Photochemistry

International Edition: DOI: 10.1002/anie.201505731
German Edition: DOI: 10.1002/ange.201505731

Visible-Light-Induced Decarboxylative Functionalization of Carboxylic Acids and Their Derivatives

Jun Xuan, Zhao-Guo Zhang, and Wen-Jing Xiao**

C–C coupling · carboxylic acids · photochemistry · radicals · synthetic methods

***V**isible-light-induced radical decarboxylative functionalization of carboxylic acids and their derivatives has recently received considerable attention as a novel and efficient method to create C–C and C–X bonds. Generally, this visible-light-promoted decarboxylation process can smoothly occur under mild reaction conditions with a broad range of substrates and an excellent functional-group tolerance. The radical species formed from the decarboxylation step can participate in not only single photocatalytic transformations, but also dual-catalytic cross-coupling reactions by combining photoredox catalysis with other catalytic processes. Recent advances in this research area are discussed herein.*

1. Introduction

Carboxylic acids are widely used in biological and chemical syntheses as one of the most fundamental and important platform molecules and their radical decarboxylative functionalization has garned much interest as an attractive synthetic method.[1] Generally, radical decarboxylation of carboxylic acids has several advantages for synthetic organic chemistry: 1) Most of the carboxylic acids are abundant and inexpensive basic chemicals; 2) the formed radical intermediates can be easily converted into many high-value chemical products; and 3) the elimination of CO_2 as the traceless by-product does not influence the reaction system. Dating back to the 1930s, Hunsdiecker et al. found that aliphatic, α,β-unsaturated, and aromatic carboxylic acids bearing electron-withdrawing substituents can efficiently undergo radical halogenative decarboxylation in the presence of dry silver salts.[2] Since this elegant discovery, numerous modifications have been exploited to simplify the procedure, because of the technical difficulties in the preparation of pure and scrupulously dry silver salts.[3] Another classic radical decarboxylative method, the Barton decarboxylation, was first discovered in 1962 and has been widely used in chemical synthesis.[4] However, the method generally requires an additional procedure to transfer carboxylic acids to the corresponding thiohydroxamate esters, thus providing 2-(alkylthio)pyridine as an undesired by-product. In addition to the reactions above, radical decarboxylative functionalizations involving high-energy UV-light induction[5] and electrochemical processes[6] have been developed as efficient options for the synthesis community. From the perspective of sustainable synthetic chemistry, the development of novel and efficient radical decarboxylation methods for the conversion of carboxylic acids into valuable fine chemicals is highly desirable.

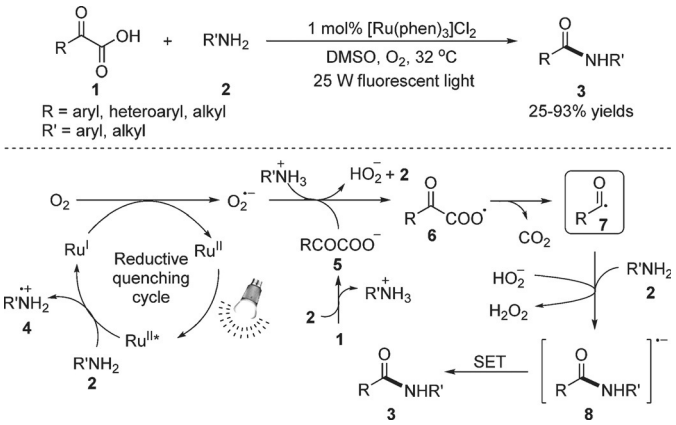
Since 2008, visible-light-induced photoredox catalysis has emerged as a powerful method for initiating radical reactions under very mild reaction conditions and low-energy irradiation.[7] Recently, the application of this strategy to radical decarboxylation reactions has resulted in a significant advancement of this field. The radical species formed from carboxylic acids can participate not only in single photocatalytic transformations but also in dual-catalytic cross-coupling reactions by combining photoredox catalysis with transition-metal catalysis.[8] In addition to carboxylic acids, some of their derivatives can also be used in photocatalyzed decarboxylative functionalization reactions. Herein, we summarize recent advances in the visible-light-mediated radical

[*] Dr. J. Xuan, Prof. Dr. W.-J. Xiao
CCNU-uOttawa Joint Research Centre, Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry
Central China Normal University (CCNU)
152 Luoyu Road, Wuhan, Hubei 430079 (China)
E-mail: wxiao@mail.ccnu.edu.cn
Homepage: http://chem-xiao.ccnu.edu.cn/
Prof. Dr. Z.-G. Zhang
School of Chemistry and Chemical Engineering
Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (China)
E-mail: zhaoguo@sjtu.edu.cn

decarboxylative functionalization of carboxylic acids and their derivatives, thus hoping to attract more research efforts to this field and encourage the development of novel chemical transformations with the radical intermediates formed. This minireview is organized according to the types of starting materials employed.

2. Radical Decarboxylative Functionalization of Carboxylic Acids

α-Keto acids are important acyl synthons in synthetic organic chemistry and the development of novel methods for the decarboxylation of α-keto acids has attracted considerable research interest.[1] However, most of the reported methods are largely limited to activating α-keto acids with transition metals at a high temperature or with strong oxidants.[9] At the end of 2013, an inspiring breakthrough in this field was reported by Lei and co-workers, who developed the first visible-light-induced decarboxylative amidation of α-keto acids, thus providing a novel and efficient route to various amides in good yields (Scheme 1).[10] One of the key



Scheme 1. Visible-light-induced decarboxylative amidation of α-keto acids. DMSO = dimethylsulfoxide, phen = 1,10-phenanthroline.

features of this work was the use of O_2 as a green terminal oxidant. Different aryl-, heteroaryl-, or alkyl-substituted α-keto acids could be successfully used in this transformation. Importantly, the method can be successfully applied to the efficient synthesis of nitrogen-containing heterocyclic compounds when *ortho*-substituted anilines are involved.

The proposed reaction mechanism consists of reductive quenching of the excited Ru^{II}* with an amine to give a Ru^{I} species, which is subsequently oxidized by O_2 to regenerate the photocatalyst and give the superoxide radical anion (Scheme 1). Simultaneously, deprotonation of **1** delivers the anion intermediate **5**, which may subsequently undergo one-electron transfer (SET) with the superoxide radical anion to generate the intermediate **6**. The decarboxylation of **6** then gives the key acyl radical **7**. Finally, the reaction of **7** with the amine **2**, followed by another SET, provides the desired amide **3**. Notably, the signal of the Ru^{I} species can be directly detected by electron paramagnetic resonance spectroscopy. Moreover, the results of a radical-trapping experiment with the addition of TEMPO suggested that **7** was a possible intermediate. All of the mentioned mechanistic studies, combined with the results of density functional calculations, support the proposed mechanism as a reasonable pathway.

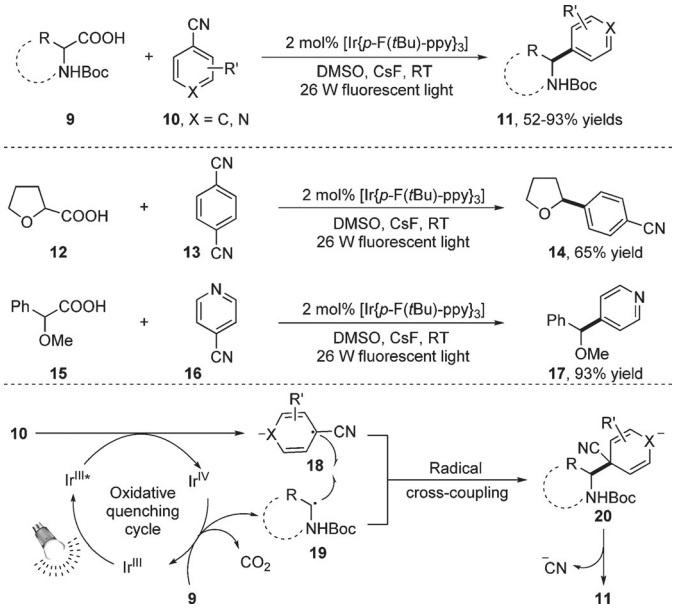
The group of MacMillan extended this type of visible-light-induced decarboxylation to various other useful transformations, and made a major contribution to this research area. In 2014, they described an elegant visible-light-mediated decarboxylative arylation of α-amino acids with cyanoarenes, thus affording the corresponding, and prevalent, benzylic amine architectures in good yields (Scheme 2).[11] A wide range of Boc-protected natural and unnatural α-amino acids, as well as α-oxygenated acids such as tetrahydro-2-furancarboxylic acid (**12**) and 2-methoxyphenylacetic acid (**15**), were successfully used with high reaction efficiencies. Notably, a major limitation of this methodology was that only cyanobenzenes possessing electron-withdrawing groups could be coupled with carboxylic acids.

The reaction is initiated by oxidative quenching of the excited photocatalyst Ir^{III}* with the cyanoarene **10** to generate the aryl radical anion **18** (Scheme 2). Then, the α-amino acid **9** functions as an electron donor to reduce the formed Ir^{IV} to the

Jun Xuan received his BSc in chemistry from Fuyang Teachers College in 2009 and completed his PhD studies in 2015 under the direction of Prof. Wen-Jing Xiao at Central China Normal University (CCNU). He is now a Humboldt postdoctoral fellow with Prof. Armido Studer at the Westfälische Wilhelms-Universität Münster. His research interests focus on the synthesis of functional heterocycles by using visible-light photoredox catalysis.

Zhao-Guo Zhang received his MSc in 1994 from Nanjing University and his PhD in 1997 from the Shanghai Institute of Organic Chemistry under the direction of Prof. Xi-Yan Lu. After postdoctoral studies with Prof. Xu-Mu Zhang at Pennsylvania State University, he became a professor at the Shanghai Institute of Organic Chemistry. Since 2005 he has been a full professor at Shanghai Jiao Tong University. His research includes transition-metal-catalyzed reactions, homogeneous catalysis, and the development of new synthetic methods.

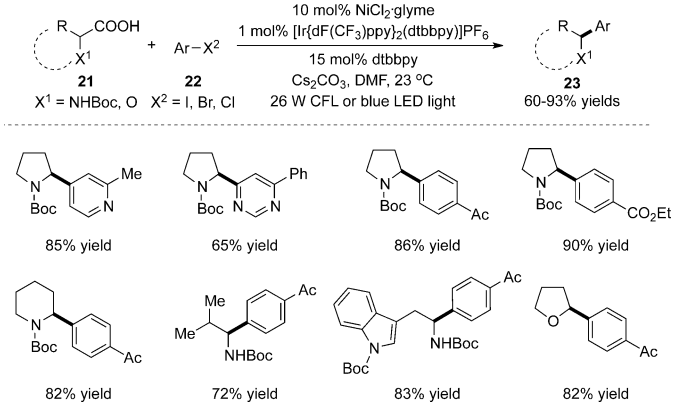
Wen-Jing Xiao received his MSc in 1990 while under the supervision of Prof. Wen-Fang Huang at CCNU. In 2000, he received his PhD under the direction of Prof. Howard Alper at the University of Ottawa. After postdoctoral studies with Prof. David W. C. MacMillan (2001–2002) at the California Institute of Technology, he became a full professor at CCNU. His current research includes the development of new synthetic methods and the synthesis of biologically active compounds.



Scheme 2. Visible-light-induced decarboxylative arylation of α-amino acids. Boc = *tert*-butoxycarbonyl, *p*-F(*t*Bu)ppy = 4-(*tert*-butyl)-2-(4-fluorophenyl)pyridine.

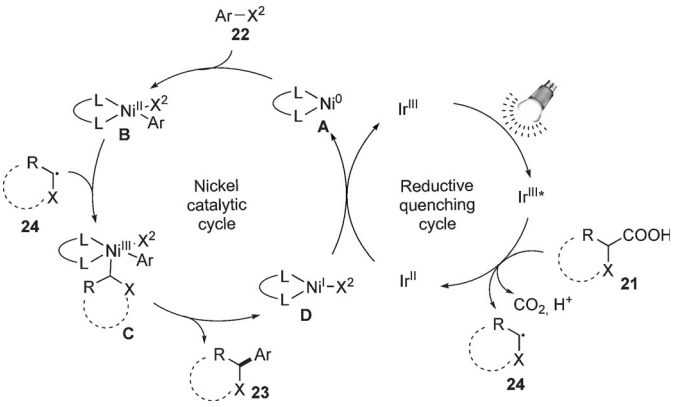
low-valent Ir^{III} so as to complete the photocatalytic cycle. The generated carboxyl radical species subsequently looses CO_2, thereby delivering another key α-amino alkyl radical (**19**). Finally, a radical–radical cross-coupling of the persistent radical **18** with the transiently formed **19**, followed by cyanide elimination, provides product **11**. One of the most attractive features of the reaction is that the two coupling partners, **9** and **10**, are simultaneously activated in a single photocatalytic cycle without requiring an external reductant or oxidant.

In 2014, Doyle, MacMillan, and co-workers described an unprecedented decarboxylative cross-coupling of carboxylic acids with aryl halides by merging nickel catalysis with visible-light photoredox catalysis (Scheme 3).[12a] This novel methodology tolerated differently electron-rich aryl halides and provided a new option for the visible-light-induced decarboxylative arylation of carboxylic acids, albeit with a relatively high loading of the nickel catalyst (10 mol%). Apart from several types of carboxylic acids, *N*,*N*-dimethylaniline was also shown to be a suitable coupling partner with a variety of aryl halides under optized reaction conditions. In a contribution of 2015, MacMillan and co-workers described the decarboxylative arylation of α-oxo acids using this visible-light-promoted dual-catalytic system , and thus provided efficient access to many aryl and alkyl ketones in good yields.[12b]



Scheme 3. Visible-light-induced decarboxylative cross-coupling of carboxylic acids. glyme = monoethylene glycol dimethyl ether; [dF(CF$_3$)ppy] = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, DMF = *N*,*N*-dimethylformamide, CFL = compact fluorescent lamp.

This cross-coupling process starts with the reductive quenching of Ir^{III}* with an carboxylic acid **21** to generate a Ir^{II} species and a carboxyl radical (Scheme 4). The latter subsequently loses CO_2, thus delivering the carbon-centered radical species **24**. Simultaneously, the oxidative addition of

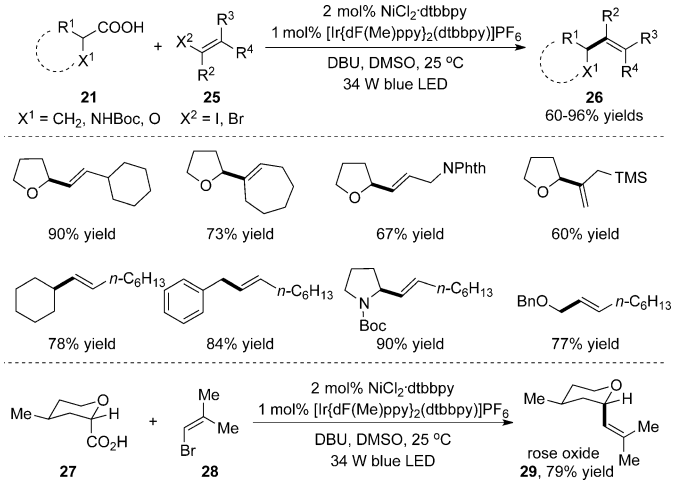


Scheme 4. Plausible mechanism of the visible-light-induced decarboxylative cross-coupling of carboxylic acids.

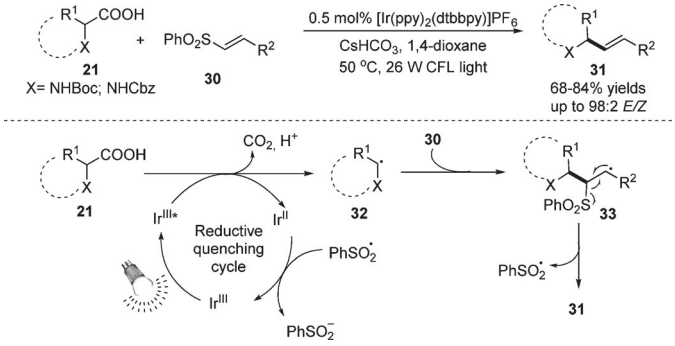
Ni^0 to an aryl halide **22** provides a Ni^{II} complex (**B**), which rapidly intercepts **24** to afford the Ni^{III} complex **C**. Reductive elimination provides the C_{sp^3}–C_{sp^2} coupling products **23** and the Ni^I species **D**. Finally, one-electron transfer from the Ir^{II} to the Ni^I species completes both catalytic cycles.

Shortly after its discovery, this dual-catalytic decarboxylative cross-coupling reaction was elegantly expanded to carboxylic acids and vinyl halides by the group of MacMillan (Scheme 5).[13] The method provides an ideal platform for the formation of new C–C bonds and thus allows direct access to complex allylic amino, allylic oxy, and alkyl vinyl products with good results. Importantly, the loading of the nickel catalyst could be decreased to 2 mol% in this case. Furthermore, the specific use of this methodology is well demonstrated by its utilization in the construction of rose oxide **29**, a widely used natural product, in good yield. These two dual-catalytic cross-coupling processes may open up a new avenue for the combination of visible-light photoredox catalysis with other catalysis approaches.

Another impressive example of decarboxylative vinylation of α-amino acids developed by the group of MacMillan was based on the use of a radical conjugate addition as a key step (Scheme 6).[14] Good to excellent yields of the corresponding allylic amines **31** can be obtained with the assistance of 0.5 mol% $[Ir(ppy)_2(dtbbpy)]PF_6$ as the photoredox catalyst



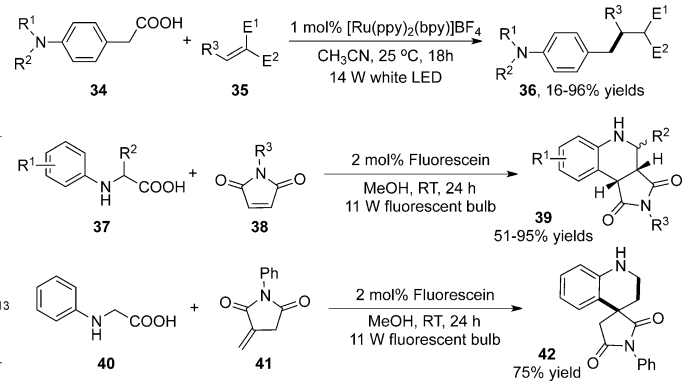
Scheme 5. Decarboxylative cross-coupling of carboxylic acids with vinyl halides. [dF(Me)ppy] = 2-(2,4-difluorophenyl)-5-methylpyridine, DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene, NPhth = *N*-phthalimido.



Scheme 6. Visible-light-induced decarboxylative vinylation of α-amino acids. Cbz = benzyloxycarbonyl.

and vinyl sulfones as α-amino radical acceptors.[15] Advantages of this strategy are the broad scope with respect to both starting materials, good functional-group tolerance, and excellent control of the olefin geometry. An additional attractive feature of the method is that several natural products and many established pharmacophores can be easily accessed using the decarboxylative vinylation reaction as the key step. The formation of α-amino radical species **32** is also based on reductive quenching of the excited photocatalyst, in this case with an α-amino acid **21**, as shown in the mechanistic pathway (Scheme 6). Then, the radical addition of **32** to a vinyl sulfone **30** delivers another radical intermediate (**33**), which subsequently looses a sulfinyl radical to provide the final allylic amine **31**. Finally, one-electron reduction of the sulfinyl radical with Ir^{II} gives a sulfinate anion and regenerates the photoredox catalyst to complete the photocatalytic cycle.

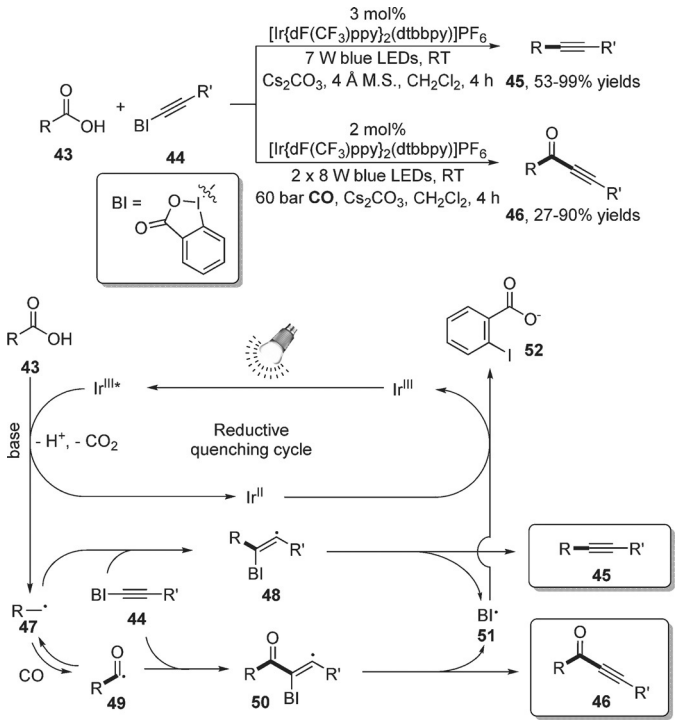
Actually already in 2013, a visible-light-mediated decarboxylative radical conjugate addition reaction was successfully achieved by Nishibayashi and co-workers (Scheme 7).[16] Note that only an arylacetic acid bearing an amino group at its *para*-position can efficiently undergo the decarboxylation process to generate the key benzyl radical. The fact that this



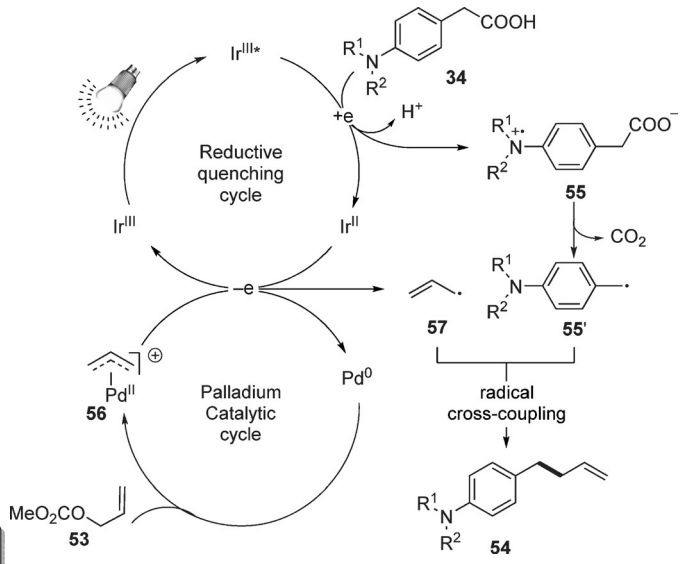
Scheme 7. Visible-light-induced decarboxylative radical conjugated addition with aryl acetic and α *N*-aryl amino acids. ppy = 2-phenylpyridine; bpy = 2,2′-bipyridine.

visible-light-mediated decarboxylative radical conjugate addition process is completely shut down when either the visible light or the ruthenium catalyst are excluded, strongly demonstrates the photoredox characteristics of this transformation. At approximately the same time, Wang, Tan and co-workers described an elegant visible-light-mediated decarboxylative annulation of *N*-aryl glycines **37** using decarboxylative radical conjugate addition as a key step (Scheme 7).[17] The reaction uses fluorescein as simple organic photoredox catalyst and leads to the corresponding natural-product-like heterocyclic ring structures **39** in generally good yields. More notably, the method can be efficiently extended to synthesize the spiro-bicyclic amine **42** by using the methylene succinimide **41** as the radical acceptor. In a later effort, MacMillan and co-workers further expanded the scope of the carboxylic acids from aminoaryl acetic acids and *N*-aryl glycines to a variety of generic acids, including α-amino acids, α-oxy acids, as well as many cyclic and acyclic alkanoic acids, which greatly enriched the synthetic potential of the method.[18] Notably, the successful three-step synthesis of pregabalin, an anticonvulsant drug,[19] represents a good example of the synthetic application.

In 2015, we described a visible-light-mediated decarboxylative alkynylation reaction using BI–alkyne[20] as electrophilic alkynylating agent (Scheme 8).[21] Remarkably, in the presence of 60 bar carbon monoxide, this reaction becomes a decarboxylative carbonylative alkynylation reaction, and affords valuable ynones **46** in good yields. The reaction is quite general. Importantly, the synthetic application of the method was elegantly demonstrated by the preparation of naturally occurring ursolic acid and the synthesis of oxazolidinones. Similar to the mechanism discussed above, the radical intermediate **47** is formed through reductive quenching of the excited Ir^{III}*. Then, radical addition of **47** to the BI–alkyne **44** generates the intermediate **48**, which eliminates a radical to afford the decarboxylative alkynylation product **45**. In the presence of CO, **47** can be firstly trapped by CO to give the acyl radical **49**, which undergoes a similar radical addition/elimination process to provide the decarboxylative carbonylative alkynylation product **46**. In both cases, the formed BI radical **51** is considered to be the oxidant for completion of the photocatalytic cycle.



Scheme 8. Visible-light-mediated decarboxylative alkynylation and carbonylative alkynylation of carboxylic acids. M.S. = molecular sieve.

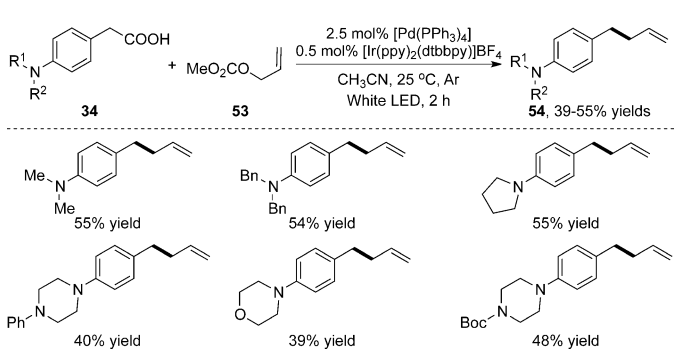


Scheme 10. Plausible reaction mechanism for dual-catalytic decarboxylative allylation of aminoarylacetic acids.

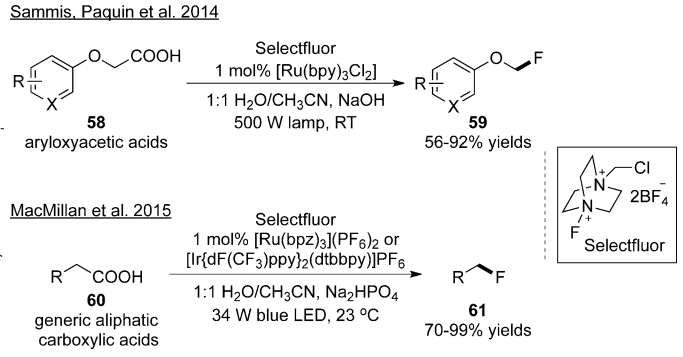
As part of their continuing studies focusing on the development of palladium-catalyzed decarboxylative coupling reactions,[22a] the group of Tunge described an impressive dual-catalytic decarboxylative allylation of aminoaryl acetic acids by combining palladium and visible-light photoredox catalysis to provide novel access to allylated alkanes in moderate yields (Scheme 9).[22b] Compared with the previously reported palladium-catalyzed benzylic allylation processes,[23] this reaction is characterized by its mild reaction conditions and does not require additional activating agents.

As depicted in Scheme 10, a radical dual-catalysis mechanism is proposed to explain this reaction. The photocatalytic cycle starts with reductive quenching of an excited Ir^{III}* photocatalyst with an aminoarylacetic acid **34** to give intermediate **55**, which after loss of CO_2, affords the benzyl radical intermediate **55′**. Simultaneously, the reaction of Pd^0 with allyl methyl carbonate (**53**) delivers a π-allylpalladium complex (**56**), which is subsequently reduced by low-valent Ir^{II} to give the allylic radical **57**, and thus completes the photoredox and palladium catalytic cycle. At last, the radical cross-coupling of **55′** with **57** generates the desired benzylic allylation product **54**. Note that the addition of **55′** to the palladium center of the π-allylpalladium complex **56**, followed by sequential reduction of the formed Pd^{III} species with the low-valent Ir^{II} and reductive elimination, is thought to be an alternative reaction pathway.

Fluorinated compounds have been widely used in materials, agrochemical, and pharmaceutical chemistry applications, and the incorporation of fluorine atoms into organic molecules can significantly alter not only their chemical properties, but also their physical and biological properties.[24] Based on their previous work on UV-mediated decarboxylative fluorinations,[25] the first example of visible-light-mediated decarboxylative C–F bond formation was realized by Sammis, Paquin, and co-workers in 2014, by using Selectfluor as the fluorine source (Scheme 11).[26] A mechanistic study involving transient absorption spectroscopy revealed that a SET from the ^{3}MLCT state of the Ru^{II} photoredox catalyst to Select-



Scheme 9. Dual-catalytic decarboxylative allylation of aminoarylacetic acids by combining palladium and visible light photoredox catalysis.

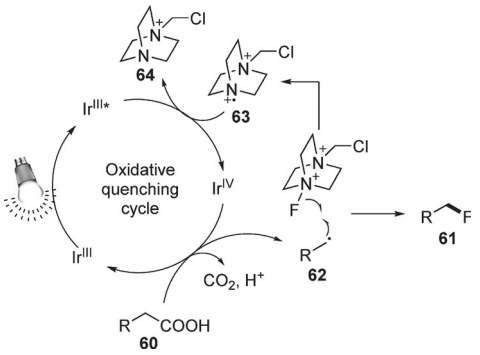


Scheme 11. Visible-light-mediated decarboxylative C–F bond formation. bpz = 2,2′-bipyrazine.

fluor was involved as a key step in this reaction. Although the method made an impressive breakthrough in this research area, the limitation to the utilization of aryloxyacetic acids is a major shortcoming.

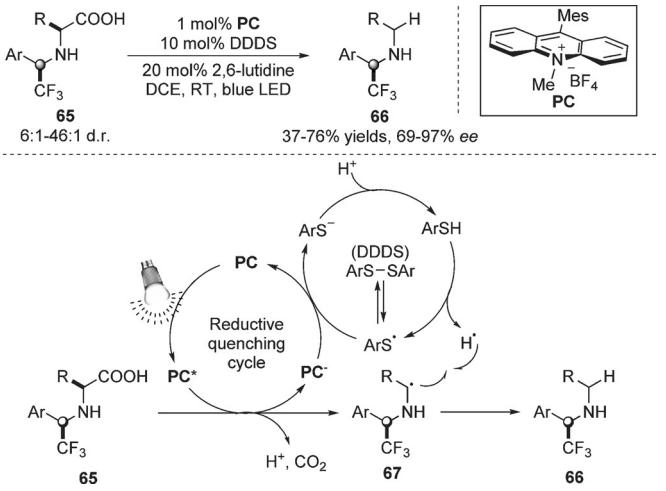
To overcome this obstacle, MacMillan et al. developed a versatile decarboxylative fluorination protocol for a wide range of aliphatic carboxylic acids by employing either $[Ru(bpz)_3](PF_6)_2$ or $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ as the photoredox catalyst under irradiation with a 34 W blue LED light (Scheme 11).[27a] This kind of reaction can also be performed under transition-metal-free condition by organic photoredox catalysis.[27b] The reaction itself features a simple operation under mild reaction conditions, and gives the corresponding valuable fluorinated products in excellent yields. Different substituted alkyl carboxylates, such as primary, secondary, and tertiary alkyl carboxylic acids and their sodium salts, are well tolerated. It is of note that in the cases of some unactivated primary and tertiary carboxylic acids, a relatively long reaction time is required for their full conversion.

A plausible reaction mechanism based on the oxidative quenching cycle is proposed (Scheme 12). Initially, the irradiation of the Ir^{III} photocatalyst with visible light generates the excited $Ir^{III}*$ complex, which is subsequently oxidized by a sacrificial quantity of Selectfluor to give the high-valent Ir^{IV} species. This step is proven to be feasible by the fluorescence-quenching experiments and the reported results from the group of Sammis.[26] Under basic conditions, facile deprotonation of carboxylic acid **60**, followed by a one-electron oxidation of the formed carboxylate by Ir^{IV} regenerates the iridium photocatalyst. The formed carboxyl radical immediately looses CO_2 to give the radical intermediate **62**. Finally, direct fluorine transfer from Selectfluor to **62** provides the desired C–F bond-formation product. The concomitantly generated Selectfluor radical cation (**63**) is thought to replace Selectfluor as an oxidative quencher in the subsequent photocatalytic cycles to oxidize $Ir^{III}*$ to Ir^{IV}.



Scheme 12. Plausible mechanism for visible-light-mediated decarboxylative C–F bond formation.

In 2014, the group of Wallentin used an organocatalytic photoredox system to achieve an impressive visible-light-promoted decarboxylative reduction of carboxylic acids (Scheme 13).[28] Similar to Nicewicz and co-workers,[29c] they

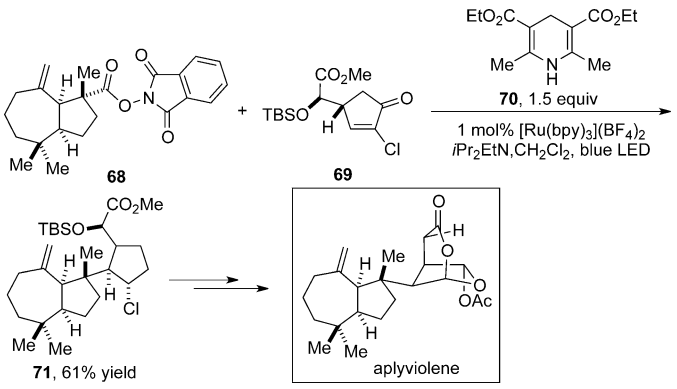


Scheme 13. Visible-light-mediated decarboxylative reduction of carboxylic acids. DCE = dichloroethane, DDDS = bis(4-chlorophenyl)disulfide.

exploited Fukuzumi's mesityl acridinium salt **PC**[29a,b] as the organic photoredox catalyst and DDDS as a redox-coupled hydrogen shuttle. α-Amino acids, α-hydroxy acids, and phenylacetic acids are suitable radical precursors for this decarboxylative reduction process. In addition, a variety of sensitive functional groups, such as esters, ethers, amines, alcohols, and thioethers, are well-tolerated. More importantly, no obvious loss in optical activity based on the benzylic stereogenic center is observed when chiral α-amino acids **65** are subjected to the optimal reaction conditions. The authors proposed the reaction mechanism shown in Scheme 13 to explain this decarboxylative reduction process according to a previous study reported by Nicewicz and co-workers .[29c] Initially, the carboxylic acid **65** acts as a reductive quencher to reduce the excited photocatalyst, thus providing the radical intermediate **67** along with the release of CO_2 and a proton. The thiyl radical that exists in equilibrium with DDDS functions as an oxidant to complete the photocatalytic cycle. The formed thiolate anion is then protonated to give thiophenol, which is thought to act as the hydrogen-atom donor to react with **67** and furnish the final product **66**.

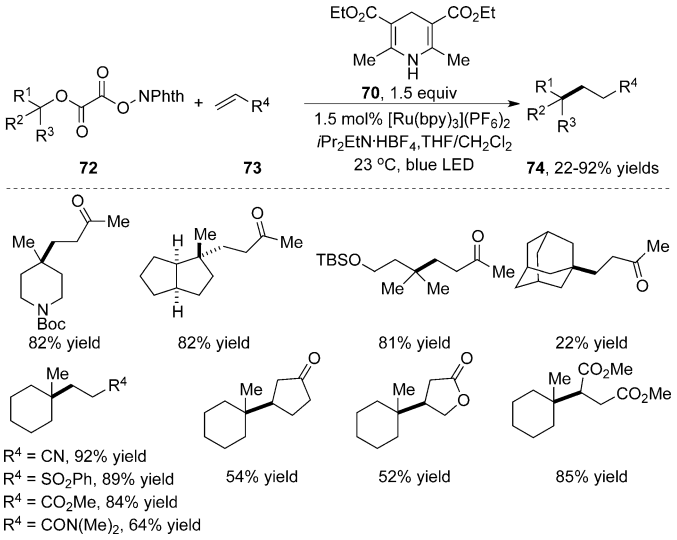
3. Radical Decarboxylative Functionalization of Carboxylic Acid Derivatives

The visible-light-induced radical decarboxylative fragmentation of acyloxyphthalimides was discovered by Okada, Oda, and co-workers in 1991.[30a] The formed radical species have been impressively applied to the construction of new C–C, C–H, and C–Se bonds.[30b–d] Based on these elegant prior contributions, Overman and co-workers accomplished a modified second-generation total synthesis of aplyviolene using the visible-light-promoted radical decarboxylative fragmentation of the acyloxyphthalimide **68** as the key step (Scheme 14).[31a] The generated tertiary radical species can efficiently undergo radical conjugate addition to the carbon–carbon double bond of the α-chlorocyclopentenone **69** to form a new quaternary carbon stereocenter with high stereoselectivity.



Scheme 14. Visible-light-mediated decarboxylative fragmentation of acyloxyphthalimide **68**. TBS = *tert*-butyldimethylsilyl.

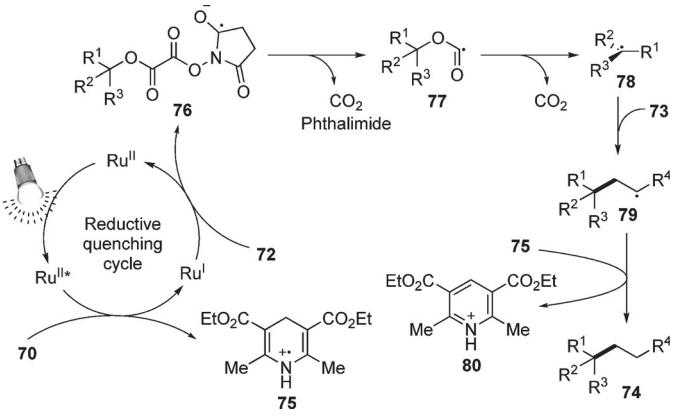
Shortly after this discovery, Overman et al. expanded the strategy to the photoredox-catalyzed fragmentation of *tert*-alkyl *N*-phthalimidoyl oxalates (Scheme 15).[31b–d] The method offered direct and efficient access to quaternary carbon centers from a variety of tertiary alcohols. Note that the



Scheme 15. Visible-light-mediated decarboxylative fragmentation of *tert*-alkyl *N*-phthalimidoyl oxalates.

Hantzsch ester **70** serves as both the reductive quencher and the hydrogen donor in this fragmentation process. In addition, many commonly used electron-deficient olefins, such as acrylonitrile, vinylsulfone, dimethylacrylamide, dimethylfumarate, and various cyclic unsaturated systems, are shown to be suitable conjugate acceptors. Interestingly, it was found that an ammonium additive (iPr$_2$NEt·HBF$_4$) plays an important role in this process. The authors speculated that the role of the additive might involve: 1) protonation of radical anion **76** (Scheme 16), and 2) exchange of the anion with [Ru(bpy)$_3$](PF$_6$)$_2$ to provide [Ru(bpy)$_3$](BF$_4$)$_2$ as a more soluble photoredox catalyst.

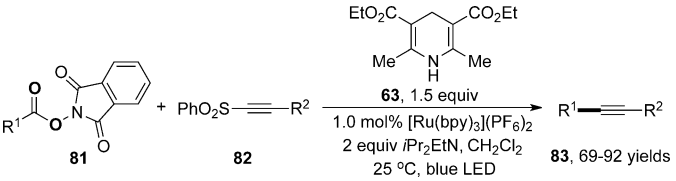
The proposed mechanism of this reaction starts with the one-electron oxidation of the Hantzsch ester **70** by Ru^{II}* to give low-valent Ru^{I} and the ester radical cation **75** (Scheme 16). Then, one-electron transfer from the Ru^{I} species to the *tert*-alkyl *N*-phthalimidoyl oxalate **72** generates the radical anion **76** and completes the photocatalytic cycle. Homolytic cleavage of the N–O bond of **76**, followed by



Scheme 16. Plausible mechanism for photoredox-catalyzed decarboxylative fragmentation of *tert*-alkyl *N*-phthalimidoyl oxalates.

decarboxylation, generates the alkoxycarbonyl radical **77**. Later, a slower second decarboxylation process occurs to give the tertiary radical **78** which is then trapped by the olefin **73** to provide the radical species **79**. Finally, hydrogen abstraction of **79** from **75** delivers the final product.

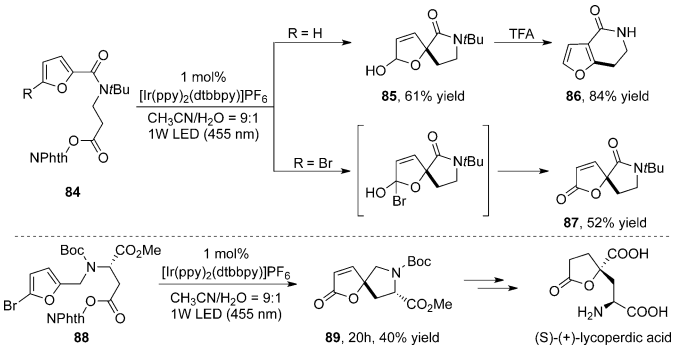
In 2015, Chen and co-workers described a visible-light-promoted reductive decarboxylative alkynylation reaction using alkynyl phenylsulfones as the alkynyl precursors (Scheme 17).[32] The reaction can occur smoothly in both



Scheme 17. Visible-light-mediated decarboxylative alkynylation of *N*-acyloxyphthalimides.

organic solvents and neutral aqueous solutions, thus making it compatible with a wide range of functional groups and biomolecules. Similar to previous reports,[30,31] reductive decarboxylative fragmentation of the *N*-acyloxyphthalimide **81**, followed by α-addition of the formed alkyl radical to the alkynyl sulfone **82** is considered as the critical step.

In another effort in this area, Reiser et al. impressively applied this visible-light-mediated decarboxylatve fragmentation of *N*-acyloxyphthalimides to the construction of anellated furans or spirobutenolides (Scheme 18).[33] More significantly, the reported photoannulation reaction was successfully used to prepare the key intermediate **89** in the synthesis of (*S*)-(+)-lycoperdic acid (Scheme 18). Although the mechanism required further investigation, the authors proposed that [Ir(ppy)$_2$(dtbbpy)]PF$_6$ might function as a pho-

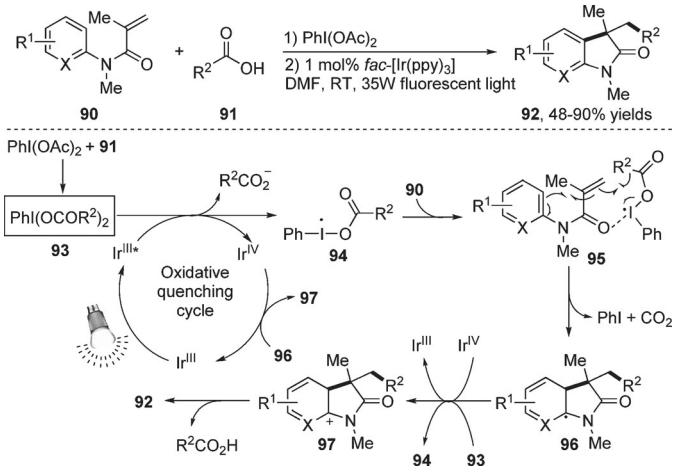


Scheme 18. Visible-light-mediated construction of anellated furans or spirobutenolides.

tosensitizer to transfer energy from its photoexcited state to the phthalimide moiety of **84**. The result of UV irradiation of the substrate and the influence of the N substituent in the starting materials appeared to support the proposed sensitization mechanism and the intramolecular electron transfer process.

The decarboxylation of carboxylic acids with phenyliodine(III) diacetate (DIB) generally requires high reaction temperatures (110–160 °C) or high-energy UV light irradiation.[34] In 2013, Zhu and co-workers developed a novel visible-light-induced decarboxylative tandem coupling of DIB at room temperature, thus giving the corresponding 3,3-disubstituted oxindole scaffolds in good yield (Scheme 19).[35] After a facile ligand metathesis with DIB, a wide range of primary, secondary, and tertiary aliphatic carboxylic acids can successfully undergo this decarboxylation/C–H functionalization cascade reaction. It should be noted that benzoic acid is not suitable for the transformation presumably because of the slower decarboxylation process of the ligand-metathesis product $PhI(OCOPh)_2$ and the decreased nucleophilic ability of the formed aryl radical.

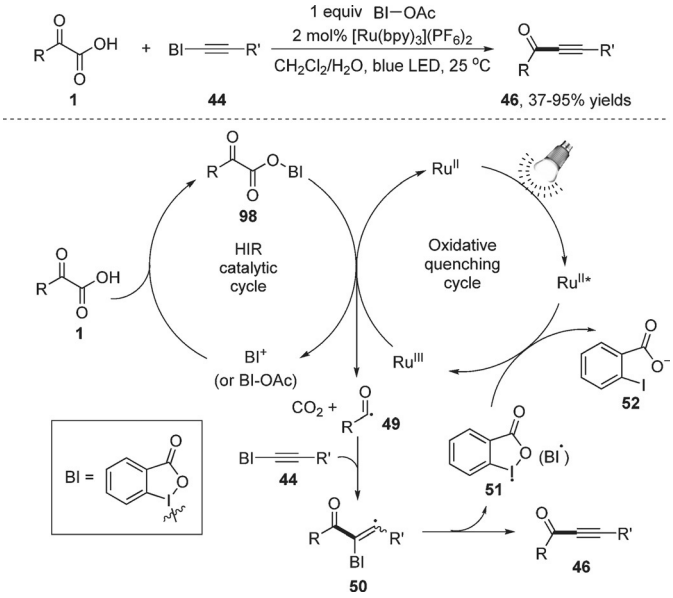
It was proposed that the ligand-metathesis product, $PhI(OCOR^2)_2$ (**93**), acts as the oxidative quenching reagent to oxidize the excited Ir^{III}* to Ir^{IV}, and to simultaneously provide the radical species **94** (Scheme 19). Coordination of



Scheme 19. Visible-light-mediated decarboxylation/C–H functionalization cascade.

the carbonyl group of **90** with **94** generates the intermediate **95**, which may subsequently undergo a decarboxylation/radical cyclization cascade to give another carbon-centered radical species (**96**). A SET from **96** to Ir^{IV} completes the photocatalytic cycle and delivers the cation intermediate **97**. Finally, the carboxylate-anion-assisted deprotonation of **97** affords the desired oxindole **92**. Note that a radical-chain process is also a plausible reaction pathway for the formation of **97**.

Another impressive example of the combination of visible-light photoredox catalysis with hypervalent iodine(III) reagents (HIR) was realized by Chen and co-workers in 2015 (Scheme 20).[36a] The reaction provides an efficient method to



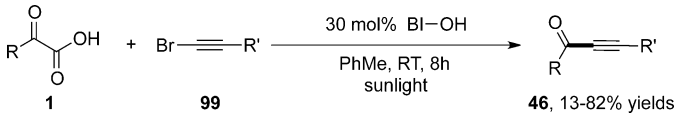
Scheme 20. Dual-catalytic decarboxylative ynonylation reactions.

obtain various substituted ynones, ynamides, and ynoates in good yields and with excellent chemoselectivities. Some commonly used simple alkynyl precursors, such as alkynyl bromides or alkynyl sulfones, were ineffective for this dual-catalytic decarboxylative ynonylation reaction in the presence of BI as an additive. The best result was obtained when the electrophilic reagent BI–alkyne **44** was involved. Control experiments in the absence of the photoredox catalyst and blue LED irradiation further confirmed the photocatalytic nature of the transformation. Notably, a wide range of functional groups, including alkenyl, amine, ester, azide, hydroxy, and cyano groups, are well-tolerated.

Based on the results of TEMPO trapping, ^1H NMR spectroscopy, and ^{13}C-labeling experiments, a plausible dual-catalytic reaction pathway was proposed (Scheme 20). First, the reaction of the α-keto acid **1** with BI–OAc afforded the BI/ketoacid complex **98**. Note that similar to their previous reports,[36b,c] Chen and co-workers proposed that BI–OAc might play a role in oxidizing Ru^{II}* to Ru^{III} for reaction initiation. Then, SET from **98** to Ru^{III}, followed by decarboxylation, gives the acyl radical intermediate **49** and regenerates the Ru^{II} photoredox catalyst. The simultaneously formed BI

cation (or BI–OAc) participates in another new HIR catalytic cycle. Next, the α-addition of **49** to the BI–alkyne **44** affords ynone **50**, which subsequently eliminates the BI radical **51** to give the final product. It is noteworthy that the generated BI radical will act as the final oxidant to oxidize Ru^{II}* to Ru^{III} in the subsequent photocatalytic cycle.

Soon after the discovery of Chen's group,[36] Li, Wang, and co-workers found that a very similar visible-light-induced decarboxylative alkynylation reaction of α-keto acids occurred smoothly without the addition of a photoredox catalyst (Scheme 21).[37] In this reaction bromoacetylenes (**99**) were employed as alkynyl precursors with the assistance of 30 mol% BI–OH as a hypervalent iodine catalyst. Generally, the corresponding ynones were obtained in good yield under the irradiation of sunlight or blue LED light. Based on the results of mechanism studies, the in situ generated BI derivatives **44** and **98** were proposed to be important intermediates for this sunlight-driven decarboxylative alkynylation process.



Scheme 21. Sunlight-driven decarboxylative alkynylation of α-keto acids.

4. Conclusion

Herein we summarized recent advances in the visible-light-mediated radical decarboxylative functionalization of carboxylic acids and their derivatives with a focus on the discussion of reaction mechanisms. The mild and environmentally benign decarboxylation conditions, which include visible light as a green energy source, make this protocol quite attractive. Recent discoveries in this rapidly developing research area strongly demonstrate that the carbon-centered radical species formed in the decarboxylation step could be utilized in not only the creation of simple C–C or C–X bonds, but also the highly efficient construction of structurally complex heterocycles and natural products. From the viewpoint of green and sustainable chemistry, it can be clearly forecasted that carboxylic acids and their derivatives as radical precursors will continue to be developed in the area of visible-light photoredox catalysis. Although there has been excellent progress, additional development of catalytic asymmetric reactions of the radical intermediates, together with more insightful mechanistic investigations, is highly warranted.

Acknowledgements

We would like to thank the National Science Foundation of China (NO. 21232003, 21202053, 21272087, and 21472057) and the National Basic Research Program of China (2011CB808603) for the financial support for the work we have performed in this area.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 15632–15641
Angew. Chem. **2015**, *127*, 15854–15864

[1] a) N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030–5048; b) P. Gallezot, *Chem. Soc. Rev.* **2012**, *41*, 1538–1558; c) A. J. J. Straathof, *Chem. Rev.* **2014**, *114*, 1871–1908.

[2] a) H. Hunsdiecker, C. Hunsdiecker, E. Vogt, US 2176181, **1939**; b) H. Hunsdiecker, C. Hunsdiecker, *Ber. Dtsch. Chem. Ges. B* **1942**, *75*, 291–297; c) R. G. Johnson, R. K. Ingham, *Chem. Rev.* **1956**, *56*, 219–269.

[3] a) F. A. Rice, *J. Am. Chem. Soc.* **1956**, *78*, 3173–3175; b) G. M. Lampman, J. C. Aumiller, *Org. Synth.* **1971**, *51*, 106–108; c) A. McKillop, D. Bromley, *Tetrahedron Lett.* **1969**, *10*, 1623–1626; d) J. I. Concepción, C. G. Francisco, R. Freire, R. Hernández, J. A. Salazar, E. Suárez, *J. Org. Chem.* **1986**, *51*, 402–404; e) J. P. Das, S. Roy, *J. Org. Chem.* **2002**, *67*, 7861–7864; f) Z. Wang, L. Zhu, F. Yin, Z. Su, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 4258–4263.

[4] a) D. H. R. Barton, E. P. Serebryakov, *Proc. Chem. Soc.* **1962**, 309; b) D. H. R. Barton, H. A. Dowlatshahi, W. B. Motherwell, D. Villemin, *J. Chem. Soc. Chem. Commun.* **1980**, 732–733.

[5] a) A. G. Griesbeck, W. Kramer, M. Oelgemöller, *Synlett* **1999**, 1169–1178; b) Y. Yoshimi, T. Itou, M. Hatanaka, *Chem. Commun.* **2007**, 5244–5246; c) Y. Yoshimi, M. Masuda, T. Mizunashi, K. Nishikawa, K. Maeda, N. Koshida, T. Itou, T. Morita, M. Hatanaka, *Org. Lett.* **2009**, *11*, 4652–4655.

[6] a) J. M. Anderson, J. K. Kochi, *J. Am. Chem. Soc.* **1970**, *92*, 2450–2460; b) W. S. Trahanovsky, J. Cramer, D. W. Brixius, *J. Am. Chem. Soc.* **1974**, *96*, 1077–1081.

[7] For selected reviews, see: a) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527–532; b) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859–917; c) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102–113; d) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828–6838; *Angew. Chem.* **2012**, *124*, 6934–6944; e) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687–7697; f) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; g) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387–2403; h) J. Xuan, L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Eur. J. Org. Chem.* **2013**, 6755–6770; i) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734–4743; *Angew. Chem.* **2013**, *125*, 4832–4842; j) M. N. Hopkinson, B. Sahoo, J. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874–3886; k) M. Peña-López, A. Rosas-Hernández, M. Beller, *Angew. Chem. Int. Ed.* **2015**, *54*, 5006–5008; *Angew. Chem.* **2015**, *127*, 5090–5092.

[8] For selected examples of combining photoredox catalysis with transition-metal catalysis, see: a) M. Osawa, H. Nagai, M. Akita, *Dalton Trans.* **2007**, 827–829; b) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566–18569; c) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034–9037; d) B. Sahoo, M. N. Hopkinson, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 5505–5508; e) X.-Z. Shu, M. Zhang, Y. He, H. Frei, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5844–5847; f) M. N. Hopkinson, B. Sahoo, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 2794–2800; g) J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433–436; h) D. C. Fabry, J. Zoller, S. Raja, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 10228–10231; *Angew. Chem.* **2014**, *126*, 10392–10396; i) J. Xuan, T.-T. Zeng, Z.-J. Feng, Q.-H. Deng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, H. Alper, *Angew. Chem. Int. Ed.* **2015**, *54*, 1625–1628; *Angew. Chem.* **2015**, *127*, 1645–1648; j) D. C. Fabry, M. A. Ronge, J. Zoller, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, *54*, 2801–2805; *Angew. Chem.* **2015**, *127*, 2843–2847; k) J. Xuan, T.-T. Zeng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, *Chem. Eur. J.* **2015**, *21*, 4962–4965.

[9] a) L. J. Gooßen, F. Rudolphi, C. Oppel, N. Rodríguez, *Angew. Chem. Int. Ed.* **2008**, *47*, 3043–3045; *Angew. Chem.* **2008**, *120*,

3085 – 3088; b) L. J. Gooßen, B. Zimmermann, T. Knauber, *Angew. Chem. Int. Ed.* **2008**, *47*, 7103 – 7106; *Angew. Chem.* **2008**, *120*, 7211 – 7214; c) H. Wang, L.-N. Guo, X.-H. Duan, *Org. Lett.* **2012**, *14*, 4358 – 4361; d) J. Miao, H. Ge, *Synlett* **2014**, 911 – 919.

[10] J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, *Angew. Chem. Int. Ed.* **2014**, *53*, 502 – 506; *Angew. Chem.* **2014**, *126*, 512 – 516.

[11] Z.-W. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5257 – 5260.

[12] a) Z.-W. Zuo, D. T. Ahneman, L.-L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437 – 440; b) L.-L. Chu, J. M. Lipshultz, D. W. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 7929 – 7933; *Angew. Chem.* **2015**, *127*, 8040 – 8044.

[13] A. Noble, S. J. McCarver, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 624 – 627.

[14] A. Noble, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 11602 – 11605.

[15] For selected examples using vinyl sulfones as radical acceptors, see: a) N. Miyamoto, D. Fukuoka, K. Utimoto, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 503 – 504; b) J. Xiang, W. Jiang, J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1997**, *119*, 4123 – 4129; c) A.-P. Schaffner, V. Darmency, P. Renaud, *Angew. Chem. Int. Ed.* **2006**, *45*, 5847 – 5849; *Angew. Chem.* **2006**, *118*, 5979 – 5981.

[16] Y. Miyake, K. Nakajima, Y. Nishibayashi, *Chem. Commun.* **2013**, *49*, 7854 – 7856.

[17] L. Chen, C. S. Chao, Y. Pan, S. Dong, Y. C. Teo, J. Wang, C.-H. Tan, *Org. Biomol. Chem.* **2013**, *11*, 5922 – 5925.

[18] a) L. L. Chu, C. Ohta, Z.-W. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 10886 – 10889; for similar work, see: b) T. Chinzei, K. Miyazawa, Y. Yasu, T. Koike, M. Akita, *RSC Adv.* **2015**, *5*, 21297 – 21300.

[19] a) C. A. Martinez, S. Hu, Y. Dumond, J. Tao, P. Kelleher, L. Tully, *Org. Process Res. Dev.* **2008**, *12*, 392 – 398; b) M. Mujahid, M. Muthukrishnan, *Chirality* **2013**, *25*, 965 – 969.

[20] a) J. P. Brand, J. Waser, *Chem. Soc. Rev.* **2012**, *41*, 4165 – 4179; b) E. A. Merritt, B. Olofsson, *Eur. J. Org. Chem.* **2011**, 3690 – 3694; c) M. J. Bouma, B. Olofsson, *Chem. Eur. J.* **2012**, *18*, 14242 – 14245.

[21] Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 11196; *Angew. Chem.* **2015**, *127*, 11348.

[22] a) J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846 – 1913; b) S. B. Lang, K. M. O'Nele, J. A. Tunge, *J. Am. Chem. Soc.* **2014**, *136*, 13606 – 13609.

[23] a) S. R. Waetzig, J. A. Tunge, *J. Am. Chem. Soc.* **2007**, *129*, 14860 – 14861; b) B. M. Trost, D. A. Thaisrivongs, *J. Am. Chem. Soc.* **2009**, *131*, 12056 – 12057; c) B. M. Trost, D. A. Thaisrivongs, J. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 12439 – 12441; d) J. Zhang, C. Stanciu, B. Wang, M. M. Hussain, C.-S. Da, P. J. Carroll, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2011**, *133*, 20552 – 20560.

[24] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886; b) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308 – 319; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; d) C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2015**, *54*, 3216 – 3221; *Angew. Chem.* **2015**, *127*, 3261 – 3267.

[25] a) M. Rueda-Becerril, C. Chatalova Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquin, G. M. Sammis, *J. Am. Chem. Soc.* **2012**, *134*, 4026 – 4029; b) J. C. T. Leung, C. Chatalova-Sazepin, J. West, M. Rueda-Becerril, J.-F. Paquin, G. M. Sammis, *Angew. Chem. Int. Ed.* **2012**, *51*, 10804 – 10807; *Angew. Chem.* **2012**, *124*, 10962 – 10965.

[26] a) M. Rueda-Becerril, O. Mahe, M. Drouin, M. B. Majewski, J. G. West, M. O. Wolf, G. M. Sammis, J. F. Paquin, *J. Am. Chem. Soc.* **2014**, *136*, 2637 – 2641; b) J. C. T. Leung, G. M. Sammis, *Eur. J. Org. Chem.* **2015**, 2197 – 2204.

[27] a) S. Ventre, F. R. Petronijevic, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 5654 – 5657; b) X. Wu, C. Meng, X. Yuan, X. Jia, X. H. Qian, J. Ye, *Chem. Commun.* **2015**, *51*, 11864 – 11867.

[28] C. Cassani, G. Bergonzini, C. J. Wallentin, *Org. Lett.* **2014**, *16*, 4228 – 4231.

[29] a) S. Fukuzumi, H. Kotani, K. Ohkubo, S. Ogo, N. V. Tkachenko, H. Lemmetyinen, *J. Am. Chem. Soc.* **2004**, *126*, 1600 – 1601; b) K. Ohkubo, K. Mizushime, R. Iwata, K. Souma, S. Suzuki, S. Fukuzumi, *Chem. Commun.* **2010**, *46*, 601 – 603; c) T. M. Nguyen, N. Manohar, D. A. Nicewicz, *Angew. Chem. Int. Ed.* **2014**, *53*, 6198 – 6201; *Angew. Chem.* **2014**, *126*, 6312 – 6315.

[30] a) K. Okada, K. Okamoto, N. Morita, K. Okubo, M. Oda, *J. Am. Chem. Soc.* **1991**, *113*, 9401 – 9402; b) K. Okada, K. Okubo, N. Morita, M. Oda, *Tetrahedron Lett.* **1992**, *33*, 7377 – 7380; c) K. Okada, K. Okubo, N. Morita, M. Oda, *Chem. Lett.* **1993**, 2021 – 2024; d) M. Zlotorzynska, G. M. Sammis, *Org. Lett.* **2011**, *13*, 6264 – 6267.

[31] a) M. J. Schnermann, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 9576 – 9580; *Angew. Chem.* **2012**, *124*, 9714 – 9718; b) G. L. Lackner, K. W. Quasdorf, L. E. Overman, *J. Am. Chem. Soc.* **2013**, *135*, 15342 – 15345; c) G. L. Lackner, K. W. Quasdorf, G. Pratsch, L. E. Overman, *J. Org. Chem.* **2015**, *80*, 6012 – 6024; d) G. Pratsch, G. L. Lackner, L. E. Overman, *J. Org. Chem.* **2015**, *80*, 6025 – 6036.

[32] J. Yang, J. Zhang, L. Qi, C. Hu, Y. Chen, *Chem. Commun.* **2015**, *51*, 5275 – 5278.

[33] G. Kachkovskyi, C. Faderl, O. Reiser, *Adv. Synth. Catal.* **2013**, *355*, 2240 – 2248.

[34] a) J. Leffler, L. Story, *J. Am. Chem. Soc.* **1967**, *89*, 2333 – 2338; b) H. Togo, M. Aoki, M. Yokoyama, *Tetrahedron* **1993**, *49*, 8241 – 8256; c) T. Wu, H. Zhang, G. Liu, *Tetrahedron* **2012**, *68*, 5229 – 5233.

[35] J. Xie, P. Xu, H. Li, Q. Xue, H. Jin, Y. Cheng, C. Zhu, *Chem. Commun.* **2013**, *49*, 5672 – 5674.

[36] a) H. Huang, G. Zhang, Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 7872 – 7876; *Angew. Chem.* **2015**, *127*, 7983 – 7987; b) H. Huang, G. Zhang, L. Gong, S. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2014**, *136*, 2280 – 2283; c) H. Huang, K. Jia, Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 1881 – 1884; *Angew. Chem.* **2015**, *127*, 1901 – 1904.

[37] H. Tan, H. Li, W. Ji, L. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 8374 – 8377; *Angew. Chem.* **2015**, *127*, 8494 – 8497.

Received: June 22, 2015
Published online: October 28, 2015