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Generation of the Methoxycarbonyl Radical by Visible-Light Photoredox Catalysis and Its Conjugate Addition with Electron-Deficient Olefins

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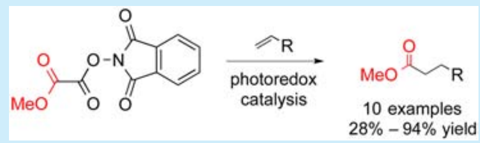
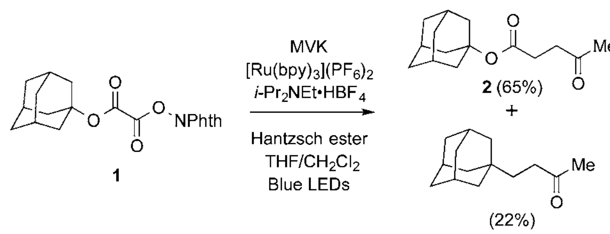
Ⓢ *Supporting Information*

ABSTRACT: Visible-light photoredox-catalyzed fragmentation of methyl *N*-phthalimidoyl oxalate allows the direct construction of a 1,4-dicarbonyl structural motif by a conjugate addition of the methoxycarbonyl radical to reactive Michael acceptors. The regioselectivity of the addition of this alkoxyacyl radical species to electron-deficient olefins is heavily influenced by the electronic nature of the acceptor, behavior similar to that exhibited by nucleophilic alkyl radicals.



The normal reactivity of carbonyl compounds renders 1,3- or 1,5-dicarbonyl functionality much easier to incorporate into organic molecules than 1,4-dicarbonyl functionality.[1] The 1,4-addition of acyl-anion equivalents to α,β-unsaturated carbonyl compounds is a general approach for constructing 1,4-dicarbonyl products. However, several steps are needed to introduce an alkoxycarbonyl group in this way.[1] Transition-metal-catalyzed alkoxycarbonylation is a widely practiced and immensely important method to incorporate carbonyl functionality into alkenes;[2] however, the use of this chemistry to alkoxycarbonylate electron-deficient alkenes has not been widely developed.[3] A potentially attractive approach for preparing γ-ketoesters would be the direct 1,4-addition of an alkoxycarbonyl radical to α,β-unsaturated carbonyl compounds.[4] Although intramolecular additions of alkoxycarbonyl radicals to alkenes are well-known and used productively to construct 5- and 6-membered lactones,[5] there are only a few examples of synthetically useful bimolecular coupling reactions of alkoxycarbonyl radicals with alkenes.[6] In these cases, the alkoxycarbonyl radical is generated by Fe- or Pd-catalyzed oxidation of carbazate precursors.

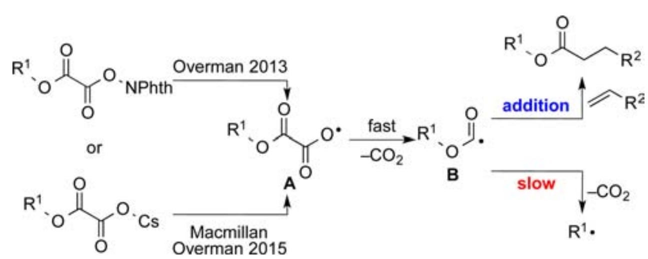
Computational studies suggest that alkoxycarbonyl radicals are less nucleophilic than acyl radicals, leading them to be termed as either ambiphilic or in some contexts electrophilic radicals.[7] These studies raise some concern about whether an alkoxycarbonyl radical would be sufficiently nucleophilic to add efficiently to an electron-deficient C−C π-bond. However, in our recent investigations on the generation of tertiary radicals from tertiary alkyl *N*-phthalimidoyl oxalate precursors, we observed that the intermediate alkoxycarbonyl radical formed from adamantanol precursor **1** reacted efficiently with methyl vinyl ketone to give γ-ketoester **2** (eq 1).[8,9] As a result, we became interested in the possibility of using an oxalate precursor and visible-light photoredox catalysis to conveniently generate alkoxycarbonyl radicals in the context of their conjugate addition to α,β-unsaturated carbonyl compounds and related electron-deficient alkenes. Two potential precursors



(1)

for producing alkoxycarbonyl radicals by visible-light photoredox catalysis would be alkyl *N*-phthalimidoyl oxalates[8] or a salt of an alkyl hemioxalate (Scheme 1).[10,11] For this method to

Scheme 1. Two Potential Precursors of Alkoxycarbonyl Radicals



be successful, β-scission of the alkoxycarbonyl radical **B** to give an alkyl radical must be slower than its reaction with the radical acceptor.[12] The rate of decarboxylation of alkoxycarbonyl radicals is known to reflect the stability of the forming alkyl radical with the rate of decarboxylation of the *tert*-butoxycarbonyl radical estimated to be ∼500 times faster than that of a primary alkoxycarbonyl radical.[13] As the methoxycarbonyl radical would be expected to decarboxylate even more slowly, our studies focused on developing a

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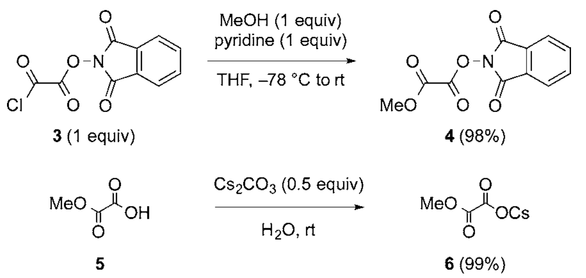
convenient method to generate this carbon radical and surveying its reactivity with alkenes.

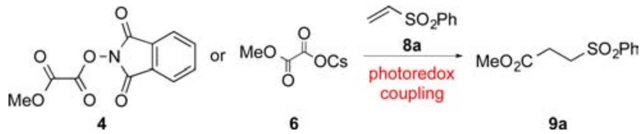
Methyl *N*-phthalimidoyl oxalate (**4**) was obtained by acylation of methanol with *N*-phthalimidoyl chlorooxalate (**3**) using a modification of a procedure developed previously in our laboratory for the preparation of tertiary alkyl *N*-phthalimidoyl oxalates (Scheme 2).[8] The reaction was carried out in the absence of DMAP at 0 °C to prevent formation of dimethyl oxalate. Additionally, the use of pyridine in place of Et_3N led to more reproducible results. Phthalimidoyl oxalate **4** was not stable to silica gel chromatography; however, upon careful trituration it was isolated on a multigram scale as a colorless solid in high yield and acceptable purity. Reagent **4** is stable to light and can be stored in a −20 °C freezer for prolonged periods of time without decomposition. Cesium methyl oxalate **6** was generated from commercially available methyl hemioxalate **5** upon reaction with 0.5 equiv of Cs_2CO_3 in water, followed by concentration to give **6** as a colorless solid.

Scheme 2. Preparation of Methyl *N*-Phthalimidoyl Oxalate (4) and Cesium Methyl Oxalate 6



Using conditions optimized earlier for the coupling of tertiary radicals generated from related precursors with electron-deficient alkenes,[8,10] the reaction of radical precursors **4** and **6** with phenyl vinyl sulfone (**8a**) was examined (Table 1). Coupling of *N*-phthalimidoyl oxalate **4** (1.5 equiv) with phenyl vinyl sulfone in the presence of 1.5 mol % of $[Ru(bpy)_3](PF_6)_2$, 1.5 equiv of diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**7**), and 1 equiv of *i*-$Pr_2NEt·HBF_4$ in 1:1 THF/CH_2Cl_2 with irradiation at room temperature with low-intensity blue LEDs gave product **9a** in 50% yield (Table 1, entry 1). In contrast, the reaction of methyl cesium oxalate **6** (1.5 equiv) with phenyl vinyl sulfone in the presence of 2 mol % of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and 10 equiv of water in 3:1 DME/DMF irradiated with 35 W blue LEDs provided adduct **9a** in only 2% yield (Table 1, entry 2). As low yields were also obtained in further screening of the reaction of oxalate salt **6** with benzyl acrylate,[14] we chose to focus on optimizing the coupling of phthalimidoyl oxalate **4** with acceptor **8a**. The major byproduct of the reaction of entry 1 was identified as the product of addition of the 2-tetrahydrofuryl radical to phenyl vinyl sulfone (~30%). To suppress this unwanted reactivity, a solvent screen was performed that identified CH_2Cl_2 as the optimal solvent (entry 3). The choice of a polar aprotic solvent was important, as reactions run in nonpolar solvents such as benzene led to lower yields, likely because of the low solubility of Hantzsch ester **7** (entry 4). Employing alternative reductive quenchers such as 1,3-dimethyl-2-arylbenzimidazolines,[15] or 2-phenylbenzothiazoline,[16] led to greatly diminished yields of addition product **9a**. The yield of **9a** was improved substantially by increasing the amounts of phthalimidoyl oxalate **4** and Hantzsch ester **7** to 3 equiv (entry 5). Raising the temperature of the reaction proved to be detrimental (entry 6), whereas omission of the ammonium additive resulted in a slight increase in yield (entry 7). Finally, by varying the concentration of the reaction mixture, we were able to reduce the excess of the radical precursor **4** and the Hantzsch ester **7** from 3 to 2 equiv without compromising the isolated yield of **9a** (entry 8). In the absence of visible light, no product was formed (entry 9), whereas reactions carried out in absence of the photocatalyst or for 6 h instead of 18 h led to greatly reduced formation of coupled product **9a** (entries 10 and 11).[17]

Table 1. Initial Studies and Reaction Optimization



entry[a]	radical precursor (equiv)	solvent (M)	temp (°C)	7 (equiv)	yield[b] (%)
1[c]	4 (1.5)	1:1 CH_2Cl_2/THF (0.1)	23	1.5	50
2	6 (1.5)	3:1 DME/DMF (0.1)	40		2
3[c]	4 (1.5)	CH_2Cl_2 (0.1)	23	1.5	55
4[c]	4 (1.5)	benzene (0.1)	23	1.5	38
5[c]	4 (3.0)	CH_2Cl_2 (0.1)	23	3.0	90
6[c]	4 (3.0)	CH_2Cl_2 (0.1)	80	3.0	50
7	4 (3.0)	CH_2Cl_2 (0.1)	23	3.0	94[d]
8	**4 (2.0)**	**CH_2Cl_2 (0.6)**	**23**	**2.0**	**94[d]**
9[e]	4 (2.0)	CH_2Cl_2 (0.6)	23	2.0	0
10[f]	4 (2.0)	CH_2Cl_2 (0.6)	23	2.0	16
11[g]	4 (2.0)	CH_2Cl_2 (0.6)	23	2.0	56

[a]Reaction conditions for radical precursor **4**: 1 equiv of **8a**, 1.5 mol % of $[Ru(bpy)_3](PF_6)_2$, low-intensity blue LEDs, 18 h. Reaction conditions for radical precursor **6**: 1 equiv of **8a**, 2 mol % of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, 35 W blue LEDs, 18 h. [b]Yield determined by ^1H NMR analysis of the crude reaction mixture using 1,4-dimethoxybenzene as an internal standard. [c]Reaction was performed in the presence of *i*-$Pr_2NEt·HBF_4$ (1 equiv) as an additive. [d]Isolated yield after silica gel chromatography. [e]Reaction performed in the absence of visible light. [f]Reaction performed in the absence of photocatalyst. [g]Reaction was stopped after 6 h.

With optimal reaction conditions identified, the scope of the conjugate addition of the methoxycarbonyl radical to a range of alkene coupling partners was investigated (Table 2). Acceptors containing a terminal double bond and activated by sulfone, ketone, ester, amide, nitrile, or phosphonate functional groups performed best in the reaction, furnishing the corresponding products in moderate to high yields (entries 1−6). However, introduction of either an α methyl or α phenyl substituent to methyl vinyl ketone resulted in no detectable formation of the coupled product, as did incorporation of such substituents into benzyl acrylate.[18] Cyclopent-2-en-1-one was a poor coupling partner, yielding the desired product in 27% yield, whereas 5-oxocyclopent-1-ene-1-carbonitrile underwent conjugate hydride reduction by the Hantzsch ester **7**.[19] However, acyclic enones containing a second electron-withdrawing substituent at the β-carbon, such as dimethyl fumarate or *trans*-3-cyanoacrylate, did react in high yield (entries 7 and 8). The outcome of the latter reaction is noteworthy, as acceptor **8h** possessing two electron-withdrawing groups of different steric and electronic properties underwent exclusive addition α to methyl ester substituent. This sense of regioselectivity, which was attributed by Giese to larger LUMO coefficient at C-2,[4a] has been observed

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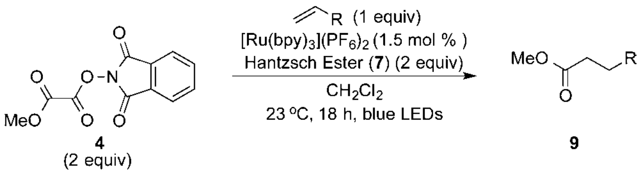
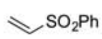
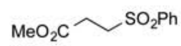
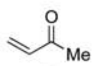
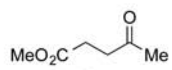
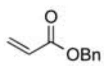
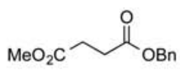
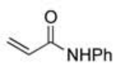
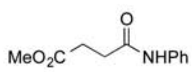
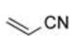
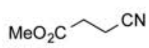
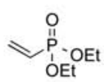
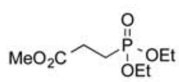
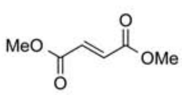
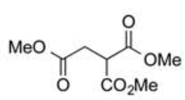
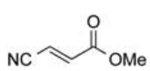
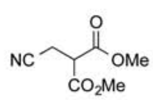
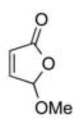
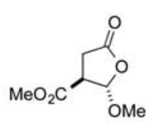
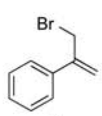
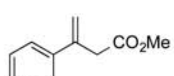
Table 2. Acceptor Scope with *N*-Phthalimidoyl Oxalate 4



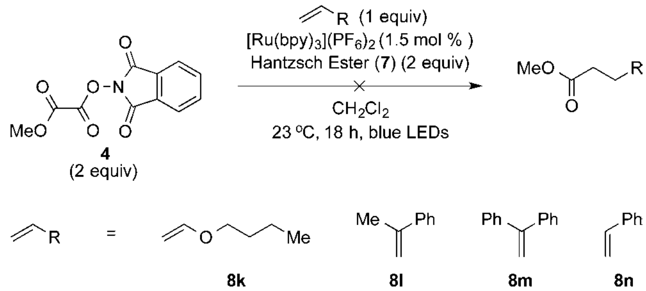
entry[a]	acceptor	product	yield (%)
1	 8a	 9a	94
2	 8b	 9b	74
3	 8c	 9c	89
4	 8d	 9d	60
5	 8e	 9e	74
6	 8f	 9f	66
7	 8g	 9g	80
8	 8h	 9h	91
9	 8i	 9i	28
10	 8j	 9j	47

[a]Reaction performed using the optimized conditions (see the Supporting Information). All yields are yields of pure products isolated after silica gel chromatography.

previously; however, in the previous cases the magnitude of regioselection was much lower: 5–6:1.[20] 4-Methoxybutenolide (**8i**), which was shown previously to react in good yield with a nucleophilic tertiary carbon radical,[8,10] coupled in low yield with the methoxycarbonyl radical (entry 9). Coupling of the methoxycarbonyl radical with 2-phenylallyl bromide (**8j**) gave allylic substitution product **9j** in 47% yield. To our surprise, methyl 2-(bromomethyl)acrylate was unreactive.[18]

As alkoxycarbonyl radicals had been suggested to be ambiphilic or electrophilic, we examined the reactivity of the methoxycarbonyl radical generated from *N*-phthalimidoyl oxalate **4** with electron-rich alkenes and styrenes (Scheme 3).[18] For example, performing the reaction in the presence of a

Scheme 3. Coupling of *N*-Phthalimidoyl Oxalate with Electron-Rich Alkenes and Styrenes



prototypical electron-rich alkene, butyl vinyl ether (**8k**), led to no detectable coupled product. Reactions carried out in the presence of styrene derivatives **8l–n** led to broad peaks in the ^{1}H NMR spectra of crude reaction mixtures, indicating likely polymerization of the intermediate stabilized benzylic radicals formed upon addition of the methoxycarbonyl radical.

In summary, methyl *N*-phthalimidoyl oxalate (**4**) was shown to be a convenient precursor of the methoxycarbonyl radical under visible-light photoredox conditions. It reacts in good yield with terminal alkenes harboring a variety of electron-withdrawing substituents, thus providing a convenient method for the direct construction of γ-ketoesters and related products. It also reacts in high yield with 1,2-disubstituted alkenes activated by two electron-withdrawing substituents and in one relevant case with regioselectivity higher than that of alkyl radicals. We attribute the somewhat limited scope of reactivity of the methoxycarbonyl radical to it being less nucleophilic than alkyl carbon radicals. No indication that the methoxycarbonyl radical shows ambiphilic reactivity was observed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00895.

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

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Notes

The authors declare no competing financial interest.

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(1F31GM113494). NMR and mass spectra were obtained at UC Irvine using instrumentation acquired with the assistance of NSF and NIH Shared Instrumentation grants.

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