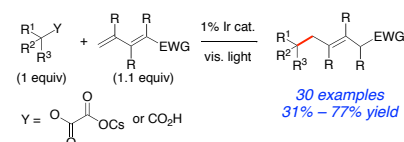


1,6-Addition of Tertiary Carbon Radicals Generated From Alcohols or Carboxylic Acids by Visible-Light Photoredox Catalysis

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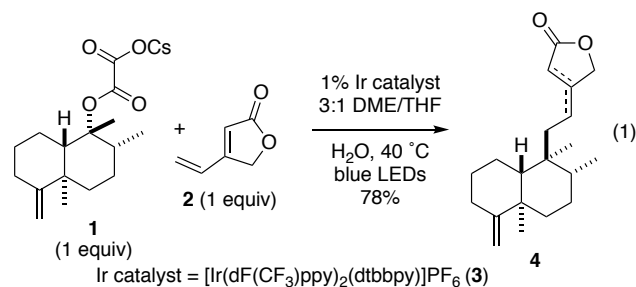


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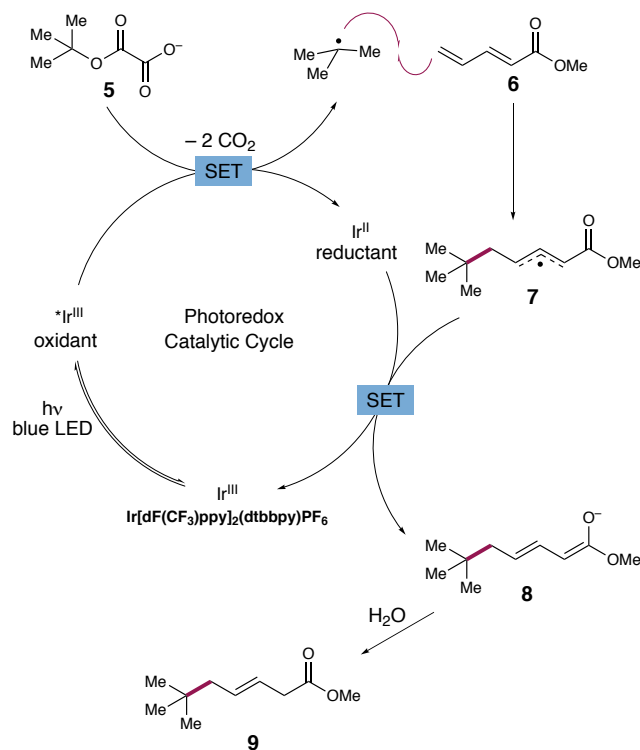
Supporting Information Placeholder

ABSTRACT: The addition of tertiary carbon radicals generated by Ir-catalyzed visible-light photocatalyst to electron-deficient 1,3-dienes proceeds in good yields to append a δ -substituted β,γ -unsaturated carbonyl fragment to a tertiary alcohol or carboxylic acid precursor and construct a new quaternary carbon center.

Classical Michael reactions and organometallic conjugate addition reactions are among the most important C–C bond-forming transformations.¹ Related addition reactions that take place in a 1,6-fashion allow C–C bonds to be formed at the distal end of electron-deficient dienes.² Active methylene compounds were nucleophiles in early examples.^{2a} However since the early 1970s organometallic nucleophiles,³ formed stoichiometrically or in a catalytic fashion, are employed most commonly in 1,6-additions.² Conspicuously absent are 1,6-additions of nucleophilic carbon radicals, undoubtedly reflecting competing oligomerization and polymerization brought about by further reactions of the persistent allylic radical intermediates with the diene.⁴ In recent studies in our laboratories, we found that the *trans*-decalin tertiary radical generated from oxalate precursor **1** in the presence of visible light and Ir(II) photocatalyst **3**⁵ reacted cleanly with 4-vinylfuran-2-one (**2**) to give 1,6-addition products **4** in high yield (eq 1)^{6,7} It was significant that product **4** was formed in good yield using equal amounts of the radical precursor and the 1,3-diene. To our knowledge there is only one previous example of the reaction of a tertiary carbon radical with a 1,3-diene, the Bu_3SnH /AIBN-promoted reaction of adamantyl bromide with methyl sorbate, a reaction described as producing many products with the 1,4- and 1,6-addition products isolated in a combined yield of 41%.^{8,9}



Scheme 1. Proposed Photoredox Reaction of Tertiary Oxalate Anions with Electron-Deficient 1,3-Dienes.

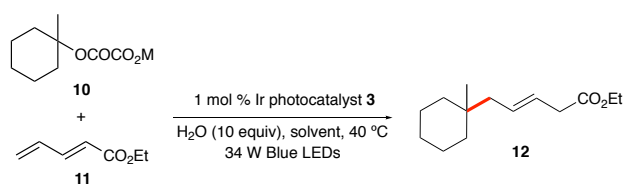


We anticipated that the generation of tertiary carbon radicals from carboxylate or oxalate⁵ salts using the Ir-catalyzed redox-neutral photoredox method first reported by MacMillan¹⁰ might avert the competing oligomerization problems typically encountered in radical additions to 1,3-dienes. This prospect follows from

the expected photoredox catalytic cycle, which is depicted in Scheme 1 for the reaction of *tert*-butyl oxalate salt **5** with pentadienoic ester **6**. In particular, if single-electron transfer from the reduced Ir(II) photocatalyst to the coupled allylic radical intermediate **7** was fast, further addition reactions of this intermediate might be prevented. Ultimate α -protonation of dienolate intermediate **8** might then cleanly deliver the reductively coupled product **9**.¹¹ Our exploration of the scope and limitations of this approach to the 1,6-addition of tertiary carbon radicals to electron-deficient dienes is the subject of this report.

Our investigations began by examining the coupling reaction of the cesium oxalate salt of 1-methylcyclohexanol **10** with ethyl 2,4-pentadienoate (**11**) (Table 1). Using conditions optimized earlier for the reaction of tertiary cesium oxalates with electron deficient alkenes,⁵ coupled product **12** was formed in moderate yield (Table 1, entries 1 and 2). The yield of **12** was improved somewhat by replacing DMF with THF and using 1.5 equiv of the diene (entries 3–5). Reaction concentration was found to be the most important variable, with the yield of **12** increasing to 74–82% in reactions carried out at 0.025–0.03 M (entries 6–9). Moreover, the yield of **12** was depressed only slightly when 1.1 equiv, rather than 1.5 equiv, of the diene was employed (entry 10). The use of pure DME or THF, instead of a 3:1 mixture of these solvents, resulted in lower yields (entries 11 and 12). Yields were similarly high using the lithium oxalate salt (entries 10 and 13).

Table 1. Optimization Studies



entry	M	10:11 (equiv)	solvent	concentration (M)	yield ^a
1	Cs	1:1	3:1 DME/DMF	0.05	40%
2	Cs	1:1.5	3:1 DME/DMF	0.05	36%
3	Cs	1:1	3:1 DME/THF	0.05	42%
4	Cs	1:1.5	3:1 DME/THF	0.05	51%
5	Cs	1.5:1	3:1 DME/THF	0.05	45%
6	Cs	1:1.5	3:1 DME/THF	0.10	30%
7	Cs	1:1.5	3:1 DME/THF	0.03	77%
8	Cs	1:1.5	3:1 DME/THF	0.025	74–82%
9	Cs	1:1.5	3:1 DME/THF	0.010	64%
10	Cs	1:1.1	3:1 DME/THF	0.025	74%
11	Cs	1:1.5	DME	0.025	41%
12	Cs	1:1.1	THF	0.025	57%
13	Li	1:1.1	3:1 DME:THF	0.025	74%

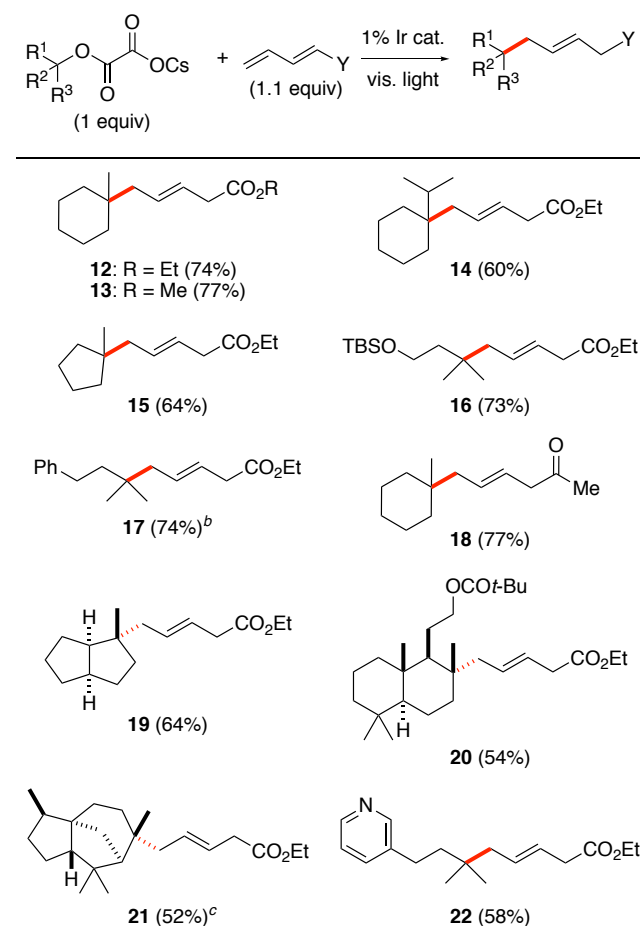
^aYield by ¹H NMR analysis using an internal standard.

The results of our exploration of the scope of the coupling of oxalate-derived tertiary carbon radicals with electron-deficient 1,3-dienes using a 1.0:1.1 ratio of the cesium (or lithium) oxalate salt to the 1,3-diene and a reaction concentration of 0.025 M in 3:1 DME/THF are shown in Schemes 2 and 3. Reactions of ten representative tertiary cesium oxalates with esters of 2,4-pentadienoic acid or hexa-3,5-dien-2-one gave products **12–22** in 52–77% yield (Scheme 2). In each case, the *E* stereoisomer ($J_{\text{vic}} = 15\text{--}16$ Hz) was formed predominately; only trace amounts (2–8%) of the *Z* stereoisomer, which showed signals for its vinylic carbons 1–2 ppm up-

field of those for the major *E* stereoisomer, were observed. Neither products of 1,4-addition, nor 1,6-addition products having the double bond conjugated to the carbonyl group,¹² were formed in significant amounts.

Pentadienoic esters containing methyl substituents at C-2 and/or C-4 also underwent clean 1,6-addition to give products **23–29** in 56–74% yield (Scheme 3). In each case, the *E* stereoisomer was formed predominantly. For products **26–29** containing a tri-substituted double bond, the *E* configuration was confirmed by the upfield shift of the vinylic methyl carbon in the ¹³C NMR spectra (~20 ppm).

Scheme 2. Scope of the Reaction of Tertiary Cesium (or Lithium) Oxalates with Unsubstituted 1,3-Diene Esters or Ketones.^a

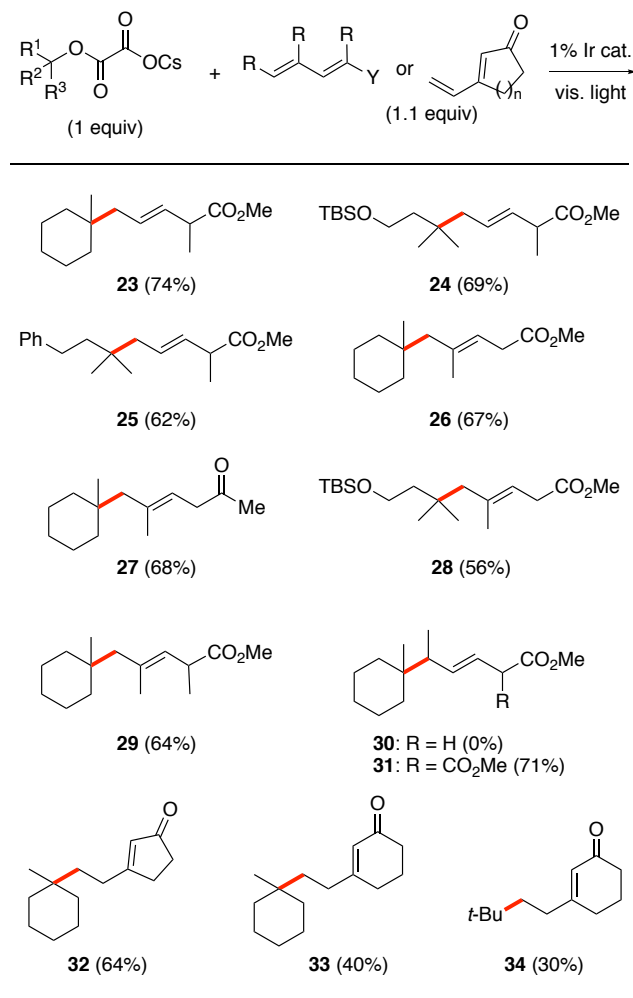


^aReaction conditions: 1 mol % [Ir(dF(CF₃)ppy)₂(dtbpy)]PF₆, H₂O (10 equiv), 3:1 DME/THF (0.025 M), 2 x 34 W Blue LEDs, 60 °C, 18 h. Isolated yield of purified product. ^bReaction was conducted on a 1 mmol scale. ^cThe lithium oxalate salt was employed.

Successful 1,6-addition reactions to dienes containing terminal substituents were observed in two situations. Product **31** was formed in 71% yield from the reaction of the 1-methylcyclohexyl radical with methyl 2-carbomethoxy-2,4-hexadienoate. In contrast, methyl sorbate, which lacks the second activating ester substituent, gave none of the corresponding product **30** under identical conditions. Also useful was the related reaction with 3-vinylcyclopent-2-en-1-one, which gave 3-substituted cyclopent-2-en-1-one **32** in 64% yield. Corresponding reactions with 3-vinylcyclohex-2-en-1-one were less efficient providing

products **33** and **34** in low yield. Differing from related reactions of dienyl methyl ketones, the major or exclusive product isolated in additions to 3-vinylcycloalkenones was the conjugated cycloalkenone.¹³

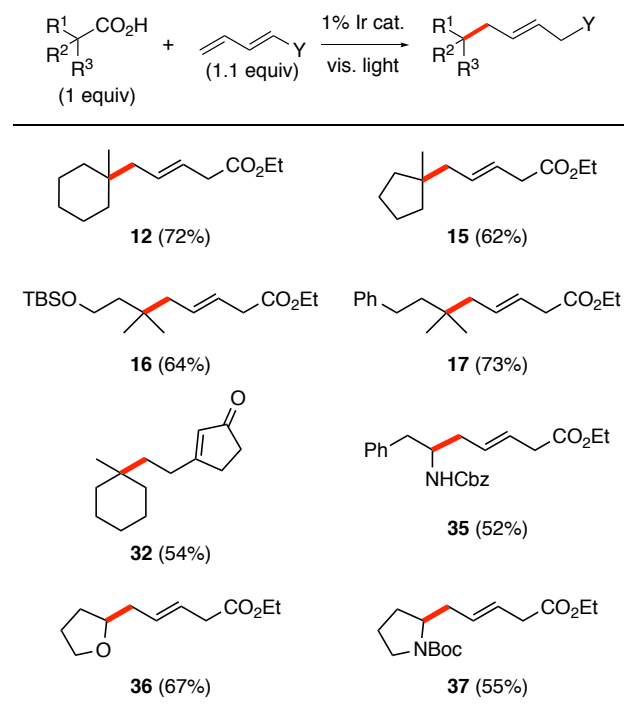
Scheme 3. Scope of the Reaction of Tertiary Cesium Oxalates with Substituted Electron-Deficient 1,3-Dienes.^a



^aReaction conditions: 1 mol % [Ir(dF(CF₃)ppy)₂(dtbpy)]PF₆, H₂O (10 equiv), 3:1 DME/THF (0.025 M), 2 x 34 W Blue LEDs, 60 °C, 18 h. Isolated yield of purified product.

We briefly examined under identical conditions visible-light promoted photoredox reactions in which the carbon radical was generated from a carboxylic acid precursor (Scheme 4).¹⁰ In reactions of tertiary radical intermediates, the yield of coupled products **12**, **15** and **17** was essentially identical to that observed with the corresponding tertiary oxalate precursors, whereas products **16** and **32** were formed in ~10% lower yields from the carboxylic acid precursors. With carboxylic acid precursors, 1,6-additions of secondary carbon radicals with ethyl 2,4-pentadienoate (**11**) proceeded to deliver products **35**–**37** in 52–67% yields.¹⁴

Scheme 4. Scope of the reaction of carboxylic acids with electron-deficient 1,3-dienes.



^aReaction conditions: 1 mol % [Ir(dF(CF₃)ppy)₂(dtbpy)]PF₆, K₂HPO₄ (1.3 equiv), H₂O (10 equiv), 3:1 DME/THF (0.025 M), 2 x 34 W Blue LEDs, 60 °C, 18 h. Isolated yield of purified product.

Conclusion. This study demonstrates that using Ir-catalyzed photocatalysis,^{5,10} the addition of tertiary-carbon radicals to electron-deficient dienes is a useful reaction for constructing new quaternary carbon centers by appending a δ -substituted β,γ -unsaturated carbonyl fragment to a tertiary alcohol or tertiary-carbinyl carboxylic acid precursor. This reaction will be of particular utility in cases where one of these precursors is more readily available than the corresponding halide precursor of a tertiary organometallic intermediate.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data of new compounds, and copies of ¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

1. For example, see: Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH: Weinheim, 2007.
2. Selected reviews: (a) Ralls, J. W. *Chem. Rev.* **1959**, *59*, 329–344. (b) Csáky, A. G.; de la Herráan, G.; Murci, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080–4102. (c) Silva, E. M. P.; Silva, A. M. S. *Synlett* **2012**, *44*, 3109–3128. (d) Chauhan, P.; Kaya, U.; Enders, D. *Adv. Synth. Catal.* **2017**, *359*, 888–912.
3. (a) Naf, F.; Degan, P.; Ohloff, G. *Helv. Chem. Acta* **1972**, *55*, 82–85. (b) Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *J. Am. Chem. Soc.* **1972**, *94*, 4395–4396.
4. Fischer, H. *Chem. Rev.* **2001**, *101*, 3581–3610.
5. Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.
6. (a) Müller, D. S.; Untiedt, N. L.; Dieskau, A. P.; Lackner, G. L. Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 660–663. (b) Slutskyy, Y.; Jamison, C. R.; Lackner, G. L.; Müller, D. S.; Dieskau, A. P.; Untiedt, N. L.; Overman, L. E. *J. Org. Chem.* **2016**, *81*, 7029–2035.
7. The initially produced coupled product contained variable small amounts of the β,γ -unsaturated butenolide regioisomers.⁶
8. Ohno, M.; Ishizaki, K.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 1285–1288.
9. A few higher yielding 1,6-additions of primary and secondary carbon radicals have been reported: (a) Mao, S.; Fang, X.; Ba, L.; Wu, F. *J. Fluorine Chem.* **2007**, *128*, 5–11. (b) Gong, H.; Andrews, R. S.; Zuccarello, J. L.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 879–882. (c) Liu, X.-K.; Zheng, X.; Ruan, Y.-P.; Ma, J.; Huang, P.-Q. *Org. Biomol. Chem.* **2012**, *10*, 1275–1284.
10. Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886–10889.
11. For a conceptually similar approach using SmI₂ to reduce an allylic radical intermediate, see: Takai, K.; Matsukawa, N.; Takahashi, A.; Fugii, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 152–155.
12. Heating product **12** with 1.5 equiv of DBU in refluxing THF for 36 h established an ~1:1 equilibrium mixture of **12** and its (*E*)- α,β -unsaturated isomer, the latter showing a diagnostic signal in the ¹H NMR spectra for the β -vinylic hydrogen at 7.05 ppm.
13. In some experiments, substantial amounts of the non-conjugated product were seen in radical additions to 3-vinylcyclohex-2-en-1-one.
14. The generation of secondary radicals from oxalate precursors and their reaction with dienes was not explored, because competitive trapping of secondary-alkoxyacyl radical intermediates was expected to be problematic.⁵