

Room-Temperature Decarboxylative Alkynylation of Carboxylic Acids Using Photoredox Catalysis and EBX Reagents

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Abstract: Alkynes are used as building blocks in synthetic and medicinal chemistry, chemical biology, and materials science. Therefore, efficient methods for their synthesis are the subject of intensive research. Herein, we report the direct synthesis of alkynes from readily available carboxylic acids at room temperature under visible-light irradiation. The combination of an iridium photocatalyst with ethynylbenziodoxolone (EBX) reagents allowed the decarboxylative alkynylation of carboxylic acids in good yields under mild conditions. The method could be applied to silyl-, aryl-, and alkyl- substituted alkynes. It was particularly successful in the case of α -amino and α -oxo acids derived from biomass.

Alkynes are among the most versatile functional groups in synthetic chemistry, as they are sufficiently stable, yet reactive enough to be easily modified. These properties make them ideally suited for applications not only in organic synthesis, but also in chemical biology and materials science (Figure 1).^[1] All the potential applications of alkynes are dependent on their efficient synthesis. In particular, the metal-catalyzed Sonogashira cross-coupling reaction is now broadly applicable to the formation of alkynes (Figure 1 A).^[2] However, the Sonogashira reaction requires starting materials that are functionalized with adequate leaving groups,

which themselves need to be introduced into the molecules. New approaches are urgently needed to make the synthesis of structurally diverse alkynes more efficient. To meet this challenge, the direct alkynylation of $sp^{2[3]}$ or $sp^3[4]$ C–H bonds has been intensively investigated in the last decade (Figure 1 B). Nevertheless, many of these methods still suffer from limited scope and the need for harsh conditions, and directing groups or adjacent heteroatoms to control the selectivity in C–H functionalization reactions.

As an alternative to classical cross-coupling or C–H functionalization reactions, decarboxylative methods have recently attracted strong interest (Figure 1 C).^[5] Indeed, the required carboxylic acid starting materials are derived from biomass, and are therefore often even cheaper than the corresponding C–H compounds. Furthermore, the carboxyl group allows control of the site of functionalization and only carbon dioxide is generated as waste. Despite these advantages, examples of decarboxylative alkynylation of aliphatic carboxylic acids are rare (Scheme 1). In 2009, Chao-Jun Li and co-workers reported the decarboxylative alkynylation of amino acids using a copper catalyst and di-*tert*-butyl peroxide as stoichiometric oxidant at 110 °C (Scheme 1 A).^[6] In 2010, Seidel and co-workers^[7] and Chao-Jun Li and co-workers^[8]

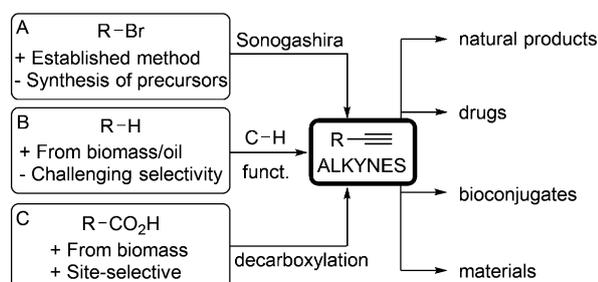
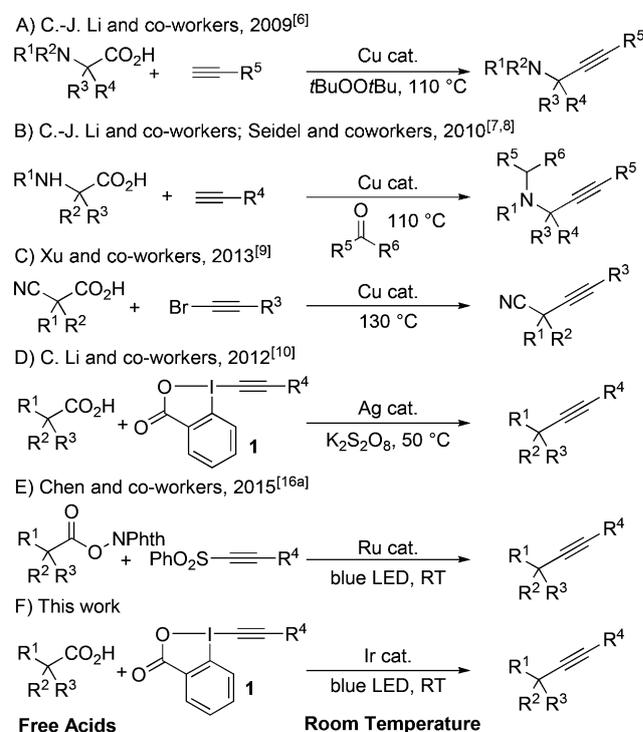


Figure 1. Synthesis and applications of alkynes.

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Scheme 1. Synthesis of acetylenes by decarboxylative alkynylation.

reported the condensation of aldehydes or ketones instead of the peroxide oxidant (Scheme 1B). The copper-catalyzed method was extended to α -cyano carboxylic acids by using alkynyl bromides, as reported by Xu and co-workers in 2013 (Scheme 1C).^[9] Finally, in 2012, Chaozhong Li and co-workers reported a different approach based on the oxidative generation of radicals from carboxylic acids using a persulfate and a silver catalyst at 50 °C (Scheme 1D).^[10] Key to success was the use of ethynylbenziodoxolone (EBX, **1**) reagents, a class of reagents discovered by Ochiai and Zhdankin,^[11] and intensively investigated by our group^[12] and others,^[13] to intercept the formed radical. Nevertheless, the use of these methods remains limited by the higher temperatures needed and/or the use of strong stoichiometric oxidants.

In order to develop a decarboxylative alkylation method under milder conditions, we envisaged the use of photoredox catalysis.^[14] Indeed, this approach has been highly successful for the decarboxylative functionalization of carboxylic acids.^[15] In 2015, Chen and co-workers reported a decarboxylative alkylation method with alkynyl sulfones as reagents,^[16] but in this case activation of the carboxylic acid as a N-hydroxy phthalimide ester was required,^[17] which diminished the efficiency of the reaction (Scheme 1E). Based on the exceptional reactivity of EBX reagents, we considered them to be well-suited for the development of a photoredox process starting directly from the free acids. Indeed, Chen and co-workers had demonstrated that EBX reagents were compatible with a photoredox process in the alkylation of boronic acid esters.^[13g] Herein, we report a method for the decarboxylative alkylation of free carboxylic acids under photoredox conditions (Scheme 1F). The reaction proceeds at room temperature for a broad range of acids, and allows the introduction of silyl-, alkyl-, and aryl- substituted alkynes.

We started our investigations with Cbz-protected proline (**2a**) as substrate using iridium complex **3a** as photocatalyst and a simple commercially available blue LED as light source (Table 1) as MacMillan and co-workers have reported that similar conditions are highly successful.^[15d-h] We decided to target specifically silylated alkynes as products, as they give easy access to the most versatile terminal acetylenes. Gratifyingly, when TIPS-EBX (**1a**; TIPS = triisopropylsilyl) was used as reagent^[18] and cesium acetate as base, the desired alkylation product **4a** could be isolated in 31% yield (entry 1). Intensive investigation of the reaction conditions showed that both the composition and amount of the base were essential to obtain a good yield.^[19] With four equivalents of cesium acetate, the yield could be raised to 68% (entry 2). Other acetate salts such as potassium and sodium acetates were less efficient (entries 3–4). Use of cesium carbonate gave the desired product **4a** only in 35% yield (entry 5).^[20] The best yield (74%) was finally obtained when cesium benzoate was used as base (entry 6). Compound **4a** was obtained in 68% yield when catalyst **3b** was used, whereas the use of other iridium (**3c** and **3d**) and ruthenium (**3e** and **3f**) complexes or organocatalyst **3g** did not lead to formation of the desired product (entries 7–12). A final optimization of base stoichiometry, concentration, and reaction flask (the use of a thin long test tube with efficient stirring and maximal light exposition was important) finally allowed to improve the

Table 1: Optimization of the decarboxylative alkylation.

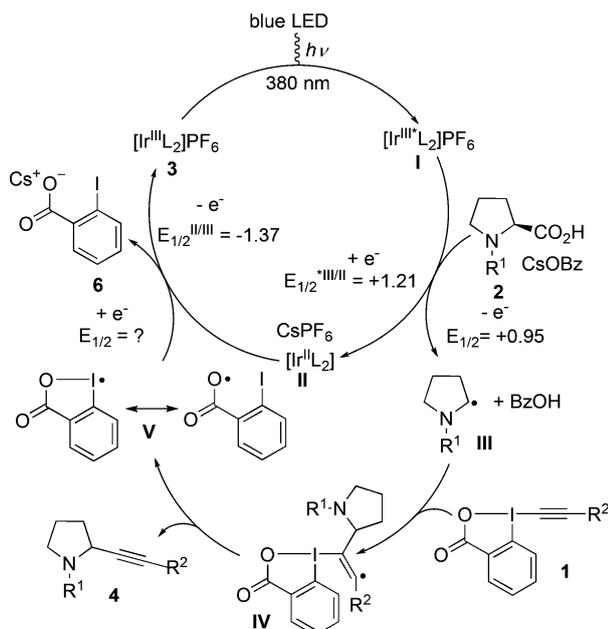
Entry	Catalyst	Base	Reagent	Conversion ^[a]	Yield ^[b]
1	3a	1.1 equiv CsOAc	1a	> 95%	31%
2	3a	4.0 equiv CsOAc	1a	> 95%	68%
3	3a	4.0 equiv KOAc	1a	< 50%	9%
4	3a	4.0 equiv NaOAc	1a	< 50%	22%
5	3a	4.0 equiv Cs ₂ CO ₃	1a	> 95%	35%
6	3a	4.0 equiv CsOBz	1a	> 95%	74%
7	3b	4.0 equiv CsOBz	1a	> 95%	68%
8	3c	4.0 equiv CsOBz	1a	< 10%	< 5%
9	3d	4.0 equiv CsOBz	1a	< 10%	< 5%
10	3e	4.0 equiv CsOBz	1a	< 10%	< 5%
11	3f	4.0 equiv CsOBz	1a	< 10%	< 5%
12	3g	4.0 equiv CsOBz	1a	< 10%	< 5%
13 ^[c]	3a	3.0 equiv CsOBz	1a	> 95%	92%
14 ^[c]	3a	3.0 equiv CsOBz	1b	> 95%	38%
15 ^[c]	3a	3.0 equiv CsOBz	1c	> 95%	< 5%
16 ^[c]	3a	3.0 equiv CsOBz	1d	> 95%	82%
17 ^[c]	3a	3.0 equiv CsOBz	1e	> 95%	< 5%

[a] Reaction conditions: 0.1 mmol **2a** (1 equiv), 0.15 mmol **1** (1.5 equiv), 1 μ mol **3** (0.01 equiv) in dichloroethane (DCE; 1 mL) for 22 h at RT. The conversion of **2a** by NMR is given. The values for reduction potentials are given in volts for catalyst **3** relative to the SCE, except for **3b** which is reported relative to ferrocene.^[14f,22] [b] Isolated yield after preparative TLC. [c] In 0.5 mL DCE. Bz = benzoyl.

yield to 92% using commercially available catalyst **3a** (entry 13).^[21] As a final control, we then decided to examine other alkylation reagents under the optimized reaction conditions (entries 14–17). With benziodoxole **1b**, compound **4a** was obtained in 38% yield (entry 14), whereas no product was formed with alkynylodonium salt **1c**, (entry 15). Alkyne **4a** could still be obtained in 82% yield using simple alkynyl iodide **1d** (entry 16). Although the yield was lower than with EBX reagent **1a**, this result is noteworthy and in good agreement with the alkylation of C–H bonds under photo-

using TIPS-EBX (**1a**) is that the obtained products are easily deprotected to give the versatile terminal acetylenes. For example, proline derivative **4a** was obtained on the millimole scale in 89% yield. Desilylation and [3+2] cycloaddition with benzyl azide gave then triazole **5** in 90% yield (Scheme 4B).

In the future, in-depth investigations will be needed to gain a good understanding of the reaction mechanism. Nevertheless, based on the extensive research already done in the field of photoredox catalysis,^[14,15] a tentative mechanism can be proposed (Scheme 5). The catalytic cycle would



Scheme 5. Tentative mechanism for the decarboxylative alkylation. The values for reduction potentials are given in volts for catalyst **3a** and substrate **2b**.

start with the activation of the iridium catalyst **3** by visible light, which occurs at 380 nm for **3a**. The obtained activated complex **I** has a reduction potential of +1.21 V and should be able to oxidize the cesium carboxylate salt of protected proline derivatives (reduction potential of +0.95 V for the Boc protected derivative **2b**).^[15f] This process would lead to reduced iridium complex **II** and α -amino radical **III**. Addition of **III** onto EBX reagent **1** in the α position to the iodine could then lead to adduct **IV**, although addition onto the β position followed by a 1,2-shift or a concerted mechanism cannot be excluded at this stage. β -elimination of iodine radical **V** would then lead to the alkylation product **4**. A final key step of the catalytic cycle would be then reduction of radical **V** by iridium complex **II** to give cesium salt **6** and regenerate catalyst **3**. With **3a**, Ir^{II} complex **II** is an especially strong reductant, with a reduction potential of -1.37 V. This value is higher than most of the tested catalysts, and could explain the exceptional performance of **3a**. A similar mechanism could be proposed with alkynyl iodide, as reduction of a potentially formed iodine radical is easy (reduction potential of +1.3 V).^[25]

In conclusion, we have reported the decarboxylative alkylation of free carboxylic acids that proceeds under

photoredox catalysis. The process can be carried out at room temperature by using visible light with only 0.5 mol% of an iridium photocatalyst. α -amino acids could be converted to the corresponding alkynes in good yields. The process was also successful in the case of α -oxo acids and simple aliphatic carboxylic acids, and could be applied to the transfer of silyl-, aryl- and alkyl- substituted alkynes. The obtained products could be easily further functionalized. When considering the mild reaction conditions and broad functional-group tolerance, the method is expected to become highly useful for the alkylation of complex organic compounds and biomolecules in the future.

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Keywords: alkynes · amino acids · carboxylic acids · hypervalent iodine · photocatalysis

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