Photocatalysis

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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]

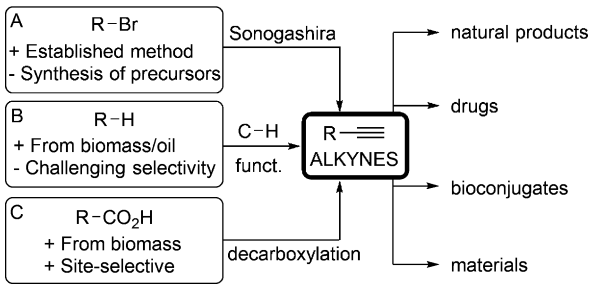

Figure 1. Synthesis and applications of alkynes.

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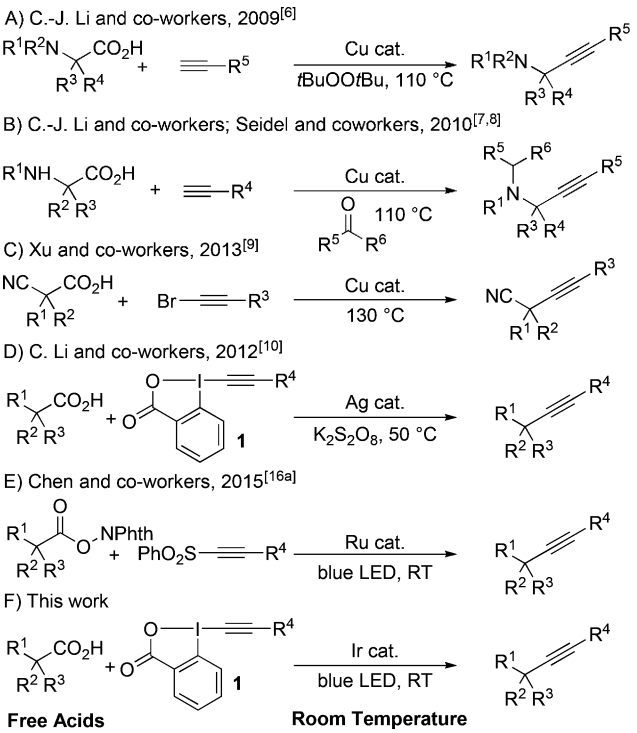


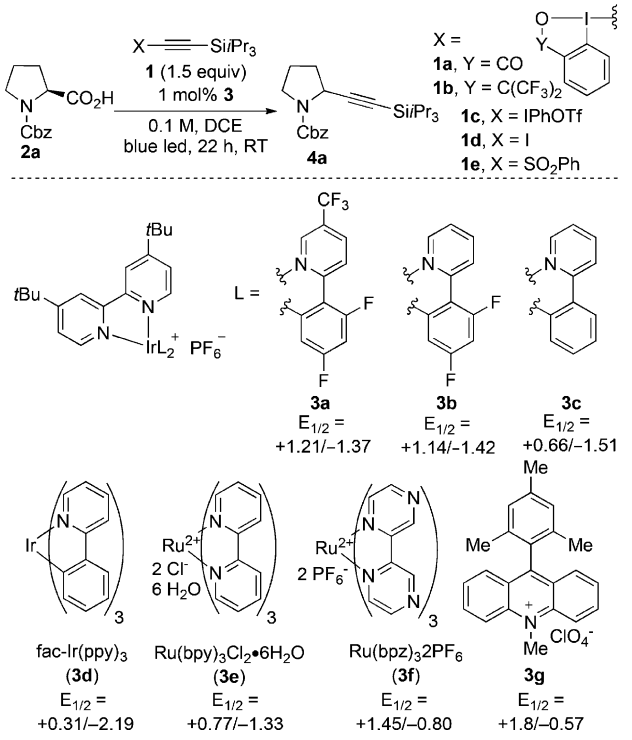
Scheme 1. Synthesis of acetylenes by decarboxylative alkynylation.

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 alkynylation 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 alkynylation 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 alkynylation of boronic acid esters.[13g] Herein, we report a method for the decarboxylative alkynylation 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 alkynylation 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 yield to 92% using commercially available catalyst **3a** (entry 13).[21] As a final control, we then decided to examine other alkynylation 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 alkynyliodonium 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 alkynylation of C–H bonds under photo-

Table 1: Optimization of the decarboxylative alkynylation.

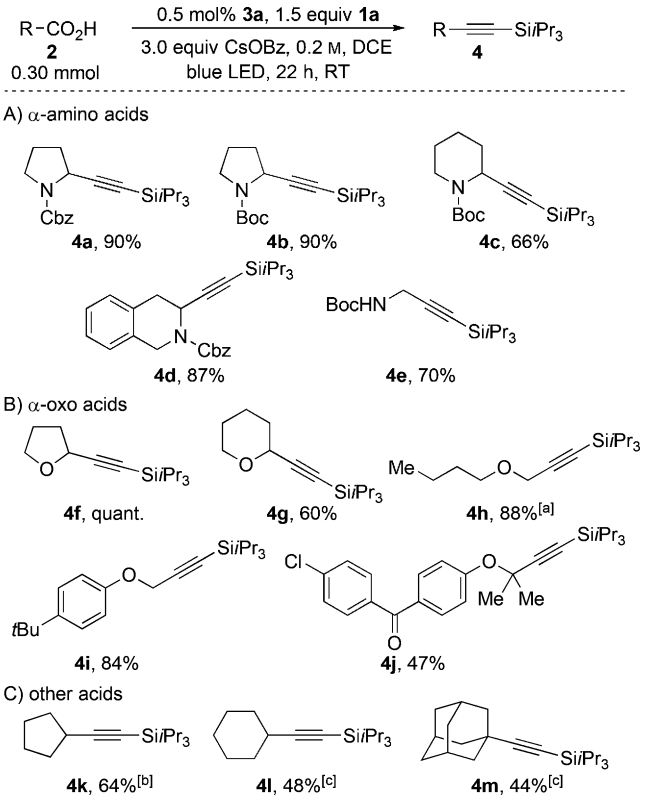


Entry	Catalyst	Base	Reagent	Conversion[a]	Yield[b]
1	**3a**	1.1 equiv CsOAc	**1a**	>95%	31%
2	**3a**	4.0 equiv CsOAc	**1a**	>95%	68%
3	**3a**	4.0 equiv KOAc	**1a**	<50%	9%
4	**3a**	4.0 equiv NaOAc	**1a**	<50%	22%
5	**3a**	4.0 equiv Cs_2CO_3	**1a**	>95%	35%
6	**3a**	4.0 equiv CsOBz	**1a**	>95%	74%
7	**3b**	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 μmol **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.

redox conditions using alkynyl iodides recently developed by Hashmi and co-workers.[4d] No product was obtained when using alkynyl sulfone **1e** as reagent (entry 17).

With the optimized conditions etablished, we investigated the scope of the decarboxylative alkynylation (Scheme 2). We



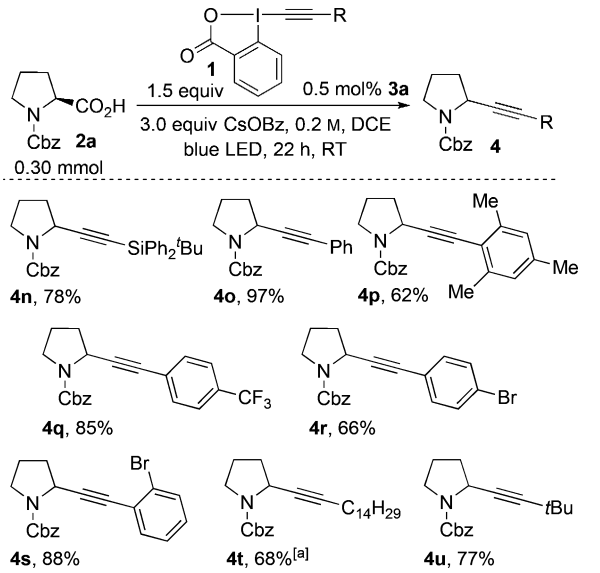
Scheme 2. Scope of carboxylic acids in the decarboxylative alkynylation. [a] Yield determined by NMR spectroscopy. [b] Using 1 mol% of catalyst **3a**. [c] Using 2 mol% of catalyst **3a**.

started with the examination of amino acids (Scheme 2A). On the preparative scale with only 0.5 mol% of catalyst **3a**, both Cbz- and Boc-protected proline derivatives **4a** and **4b** could be obtained in 90% yield. Piperidine **4c** could also be obtained in 66% yield. Tetrahydroquinoline **4d** was formed in 87% yield. This result is particularly interesting when considering that direct C–H alkynylation cannot be used to obtain this regioisomer, as the C–H bond adjacent to the benzene ring is more reactive. The reaction was not limited to cyclic amino acids: propargylic amine **4e** could also be isolated in 70% yield.

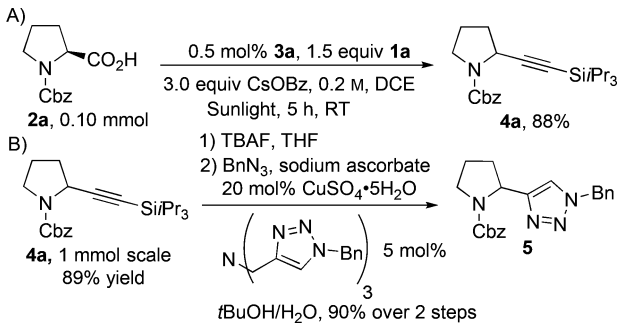
We then turned to the alkynylation of α-oxo acids (Scheme 2B). Alkynylated tetrahydrofuran **4f** could be obtained in quantitative yield. The reaction also worked well in the case of a pyran derivative (product **4g**) or simple acyclic substrates (product **4h** and **4i**). As an example of the formation of an alkyne at a tertiary position, we attempted the more challenging functionalization of the drug fenofibric acid, which has been extensively used to treat hyperlipidemia and diabetes.[23] Gratifyingly, the desired product **4j** could still be obtained in 47% yield. Finally, carboxylic acids lacking the adjacent heteroatom were examined (Scheme 2C). The desired products were obtained in moderate yields without further optimization for secondary (products **4k** and **4l**) and tertiary (product **4m**) carboxylic acids.

The scope of alkynes in the decarboxylative alkynylation reaction was examined next (Scheme 3). In the case of silyl alkynes, a bulky group was required: The *tert*-butyldimethylsilyl-protected proline derivative **4n** was obtained in 78% yield, whereas no product could be isolated with triethylsilyl or trimethylsilyl groups (results not shown). This is probably due to the lower stability of these reagents under basic conditions. Aryl-substituted EBX reagents worked very well in the alkynylation process, giving products **4o–s** in 62–97% yield. In particular, the introduction of bromide-substituted benzene rings in **4r** and **4s** will allow easy further functionalization. Finally, EBX reagents bearing both primary and tertiary alkyl groups could also be used (products **4t** and **4u**).

We then wondered if the reaction could also be carried out using natural sunlight. Indeed, product **4a** was obtained in 88% yield after only five hours at room temperature when the reaction flask was directly exposed to sunlight (Scheme 4A).[24] One of the main advantages of the alkynylation



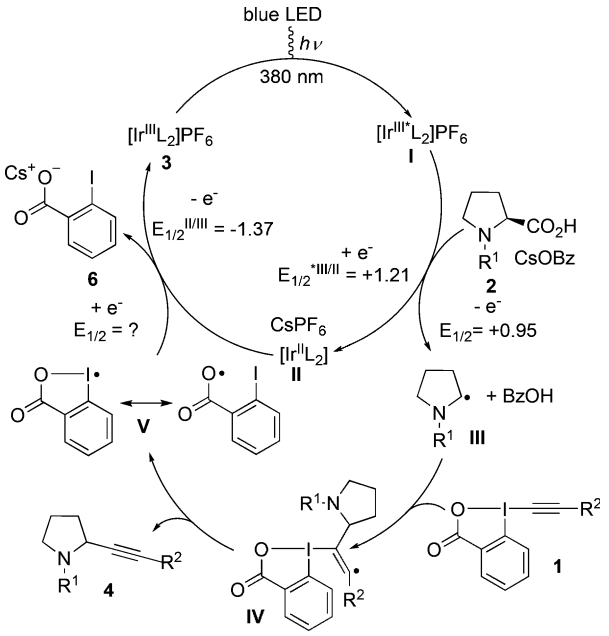
Scheme 3. Scope of alkynes in the decarboxylative alkynylation. [a] Using 1 mol% of catalyst **3a**.



Scheme 4. Reaction with natural sunlight (A) and derivatization of product **4a** (B). CBz = benzyloxycarbonyl.

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 alkynylation. 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 alkynylation 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 alkynylation 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 alkynylation of complex organic compounds and biomolecules in the future.

Acknowledgements

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

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[19] See the Supporting Information for a full list of tested solvents and reaction conditions.

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[21] See the Supporting Information for details. No product was observed in the absence of either light or catalyst **3a**.

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