Cross-Coupling Reaction

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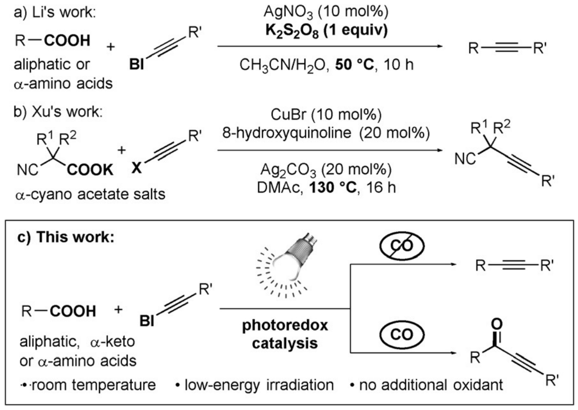
Decarboxylative Alkynylation and Carbonylative Alkynylation of Carboxylic Acids Enabled by Visible-Light Photoredox Catalysis**

Quan-Quan Zhou, Wei Guo, Wei Ding, Xiong Wu, Xi Chen, Liang-Qiu Lu, and Wen-Jing Xiao**

Abstract: *Visible-light-induced photocatalytic decarboxylative alkynylations of carboxylic acids have been developed for the first time. The reaction features extremely mild conditions, broad substrate scope, and avoids additional oxidants. Importantly, a decarboxylative carbonylative alkynylation has also been carried out in the presence of carbon monoxide (CO) under photocatalytic conditions, which affords valuable ynones in high yields at room temperature.*

Carboxylic acids are fundamental feedstocks which are manufactured in large amounts. They are often employed as robust and versatile precursors in the synthesis of pharmaceuticals, agro-, and fine chemicals, among which decarboxylative cross-coupling reactions of carboxylic acids have received increasing interests from academic and industrial settings in the past decade.[1] Despite advances, an important challenge that has not been fully addressed in this field is how to activate carboxylic acids for further transformations under environmentally friendly and sustainable conditions. Very recently, visible-light-induced photoredox catalysis[2] has been identified as an ideal approach to generate radicals from carboxylic acids.[3] Therefore, a wealth of radical transformations have been achieved using this strategy at room temperature (i.e., decarboxylative reduction,[4a] arylation,[3d,4b] vinylation,[4c,d] alkylation,[4e,f] oxidative amidation,[3c] and fluorination[4g–i]). However, to the best of our knowledge, no direct radical decarboxylative alkynylations or their related carbonylative alkynylations of carboxylic acids through visible-light photoredox catalysis have been reported.

Transition-metal-catalyzed decarboxylative alkynylation of carboxylic acids is among the most direct conversions for the preparation of alkynes.[1b,f,5] However, only a handful of works on radical decarboxylative alkynylations of carboxylic acids have been disclosed. In this regard, Li and co-workers[6a] in 2012 reported a silver-catalyzed, radical decarboxylative alkynylation of carboxylic acids with ethynylbenziodoxolones (EBX) as the alkynylating agent in the presence of stoichiometric oxidants (Scheme 1 a). Shortly after, the Xu group developed a copper-catalyzed decarboxylative alkynylation reaction of quaternary α-cyano acetate salts using an alkynyl halogen (X = Br, Cl) as the starting material at 130 °C in DMAc (*N*,*N*-dimethylacetamide; Scheme 1 b).[6b] To further improve the radical decarboxylative alkynylation reaction of carboxylic acids and exploit new transformations of these chemicals, we disclosed a decarboxylative alkynylation and carbonylative alkynylation of carboxylic acids through visible-light photoredox catalysis for the first time (Scheme 1 c). These reactions feature very mild conditions (i.e., room temperature and low-energy visible-light irradiation), no additional oxidant, and a broad substrate scope.



Scheme 1. Decarboxylative alkynylation/carbonylative alkynylation reactions of carboxylic acids. **BI** = benziodoxolone; **X** = Br or Cl.

Initially, the decarboxylative alkynylation reaction was examined with cyclohexyl carboxylic acid (**1a**) and phenyl-EBX[6c–e] (**2a**) as model substrates in the presence of 3 mol % $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**PC1**, $dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4-di-*tert*-butyl-2,2′-bipyridine) as a photocatalyst and 1.5 equiv of K_2HPO_4 as a base.[7] To our delight, this reaction does indeed proceed under the irradiation of a bulb of 7 W blue LEDs, to afford the desired alkynylation product **3aa** in modest yield as determined by gas chromatography (GC; Table S1, entry 1: 29 % yield). Then, various metal or organic photocatalysts, bases, solvents, additives, and the ratio of **1a** to **2a** were tested to improve the reaction efficiency (Tables S1–S2). Finally, we could isolate the desired product **3aa** in 81 % yield under the optimal conditions (see the footnote in Table 1). Control experiments indicated that both photocatalyst and visible

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[*] Q.-Q. Zhou,[+] W. Guo,[+] W. Ding, X. Wu, X. Chen, Prof. Dr. L.-Q. Lu, Prof. Dr. W.-J. Xiao
Key Laboratory of Pesticide & Chemical Biology
College of Chemistry, Central China Normal University (CCNU)
152 Luoyu Road, Wuhan, Hubei 430079 (China)
E-mail: luliangqiu@mail.ccnu.edu.cn
wxiao@mail.ccnu.edu.cn

[+] These authors contributed equally to this work.

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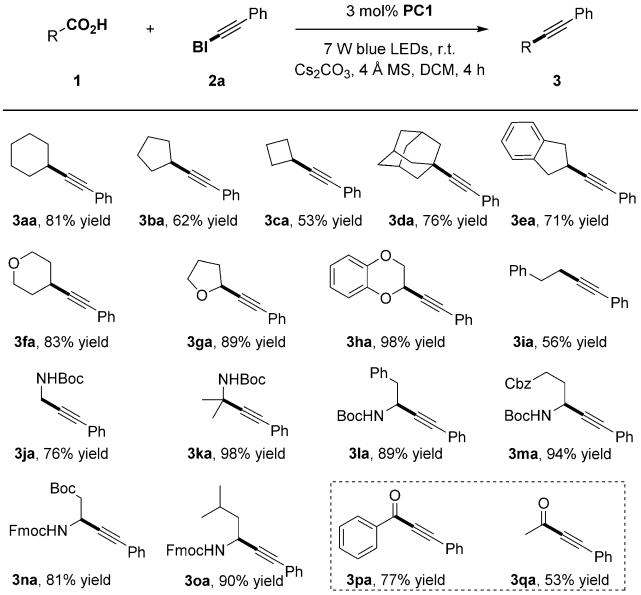
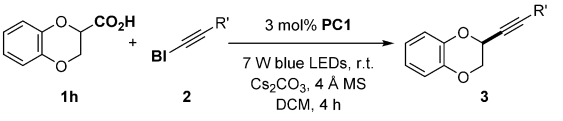
Table 1: Scope of carboxylic acids in the decarboxylative alkynylation reaction.[a]



[a] Standard condition A: **1** (0.40 mmol), **2** (0.60 mmol), Cs_2CO_3 (0.60 mmol), **PC1** (0.012 mmol), and 40 mg 4 Å MS in DCM (6 mL) at room temperature under the irradiation of a bulb of 7 W blue LEDs for 4 h. Yield of the isolated products.

Table 2: Scope of EBX reagents in the decarboxylative alkynylation reaction.[a]



Entry	**2:** R′	Product	Yield [%][b]
1	**2a:** phenyl	**3ha**	98
2	**2b:** 4-methylphenyl	**3hb**	97
3	**2c:** 4-fluorophenyl	**3hc**	99
4	**2d:** 4-chlorophenyl	**3hd**	99
5	**2e:** 4-phenyl phenyl	**3he**	96
6	**2f:** 3,5-dimethylphenyl	**3hf**	94
7	**2g:** 2-thiophenyl	**3hg**	87
8	**2h:** *tert*-butyl	**3hh**	82
9	**2i:** *n*-pentyl	**3hi**	70

[a] Please see the footnote in Table 1.

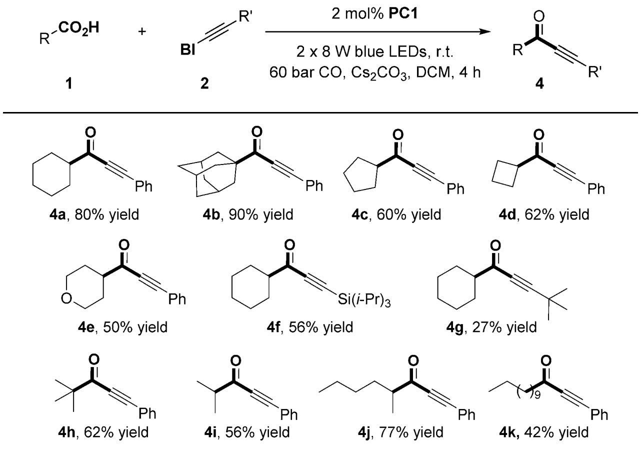
light were essential in this decarboxylative alkynylation reaction.

Next, the generality of this alkynylation reaction was investigated under optimal conditions. As summarized in Table 1, a broad range of carboxylic acids was determined to be applicable to this transformation. The decarboxylative alkynylation reaction of various carbocyclic carboxylic acids proceeded smoothly, affording the corresponding alkynylation products in high yields (**3aa**–**3ea**: 53–81 % yield). Significantly, this reaction tolerates a broad range of oxa-heterocyclic carboxylic acids. For example, carboxylic acids with α- and γ-oxygen atoms are excellent reaction partners, providing the decarboxylative alkynylation products in high yields (**3fa**–**ha**: 83–98 % yield). Perhaps more importantly, primary carboxylic acids and acyclic α-amino acids can readily undergo this transformation under our standard conditions, thus resulting in the formation of structurally diverse alkynes (**3ia**: 56 % yield) and α-alkynyl amines in good to excellent yields (**3ja**–**oa**: 76–98 % yield). Notably, this photocatalytic strategy was also tolerant to α-ketonic carboxylic acids. When aryl- or alkyl-substituted α-ketonic acids were employed, the desired ynone products were obtained in good yields (**3pa**: 77 % yield; **3qa**: 53 % yield).

Experiments that probe the scope of EBX reagents were performed for this visible-light photocatalytic carbonylative alkynylation reaction. As highlighted in Table 2, various aryl-substituted EBXs works well in this reaction. The electronic and steric properties of substituents on the benzene ring did not significantly influence the reaction efficiency, and the corresponding coupling products were isolated in excellent yields (Table 2, entries 1–6: 94–99 % yield). Remarkably, the heteroaryl-substituted EBX reagent **2g** was applicable as well, affording the desired product in good yield (Table 2, entry 8: **3hg**, 87 % yield). To extend the reaction scope, alkyl-substituted EBX reagents were investigated. It has been found that, for example, EBX reagents with bulky *tert*-butyl (**2h**) and linear *n*-pentyl (**2i**) groups can be readily employed in the reaction, providing the corresponding products in good yields (Table 2, entry 8: **3hh**, 82 % yield; entry 9: **3hi**, 70 % yield).

It is well known that ynones serve as important structural motifs in bioactive molecules, as well as useful building blocks in heterocycle synthesis.[8] To access such chemicals, palladium-catalyzed carbonylation reactions of alkynylating reagents, carbon monoxide (CO), and organic iodides[8a,c] or aryl diazonium salts[7b] have been recently developed. At the beginning of this year, the Wangelin group[9a] and our group[9b] independently discovered a multicomponent coupling reaction of aryldiazonium salts, CO,and alcohols, namely radical alkoxycarbonylation reactions, through visible-light photoredox catalysis. Based on the above-mentioned results, we have successfully carried out the decarboxylative carbonylative alkynylation of carboxylic acids with CO and EBX reagents. After briefly screening the reaction conditions,[10] ynone **4a** was isolated in high yield under our optimal conditions (Table 3, **4a**: 80 % yields). As highlighted in Table 3, a variety of cyclic carboxylic acids exhibit good reactivity in this radical carbonylative alkynylation reaction (**4a**–**e**: 50–90 % yield). Importantly, triisopropylsilyl- and *tert*-butyl-substituted EBX reagents were well tolerant with this reaction, providing the corresponding ynone products **4f** and **4g** in 56 % and 27 % yield, respectively. Note that the silicon group on the product (**4f**) can be easily removed or converted into other groups. Furthermore, this photocatalytic carbonylative alkynylation is quite general with respect to acyclic carboxylic acids. It is feasible to convert primary, secondary, and tertiary acyclic carboxylic acids into linear or branched ynone products, generally in moderate to good yields (**4h**–**4k:** 42–77 % yield). A limitation of this transformation is that the carbonylative alkynylation reactions of α-amino- or α-oxygen-substituted carboxylic acids cannot occur. Reactions

Table 3: Representative results of decarboxylative carbonylative alkynylation reactions.[a]



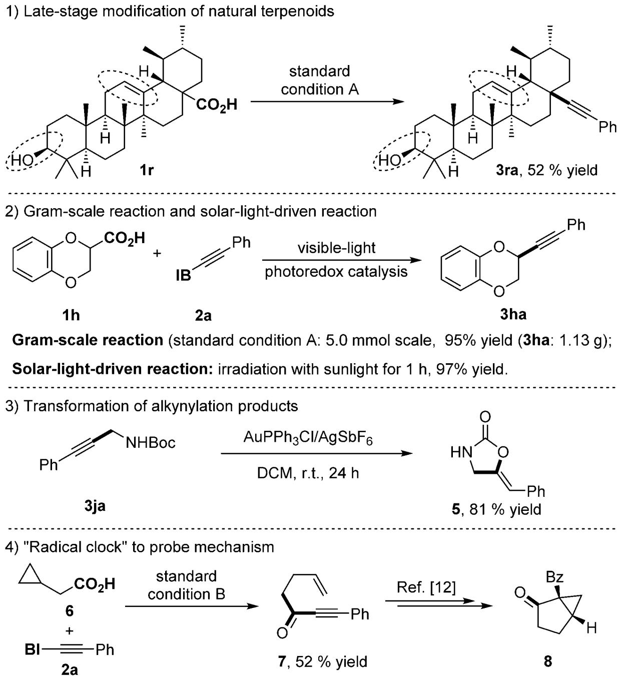
[a] Standard condition B: **1** (0.20 mmol), **2** (0.30 mmol), Cs_2CO_3 (0.15 mmol), **PC1** (0.004 mmol) in DCM (4 mL) at room temperature under the atmosphere of CO (60 bar) and the irradiation of two bulbs of 8 W blue LEDs for 4 h. Yield of the isolated products.

of these substrates usually produce the alkynylation products as the major product rather than the expected carbonylation products.[11]

Demonstrations of the synthetic utility of our decarboxylative alkynylation as well as carbonylative alkynylation processes have been performed. Very delightfully, this visible-light photocatalytic protocol allows the decarboxylative alkynylation of complex molecules under extremely mild reaction conditions. As presented in the top of Scheme 2, decarboxylative alkynylation of a natural terpenoid, ursolic acid (**1r**),[12] was successful (Scheme 2, Eq. (1): **3ar**, 52% yield), leaving the hydroxy and alkene group untouched. Moreover, a gram-scale decarboxylative alkynylation reaction of substrates **1h** and **2a** was carried out under standard conditions. This reaction proceeded well and afforded the desired coupling product **3ha** in an excellent yield (Scheme 2, Eq. (2): 95% yield). Significantly, the decarboxylative alkynylation reaction can be successfully carried out under irradiation with natural solar light, affording the desired product **3ha** in a shortened reaction time (Scheme 2, Eq. (2): 97% yield). In addition, one of the reaction products, *N*-Boc-protected propargylamine (**3ja**), can be elegantly converted to oxazolidinone **5** through a Au^I-catalyzed annulation reaction (Scheme 2, Eq. (3): 81% yield).[13] When 2-cyclopropylacetic acid was used as the substrate, a ring-opened product **7** was afforded in a moderate yield (Scheme 2, Eq. (4): 52% yield). This result not only supported the radical mechanism for the carbonylative alkynylation reaction, but also provided an important precursor (**7**), which can be used in the preparation of the fused-ring molecule **8**.[14]

To understand these two transformations, plausible reaction pathways were proposed with carboxylic acid **1a** and phenyl-substituted EBX **2a** as the model substrates. As shown in Scheme 3, an initial single-electron oxidation of carboxylic acid **1a** by the excited state of the iridium (III) photocatalyst delivers the cyclohexyl radical (**A**) while the photocatalyst is reduced to its low-valence state [Ir^{II}].[15] The radical addition of **A** to the alkynylating reagent **2a** generates the intermediate **B**, which undergoes a subsequent radical elimination reaction to yield the desired product **3aa**, with the generation of benziodoxolonyl radical (**BI·**).[6a,16] Finally, the [Ir^{II}] species was oxidized by **BI·** to [Ir^{III}] to complete the photocatalytic cycle. In the case of the decarboxylative carbonylative alkynylation reaction in the presence of carbon monoxide, radical **A** can be trapped by CO to produce an acyl radical **C**. This newly generated radical reacts with **2a**, followed by the generation of **BI·**, to provide the ynone **4a**.[8a,e]

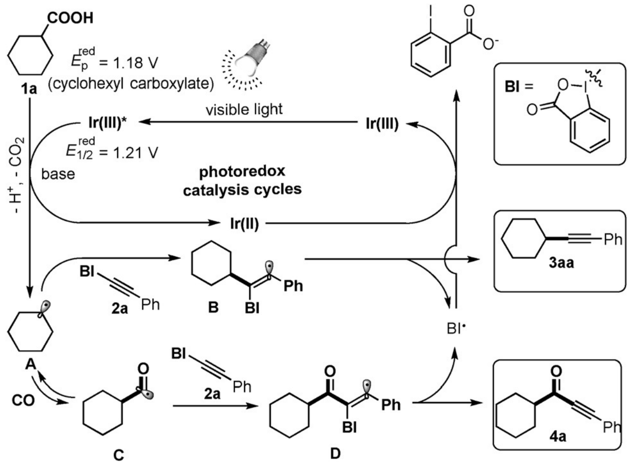
In conclusion, we have successfully developed photocatalytic direct radical decarboxylative alkynylation and



Gram-scale reaction (standard condition A: 5.0 mmol scale, 95% yield (**3ha**: 1.13 g);

Solar-light-driven reaction: irradiation with sunlight for 1 h, 97% yield.

Scheme 2. Synthetic utility of methodology.



Scheme 3. Possible reaction mechanism.

carbonylative alkynylation reactions of carboxylic acids for the first time. These reactions allow the preparation of various alkynes and ynones in good to excellent yields under very mild conditions. Unique from other transition-metal-catalyzed protocols, the current carbonylative alkynylation reactions can directly use readily available carboxylic acids as the starting materials. More importantly, the utilization of these two reactions has been demonstrated by the derivatization of naturally occurring ursolic acid and the preparation of oxazolidinones.

Keywords: alkynylation · carbonylation · decarboxylation · photocatalysis · visible light

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