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Oxalates as Activating Groups for Alcohols in Visible Light Photoredox Catalysis: Formation of Quaternary Centers by Redox-Neutral Fragment Coupling

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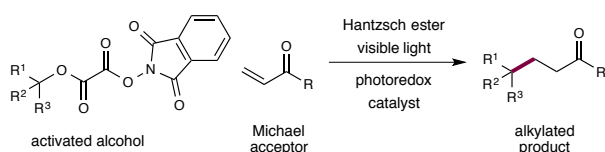
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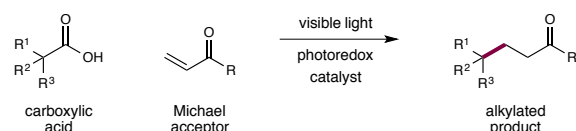
Abstract. Alkyl oxalates are new bench-stable alcohol-activating groups for radical generation under visible light photoredox conditions. Using these precursors, the first net redox-neutral coupling of tertiary and secondary alcohols with electron-deficient alkenes is achieved.

Nucleophilic tertiary carbon radicals are useful intermediates for combining structurally complex carbon fragments with the formation of new quaternary carbons.¹ These alkyl radicals are formed most commonly from halide precursors; however, competing elimination and rearrangement reactions can undermine the preparation of structurally complex tertiary halides.² In contrast, tertiary alcohols would be ideal precursors of tertiary radicals, as they can be prepared by various reliable methods and are also widely commercially available. Taking inspiration from Barton's introduction of *tert*-alkyl *N*-hydroxypyridine-2-thionyl oxalates for generating carbon radicals from alcohols,^{2b} the Overman group recently introduced *N*-phthalimidoyl oxalate derivatives of tertiary alcohols for the reductive coupling of tertiary carbon radicals with Michael acceptors using visible light and [Ru(bpy)₃](PF₆)₂ (Eq 1).³⁻⁵ Although this method was demonstrated to possess a wide substrate scope, its mechanism necessitates the use of a stoichiometric reductant to produce the tertiary alkyl radical and also forms phthalimide as a byproduct. Further, the inherent sensitivity of the *N*-phthalimidoyl oxalate moiety can present complications for purification of the requisite intermediates, as *N*-phthalimidoyl oxalates are not stable to aqueous workup or silica column chromatography. As such, identifying an activating group for tertiary alcohols that is both stable and capable of generating and coupling radicals in a redox-neutral

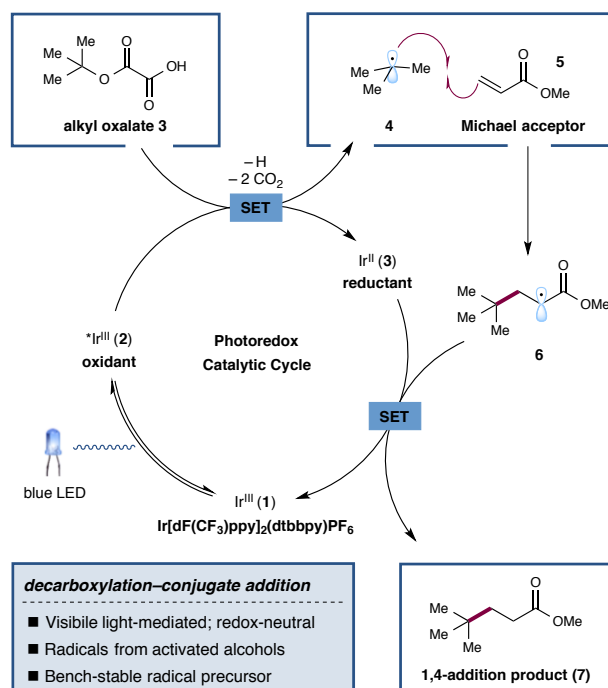
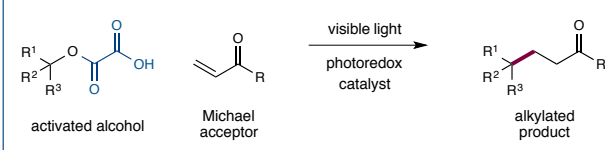
Overman, 2013: Reductive Coupling of *N*-Phthalimidoyl Oxalates (Eq 1)



MacMillan, 2014: Photocatalytic Radical Generation from Acids (Eq 2)



This Work: Redox-Neutral Coupling of Activated Alcohols (Eq 3)



Scheme 1. Proposed Mechanism for Redox-Neutral Radical Coupling Reaction using Alkyl Oxalates and Michael Acceptors

fashion (i.e., without the need for supplementary reductants or oxidants) would be a desirable goal. In a 2014 publication, the MacMillan group reported a net redox-neutral method to generate carbon radicals and couple them with Michael acceptors by visible light promoted decarboxylation of carboxylic acids using the iridium photocatalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (**1**) (Eq 2).⁶ In contrast to the reductive coupling of *N*-phthalimidoyl oxalates, this method produces no byproduct other than CO₂. We questioned whether it would be possible to combine the salient features of both the Overman and MacMillan radical generation methods in order to identify a new activating group strategy for tertiary alcohols, one that proceeds via a redox-neutral manifold utilizing stable, easily handled intermediates. In this communication, we report that simple oxalate salts of tertiary alcohols undergo high-yielding photocatalytic coupling with electron-deficient alkenes in the presence of photocatalyst **1** and visible light (Eq 3).

The mechanistic details of the proposed coupling reaction are outlined in Scheme 1. It has been shown that irradiation of heteroleptic photocatalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (**1**) [dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] with visible light leads to the formation of a long-lived ($\tau = 2.3 \mu\text{s}$) excited state ^{*}Ir^{III} **2**, which is a strong oxidant ($E_{1/2}^{\text{red}} [^*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21 \text{ V}$ vs. SCE in CH₃CN).⁷ On this basis, we hypothesized that oxidation of the conjugate base of alkyl oxalate **3** ($E_{1/2}^{\text{red}} = +1.28 \text{ V}$ vs. SCE in CH₃CN for *t*-BuOCOCOC₂Cs)⁸ by ^{*}Ir^{III} (**2**) via single-electron transfer (SET) should be thermodynamically feasible,

Table 1. Initial Studies and Reaction Optimization

| entry | X | solvent | base | yield ^a |
|-------------------|----|-------------|---------------------------------|--------------------|
| 1 | H | DMF | K ₂ HPO ₄ | 64% |
| 2 | H | DMF | CsF | 74% |
| 3 | H | DME | CsF | 82% |
| 4 | H | 3:1 DME:DMF | CsF | 91% |
| 5 | Cs | 3:1 DME:DMF | none | 65% |
| 6 ^b | Cs | 3:1 DME:DMF | none | 95% |
| 7 ^b | Li | 3:1 DME:DMF | none | 93% |
| 8 ^{b,c} | Cs | 3:1 DME:DMF | none | 66% |
| 9 ^{b,d} | Cs | 3:1 DME:DMF | none | 0% |
| 10 ^{b,e} | Cs | 3:1 DME:DMF | none | 0% |

^aReactions on 0.2 mmol scale using 1.0 equiv acceptor and 1.1 equiv oxalate. Yields determined by ¹H NMR using mesitylene as an internal standard. ^b10 equiv water added. ^cReaction performed with 26W CFL. ^dReaction performed without photocatalyst. ^eReaction performed in the absence of light.

generating alkyl radical **4** following the stepwise loss of two molecules of CO₂.^{2b,3a} This nucleophilic carbon-centered radical **4** should rapidly undergo addition to electron-deficient alkenes such as methyl acrylate **5**. Finally, we expected that reduction of the resulting adduct radical **6** ($E_{1/2}^{\text{red}} = -0.59$ to -0.73 V vs. SCE in MeCN)⁹ by SET from the available Ir^{III} species **3** ($E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37$ V vs. SCE in CH₃CN)⁷ should give after protonation coupled product **7** and regenerate ground state photocatalyst **1**, completing the proposed catalytic cycle.

We first explored the proposed decarboxylative alkylation reaction using the alkyl hydrogen oxalate derived from 1-methyl-1-cyclohexanol as the radical precursor in the presence of benzyl acrylate as an archetypal Michael acceptor (Table 1). Using Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (**1**) as photocatalyst and dipotassium phosphate as base,⁶ we were delighted to obtain the desired product in moderate yield (entry 1). Further optimization revealed cesium fluoride to be a more competent base and a 3:1 mixture of DME:DMF to be the optimal solvent (entries 2–4).

Although *tert*-alkyl hydrogen oxalates clearly function as viable radical precursors, many were observed to be intrinsically unstable species that disproportionate into a mixture of the corresponding dialkyl oxalate and oxalic acid, even during storage at -18 °C.¹⁰ Furthermore, it was apparent that the presence of a highly acidic hydrogen oxalate would likely preclude the preparation of substrates containing sensitive functional groups. Fortunately, it was found that the preformed cesium salts of the starting acids were also competent in the reaction (entry 5). In contrast to the parent acid (and, indeed, most activating groups for tertiary alcohols used for radical generation),^{2,3} we found alkyl cesium oxalates to be bench-stable, non-hygroscopic and easy to isolate and handle.¹¹ The addition of 10 equiv of water was found to be highly beneficial when utilizing the pre-formed oxalate salt, giving the coupled product in an excellent 95% yield (entry 6). Presumably, the water both assists in solubilizing the oxalate salt and provides a proton source to quench the intermediate cesium enolate after radical coupling and reduction. Additionally, oxalates bearing other alkali counterions, such as lithium (entry 7), performed comparably to cesium oxalates in the reaction.¹² The use of a 26 W CFL bulb in place of the 34 W blue LED lamp resulted in a

diminished but still useful yield (entry 8). Finally, it was observed that control experiments run in the absence of photocatalyst or a visible-light source did not generate any of the desired 1,4-addition product (entries 9 and 10).

Having identified optimal conditions, we examined the scope of the acceptor component. As shown in Table 2, a wide range of electron-deficient alkenes can be used in the reaction. As expected, various acrylates proved to be capable acceptors in the reaction (products **10** and **11**, 88 and 86% yield respectively), and the presence of α -substitution was well tolerated (products **17–20** 85–96% yield). Moreover, α,β -unsaturated acids can also be used as coupling partners, owing to the low basicity of the oxalate salt (product **20**, 85% yield). This procedure could be applied to a range of other electron-deficient alkenes, including enones, enals, acrylamides, vinyl phosphonates, and vinyl sulfones (products **12–16**, 68–86% yield). Surprisingly, acrylonitrile produced little product (11% yield),¹³ whereas methacrylonitrile proved to be a much more capable acceptor (product **17**, 85% yield). Substitution at the β -position was tolerated for more electron-deficient alkenes such as dimethyl fumarate and dimethyl ethylidene- and benzylidenemalonate, furnishing the expected adducts with good efficiency (products **21–23**; 70–99% yield). As expected, 4-vinylfuran-2-one gave exclusively the 1,6-addition product in excellent yield (product **24**, 89% yield). In the case of acceptors harboring existing stereogenic centers, high levels of diastereoselectivity were obtained (products **25** and **26**, 73–90% yield, >20:1 dr).

Table 2. Acceptor Scope with Alkyl Cesium Oxalate 9^a

| Michael Acceptors Employed (product number, yield) | | |
|--|----------------------------------|----------------------------------|
| | | |
| 10 88% yield | 11 86% yield ^b | 12 86% yield |
| | | |
| 13 82% yield | 14 77% yield | 15 68% yield |
| | | |
| 16 77% yield | 17 85% yield | 18 96% yield |
| | | |
| 19 94% yield | 20 85% yield ^b | 21 99% yield |
| | | |
| 22 73% yield ^c | 23 70% yield ^c | 24 89% yield ^d |
| | | |
| 25 73% yield ^{c,d,e} | 26 90% yield ^f | 27 >20:1 dr |

^aIsolated yields using optimized conditions from Table 1 with 1.0 equiv acceptor and 1.1 equiv oxalate (see SI). ^bPerformed with 1.5 equiv of cesium oxalate. ^cPerformed in 100% DME. ^dRun at 22 °C. ^eProduct **25** isolated as *trans*-isomer. ^fProduct **26** isolated as *cis*-isomer.

Table 3. Scope of Cesium Oxalate Salts with Benzyl Acrylate as the Acceptor^a

| Oxalate | Product | Oxalate | Product | Oxalate | Product |
|---------|---------|---------|---------|---------|---------|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

^aIsolated yields using optimized conditions from Table 1 with 1.0 equiv acceptor and 1.1 equiv oxalate (see SI). ^bPerformed with 1.5 equiv of oxalate. ^cUsing 100% DME.

Next, we turned our attention to the investigation of the cesium oxalate scope (Table 3). Owing to the long forming bond (2.2–2.5 Å) in the transition state of carbon radical conjugate addition¹⁴ and the poor solvation of carbon radicals,^{1b} the reaction proved to be quite insensitive to steric hindrance around the site of radical generation, with adjacent isopropyl and *tert*-butyl groups not greatly reducing the efficiency of the reaction (products **29** and **31**, 73–93% yield). Cyclopentanol-derived oxalates also underwent coupling in good yield (products **33** and **39**, 85–92% yield), although very low conversion was observed for 1-methylcyclopropanol- and 1-methylcyclobutanol-derived oxalates. Heterocycles including pyrrolidines, piperidines, tetrahydrofurans, pyridines, and indoles were well tolerated in the reaction (products **35**, **37**, **41**, **59**, and **63**, 54–77% yield). Underscoring the utility of this method for the constructing quaternary stereocenters in complex molecules, natural product-derived oxalates also performed well, with good levels of diastereoselectivity being observed (products **41**, **43**, **45**, **47** and **49**, 67–96% yield). Indeed, high yields were obtained even for the formation of vicinal quaternary stereocenters (product **47**, 85% yield). In addition, a number of acyclic *tert*-alkyl oxalates also undergo the coupling with high levels of efficiency (products **51**–**63**, 67–96% yield).

The reaction was examined with several secondary cesium oxalates, and two representative examples are shown in Table 4. Although still synthetically useful, lower yields of coupled products were obtained with these substrates and the product of trapping of the intermediate alkoxyacyl radical was also isolated

(products **65** and **66**). For more stabilized benzylic radicals, these side products were not observed, although the yields remained moderate (product **68**).

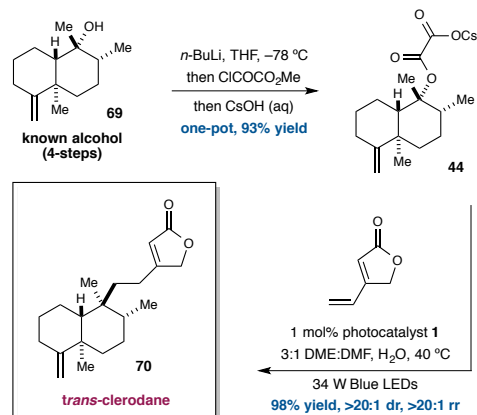
The reaction also enabled a short synthesis of **70**,¹⁵ a member of the *trans*-clerodane family of natural products (Scheme 2).¹⁶ Activation of the tertiary alcohol of known intermediate **69**¹⁷ is particularly challenging, as the *trans*-decalin ring system places the tertiary alcohol in a 1,3-diaxial relationship with the angular methyl substituent. This severe steric interaction had previously

Table 4. Examples of Secondary Oxalate Salts^a

| Oxalate | Product |
|---------|---------|
| | |
| | |
| | |

^aIsolated yields using optimized conditions from Table 1 with 1.0 equiv acceptor and 1.5 equiv oxalate (see SI).

Scheme 2: 6-Step Synthesis of a *trans*-Clerodane Natural Product



prevented the preparation of the *N*-phthalimidoyl oxalate derivative.¹⁷ However, acylation of **69** with methyl chlorooxalate proceeded in excellent yield. In-situ hydrolysis with aqueous cesium hydroxide allowed pure cesium oxalate **44** to be isolated in one step and high yield from alcohol **69** without the use of chromatography. Coupling of oxalate **44** (1.5 equiv) with commercially available 4-vinylfuran-2-one (1.0 equiv) proceeded with perfect diastereo- and regioselectivity in 98% yield to give *trans*-clerodane **70**, a natural product that is a versatile precursor of many other members of the *trans*-clerodane family.¹⁷

In summary, we have developed a new visible light photoredox-catalyzed method for the generation of alkyl radicals from secondary and tertiary alcohols and demonstrated its use in the redox-neutral formation of quaternary carbon centers through alkylation with electron-deficient alkenes. The intermediate alkyl cesium oxalates are bench-stable and easily handled and provide a notably convenient means to activate alcohols for radical generation. We believe this method will find broad application.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(2) In addition to halides, a number of activating groups to allow tertiary alcohols to be used as radical precursors have been reported.

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(8) See SI for further details about CV measurements.

(9) (a) Bortolamei, N.; Isse, A. A.; Gennaro, A. *Electrochim. Acta* **2010**, *55*, 8312. (b) See SI for evidence of an enolate intermediate.

(10) This disproportionation is unique to *tert*-alkyl hydrogen oxalates. Alkyl hydrogen oxalates derived from primary and secondary alcohols are stable and do not readily disproportionate.

(11) The cesium oxalates were most conveniently prepared via hydrolysis of the corresponding *tert*-alkyl methyl oxalates with aqueous CsOH. This route avoids the potentially unstable alkyl hydrogen oxalate moiety, and the *tert*-alkyl methyl oxalate intermediates are stable to silica column chromatography and aqueous work up. The cesium oxalates may also be prepared in a simple one-pot procedure directly from tertiary alcohols; see SI.

(12) Lithium, sodium, potassium, and cesium oxalates all gave similar results (see SI for details); however, cesium oxalates were chosen for development under the assumption that they were likely to have favorable physical properties over a wide range of oxalate substrates.

(13) Rapid reaction of the coupled radical with additional acrylonitrile is likely responsible for the low yield in this case.

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Graphical Abstract

