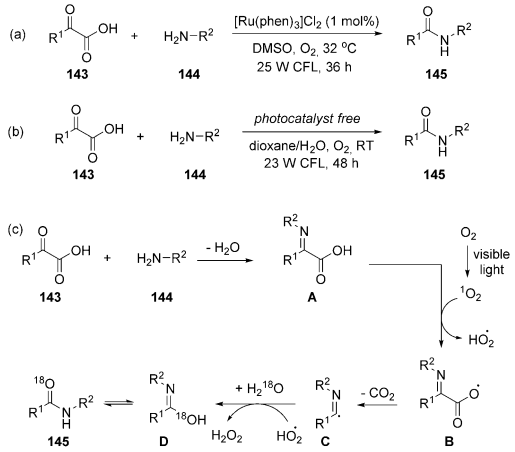
Scheme 45. Visible-light photoredox decarboxylative C–H amination reaction.

A proposed catalytic cycle for the decarboxylative C–H amination is shown in Scheme 46. Photoexcitation of $Ir(ppy)_3$ yields $Ir(ppy)_3$*, and a SET from $Ir(ppy)_3$* to **141** leads to fragmentation of *N*-acyloxyphthalimide **141** to provide the nitrogen-centered phthalimidyl radical **A** (PhthN•), the trifluoroacetate anion, and $Ir(ppy)_3^+$. The addition of **A** to arene **140** gives neutral radical intermediate **B**, which is oxidized by $Ir(ppy)_3^+$ to afford cation **C** and regenerate the $Ir(ppy)_3$ photocatalyst. The departure of a proton from **C** in the presence of the trifluoroacetate anion provides aminated product **142** and trifluoroacetic acid.



Scheme 46. Proposed mechanism for visible-light photoredox decarboxylative C–H amination.

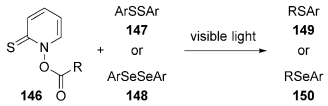
In 2013, Lei, Lan, and co-workers described an efficient method for visible-light photoredox decarboxylative and oxidative coupling reactions of α-keto acids **143** and primary amines **144** with the assistance of the $[Ru(phen)_3]Cl_2$ photocatalyst (Scheme 47 a).[53] The method exhibits good tolerance of various functional groups and provides an efficient approach to aerobic oxidative decarboxylation. Recently, Xu and co-workers reported a catalyst-free strategy for a singlet oxygen promoted decarboxylative amidation by using similar substrates (Scheme 47 b).[54] This method has some advantages such as the avoidance of metal catalysts and its high levels of functional group tolerance. In addition, the reaction could be scaled up and showed high chemoselectivity. A possible pathway for this decarboxylative amidation process is proposed in Scheme 47 c. The treatment of α-keto acid **143** with primary amine **144** leads to a condensation reactions that proceeds through the corresponding hemiaminal to give α-iminoacids **A**. Singlet oxygen, which is generated from oxygen under irradiation with visible light, abstracts an electron from **A** to yield radical **B**, and the decarboxylation of **B** delivers *N*-arylimidoyl radical **C**. The reaction with ^{18}O-labeled water ($H_2{}^{18}O$) gives enol compound **D**, and tautomerization of **D** affords amide **145**. The mechanism shows that singlet oxygen, generated from oxygen under irradiation, was the key promoter for this catalyst-free transformation.



Scheme 47. Visible-light photoredox decarboxylation/oxidative coupling of α-keto acids and amines.

3.3. Formation of C–S and C–Se Bonds

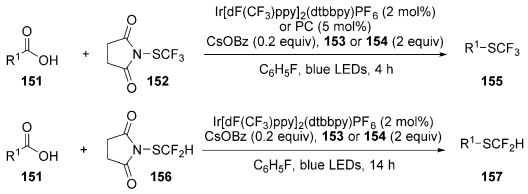
Aryl sulfides and selenides are important building blocks in organic chemistry, materials science, and the pharmaceutical industry. In 1984, Barton and co-workers reported a visible-light decarboxylation for thiohydroxamic-carboxylic mixed anhydrides **146** with disulfides **147** or diselenides **148** to give sulfides **149** or selenides **150** in reasonable to good yields (Scheme 48).[7a] The reactions proceeded well at 35–120 °C under nitrogen. In addition, Procopiou's group realized the formation of C–S bonds by using Barton's thiohydroxamate



Scheme 48. Visible-light decarboxylative coupling of thiohydroxamic-carboxylic mixed anhydrides with disulphides or diselenides.

esters under the irradiation of two 200 W tungsten filament light bulbs at 0 °C.[55]

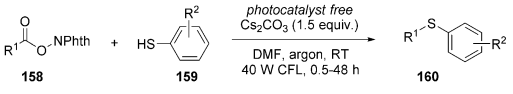
In 2016, Glorius and co-workers reported a method for the visible-light-induced decarboxylative di- and trifluoromethylthiolation of normal alkyl carboxylic acids (Scheme 49).[56] As alkyl



Scheme 49. Visible-light photoredox decarboxylative di- and trifluoromethylthiolation of alkyl carboxylic acids.

SCF_2H and SCF_3 compounds are biologically relevant, the development of an inexpensive and efficient approach to synthesize them is of great significance. In this report, both $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and 9-mesityl-10-methylacridinium perchlorate (the organic dye PC) were effectively used in the decarboxylative di- and trifluoromethylthiolation of diverse alkyl carboxylic acids that contain various functional groups. To suppress the bis(trifluoromethylthiolation) process to form by-products, either mesitylene (**153**) or methyl 3-toluate (**154**) was added to the system as a sacrificial hydrogen atom donor to avoid hydrogen atom abstraction from the products by the intermediate phthalimidyl radical.

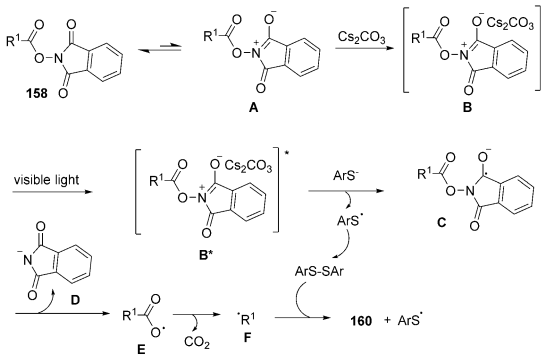
Recently, our group developed the visible-light photoredox arylthiation of *N*-(acyloxy)phthalimides **158** with aryl thiols **159**, and the acids employed to make **158** included common organic carboxylic acids, various amino acids, and a tripeptide. The reaction proceeded well at room temperature with good tolerance of various functional groups (Scheme 50).[57] Impor-



Scheme 50. Visible-light photoredox decarboxylative arylthiation.

tantly, the visible-light photoredox decarboxylative arylthiation process did not need a photocatalyst to proceed. Therefore, the economical, environmentally friendly, and practical method provided a unique strategy to synthesize aryl sulfides.

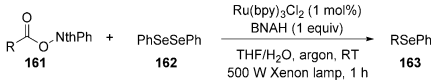
A possible mechanism for this visible-light photoredox decarboxylative arylthiation is proposed in Scheme 51. The two



Scheme 51. Proposed mechanism for visible-light photoredox decarboxylative arylthiation.

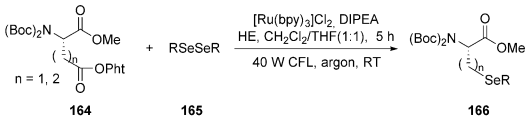
resonance structures **158** and **A** occur in the solution, and the complexation of **A** with Cs_2CO_3 gives complex **B**. The irradiation of **B** as a photosensitizer under visible light provides excited state **B***, and a single-electron transfer from ArS^- to the phthalimide moiety of **B*** delivers the two radicals, **C** and ArS•, in which the dimerization of ArS• forms a diaryl disulfide. The elimination of the phthalimide anion **D** from **C** affords carboxyl radical **E**, and upon the release of CO_2, **E** yields radical **F**. The reaction of **F** with diaryl disulfide affords the target product **160**.

In 1993, Okada, Oda and co-workers established the visible-light photoredox decarboxylative phenylselenenylation of *N*-(acyloxy)phthalimides **161** with $Ru(bpy)_3Cl_2$ as the catalyst and 1-benzyl-1,4-dihydronicotinamide as the reductant (Scheme 52).[58] This photoredox decarboxylative phenylselenenylation method affords some opportunities for the synthesis of high-value chemicals.



Scheme 52. Visible-light photoredox decarboxylative phenylselenenylation of *N*-(acyloxy)phthalimides.

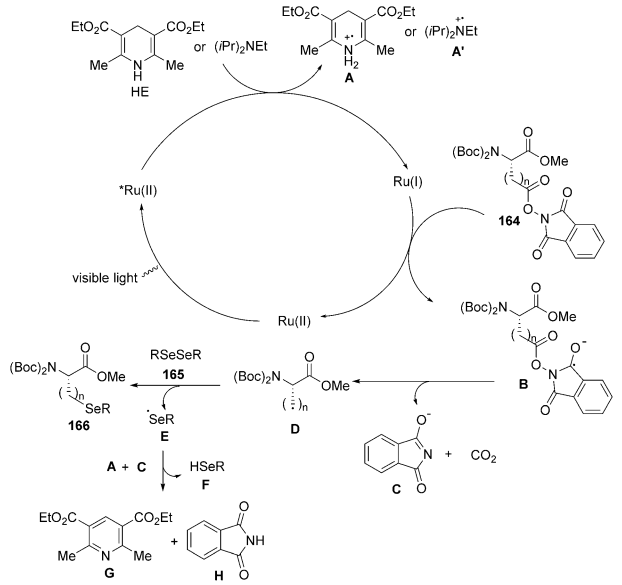
Selenoamino acids are important building blocks in the synthesis of selenoproteins. Recently, we developed an efficient visible-light photoredox synthesis of chiral α-selenoamino acids with the assistance of the $[Ru(bpy)_3]Cl_2$ photocatalyst, in which the *N*-(acyloxy)phthalimide derivatives **164** of two genetically coded proteinogenic amino acids, L-aspartic acid and glutamic acid, were used as visible-light photoredox chiral sources and radical precusors along with diorganyl diselenides **165** as radical acceptors to prepare diverse chiral α-selenoamino acid derivatives in good yields at room temperature (Scheme 53).[59] Furthermore, we investigated the decarboxylative coupling of *N*-protected dipeptide active ester by using diphenyl diselenide to give the corresponding selenodipeptide in good yield. Importantly, the configurations of the precursors, L-aspartic acid and glutamic acid, were maintained as the de-



Scheme 53. Visible-light photoredox decarboxylative synthesis of α-selenoamino acid derivatives.

carboxylative couplings occurred at the β-carbon of L-aspartic acid and the γ-carbon of L-glutamic acid. Therefore, the method afforded a useful strategy for the synthesis of other unnatural chiral α-amino acids that have biological and pharmaceutical activity.

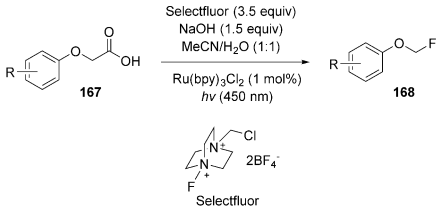
We proposed a plausible mechanism for the visible-light photoredox synthesis of chiral α-selenoamino acids as shown in Scheme 54. The irradiation of Ru^{II} with visible light yields excited state $*Ru^{II}$, which is reduced by HE or DIPEA to give Ru^{I} iand radical cations **A** or **A′**. The treatment of **164** with Ru^{I} affords radical anion **B** and regenerates the Ru^{II} catalyst. The elimination of phthalimide anion **C** and carbon dioxide from **B** provides radical **D**, which upon treatment with diorganyl diselenide **165** yields the target product **166** and releases seleno radical **E**. The combination of **A**, **C**, and **E** gives selenophene **F** and byproducts **G** and **H**.



Scheme 54. Proposed mechanism for visible-light photoredox decarboxylative synthesis of α-selenoamino acid derivatives.

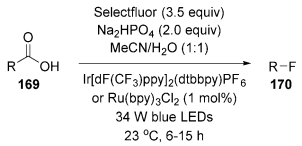
3.4. Formation of C–F Bonds

Fluorinated compounds play an important role in the pharmaceutical and agrochemical sectors, and thus it is highly desirable to develop synthetic methods for the incorporation of fluorine. In 2014, Sammis, Paquin, and co-workers developed the first example of a photoredox catalytic method for the formation of C–F bonds (Scheme 55).[60] The protocol used aryloxyacetic acid derivatives **167** as the substrates, Selectfluor [1-chloromethyl-4-fluoro-1,4-diazoniabicylco[2.2.2]octane bis(tetrafluoroborate)] as the fluorinating agent, and 1 mol% of $Ru(bpy)_3Cl_2$ as the photocatalyst under the irradiation of visible light ($\lambda = 450$ nm). The mild reaction conditions and use of visible light made this method a practical improvement over previously developed UV-mediated decarboxylative fluorinations.



Scheme 55. Visible-light photoredox decarboxylative fluorination of aryloxyacetic acid derivatives.

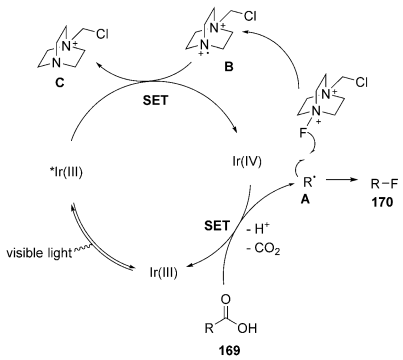
In 2015, MacMillan and co-workers described the decarboxylative fluorination of aliphatic carboxylic acids **169** in the presence of Selectfluor under photoredox catalysis (Scheme 56).[61]



Scheme 56. Visible-light photoredox decarboxylative fluorination of carboxylic acids.

This method had some advantages including its simple operation, redox-neutral fluorination, and high efficiency. Importantly, the protocol for this photoredox fluorination used readily available carboxylic acids as the substrates.

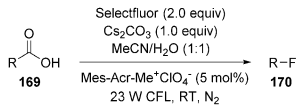
The mechanism for the visible-light-mediated photoredox decarboxylative fluorination above is proposed in Scheme 57. Irradiation of the heteroleptic iridium(III) photocatalyst with visible light leads to the formation of the long-lived excited state $*Ir^{III}$, which undergoes an oxidative quenching to give Ir^{IV}.



Scheme 57. Proposed mechanism for the visible-light photoredox decarboxylative fluorination of carboxylic acids.

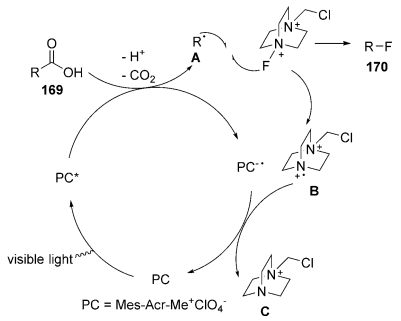
Meanwhile, the SET of alkyl carboxylate **169** to Ir^{IV} yields radical **A** upon the release of CO_2 and regenerates the Ir^{III} photocatalyst. The treatment of **A** with Selectfluor provides the target product **170** and releases radical cation **B**, and a SET of $*Ir^{III}$ to **B** affords cation **C**.

In the same year, Ye and co-workers described an efficient, green method for the decarboxylative fluorination of aliphatic carboxylic acids **169** with Selectfluor in aqueous solution by using an organic dye (i.e., Mes-Acr-$Me^+ClO_4^-$) as the photocatalyst to afford monofluoroalkanes, aryl monofluoroalkyl ethers, and fluoroesters in good to excellent yields (Scheme 58).[62] The low cost of the safe fluorine reagent, the readily available organic photocatalyst, and very mild experiment conditions made this transition-metal-free, photocatalytic radical fluorination useful.



Scheme 58. Visible-light photoredox decarboxylative fluorination of carboxylic acids by organic dye.

The proposed reaction mechanism for the visible-light-mediated photoredox decarboxylative fluorination with organic dye is shown in Scheme 59. The irradiation of the photocatalytic



Scheme 59. Proposed mechanism for visible-light photoredox decarboxylative fluorination of carboxylic acids.

organic dye (Mes-Acr-$Me^+ClO_4^-$) with visible light yields the excited state PC*, and the decarboxylation of carboxylic acid **169** under the assistance of PC* provides radical **A** and $PC^{-\bullet}$. The treatment of **A** with Selectfluor gives the target product **170** and releases radical cation **B**. The SET from $PC^{-\bullet}$ to **B** regenerates PC and gives cation **C**.

4. Conclusions

In this review, recent developments in visible-light photoredox decarboxylative coupling reactions have been summarized. The methods that are presented are characterized by a wide substrate scope, mild reaction conditions, and high efficiency and practicability. Although great advances have been achieved, this field still has some existing challenges, such as the development of inexpensive photocatalysts, the selective activation of inert C–H bonds, asymmetric synthetic strategies, and more applications to achieve total syntheses of a variety of natural products. In this regard, we anticipate that the problems will be resolved with the development of highly efficient catalysts, especially dual catalytic strategies such as the combination of photoredox with transition-metal catalysis, hydrogen-bonding catalysis, or organocatalysis. We believe that the application of visible-light photoredox decarboxylative couplings is still an active area of research, and additional methods will be discovered in the future. It should be noted that examples of other visible-light photoredox decarboxylative coupling reactions do exist, and any omission regarding this broad topic is unintentional.

Acknowledgements

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Keywords: carboxylic acids · C–C coupling · photochemistry · synthetic methods · transition metals

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