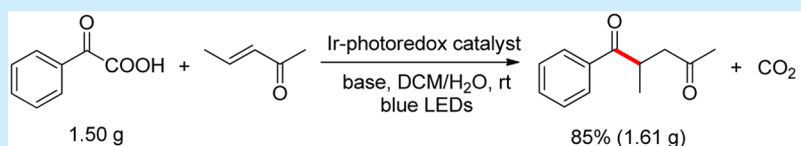


Decarboxylative 1,4-Addition of α -Oxocarboxylic Acids with Michael Acceptors Enabled by Photoredox Catalysis

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Supporting Information

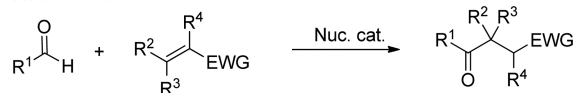


ABSTRACT: Enabled by iridium photoredox catalysis, 2-oxo-2-(hetero)arylacetic acids were decarboxylatively added to various Michael acceptors including α,β -unsaturated ester, ketone, amide, aldehyde, nitrile, and sulfone at room temperature. The reaction presents a new type of acyl Michael addition using stable and easily accessible carboxylic acid to formally generate acyl anion through photoredox-catalyzed radical decarboxylation.

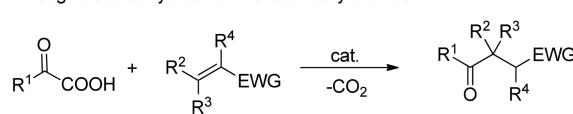
Michael addition with acyl anion is a general way to construct γ -carbonyl compounds possessing a useful electron-withdrawing functional group (Scheme 1).¹ Classic

Scheme 1. Michael Addition with Acyl Anion Equivalent

Stetter reaction



Through decarboxylation of 2-oxocarboxylic acids



methods to access such compounds include the Stetter reaction through the unpoling Breslow intermediate from aldehyde.² In the interest of utilizing carboxylic acid to generate a nucleophile in organic synthesis,³ we wondered whether such an acyl nucleophile can be generated through decarboxylation of α -oxocarboxylic acids in the Michael addition reaction.^{4,5b} Although α -oxocarboxylic acids have been successfully utilized as acyl nucleophiles in transition-metal-catalyzed decarboxylative coupling reactions,⁵ their utilization as acyl nucleophiles in addition to Michael acceptors remains underdeveloped, possibly due to the thermo-instability that Michael acceptors⁶ incompatible with the harsh conditions often require for metal-catalyzed redox neutral decarboxylation.⁷ Recently, we⁸ and other groups⁹ discovered that α -oxocarboxylic acids can decarboxylatively couple with electrophiles under mild conditions though photoredox catalysis,¹⁰ and also inspired by the recent works of photoredox catalyzed decarboxylative 1,4-addition of aliphatic carboxylic acids,¹¹ we conjectured that a photoredox catalyst may be suitable to catalyze Michael

addition of α -oxocarboxylic acids through radical decarboxylation under mild conditions. As depicted in Figure 1, a

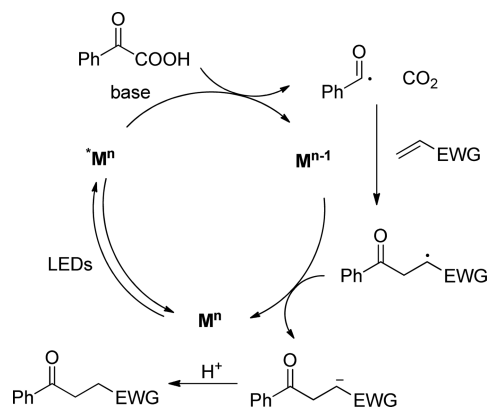


Figure 1. Hypothesized mechanism of photoredox catalyzed decarboxylative 1,4-addition of α -oxocarboxylic acid.

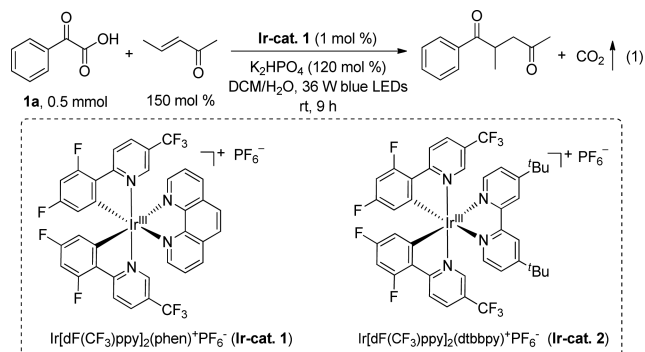
photoexcited photocatalyst $^*M^{n+}$ can be reductively quenched by α -oxocarboxylate to generate an acyl radical. The acyl radical can be trapped by a Michael acceptor to generate an enolate radical^{4b} which may oxidize the reduced $M^{(n-1)+}$ to regenerate M^{n+} and deliver the 1,4-addition product after protonation. Based on this hypothesis, we realized in this work that, when enabled by an iridium photoredox catalyst, Ir[dF(CF₃)ppy]₂(phen)PF₆, various 2-(hetero)aryl-2-oxocarboxylic acid can proceed decarboxylative 1,4-addition with a series of Michael acceptors, including unsaturated ester, ketone, amide, nitrile, sulfone, and unsaturated aldehyde, which is a challenging substrate in the Stetter reaction.² This work offers

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a new type of Michael addition with an acyl anion equivalent that was generated through decarboxylation.

A typical example after optimization is demonstrated in Table 1, entry 1. A transparent Schlenk tube charged with 2-

Table 1. Study of Parameters for Decarboxylative 1,4-Addition of 2-Oxophenylacetic Acid^a



entry	variations from the conditions in eq 1	yield ^b (%)
1	none	92 (89 ^c)
2	Ir-cat. 2 instead of Ir-cat. 1	90
3	[Ir(ppy) ₂ (dtbbpy)]PF ₆ instead of Ir-cat. 1	0
4	[Ru(bpy) ₃]Cl ₂ instead of Ir-cat. 1	0
5	[Ru(bpz) ₃]Cl ₂ instead of Ir-cat. 1	28
6	without base	0
7	K ₂ CO ₃ instead of K ₂ HPO ₄	90
8	using 50 mol % of K ₂ HPO ₄	45
9	without photoredox catalyst	0
10	without light	0

^aReaction conditions: **1a** (0.5 mmol), Michael acceptor (0.75 mmol), catalyst (1 mol %), base (0.6 mmol), and CH₂Cl₂ (1 mL)/H₂O (1 mL) at room temperature for 9 h under air. See the Supporting Information for more details. ^bGC yields using benzophenone as an internal standard. ^cIsolated yield.

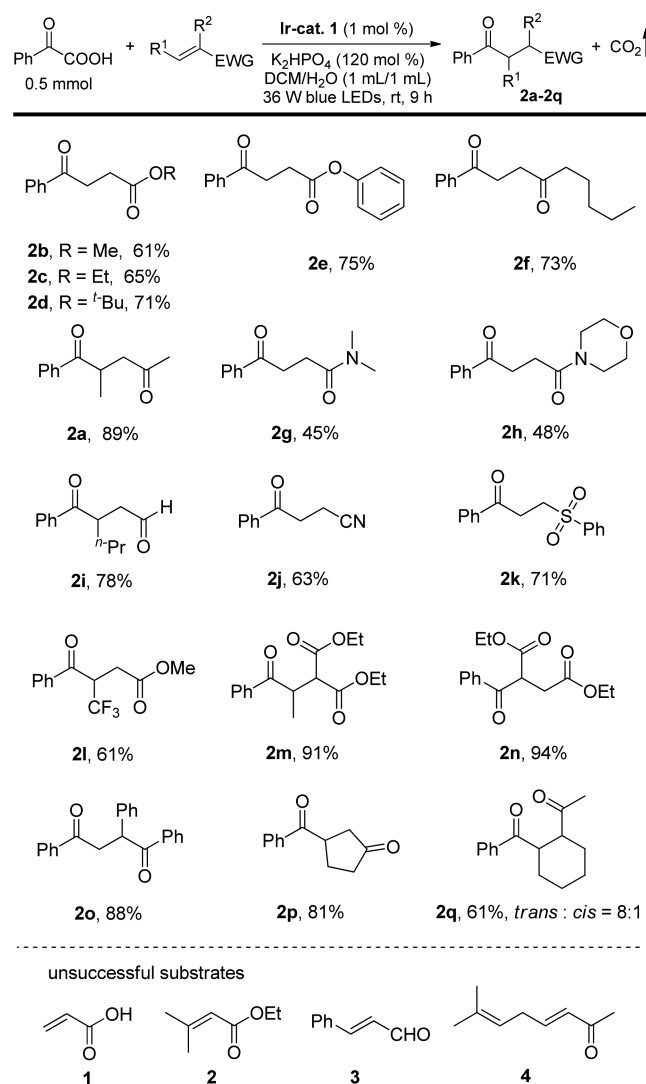
oxo-2-phenylacetic acid (0.5 mmol), (*E*)-pent-3-en-2-one (0.75 mmol), K₂HPO₄ (0.6 mmol), and Ir[dF(CF₃)ppy]₂(phen)PF₆ in a mixed solvent of dichloromethane and water (1 mL/1 mL) was exposed under the irradiation of a 36 W blue LED at room temperature. After 9 h irradiation, aqueous workup followed by column chromatography gave the addition product, 2-methyl-1-phenylpentane-1,4-dione, in 89% isolated yield. Along with the desired product, ~10% of benzaldehyde was observed as a side product. Table 1 summarizes several factors that affect the reaction outcomes. Using a similar photoredox catalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (**Ir-cat. 2**) [*E*^{1/2}(M^{•+}/M^{•-}) = 1.21 V vs SCE, τ = 2300 ns]^{10g} instead of Ir[dF(CF₃)ppy]₂(phen)PF₆ (**Ir-cat. 1**) gave almost same yield (entry 2), but using Ir(ppy)₂(dtbbpy)PF₆ [*E*^{1/2}(M^{•+}/M^{•-}) = 0.66 V vs SCE, τ = 557 ns]^{10g} gave no product at all (entry 3). Ruthenium-based photoredox catalyst [Ru(bpy)₃]Cl₂ [*E*^{1/2}(M^{•+}/M^{•-}) = 0.77 V vs SCE, τ = 1100 ns]^{10g} is totally ineffective (entry 4). [Ru(bpz)₃]Cl₂ with a high oxidative potential, but a relatively short excited-state lifetime [*E*^{1/2}(M^{•+}/M^{•-}) = 1.45 V vs SCE, τ = 740 ns],^{10g} gave the desired product in only 28% yield (entry 5).

The result of catalyst screen reveals that both the oxidative potential [*E*^{1/2}(M^{•+}/M^{•-})] and the excited state lifetime are crucial for the performance of the catalyst. The reaction cannot proceed at all without a base (entry 6). Screening of base revealed K₂CO₃ (entry 6) and K₂HPO₄ are the most suitable

bases (see the Supporting Information for more information). Although base can be used catalytically in principle for this reaction, reducing base to catalytic amount significantly decreased the yield (entry 8). The importance of base may be ascribed to the effective generation of the carboxylate anion for quenching the excited photoredox catalyst. Control experiments revealed that the reaction absolutely needs the photocatalyst and irradiation (entries 9 and 10). It should be noted this reaction proceeds well under both air (92%) and argon protection (90%) (Supporting Information).

Evaluation of the scope of Michael acceptors is summarized in Scheme 2. α , β -Unsaturated ester, such as alkyl and aryl

Scheme 2. Scope with Respect to Michael Acceptors^a



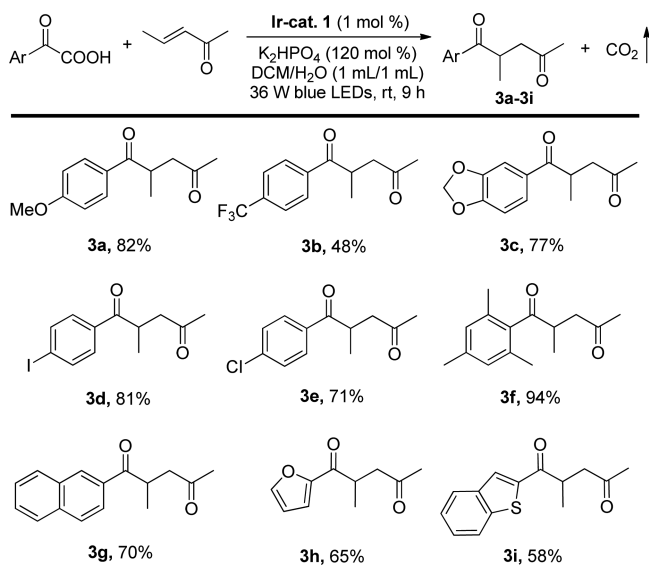
^aReaction conditions: **1a** (0.5 mmol), Michael acceptors (0.75 mmol), Ir-cat. 1 (1 mol %), K₂HPO₄ (0.6 mmol), and CH₂Cl₂/H₂O = 1:1 (2 mL) under air.

acrylate are all good substrates (**2b-2e**). α , β -unsaturated ketones are also amenable substrates (**2f, 2a**). Acrylamides gave moderate yields (**2g,h**). α,β -Unsaturated aldehyde, which is incompatible in the Stetter reaction, can also be successfully used (**2i**). Acrylonitrile and α,β -unsaturated sulfone are also suitable substrates (**2j,k**). Substituents on both the α -position (**2o**) and β -position (**2a,i**) of the Michael acceptors are

tolerated. β -CF₃ substitution on acrylate is well tolerated, and a 1,4-dicarbonyl compound possessing a useful -CF₃ substituent was generated (**2l**). Alkylidenemalonate (**2m**) and diethyl maleate (**2n**) are good substrates to generate the addition product in high yields. Except for acyclic Michael acceptors, cyclic Michael acceptors, such cyclopent-2-en-1-one, also work well (**2p**). 1-(Cyclohex-2-en-1-yl)ethan-1-one gave the addition product as a mixture of diastereomers in which the trans isomer is the major product (trans/cis = 8:1). Several unsuccessful substrates are also listed at the bottom of Scheme 2. Simple acrylic acid (**1**) is ineffective, probably due to the competition of reductive quenching with 2-oxocarboxylate. β -Dimethylated (**2**) and β -phenyl-substituted (**3**) Michael acceptors are both unreactive, which may be ascribed to the generation of a stable tertiary and benzylic radical with relatively lower oxidation potentials compared with α -carbonyl radical that is unable to reoxidize Ir^{II}.¹² Substrate **4**, which can generate a stable tertiary carbon radical, is unreactive. Styrene is unreactive.

The generality of this reaction with regard to 2-oxo-2-arylacetic acids is summarized in Scheme 3. 2-Oxo-2-phenyl-

Scheme 3. Scope with Respect to 2-Oxo-2-(hetero)arylacetic Acids^a

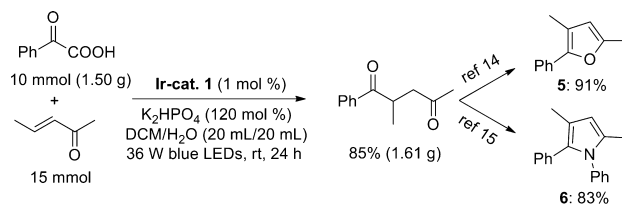


^aReaction conditions: 2-oxo-2-(hetero)arylacetic acids (0.5 mmol), Michael acceptor (0.75 mmol), Ir-cat. 1 (1 mol %), K₂HPO₄ (0.6 mmol), and CH₂Cl₂/H₂O = 1:1 (2 mL) under air.

acetic acids with both electron-donating (**3a**) and electron-withdrawing (**3b**) substituents on the phenyl ring are amenable substrates. The electron-withdrawing substituent decreases the conversion and the yield. This observation may be ascribed to the reduced reductive quenching ability toward photoexcited *Ir(III). Acetal functionality was well tolerated (**3c**). Aryl iodide (**3d**) and aryl chloride (**3e**) turned out to be compatible. No photoredox-catalyzed deiodination was observed.¹³ 2-Oxo-2-mesitylacetic acids worked well to deliver the product in high yield (**3f**). Besides 2-phenyl substitution, 2-naphthyl- (**3g**) and 2-heteroaryl-substituted glyoxylic acids (**3h,i**) are all suitable substrates, albeit in moderate yield. For reasons yet unclear, 2-alkyl-2-oxoacetic acid and 2-amino-2-oxoacetic acid were unsuccessful substrates with starting materials recovered under the optimized reaction conditions.

A gram-scale reaction further demonstrated the applicability of this photoredox-catalyzed acyl Michael addition (Scheme 4).

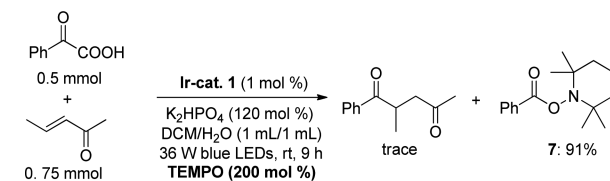
Scheme 4. Gram-Scale Reaction and Accessibly Further Transformation to 2-Arylated Heterocycles



Subjecting 1.50 g of 2-oxo-2-phenylacetic acid yielded 1.61 g (85% yield) of the desired addition product without decreasing the yield compared with small-scale reaction. Furthermore, the obtained 1,4-dicarbonyl compound can be easily transformed into 2-arylated furan¹⁴ and pyrrole,¹⁵ which are of interest in materials science and the pharmaceutical industry.

A radical-trapping experiment was tested as shown in Scheme 5. It was found that adding 1,1-diphenylethylene or TEMPO

Scheme 5. Radical Trapping Experiment with TEMPO



(2,2,6,6-tetramethylpiperidinoxy) kills this reaction. The suppressing effect of 1,1-diphenylethylene may be ascribed to the generation of a stable tertiary benzylic radical by trapping the benzoyl radical, thus ending the photoredox cycle. This observation is in accordance with the substrate limitation observed in Scheme 2. When 2.0 equiv of TEMPO was added as an additive, 2,2,6,6-tetramethylpiperidin-1-yl benzoate was observed in high yield (based on **1a**). This observation revealed TEMPO overwhelmingly traps the benzoyl radical in preference to Michael acceptor and acts as oxidant to regenerate the Ir(III) catalyst.^{4b} These observations support that the reaction proceeds through a radical decarboxylation, and the poisoning effect of 1,1-diphenylethylene suggested that the enolate radical generated is crucial for the regeneration of the Ir(III) catalyst as proposed in Figure 1.¹¹

In summary, we have shown that when enabled by iridium photoredox catalysis 2-oxocarboxylic acids can be used to generate an acyl anion equivalent to add with various Michael acceptors, including α , β -unsaturated ester, ketone, amide, aldehyde, nitrile, and sulfone under mild conditions. The reaction presents a new type of decarboxylative 1,4-addition reaction utilizing stable and easily accessible 2-oxocarboxylic acids and also demonstrates a new synthetic application of the increasing repertoire of photoredox catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02392.

Detailed experimental procedures and spectral data for all compounds(PDF)

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Notes

The authors declare no competing financial interest.

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