Decarboxylative oxidation enabled consecutive C-C bond cleavage

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Abstract

The selective cleavage of C-C bonds is of fundamental interest because it provides an alternative approach to traditional chemical synthesis, which is focused primarily on building up molecular complexity. However, current C-C cleavage methods provide only limited opportunities. For example, selective C(sp^3)-C(sp^3) bond cleavage generally relies on the use of transition-metal to open strained ring systems or iminyl and alkoxy radicals to induce β-fragmentation. Here we show that by merging photoredox catalysis with copper catalysis, we are able to employ α-trisubstituted carboxylic acids as substrates and achieve consecutive C-C bond cleavage, resulting in the scission of the inert β-CH_2 group. The key transformation relies on the decarboxylative oxidation process, which could selectively generate in-situ formed peroxide radicals and trigger consecutive C-C bond cleavage. This complicated yet interesting reaction might help the development of other methods for inert C(sp^3)-C(sp^3) bond cleavage.

Introduction

The art of making and breaking bonds has been the driving forces of innovation for chemists[1-3]. It is also the basis of metabolism, enzymology, and biochemistry as a whole[4]. In this context, the cleavage of C-C bonds is of fundamental interest for chemists because it provides an alternative approach to traditional chemical synthesis, which is focused primarily on building up molecular complexity[5-6]. Despite many impressive advances in this field, the cleavage of inert C(sp^3)-C(sp^3) bonds and their subsequent functionalization is still one of the most sought-after challenges in chemistry[7]. Generally, the known strategies for C(sp^3)-C(sp^3) bond cleavage could be divided into two classes. One focuses on the strained ring systems employing transition-metal-catalyzed processes that are triggered by C-C bond activation and β-carbon elimination[8-9]. Another process exploits the chemistry of iminyl and alkoxy radicals because of their abilities to break into an alkyl radical species and an unsaturated fragment through β-fragmentation[10-12]. Recently, the group of Sarpong developed the first homolytic C-C bond cleavage method for the deconstructive diversification of cyclic amines mediated by a silver salt by breaking one C(sp^3)-C(sp^3) bond through an in-situ installed hydroxy group[13-14]. Acids are inexpensive, highly stable, and readily available compounds. Decarboxylation enabled C(sp^2)-C(sp^3) and C(sp^2)-C(sp^2) bond cleavage has been employed for many useful transformations[15-21]. However, little studies have been performed using acids as potential substrates for C(sp^3)-C(sp^3) bond cleavage. Here we show by merging photoredox catalysis with copper catalysis, we are able to use α-trisubstituted acids as substrates and employ a decarboxylative oxidation process to achieve consecutive C-C bond cleavage, resulting in the complete scission of the inert β-CH_2 group.

We propose to generate alkoxy radicals through the decarboxylative oxidation process[22-26]. We anticipate the photoredox decarboxylation of α-trisubstituted acid **I** would produce tertiary radical **II** which could trap oxygen to create the in-situ formed peroxide radical **III**. This peroxyl radical then collapses to deliver the radical species **IV** through β-fragmentation. A few more oxidative transformations from **IV** will provide the

final product **V.** Thus, the whole catalytic process results in totally two C(sp^3)-C(sp^3) cleavage and one C(sp^2)-C(sp^3) bond cleavage.

Results

We began our investigation by using acid **1** as the substrate and examined different conditions, as shown in table 1. First we tried **Ir-1** as the photocatalyst and there was little product observed (Table 1, Entry 1). When $Cu(OAc)_2$ was added, we were able to isolate the desired product with 26% yield (Table 1, Entry 2). The yield was further improved to 48% percent when ligand **L1** was used (Table 1, Entry 3). A further screening of other ligands revealed **L4** as a better choice (Table 1, Entries 3-8). We then evaluated different copper sources (Table 1, Entries 9-11). When the reaction was carried out at 30^oC, the yield jumped to 81% after 40 hours (Table 1, Entry 12). Given the fact the whole transformation is composed of a few steps, the average yield for each step is impressingly high. At last, we tested different photocatalysts and **Ir-1** proved to be the best (Table 1, Entries 12-15). Further control experiments revealed no reactions occurred in the absence of photocatalyst, Cs_2CO_3, or blue LEDs (for a detailed account of the optimization studies, see Supplementary Table S1-S5).

With the optimized conditions in hand, we proceeded to investigate the scope of this transformation. We first evaluated this method with different aromatic substituted piperidine-4-carboxylic acids (Table 2). *N*-substituted piperidine derivatives bearing *tert*-butoxycarbonyl and benzoyl groups were well tolerated (Table 2, substrates **1-2**). A diverse range of electron-withdrawing and electron-donating functional groups were entirely compatible and delivered the products smoothly (Table 2, substrates **3-8**). F, Cl, *t*-Bu, and Ph groups furnished the products in good yields (Table 2, substrates **3**, **4**, **7**, **8**). However, strong electron-withdrawing group such as CF_3 and strong electron-donating group such as OMe only gave the product in moderate yields (Table 2, substrates **5** and **6**). Other aromatic group such as thiophene also worked well (Table 2, substrate **9**).

Reaction conditions: substrate (0.5 mmol), **Ir-1** (0.015 mmol), $Cu(OAc)_2$ (0.1 mmol), **L4** (0.125 mmol), Cs_2CO_3 (0.75 mmol), DCM (10 mL), 45W blue LEDs, 30^oC, 40 h.

We then examined aliphatic substituted piperidine-4-carboxylic acids (Table 3). For these compounds, **Ir-2** turned out to be the better catalyst. Methyl and ethyl groups provided the products in moderate yields (Table 3, substrates **10** and **11**). However, for allyl, benzyl and isopropyl substituted substrates, oxidation of these functionalities happened and the main isolated products were 4-piperidinone (Table 3, substrates **12-14**). Four-membered azetidinone substrate gave α-amino ketone product in 58% yield (Table 3, substrate **15**). For five-membered pyrrolidine-3-carboxylic acid substrate **16**, β-amino ketone product was isolated in 64% yield. As expected, piperidine-3-carboxylic acids furnished γ-amino ketone products in good yields (Table 3, substrate **17**, **18**, **20**). However, due to the oxidation of the benzyl group, the yield for substrate **19** is low.

We further applied this method to all carbon cyclic acids (Table 4). For cyclobutanecarboxylic acid substrates, 1,4-dicarbonyl compounds were isolated in good yields (Table 4, substrates **21**-**23**). When cyclopentanecarboxylic acid was used, 1,5-dicarbonyl compound was obtained instead in 70% yield (Table 4, substrates **24**).

We were pleased to find out that this method worked with acyclic acids (Table 5). For 2,2,2-triphenylacetic acid and 2,2-diphenylpentanoic acid, benzophenone was isolated as the main product in moderate yields (Table 5, substrates **25-26**). However, for 2,2-diphenylpropanoic acid, the main product was acetophenone (Table 5, substrates **27**). Different substituted 2-methyl-2-phenylpropanoic acids also furnished acetophenone type products (Table 5, substrates **28-31**). Accordingly, substrate **32** provided propiophenone as the main product in good yield. It's noteworthy that 3-phenylpropanoic acids could also be compatible and benzaldehyde type products were isolated (Table 5, substrates **33**-**35**). For 3-phenylbutanoic acid, acetophenone was isolated in 66% yield (Table 5, substrate **36**).

We also evaluated this method with β-hydroxy acids (Table 6). Interestingly, the C-C cleavage tended to happen at the α-β position, probably because the radical intermediates were stabilized by the β-hydroxy group. Thus, diketones were usually provided as the main products. For substrates which contain tertiary β-hydroxy groups (Table 6, substrates **37**-**39**), the products were isolated in good yields. However, substrates with secondary β-hydroxy groups delivered the products only in moderate yields (Table 6, substrates **40**-**41**). For substrate **42**, the C-C cleavage happened at both positions with about 3:1 ratio.

Based on our proposed mechanism (Figure 2), radical intermediate **IV** was formed during the process. To capture this intermediate, we tried to add additives. Eventually, we found the addition of Selectfluor successfully delivered ketone-alcohol as the main product. Thus, under the optimized condition, cyclobutanecarboxylic acid substrates provided 4-hydroxybutyrophenones in good yields (Table 7, substrates **43- 45**). When cyclopentanecarboxylic acid was used, 5-hydroxybutyrophenone was provided instead (Table 7, substrates **46**). For cyclohexanecarboxylic acid, 6-hydroxyhexaphenone was isolated in 75% yield (Table 7, substrates **47**). We also tested other six-member cyclic acids, all of them worked smoothly and delivered the products in moderate to good yields (Table 7, substrates **48**-**52**).

Synthetic utilities. This reaction provides a direct method to construct different diketones, which are versatile building blocks in the synthesis of natural products and bioactive compounds. Thus, we performed the synthesis of Primaperone, Melperone and Haloperidol. These drugs could be accessed in one step from product **22b** via reductive amination in good yields. We also did late-stage modification of commercial drug and complex natural products. For Sertraline derivative **53a**, the reaction worked smoothly and the product was isolated in 83% yield. For steroids **54a** and **55a**, the regioselectivities were good and we only isolated one product. However, the reactions were sluggish and much of the starting materials were recovered.

Mechanistic Studies

To better understand the mechanism, we did control experiments. First, when substrate **10a** was evaluated under the reaction condition, compound **10c** was isolated as a byproduct in 31% yield. Further analysis of the reaction mixture during the reaction through HRMS revealed **10d**, **10e** and **10f** as intermediates (for a detailed account of the mechanism study, see Supplementary Materials). However, when **10c** was submitted to the reaction condition, no **10b** was formed, which clearly indicates **10c** is a by-product, not a reacting intermediate. When amino aldehyde **56a** was subjected to the same condition, we were able to isolate one carbon shorter product **56b**. We also found that no reaction happened when compound **57** was treated with the standard condition, which means decarboxylation is the key to induce the consecutive C-C bond cleavage.

Based on the above experiments, we propose a plausible mechanism as shown in Figure 5. Photocatalyzed decarboxylation of substrate **10a** provides radical **A**, which is captured by oxygen to generate peroxide radical **B**. The reduction of radical **B** will give product **10c**. Peroxide radical **B** undergoes β-fragmentation and produces radical **C**. If radical **C** abstracts a hydrogen atom, it will give product **10d**. Radical **C** is further oxidized by copper and oxygen to deliver intermediate **10e** and **D**. Both **10d** and **10e** were identified by HRMS. Another photocatalyzed oxidative decarboxylation of **D** will give intermedaite **F**, which is further oxidized to render **10b** as the final product. If radical **F** abstracts a hydrogen atom, it will give product **10f**, which was also identified by HRMS.

Discussion

In conclusion, we have successfully developed consecutive C-C bond cleavage by taking the advantages of photoredox catalysis along with copper catalysis. This complicated process exploits the use of stable α-trisubstituted acids as substrates and efficiently breaks three C-C bonds at the same time. The key transformation features a decarboxylative oxidation process to generate the in-situ formed peroxide radical which could trig β-fragmentation and the following oxidation process. We believe this finding might shed light on the development of other methods for inert C(sp^3)-C(sp^3) bond cleavage.

Methods

General procedure for consecutive C-C bond cleavage products

To a 50 ml round bottomed flask equipped with a magnetic stirrer bar were added acid (0.5 mmol, 1.0 equiv.), **Ir-1** or **Ir-2** (0.015 mmol, 0.03 equiv.), $Cu(OAc)_2$ (18.1 mg, 0.1 mmol, 0.2 equiv.), 2,2'-bipyridine (19.5 mg, 0.125 mmol, 0.25 equiv.), Cs_2CO_3 (245 mg, 0.75 mmol, 1.5 equiv.) and DCM (10 mL). The flask was quickly degassed three times and flushed with oxygen through balloon, and then the mixture was heated to 30 ^oC in an oil bath and irradiated with three 45 W blue LEDs (5 cm away) for 40 hours or 72 hours. The reaction mixture was filtered and concentrated. The residue was purified by column chromatography on silica with petroleum ether/ethyl acetate mixture as the eluent.

General procedure for ketone-alcohol products

To a 50 ml round bottomed flask equipped with a magnetic stirrer bar were added acid (0.5 mmol, 1.0 equiv.), **Ir-1** (22.3 mg, 0.015 mmol, 0.03 equiv.), $Cu(OAc)_2$ (18.1 mg, 0.1 mmol, 0.2 equiv.), 2,2'-bipyridine (19.5 mg, 0.125 mmol, 0.25 equiv.), Cs_2CO_3 (245 mg, 0.75 mmol, 1.5 equiv.), Selectfluor (265 mg, 0.75 mmol, 1.5 equiv.) and DCM (10 mL). The flask was quickly degassed three times and flushed with oxygen through balloon, and then the mixture was heated to 30 ^oC in an oil bath and irradiated with three 45 W blue LEDs (5 cm away) for 40 hours. The reaction mixture was filtered and concentrated. The residue was purified by column chromatography on silica with petroleum ether/ethyl acetate mixture as the eluent.

Data availability

Materials and methods, experimental procedures, useful information, mechanistic studies, optimization studies, ^1H NMR spectra, ^{13}C NMR spectra and mass spectrometry data are available in the Supplementary Information. Raw data are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at

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Tables

Tables 1-7 are available in the supplementary files section.

Figures

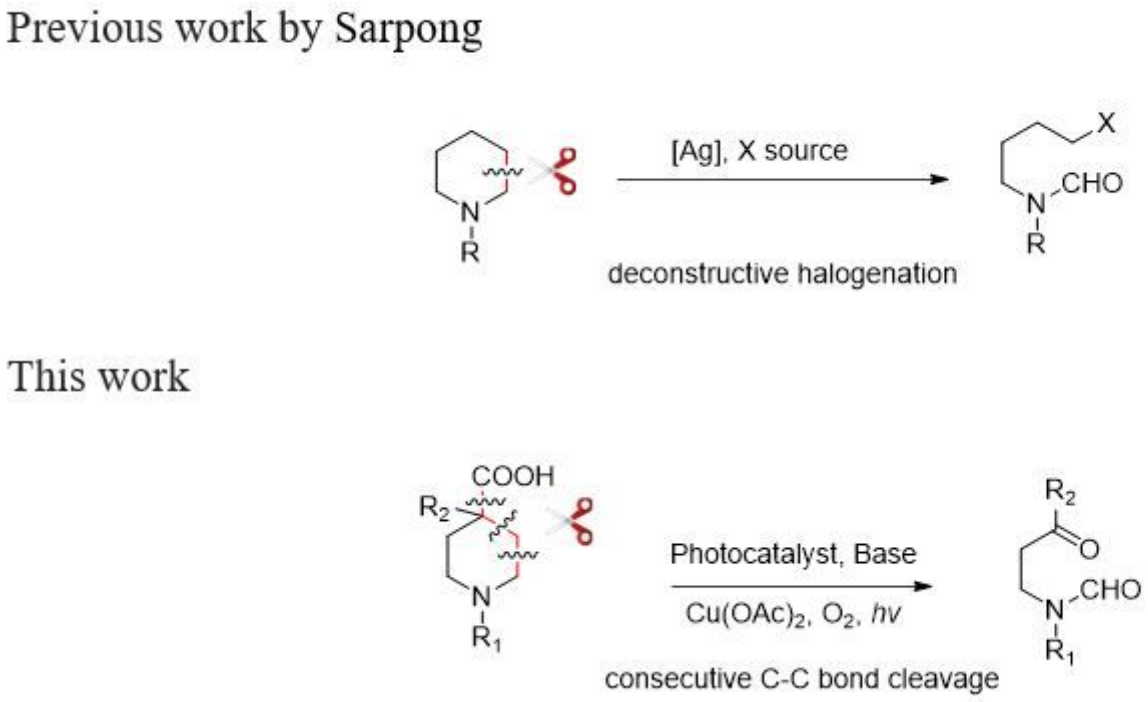

Figure 1

C-C bond cleavage of cyclic amines

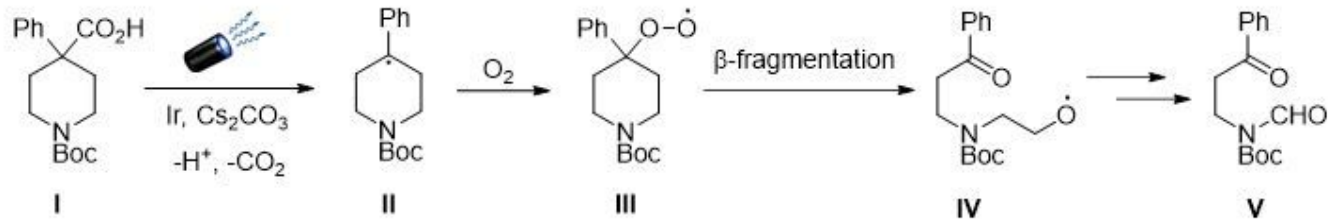

Figure 2

Proposed reaction design

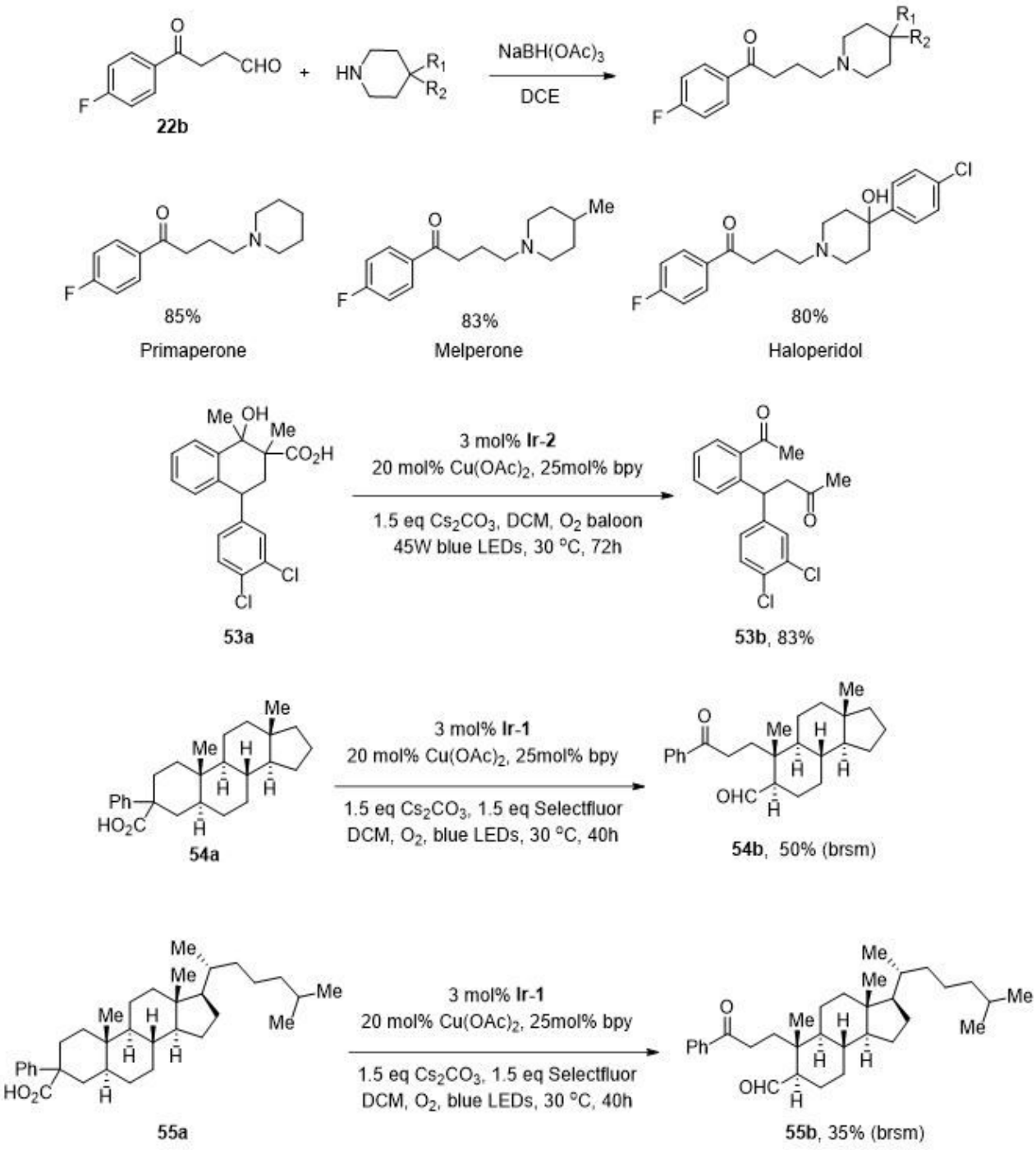

Figure 3

Synthetic utilities of the C-C cleavage reaction.

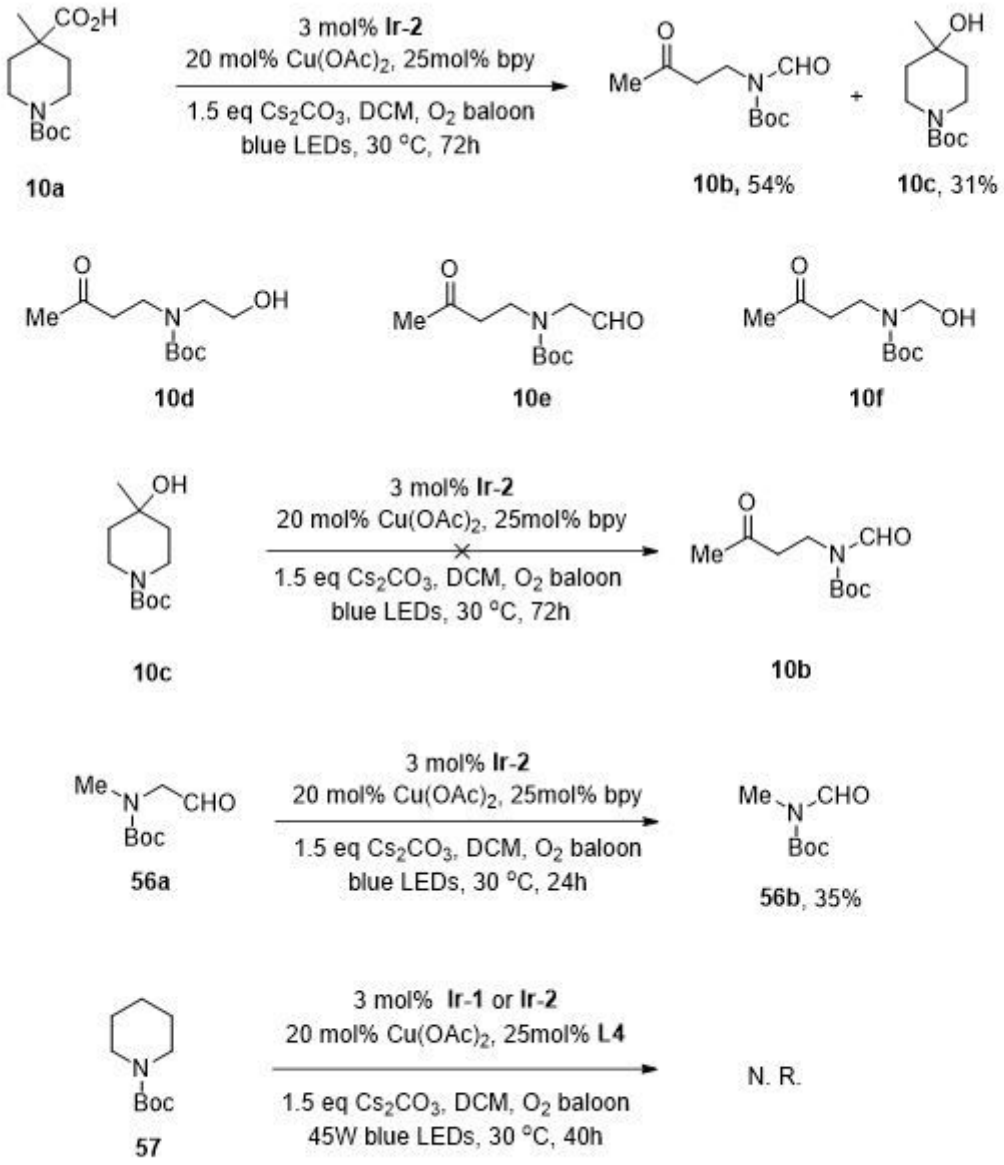

Figure 4

Experimental observations for the proposed mechanism.

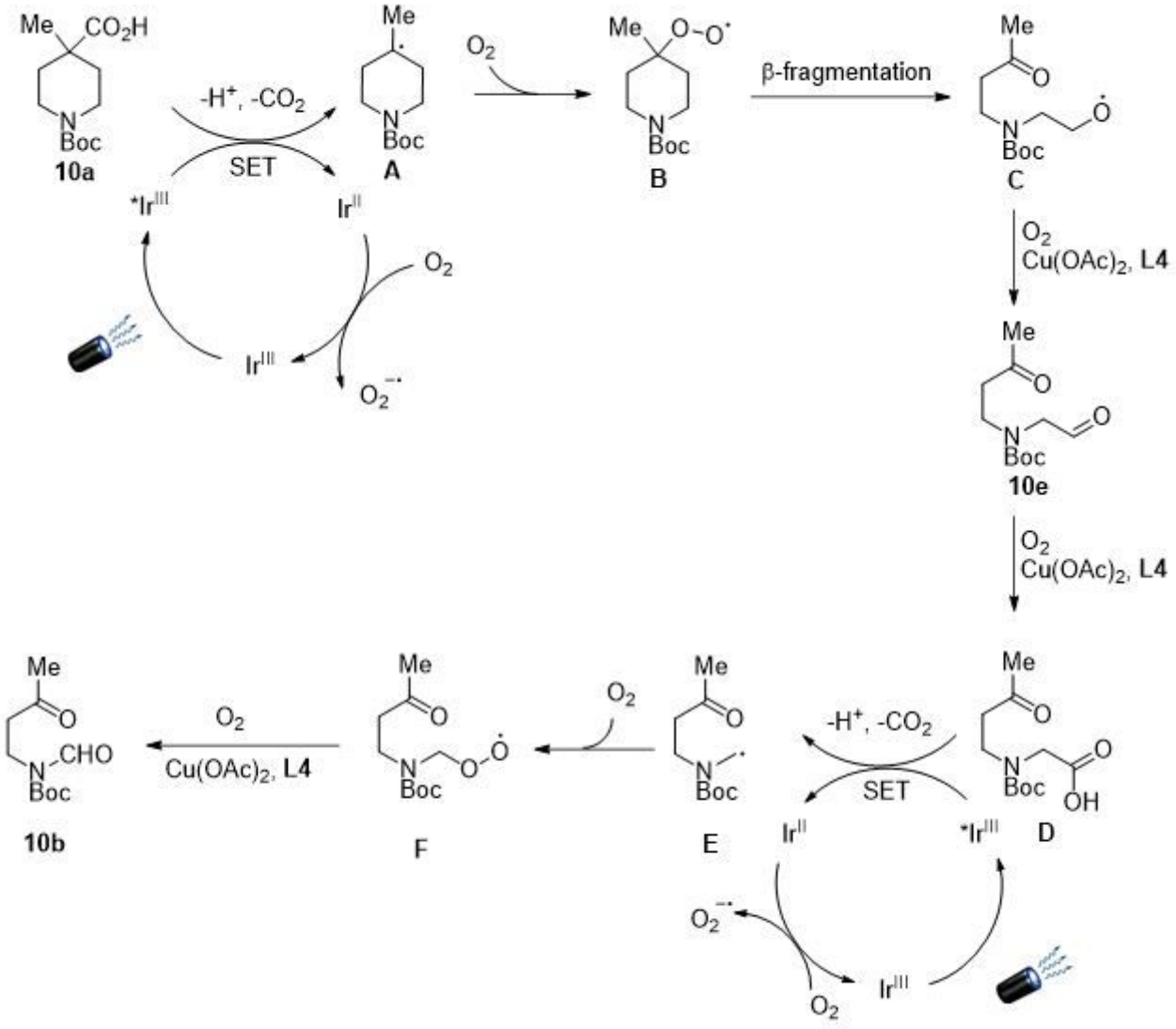

Figure 5

Proposed mechanism.

Supplementary Files

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