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Fragment Coupling and the Construction of Quaternary Carbons Using Tertiary Radicals Generated From *tert*-Alkyl *N*-Phthalimidoyl Oxalates By Visible-Light Photocatalysis

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ABSTRACT

The coupling of tertiary carbon radicals with alkene acceptors is an underdeveloped strategy for uniting complex carbon fragments and forming new quaternary carbons. The scope and limitations of a new approach for generating nucleophilic tertiary radicals from tertiary alcohols and utilizing these intermediates in fragment coupling reactions is described. In this method, the tertiary alcohol is first acylated to give the *tert*-alkyl *N*-phthalimidoyl oxalate, which in the presence of visible-light, catalytic $Ru(bpy)_3(PF_6)_2$, and a reductant fragments to form the corresponding tertiary carbon radical. In addition to reductive coupling with alkenes, substitution reactions of tertiary radicals with allylic and vinylic halides is described. A mechanism for the generation of tertiary carbon radicals from *tert*-alkyl *N*-phthalimidoyl oxalates is proposed that is based on earlier pioneering investigations of Okada and Barton. Deuterium labeling and competition experiments reveal that the reductive radical coupling of *tert*-alkyl *N*-phthalimidoyl oxalates with electron-deficient alkenes is terminated by hydrogen-atom transfer.

INTRODUCTION

The bimolecular coupling of tertiary nucleophiles with carbon-based electrophiles is a straightforward, yet underdeveloped, approach for fragment coupling with concomitant formation of sterically encumbered quaternary carbons. Recent total synthesis endeavors in our laboratories have suggested the potentially broad utility of both trialkyl-tertiary cuprates and nucleophilic carbon radicals in such constructions.[1,2,3] Tertiary carbon radicals are often generated from halide precursors. However, the synthesis of structurally elaborate tertiary halides can be complicated by competing elimination and rearrangement reactions. As a result, methods to generate tertiary carbon radicals from other common functional groups have particular significance. Barton's methods for forming carbon radicals by homolytic fragmentation of carboxylic acid-derived thiohydroxamate esters[4] or alcohol-derived thiohydroxamate oxalates,[5] introduced more than 25 years ago, are pioneering examples.[6,7]

In an early application of visible-light photocatalysis in organic synthesis, Okada reported in 1991 the utility of carboxylic acid-derived (*N*-acyloxy)phthalimides for generating nucleophilic carbon radicals and their use in radical conjugate addition reactions to construct carbon-carbon bonds.[8,9] These precursors are particularly attractive as they are readily prepared, highly stable, and often crystalline. This method for generating structurally complex tertiary radicals was a central feature of our total syntheses of the diterpenoid (–)-aplyviolene[1a,b] and several *trans*-clerodane diterpenoids.[1c] To extend this approach to other readily available precursors, we recently described the utility of *N*-phthalimidoyl oxalate derivatives of tertiary alcohols for generating tertiary radicals using visible-light photocatalysis.[3b]

Since our recent studies of photoredox-catalyzed generation of tertiary radicals and their use in fragment coupling reactions,[1b,c,3b] several other research programs contributed important new methods for accessing tertiary carbon radical intermediates. Baran described the reaction of

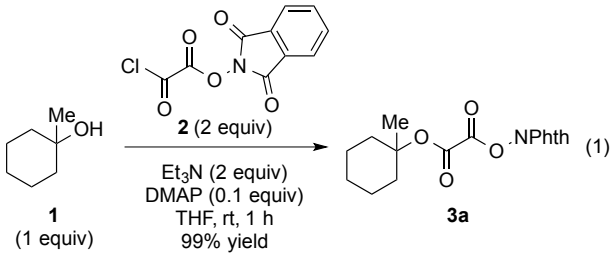
substituted alkenes with $Fe(acac)_3/PhSiH_3$ to generate secondary and tertiary radicals and their use in both intramolecular and bimolecular C–C bond-formation.[3c] In addition, recent reports by the MacMillan group detail the generation of radical intermediates by single-electron oxidation and decarboxylation of carboxylates.[3d] Although heteroatom-stabilized secondary radicals are most easily formed under these conditions, the adamantyl radical was also produced in this way.

Even though several approaches for producing tertiary carbon radicals from common precursors are now available, the prevalence and accessibility of tertiary alcohols warrants comprehensive investigation of the utility of *tert*-alkyl *N*-phthalimidoyl oxalates as precursors of these intermediates. Presented herein is a detailed exploration of the preparation and visible-light photocatalytic coupling of *tert*-alkyl *N*-phthalimidoyl oxalates with alkenes.[10,11] In addition, studies revealing how small modifications in reaction conditions and resulting changes in termination steps can affect the outcome of coupling reactions of these radical precursors are also disclosed. A comparison of *tert*-alkyl *N*-phthalimidoyl oxalates to (*N*-acyloxy)phthalimide derivatives of tertiary carboxylic acids for initiating coupling reactions of tertiary radicals is provided in the accompanying paper.[12]

RESULTS AND DISCUSSION

Synthesis of *tert*-alkyl *N*-phthalimidoyl oxalates. A general strategy for synthesizing *tert*-alkyl *N*-phthalimidoyl oxalates from tertiary alcohols consists of the direct acylation of the tertiary alcohol with *N*-phthalimidoyl chlorooxalate **2**, as exemplified in the formation of *N*-phthalimidoyl oxalate **3a** from 1-methylcyclohexanol (**1**) (eq 1). After careful optimization, the following procedure was developed. Chlorooxalate **2** was initially prepared as a colorless solid

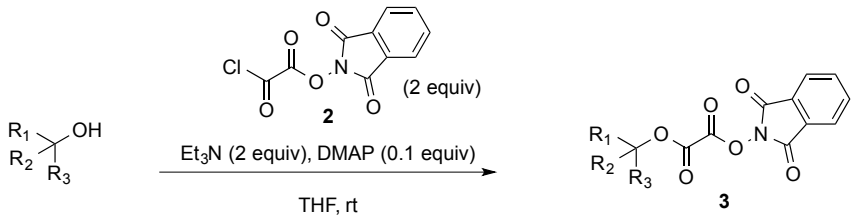
by adding an excess of oxalyl chloride (5 equiv) to a THF solution of *N*-hydroxyphthalimide at –78 °C, allowing the reaction to warm to room temperature (typically overnight), and then concentrating the reaction mixture under reduced pressure. This reactive acylating agent was then most easily manipulated as a 0.06 M solution in THF. The subsequent acylation of tertiary alcohols took place efficiently in THF in the presence of 2 equiv each of chlorooxalate **2** and triethylamine and a catalytic amount of DMAP.

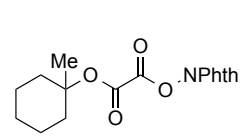


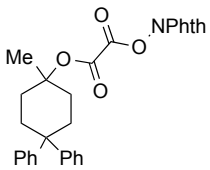
The sensitivity of tertiary *N*-phthalimidoyl oxalates towards protic nucleophiles complicates their isolation and purification. For example, oxalate **3a** could not be purified by chromatography on silica gel. Washing a dilute Et_2O solution of crude **3a** with saturated aqueous $NaHCO_3$ did remove unreacted *N*-hydroxyphthalimide from the product mixture. However, resubjection of pure phthalimidoyl oxalate **3a** to this extraction procedure resulted in substantial cleavage to release *N*-hydroxyphthalimide, suggesting that even this mild workup was problematic. *tert*-Alkyl *N*-phthalimidoyl oxalates were best isolated by diluting a concentrated CH_2Cl_2 solution of the crude acylation reaction products with hexanes (typically a 25-fold excess by volume) and filtering the resulting suspension. After concentration of the filtrate, the mixed oxalate diesters **3** were obtained in good purity (typically >95%) and high yield. As illustrated in Table 1, this method proved quite general, converting even highly hindered tertiary alcohols to the corresponding mixed oxalates efficiently (e.g., formation of **3g** and **3h**). Solid *tert*-alkyl *N*-

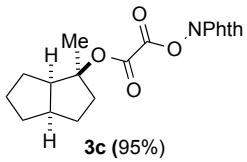
phthalimidoyl oxalates prepared in this way could be stored indefinitely at –20 °C, whereas those that are oils could be stored at this temperature for only one week before decomposition was apparent.

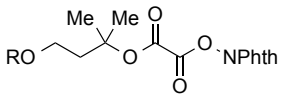
Table 1. Synthesis of *tert*-Alkyl *N*-Phthalimidoyl Oxalates (NPhth = *N*-Phthalimidoyl)

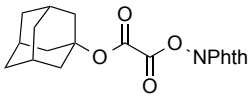


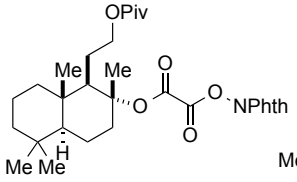

3a (95%)

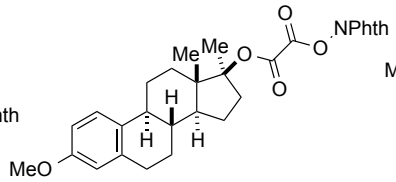

3b (95%)

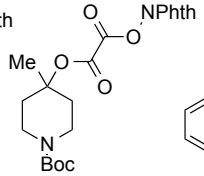

3c (95%)

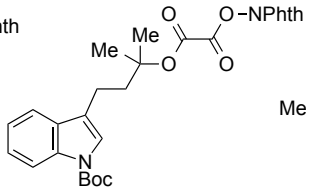

3d R = TBS (99%)
3e R = PMB (99%)

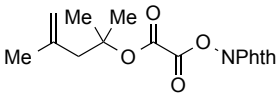

3f (97%)


3g (99%)


3h (91%)


3i (80%)

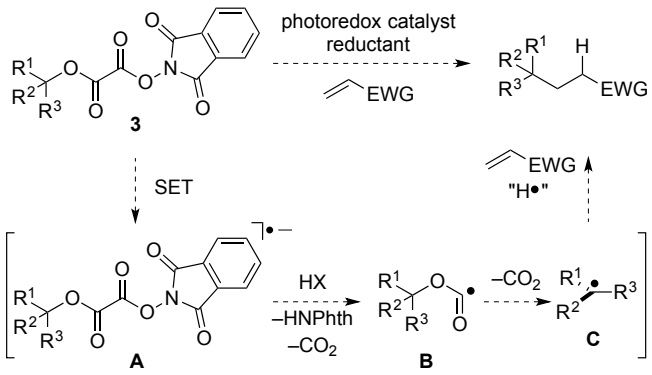

3j (65%)


3k (90%)

The structure of the adamantyl *N*-phthalimidoyl oxalate (**3f**) was confirmed by single-crystal X-ray analysis.[3b] The reduction potential of *N*-phthalimidoyl oxalate **3a** measured by CV in acetonitrile is –1.14 V vs SCE, and, as expected, is slightly less negative than that of the (*N*-acyloxy)phthalimide derivative of 1-methylcyclohexanecarboxylic acid (–1.26 V vs SCE) under identical conditions (see Supporting Information).[13]

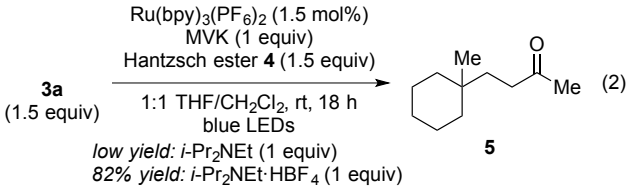
Coupling of *tert*-alkyl *N*-phthalimidoyl oxalates with conjugate acceptors. We anticipated that *tert*-alkyl *N*-phthalimidoyl oxalates would react in the presence of a photocatalyst and a stoichiometric reductant via single-electron transfer to the tetracarbonyl substrate, followed by homolytic cleavage of the N–O σ-bond with ejection of phthalimide and two equivalents of CO_2 to generate the radical intermediate (Scheme 1).[5,8] Addition of the nucleophilic tertiary radical to an electron-deficient olefin and hydrogen-atom transfer to the resulting radical intermediate would yield the product.

Scheme 1. Proposed Mechanism for the Coupling *N*-Phthalimidoyl Oxalates 3 with Conjugate Acceptors



In our earlier investigations of the use of carboxylic acid-derived (*N*-acyloxy)phthalimides in fragment coupling reactions,[1b] we found that aprotic conditions similar to those reported by Gagné for the generation and reaction of radicals derived from glucosyl halides—visible light, $Ru(bpy)_3(BF_4)_2$, diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**4**), *i*-Pr_2NEt, in CH_2Cl_2[14]—were preferable to the aqueous conditions originally described by Okada.[8,12] The reaction of *tert*-alkyl *N*-phthalimidoyl oxalate **3a** with methyl vinyl ketone (MVK) under related conditions in CH_2Cl_2 employing 1–2 mol% of the commercially available bis(hexafluorophosphate) salt of $Ru(bpy)_3^{2+}$ indeed did provide the coupled product **5**, albeit in low yield (eq 2). The low yield was easily traced to competitive

decomposition of the *N*-phthalimidoyl oxalate under these conditions, as control experiments established that the red conjugate base of *N*-hydroxyphthalimide was rapidly formed when



oxalate **3a** was exposed at room temperature to amines such as *i*-Pr_2NEt, Bu_3N, or Cy_2NMe in CH_2Cl_2. As a result of these observations, further experimentation was carried out using *i*-PrNEt•HBF_4 instead of *i*-Pr_2NEt. Additional improvement was realized by replacing CH_2Cl_2 with a 1:1 mixture of CH_2Cl_2/THF. This solvent change was necessitated because oxalate **3a** slowly decomposed in CH_2Cl_2 overnight, presumably by ionization to form the 1-methylcyclohexyl cation. In addition to commercially available blue LEDs, a commercially available compact fluorescent light was found to be equally effective as the light source.[15]

We then performed a series of reactions to evaluate the necessity of each reaction component (Table 2). Although we initially carried out the coupling reactions for 18 h, because the oxalate substrates were not amenable to TLC analysis, the yield of **5** was nearly identical when the reaction was run for only 2 h (entries 1 and 2). Visible light proved to be essential for reactivity, as no conversion of oxalate **3a** was observed when the reaction was conducted in the dark (entry 3). Omission of Hantzsch ester **4** also resulted in complete recovery of **3a** (entry 4). In contrast, we observed significant product formation in the absence of the photocatalyst (entries 5 and 6). This background reaction was slower than the photocatalyzed reaction, producing product **5** in only 28% yield after 2 h, although the yield was improved to 67% after 18 h. This background reaction, which we believe is mediated by Hantzsch ester **4**,[16] was also observed by Okada and co-workers when the photocatalyst was not present.[8] Omitting the ammonium additive resulted in a somewhat depressed yield of **5** (entry 7). Finally, revisiting the

stoichiometry of the coupling substrates (entries 8–10) confirmed that the highest yield of **5** was obtained when oxalate **3a** was used in a slight (50%) excess.

Table 2. Coupling of *N*-Phthalimidoyl Oxalate 3a with Methyl Vinyl Ketone (MVK) Under Various Reaction Conditions[a]

Entry	Modification	Yield of **5** (%)[b]
1	none	82
2	reaction time of 2 h	81
3	no light	<5%
4	no Hantzsch ester **4**	ND
5	no photocatalyst (2 h)	28
6	no photocatalyst (18 h)	67
7	no *i*-$Pr_2NEt•HBF_4$	72
8	oxalate **3a** (1 equiv)	67
9	oxalate **3a** (1.1 equiv)	68
10	oxalate **3a** (1 equiv) MVK (1.5 equiv)	57

[a]Conditions of eq 2 using *i*-$Pr_2NEt•HBF_4$; [**3a**] = 0.15 M. [b]Isolated yield after silica gel chromatography. ND = not detected.

Several other photoredox catalysts were examined to promote the formation of adduct **5** from *N*-phthalimidoyl oxalate **3a** and MVK (Table 3). Although no catalyst performed as well as $Ru(bpy)_3^{2+}$ (entry 1), several strongly reducing iridium photoredox catalysts were nearly as effective (entries 2–4).[17] Even $Ru(bpz)_3^{2+}$ ($E_{1/2}^{II/I}$ –0.80 V vs SCE),[18] a significantly weaker reductant than $Ru(bpy)_3^{2+}$ ($E_{1/2}^{II/I}$ –1.33 V vs SCE), gave a 62% yield (by NMR analysis) of ketone **5** (entry 5).

Table 3. Coupling of *N*-Phthalimidoyl Oxalate 3a with MVK in the Presence of Various Photocatalysts and Visible Light[a]

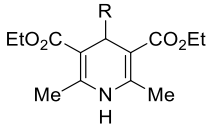
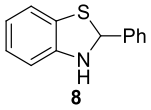
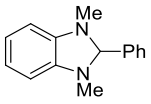
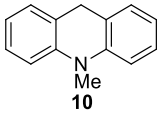
Entry	Photocatalyst	Yield of **5** (%)[b]
1	$Ru(bpy)_3(BF_4)_2$	82

2	$Ir(ppy)_3$	75
3	$Ir(df(CF_3)ppy)_2(dtbbpy)PF_6$	74
4	$Ir(dtbbpy)ppy_2PF_6$	76
5	$Ru(bpz)_3(PF_6)_2$	62

[a]Conditions of eq 2 using *i*-Pr_2NEt•HBF_4 and a reaction time of 2 h; [**3a**] = 0.15 M. [b]Yield measured by ^1H NMR relative to an internal standard (1,4-dimethoxybenzene).

We also explored replacing Hantzsch ester **4** with other potential stoichiometric reductants (Table 4). Introduction of a substituent at the 4-position of the Hantzsch ester rendered the dihydropyridine unreactive under the reaction conditions (entries 2 and 3). The use of 2-phenylbenzothiazoline (**8**) or *N*,*N'*-dimethyl-2-phenylbenzimidazoline (**9**) successfully resulted in the formation of product **5**, although the yield was somewhat less than that observed under identical conditions using Hantzsch ester **4** (entries 4 and 5).[19] No conversion to adduct **5** was observed using *N*-methylacridane (**10**), a known reductive quencher of $Ru(bpy)_3^{2+*}$ (entry 6).[20]

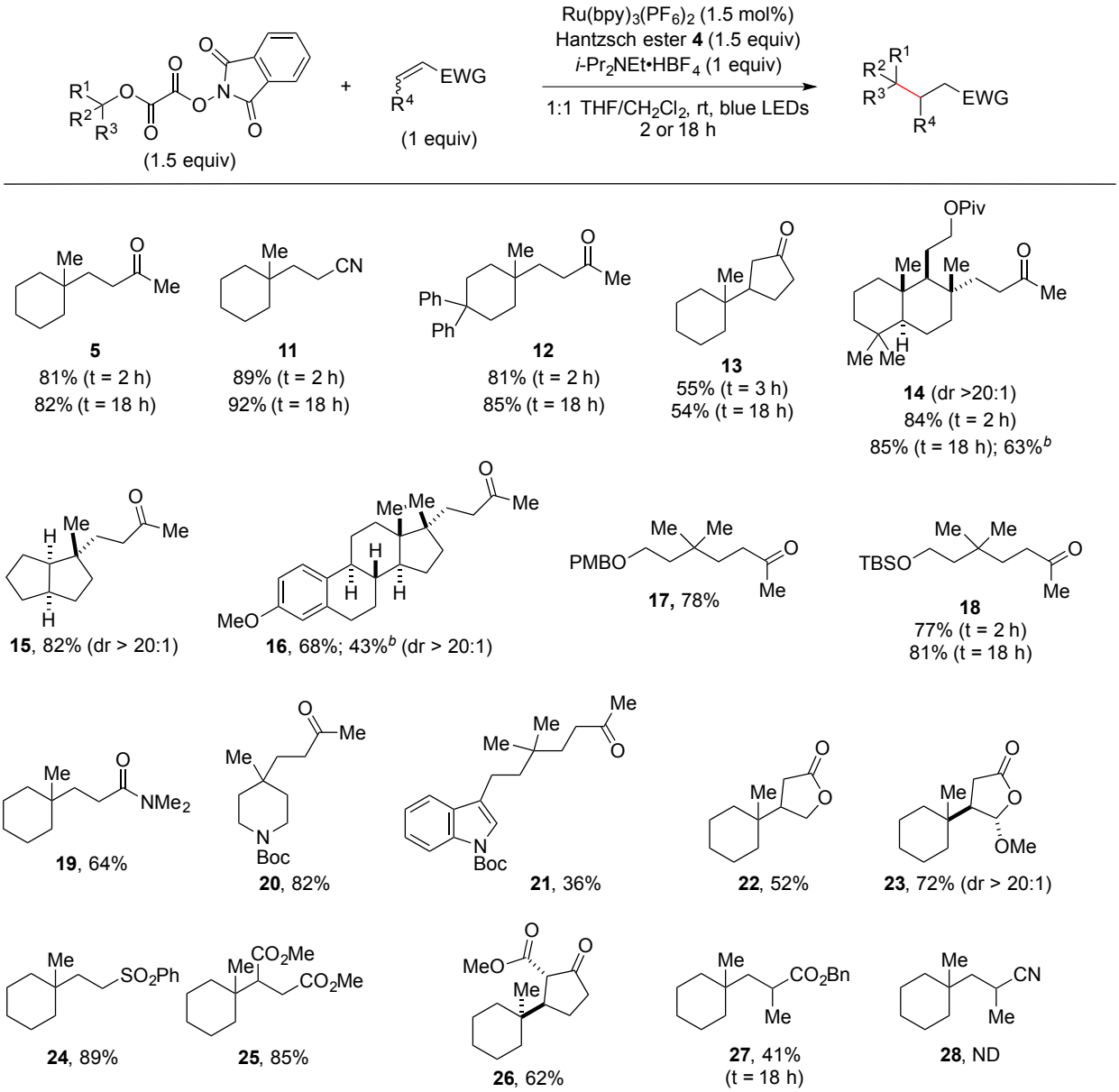
Table 4. Visible-Light Photocatalytic Coupling of *N*-Phthalimidoyl Oxalate 3a with MVK in the Presence of Potential Stoichiometric Reductants[a]

Entry	Reductant		Yield of **5** (%)
1		**4** R = H	82[b]
2		**6** R = Me	ND
3		**7** R = Ph	ND
4	 **8**		60[c]
5	 **9**		73[c]
6	 **10**		ND

[a]Conditions of eq 2 using *i*-Pr_2NEt•HBF_4; [**3a**] = 0.15 M. [b]Isolated yield after silica gel chromatography. [c]Yield measured by ^1H NMR relative to an internal standard (1,4-dimethoxybenzene); ND = not detected.

The results of our initial survey of the coupling of *tert*-alkyl *N*-phthalimidoyl oxalates with various electron-deficient alkenes are summarized in Table 5. A wide variety of *N*-phthalimidoyl oxalate substrates and conjugate acceptors are tolerated in the transformation, which generally gives good yields of the coupled products. The highest yields were realized in the coupling reactions with alkenes such as MVK, acrylonitrile and phenyl vinyl sulfone, which are unsubstituted at the β-carbon. The three chiral *N*-phthalimidoyl oxalates that we examined coupled with MVK from the less-sterically hindered face of the tertiary radical to give products **14**, **15** and **16** with >20:1 diastereoselection, with coupled products **14** and **15** being formed in >80% yield. The yield was somewhat lower in the construction of a quaternary center at C17 in the estrone series (**16**, 68%), likely reflecting the steric demand in forming vicinal quaternary carbon centers. Many of these transformations require only 2–3 h, as shown by the entries in the first row of Table 5. As expected from our exploratory studies, yields were somewhat lower when equal amounts of the *N*-phthalimidoyl oxalate and alkene were employed: 63% vs 85% in forming **14** and 43% vs 68% in forming **16**. In a number of the coupling reactions summarized in Table 5, we observed that the yield was nearly the same when *i*-$Pr_2NEt{\bullet}HBF_4$ was omitted. Nonetheless, we have found that product yields were more reproducible when this additive was present.

Table 5. Optimized Visible-Light Photocatalytic Coupling of *N*-Phthalimidoyl Oxalates with Various Electron-Deficient Alkenes[a]

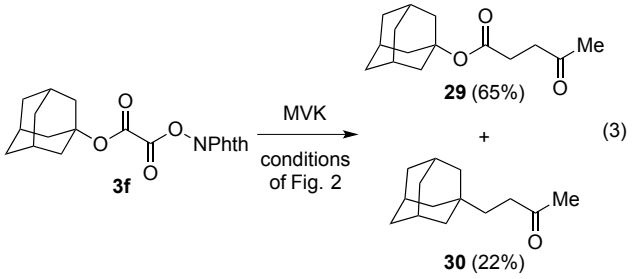


[a]Isolated yield based upon the radical acceptor after purification by silica gel chromatography (average of two experiments). The yield of **27** was measured by ^{1}H NMR relative to an internal standard (1,4-dimethoxybenzene). [b]Isolated yield using 1 equiv each of the phthalimidoyl oxalate and the alkene acceptor. ND = not detected.

Several radical acceptors having a substituent at the β-carbon also provided coupled products in useful yields. Dimethyl fumarate gave adduct **25** in 85% yield from *N*-phthalimidoyl oxalate **3a** and cyclopenten-2-one coupled with **3a** to give product **13** in 55% yield. The yield of adduct **26** resulting from the coupling of **3a** with 2-carbomethoxycyclopenten-2-one (62%) was

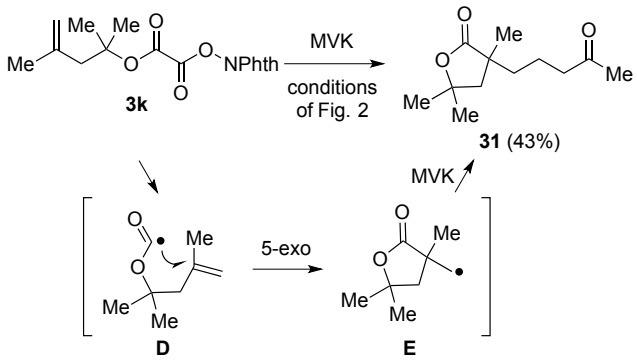
only slightly higher than that observed with cyclopenten-2-one.[21] Butenolides were also competent acceptors, with the presence of a γ-methoxy substituent enhancing the yield of the coupled product (72% for **23** and 52% for **22**) and completely regulating face-stereoselectivity. Unfortunately, radical additions to acceptors possessing electron-donating alkyl groups at the α-position were much less successful under these conditions. Benzyl methacrylate coupled with **3a** to provide product **27** in only 41% yield, whereas no product was detected in the coupling of **3a** with methacrylonitrile.[22]

It is well known that alkoxycarbonyl radicals decarboxylate many powers of ten more slowly than carboxy radicals,[23,24] with the activation barrier decreasing with the stability of the carbon radical produced.[25] In two cases, the alkoxycarbonyl radical (intermediate **B** of Scheme 1) was trapped by the radical acceptor more rapidly than it underwent decarboxylation to generate the tertiary radical intermediate. Adamantyl *N*-phthalimidoyl oxalate (**3f**) when coupled with MVK gave γ-ketoester **29** and product **30** of trapping the adamantyl radical in a 3:1 ratio (eq 3). Trapping of the adamantyl oxycarbonyl radical by MVK to give **29** as the major product is a reflection of the higher energy of the non-planar tertiary adamantyl radical than the tertiary radicals generated in the reactions reported in Table 5. In the second example illustrated in Scheme 2, it is the high rate of 5-exo radical cyclizations (**D** → **E**) that results in capture of the intermediate alkoxycarbonyl radical to yield lactone **31** from phthalimidoyl oxalate **3k**.[26]



(3)

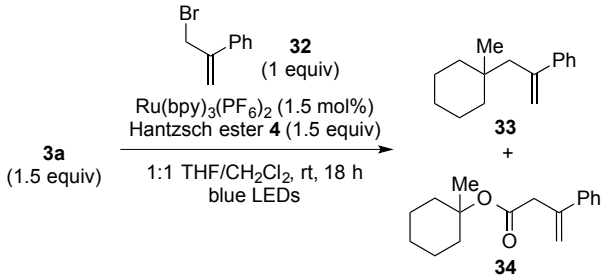
Scheme 2. Trapping of an Alkoxycarbonyl Radical by a 5-Exo Cyclization



Further investigations of the reaction scope. To expand the scope of C–C bond-formation using nucleophilic tertiary carbon radicals generated by visible-light photocatalysis, we examined the coupling of tertiary *N*-phthalimidoyl oxalates with several allylic and vinylic halide substrates to engage tertiary radical intermediates in addition-fragmentation reactions.[27] The coupling of oxalate **3a** with α-(bromomethyl)styrene (**32**) was examined in detail (Table 6). Using the reaction conditions that we had optimized for the reductive coupling reactions, substitution product **33** was obtained in 60% yield (entry 1). To our surprise, minor product **34**, arising from allylation of the intermediate alkoxycarbonyl radical, was isolated in 16% yield. Formation of this product must be the result of an unusually fast rate of addition of the alkoxycarbonyl radical to α-(bromomethyl)styrene (**32**). Attempted reactions in the absence of light (entry 2) or the Hantzsch ester (entry 3) gave no product formation or only traces of the coupled product. The photocatalyst also appears to be essential to achieve useful yields (entry 4). Stopping the reaction after 2 h led to incomplete conversion and lower yields (entries 5 and 6). It is also advantageous to use an excess of the oxalate (1.5 equiv), since reactions in which an excess of acceptor was present gave lower overall yields (entries 7–9). Finally, the additive *i*-

$Pr_2NEt•HBF_4$ has no influence on the outcome of the reaction of **3a** with α-(bromomethyl)styrene (**32**) (entry 10).

Table 6. Optimization and Control Experiments for the Reaction of *N*-phthalimidoyl Oxalate 3a with α-(Bromomethyl)styrene (32).



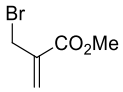
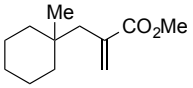
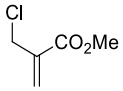
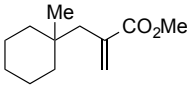
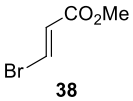
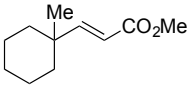
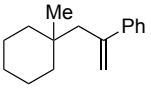
Entry	Modification	Yield of **33** (%)[a]	Yield of **34** (%)[a]
1	none	60	16
2	no light	ND[b]	ND[b]
3	no Hantzsch ester **4**	traces	ND
4	no photocatalyst (18 h)	37	7
5	no photocatalyst (2 h)	24	3
6	reaction time of 2 h	47	9
7	oxalate (1 equiv)	48	8
8	oxalate (1.1 equiv)	50	9
9	oxalate (1 equiv) acceptor (1.5 equiv)	49	16
10	*i*-$Pr_2NEt•HBF_4$ (1 equiv)	59	16

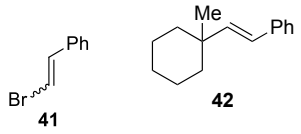
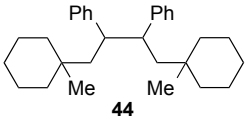
[a]Isolated yield after silica gel chromatography. [b]These products were formed when the light was turned on after 18 h. ND = not detected.

With optimized reaction conditions in hand, the coupling of *tert*-alkyl *N*-phthalimidoyl oxalate **3a** with three additional allylic halides and two vinylic halides was surveyed (Table 7). Methyl 2-(bromomethyl)acrylate (**35**) coupled with **3a** in 69% yield (entry 1). However, the reaction with the chlorine analog **37** provided no coupled product (entry 2). In lower yield,

methyl 3-bromoacrylate (**38**) gave methyl (*E*)-3-(1-methylcyclohexyl)acrylate (**39**) with high *E* stereoselectivity (entry 3). α-(Chloromethyl)styrene (**40**) and β-bromostyrene (**41**) also reacted successfully with *N*-phthalimidoyl oxalate **3a**, albeit in yields of only 47% and 19%, respectively (entries 4 and 5). The efficiency of vinylic substitution reactions was enhanced by the use of 5 equiv of the radical acceptor (entries 3 and 5). Allylic substitution products **36** and **33** are potentially good radical acceptors themselves, nonetheless products resulting from a second addition of the tertiary radical were not observed. We attribute this selectivity to the steric shielding provided by the quaternary carbon fragment in these products. Furthermore, products resulting from the addition of the intermediate alkoxycarbonyl radical to the acceptor were not detected with any substrate other than α-(bromomethyl)styrene (**32**).

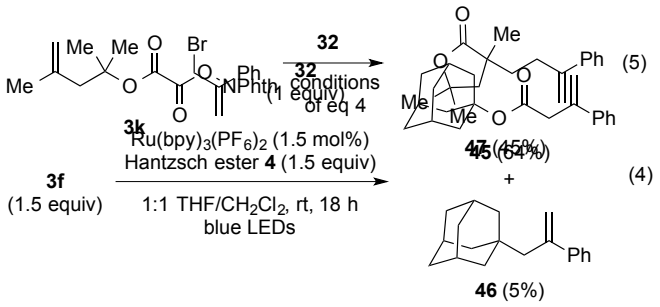
Table 7. Visible-Light Photocatalytic Allylic and Vinylic Substitution Reactions of *N*-phthalimidoyl Oxalate 3a[a]

Entry	Acceptor	Product	Yield (%)[b]
1	 **35**	 **36**	69
2	 **37**	 **36**	ND
3	 **38**	 **39**	35[c] (*E*/*Z* > 20:1)
4	 **40**	 **33**	47

5	 **41**	**42**	19[c] (*E*/*Z* > 20:1)
6	 **43**	 **44**	42 (dr 1:1)

[a]Reaction conditions of Table 6, entry 1. [b]Isolated yield after silica gel chromatography (average of two experiments). [c]5 equiv of the acceptor and 1 equiv of the oxalate were used. ND = not detected.

The reaction of *N*-phthalimidoyl oxalate **3a** with styrene (**43**) was also investigated (entry 6). In this case, only product **44**, resulting from recombination of two benzylic radical intermediates, was formed in 42% as a 1:1 mixture of stereoisomers.[28] Efforts to capture the benzylic radical in different fashions by modifying the reaction conditions or by adding common hydrogen atom transfer reagents such as Bu_3SnH, Et_3SiH, Ph_3SiH, and PhSH were unsuccessful.[29] As expected, couplings of adamantyl *N*-phthalimidoyl oxalate (**3f**) and homoallylic *N*-phthalimidoyl oxalate **3k** with α-(bromomethyl)styrene (**32**) resulted in the first

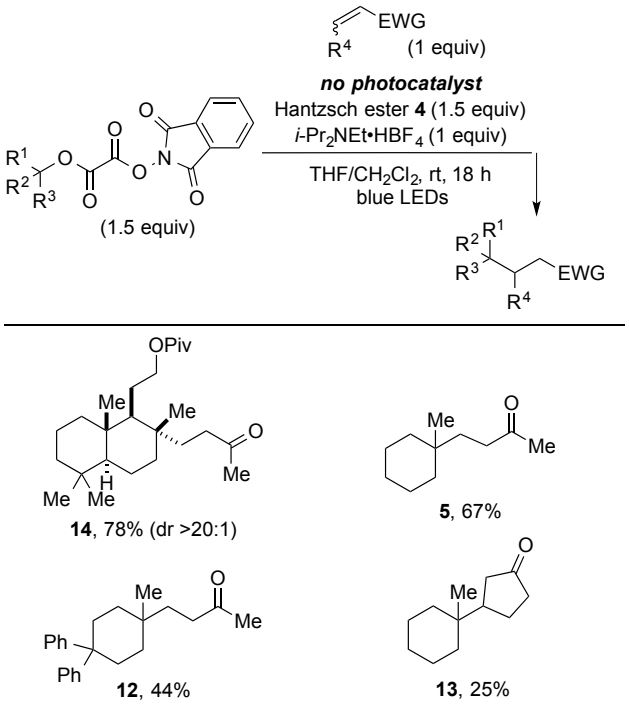


case in predominant formation of ester **45** (eq 4) and in the latter of γ-butyrolactone **47** (eq 5).

Radical coupling in the absence of $Ru(bpy)_3^{2+}$. To pursue whether the reductive coupling reaction in the absence of the photocatalyst could be a suitable method, we repeated four of the reductive radical coupling reactions reported earlier with omission of the

photocatalyst. In all cases the yield of the coupled product was lower than that obtained using the photocatalyst (compare results in Tables 2 and 8). Useful yields of products after 18 h were obtained in the coupling of two oxalates with MVK: formation of product **14** in 78% yield and **5** in 67% yield. In general, the conversion to coupled products was sluggish and yields were inconsistent in the absence of the photocatalyst.

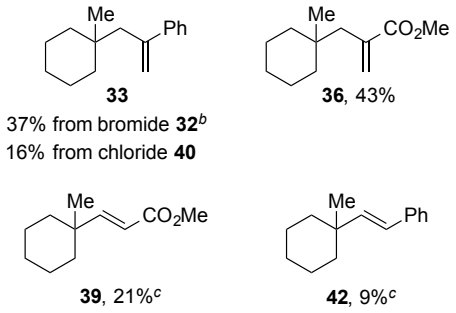
Table 8. Coupling of *N*-Phthalimidoyl Oxalates with Conjugate Acceptors in the Presence of Visible Light and Absence of a Photocatalyst



To further investigate the influence of the photocatalyst, addition-fragmentation reactions were also carried out in the absence of $Ru(bpy)_3(PF_6)_2$ (Table 9). Using five different acceptors,

allylic substitution products were formed in yields approximately half of that (47–62%) realized in the presence of the photocatalyst.[30]

Table 9. Products and Yields Obtained in Reactions of *N*-phthalimidoyl Oxalate 3a With Allylic and Vinylic Halides in the Presence of Visible Light and Absence of a Photocatalyst[a]



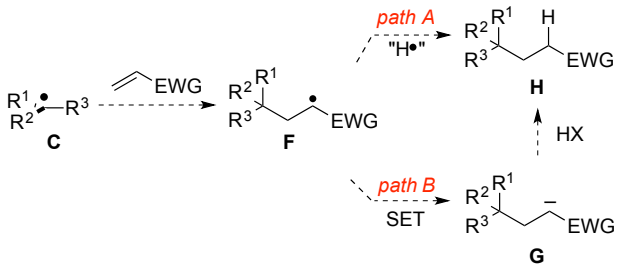
[a]Reaction conditions of Table 8, but no *i*-$Pr_2NEt•HBF_4$; isolated yield after silica gel chromatography. [b]Ester **34** is formed in 7% yield. [c]5 equiv of the acceptor and 1 equiv of the oxalate were used.

Similar radical coupling reactions of (*N*-acyloxy)phthalimides carried out in the absence of a photocatalyst and a discussion of possible mechanisms of such reactions of tertiary radicals generated from both *N*-phthalimidoyl oxalate and (*N*-acyloxy)phthalimide precursors is provided in the accompanying article.[12]

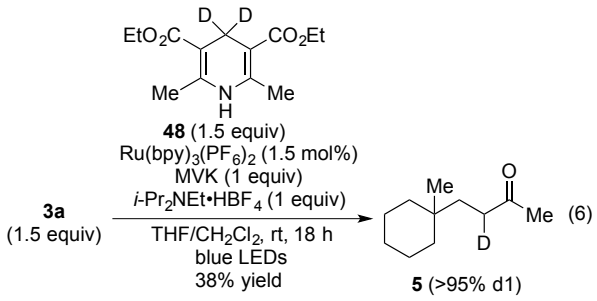
Mechanistic investigations and discussion. The results of our exploratory studies and substantial precedent are consistent with the generation of tertiary carbon radicals from the visible-light photoredox catalyzed fragmentation of both tertiary *N*-phthalimidoyl oxalates and (*N*-acyloxy)phthalimide derivatives of tertiary carboxylic acids. With the oxalate precursors, the slower rate of the second decarboxylation step (**B** → **C**, Scheme 1) can lead to the alkoxycarbonyl radical being intercepted by competing fast intramolecular or bimolecular reactions. In the reductive coupling reactions discussed herein, the radical intermediate **F** produced upon addition of a tertiary radical to an alkene could in principle be terminated by

hydrogen-atom transfer (path A, Scheme 3) or by a two-step process involving single-electron reduction to give the resonance-stabilized anion **G** followed by protonation to give product **H** (path B).

Scheme 3. Two Potential Termination Pathways

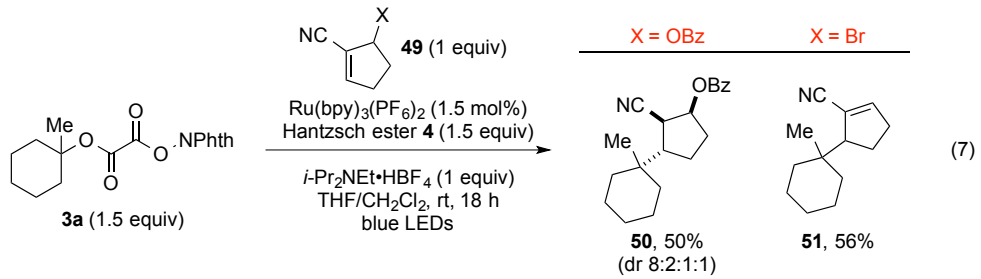


The role of the Hantzsch dihydropyridine **4** in the termination mechanism is readily examined by using its 4,4-dideuterio derivative **48**.[31] The coupling of *N*-phthalimidoyl oxalate **3a** with MVK under our standard conditions using Hantzsch dihydropyridine **48** gave coupled product **5** with nearly quantitative incorporation of deuterium at carbon 2 of the ketone side chain (eq 6).[32] This result is consistent with hydrogen atom-transfer being the predominant termination step in reductive coupling of tertiary *N*-phthalimidoyl oxalates.[33]



To further explore whether hydrogen-atom transfer or single-electron reduction is involved in the termination steps of radical coupling reactions of *N*-phthalimidoyl oxalate precursors, we examined coupling reactions of *N*-phthalimidoyl oxalate **3a** with an α,β-unsaturated nitrile

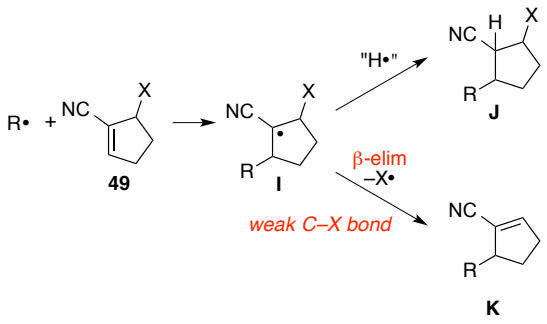
containing a leaving group at the allylic α' position (eq 7). The reaction of **3a** with allylic benzoate **49a** (X = OBz) under our optimized reaction conditions provided addition products **50** in 50% yield, with the depicted isomer being formed predominantly. No trace of the allylic



(7)

substitution product **51** was seen. In contrast, the coupling of **3a** under identical conditions with allylic bromide **49b** (X = Br) gave exclusively allylic substitution product **51** in 56% yield. Both results are fully consistent with the absence of single-electron reduction of the radical intermediate **I**, which undergoes β-scission only when the leaving group is bromide (Scheme 4).

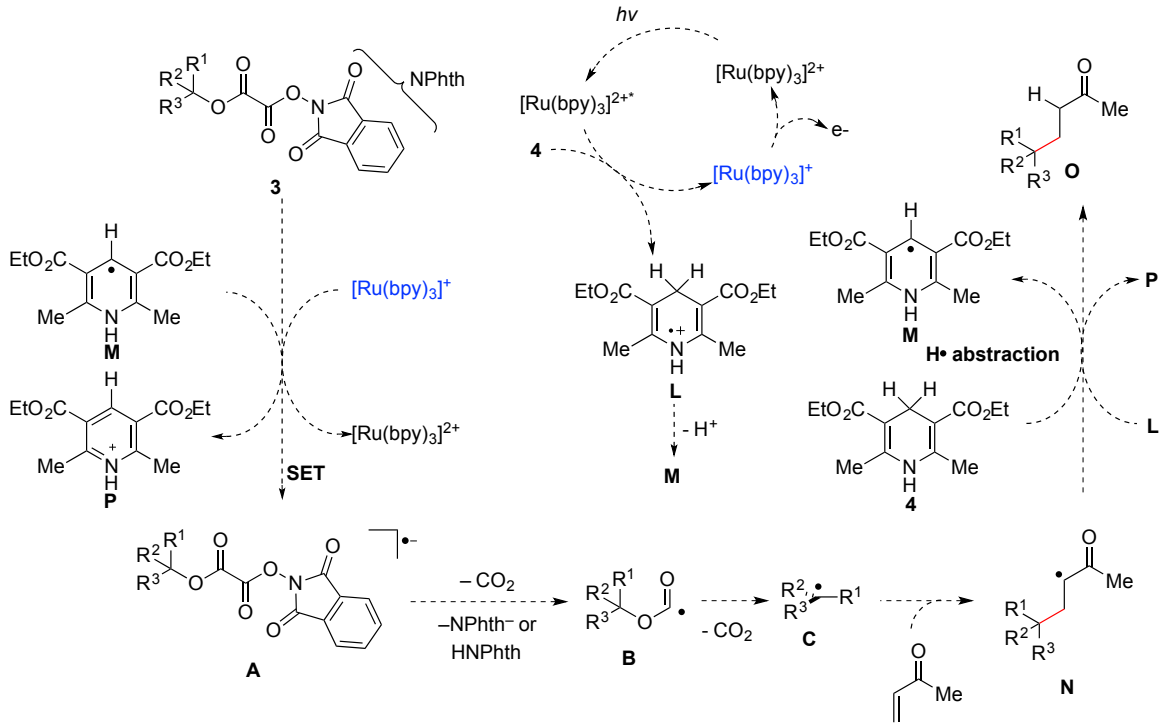
Scheme 4. Potential Homolytic Termination Pathways of the Carbon Radical Intermediate Generated Upon Coupling in the Absence of Single-Electron Transfer



The overall mechanism that we suggest for the reductive coupling reactions of tertiary *N*-phthalimidoyl oxalates is summarized in Scheme 5. Visible-light excitation of $Ru(bpy)_3^{2+}$

provides access to the excited state $Ru(bpy)_3^{2+}$*. This complex is quenched by Hantzsch ester **4**, which produces radical cation **L** and the strongly reducing $Ru(bpy)_3^{+}$. Single-electron transfer from $Ru(bpy)_3^{+}$ to the substrate oxalate then occurs to form radical anion **A** and regenerate the ground-state photocatalyst. Alternatively, electron transfer to the oxalate substrate could be accomplished by the strongly reducing dihydropyridine radical **M**, formed by deprotonation of **L** at C4.[34] Homolytic fragmentation of **A** next occurs to release phthalimide anion, CO_2, and alkoxycarbonyl radical intermediate **B**; alternatively, fragmentation of the N–O bond occurs subsequent to proton donation to the phthalimide fragment by pyridinium acid **P**.[35] A second slower decarboxylation then ensues, forming tertiary carbon radical intermediate **C**. Addition of this radical to an acceptor provides stabilized radical **N**, which abstracts a hydrogen atom from Hantzsch ester **4**.[36] This event forms the product **O** and regenerates intermediate **M,** which is capable of propagating the reaction as a radical chain carrier. In the absence of a photoredox catalyst, we propose that a radical chain mechanism mediated by Hantzsch ester **4** is operative. This sequence is discussed in more detail in the accompanying article.[12]

Scheme 5. Proposed Mechanism for Reductive Coupling of *N*-Phthalimidoyl Oxalates with MVK in the Presence of the $Ru(bpy)_3^{2+}$



CONCLUSION

A new method for directly transforming a tertiary alcohol to a quaternary carbon was developed. In this method, the tertiary alcohol is first acylated to give a *tert*-alkyl *N*-phthalimidoyl oxalate derivative, which in the presence of visible light, 1.5 mol% $Ru(bpy)_3(PF_6)_2$, and Hantzsch dihydropyridine **4** fragments at room temperature to form the corresponding tertiary carbon radical. Nucleophilic tertiary radicals generated in this way add to electrophilic alkenes to give reduced products in good to moderate yield, and react with allylic and vinylic bromides to provide allylation and vinylation products in moderate yield. With chiral precursors, stereoselection in forming a new quaternary stereocenter can be high (>20:1). This method offers advantages over the original Barton method for forming tertiary radicals from tertiary alcohols,[5] as a result of the higher stability of the intermediate mixed oxalate diester in the present method.[37]

A mechanism for the generating tertiary carbon radical from *tert*-alkyl *N*-phthalimidoyl oxalates is proposed that is based on the earlier pioneering investigations of Okada[8] and Barton (Scheme 5).[5] The high incorporation of deuterium in a coupled product when using 4,4-dideuterio Hantzsch ester **48** (eq 6), and the observation that allylic substitution products are formed from allylic bromide but not allylic ester reactants (eq 7), are consistent with the reductive radical coupling of *tert*-alkyl *N*-phthalimidoyl oxalates with electron-deficient alkenes being terminated by hydrogen-atom transfer. The importance of the reaction conditions in determining the fate of the coupled radical intermediate is discussed in detail in the accompanying article.[12] In the absence of the photocatalyst, a slower background reaction has been identified that appears to be mediated by Hantzsch ester **4**. This sequence is also considered in more detail in the accompanying article.[12]

EXPERIMENTAL SECTION

Materials and Methods. Unless stated otherwise, reactions were conducted in oven-dried glassware under an atmosphere of nitrogen or argon using anhydrous solvents (either freshly distilled or passed through activated alumina columns). For all radical coupling reactions, THF and CH_2Cl_2 were sparged with argon for 5 min prior to use. All commercially obtained reagents were used as received. $Ru(bpy)_3(PF_6)_2$ and other photocatalysts were obtained from Sigma Aldrich. Methyl vinyl ketone (MVK), acrylonitrile, benzyl methacrylate and methacrylonitrile were distilled from neat solutions prior to use. All reaction components Hantzsch ester **4**,[38] 4,4-d_2-Hantzsch ester **48**,[27a] 4-Me Hantzsch ester **6**,[39] 4-Ph Hantzsch ester **7**,[39] 2-Ph-benzothiazoline **8**,[40] *N*,*N'*-dimethyl-2-phenylbenzimidazoline **9**,[19b] *N*-methylacridane **10**,[41], *i*-$Pr_2NEt{\bullet}HBF_4$,[14] methyl 2-(bromomethyl)acrylate (**35**),[42] methyl 2-(chloromethyl)acrylate (**37**),[43] (*E*)-methyl 3-bromoacrylate (**38**),[44] α-(chloromethyl)styrene (**40**),[45] α-(bromomethyl)styrene (**32**)[45] were

prepared according to literature procedures. Usually one representative coupling reaction and yield of the product is described in detail; isolated yields reported in the Results section are the average yields obtained from duplicate experiments. Reaction temperatures were controlled using a temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or by anisaldehyde, ceric ammonium molybdate, iodine, and potassium permanganate staining. EMD silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded at 500 or 600 MHz and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded at 125 or 150 MHz, and chemical shifts reported in ppm. IR spectra were recorded on a FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Blue LEDs (30 cm, 1 watt) were purchased from http://www.creativelightings.com (product code CL-FRS5050-12WP-12V) and powered by 8 AA batteries.

4-(1-Methylcyclohexyl)butan-2-one (5). (Table 2, entry 1 and general procedure for optimization experiments, photocatalyst screen (Table 3) and reductant screen (Table 4)). A 1-dram vial was charged with oxalate **3a** (100 mg, 0.30 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (3 mg, 3.0 μmol, 0.015 equiv), Hantzsch ester **4** (76 mg, 0.30 mmol, 1.5 equiv), *i*-$Pr_2NEt{\bullet}HBF_4$ (44 mg, 0.20 mmol, 1 equiv) and a magnetic stir bar under argon. After sequential addition of CH_2Cl_2, (1 mL, sparged with Ar for 5 min), THF (1 mL, sparged with Ar for 5 min), and methyl vinyl ketone (17 μL, 0.20 mmol, 1 equiv), the vial was capped and placed in the center of a 30 cm loop of blue LEDs. The reaction mixture was stirred for 18 h, after which time it was

concentrated under reduced pressure. For all experiments reported in Table 2, the crude residue was purified by silica gel chromatography (3% EtOAc/hexanes) to yield ketone **5** as a colorless oil. For all experiments reported in Tables 3 and 4, the yield of product obtained was determined by comparison of diagnostic ^{1}H NMR signals in the crude reaction mixture to those of an internal standard (1,4-dimethoxybenzene). Characterization data for **5** matched those previously reported.[3b]

(±)-Benzyl 2-methyl-3-(1-methylcyclohexyl)propanoate (27). Following the general procedure for optimization experiments, oxalate **3a** (100 mg, 0.30 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (3 mg, 3.0 μmol, 0.015 equiv), Hantzsch ester **4** (76 mg, 0.30 mmol, 1.5 equiv), *i*-$Pr_2NEt{\bullet}HBF_4$ (44 mg, 0.20 mmol, 1 equiv) and benzyl methacrylate (34 μL, 0.20 mmol, 1 equiv) in a mixture of CH_2Cl_2, (1 mL, sparged with Ar for 5 min) and THF (1 mL, sparged with Ar for 5 min) gave a crude product mixture. The yield of **27** obtained (41%) was determined by comparison of diagnostic ^{1}H NMR signals to those of an internal standard (1,4-dimethoxybenzene). An analytically pure sample was obtained by silica gel chromatography (2.5% EtOAc/hexanes) to provide **27** as a colorless oil. R_f 0.57 (10% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.30 (m, 5H), 5.12–5.07 (m, 2H), 2.61–2.55 (m, 1H), 1.90 (dd, *J* = 14.2, 9.0, 1H), 1.44–1.31 (m, 5H), 1.28–1.15 (m, 9H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0, 136.3, 128.6, 128.4, 128.2, 66.3, 38.1, 37.7, 35.4, 33.3, 26.5, 22.11, 22.10, 20.7; IR (thin film): 2925, 2850, 1736, 1455, 1145 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{18}H_{26}O_2Na$ 297.1830, found 297.1835.

(3-(1-Methylcyclohexyl)prop-1-en-2-yl)benzene (33) and 1-methylcyclohexyl 3-phenylbut-3-enoate (34). (Table 6, entry 1, and general procedure for allylic and vinylic substitution). A 1-dram vial was charged with oxalate **3a** (50 mg, 0.15 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (1 mg,

1.5 μmol, 0.015 equiv), Hantzsch ester **4** (38 mg, 0.15 mmol, 1.5 equiv), and a magnetic stir bar under argon. After sequential addition of CH_2Cl_2, (0.5 mL, sparged with Ar for 5 min), THF (0.5 mL, sparged with Ar for 5 min) and α-(bromomethyl)styrene (**32**, 15 μL, 0.10 mmol, 1 equiv), the vial was capped and placed in the center of a 30 cm loop of blue LEDs. The reaction mixture was stirred for 18 h, after which it was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0-5% diethyl ether/pentane) to provide **33** (13 mg, 0.062 mmol, 62%) and **34** (3.4 mg, 0.013 mmol, 13%) as colorless oils.

Data for **33**: R_f 0.74 (100% pentane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 7.5, 2H), 7.30 (t, J = 7.4, 2H), 7.25-7.22 (m, 1H), 5.23 (d, J = 1.7, 1H), 5.03 (bs, 1H), 2.49 (s, 2H), 1.45-1.32 (m, 5H), 1.27-1.12 (m, 5H), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 144.3, 128.2, 127.0, 126.7, 116.7, 38.4, 34.3, 26.5, 22.3; IR (thin film): 3079, 2924, 2855, 1622, 1491, 1445 cm^{-1}; HRMS-CI (*m/z*) $[M + H]^+$ calculated for $C_{16}H_{22}H$ 215.1800, found, 215.1798.

Data for **34**: R_f 0.29 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 7.8, 2H), 7.32 (t, J = 7.7, 2H), 7.29–7.26 (m, 1H), 5.52 (s, 1H), 5.23 (s, 1H), 3.47 (s, 2H), 2.07–2.02 (m, 2H), 1.46–1.40 (m, 1H), 1.38–1.33 (m, 4H), 1.31–1.22 (m, 5H), 1.20-1.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 141.7, 140.1, 128.4, 127.8, 126.1, 116.0, 82.5, 43.0, 36.6, 25.4, 21.9; IR (thin film): 2932, 2860, 1726, 1447, 1243, 1146 cm^{-1}; HRMS-CI (*m/z*) $[M + NH_4]^+$ calculated for $C_{17}H_{22}O_2NH_4$ 276.1964, found 276.1956.

Methyl 2-((1-methylcyclohexyl)methyl)acrylate (36). In an identical fashion, oxalate **3a** (50 mg, 0.15 mmol, 1.5 equiv) was coupled with methyl 2-(bromomethyl)acrylate (**35**, 12 μL, 0.10 mmol, 1 equiv) to give a crude residue, which was purified by silica gel chromatography (3% diethyl ether/pentane) to provide **36** (14 mg, 0.069 mmol, 70%) as a colorless oil. R_f 0.78

(10% diethyl ether/pentane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.16 (d, *J* = 1.3, 1H), 5.44 (bs, 1H), 3.73 (s, 3H), 2.30 (s, 2H), 1.50-1.38 (m, 5H), 1.26-1.21 (m, 5H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 138.4, 127.4, 52.0, 37.5, 34.0, 26.5, 22.2; IR (thin film): 2926, 2850, 2359, 2342, 1726, 1457, 1445, 1201, 1154 cm^{-1}; HRMS-CI (*m/z*) $[M + NH_4]^+$ calculated for $C_{12}H_{20}NO_2NH_4$ 214.1807, found, 214.1813.

Methyl (*E*)-3-(1-methylcyclohexyl)acrylate (39). In an identical fashion, oxalate **3a** (50 mg, 0.15 mmol, 1.5 equiv) was coupled with (*E*)-methyl 3-bromoacrylate (**38**, 72 μL, 0.75 mmol, 5 equiv) to give a crude residue, which was purified by silica gel chromatography (3% diethyl ether/pentane) to provide **39** (11 mg, 0.058 mmol, 39%) as a colorless oil. R_f 0.51 (10% diethyl ether/pentane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (d, *J* = 16.2, 1H), 5.77 (d, *J* = 16.1, 1H), 3.73 (s, 3H), 1.55-1.31 (m, 10H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 159.1, 117.7, 51.6, 37.2, 26.2, 22.4; IR (thin film): 2929, 2853, 1727, 1650, 1435, 1310, 1274, 1171 cm^{-1}; HRMS-CI (*m/z*) $[M + NH_4]^+$ calculated for $C_{11}H_{18}O_2NH_4$ 200.1651, found 200.1648.

Preparation of 33 from α-(chloromethyl)styrene) (40). In an identical fashion, oxalate **3a** (50 mg, 0.15 mmol, 1.5 equiv) was coupled with α-(chloromethyl)styrene (**40**, 14 μL, 0.10 mmol, 1 equiv) to give **33** (10 mg, 0.048 mmol, 48%).

(*E*)-(2-(1-Methylcyclohexyl)vinyl)benzene (42). In an identical fashion, oxalate **3a** (50 mg, 0.15 mmol, 1.5 equiv) was coupled with β-bromostyrene (**41**, 97 μL, 0.75 mmol, 5 equiv) to give a crude residue, which was purified by silica gel chromatography (100% pentane) to provide **42** (6 mg, 0.029 mmol, 19%) as a colorless oil. R_f 0.78 (100% pentane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.1, 2H), 7.32-7.28 (m, 2H), 7.21-7.17 (m, 1H), 6.32 (d, *J* = 16.5, 1H), 6.22 (d, *J* = 16.3, 1H), 1.62-1.58 (m, 1H), 1.55-1.49 (m, 5H), 1.44-1.35 (m, 4H), 1.07 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 128.6, 126.8, 126.1, 38.1, 26.5, 22.6; IR (thin film): 2926, 2855, 1491, 1447, 1260 cm^{-1}; HRMS-CI (*m/z*) $[M]^+$ calculated for $C_{15}H_{20}$ 200.1565, found, 200.1558.

(±)-(1,4-Bis(1-methylcyclohexyl)butane-2,3-diyl)dibenzene (44). A 1-dram vial was charged with oxalate **3a** (50 mg, 0.15 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (1 mg, 1.5 μmol, 0.015 equiv), Hantzsch ester **4** (38 mg, 0.15 mmol, 1.5 equiv), and a magnetic stir bar under argon. After sequential addition of CH_2Cl_2, (0.5 mL, sparged with Ar for 5 min), THF (0.5 mL, sparged with Ar for 5 min) and styrene (**43**, 12 μL, 0.10 mmol, 1 equiv), the vial was capped and placed in the center of a 30 cm loop of blue LEDs. The reaction mixture was stirred for 18 h, after which it was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (100% pentane) to provide **44** (9 mg, 0.022 mmol, 44%), a 1:1 mixture of stereoisomers, as a colorless solid.

Data for diastereomer 1: R_f 0.66 (100% hexanes); mp: 90-92 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.21 (m, 4H), 7.16 (d, *J* = 7.3, 2H), 7.12 (d, *J* = 7.4, 4H), 2.72 (d, *J* = 9.0, 2H), 1.58-1.53 (m, 2H), 1.39 (d, *J* = 14.1, 2H), 1.26-1.19 (m, 6H), 1.14-1.08 (m, 5H), 1.05-0.98 (m, 5H), 0.83 (bs, 4H), 0.46 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 129.5, 127.9, 125.8, 49.2, 38.8, 38.4, 33.4, 29.9, 26.4, 22.1, 21.9; IR (thin film): 2924, 2854, 1494, 1452 cm^{-1}; HRMS-CI (*m/z*) $[M + NH_4]^+$ calculated for $C_{30}H_{46}N$ 420.3630, found, 420.3647.

Data for diastereomer 2: R_f 0.50 (100% hexanes); mp: 87-89 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10-7.07 (m, 4H), 7.04-7.00 (m, 2H), 6.95 (d, *J* = 7.1, 4H), 2.82 (d, *J* = 7.3, 2H), 1.79-1.70 (m, 4H), 1.37-1.32 (m, 6H), 1.22-1.17 (m, 10H), 1.00-0.95 (m, 4H), 0.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.4, 129.7, 127.3, 125.4, 49.1, 38.6, 33.8, 29.9, 26.6, 22.2, 22.1; IR (thin

film): 2924, 2858, 1494, 1452 cm^{-1}; HRMS-CI (*m/z*) $[M + NH_4]^+$ calculated for $C_{30}H_{46}N$ 420.3630, found, 420.3627.

Adamantan-1-yl 3-phenylbut-3-enoate (45) and 1-(2-phenylallyl)adamantane (46). In an identical fashion, oxalate **3f** (55 mg, 0.15 mmol, 1.5 equiv) was coupled with α-(bromomethyl)styrene (**32**, 15 μL, 0.10 mmol, 1 equiv), to give a crude residue, which was purified by silica gel chromatography (0-3% diethyl ether/pentane) to provide **45** (20 mg, 0.066 mmol, 66%) and **46** (1 mg, 5.0 μmol, 5%) as colorless solids.

Data for **45**: R_f 0.36 (4% EtOAc/hexanes); mp 47–49 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.1, 2H), 7.32 (t, *J* = 7.6, 2H), 7.29–7.25 (m, 1H), 5.50 (s, 1H), 5.21 (s, 1H), 3.43 (s, 2H), 2.11 (s, 3H), 2.00 (d, *J* = 3.1, 6H), 1.61 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 141.8, 140.3, 128.4, 127.7, 126.0, 115.8, 80.9, 42.9, 41.2, 36.3, 30.9; IR (thin film): 2911, 2853, 1727, 1455, 1342, 1252, 1165, 1057 cm^{-1}; HRMS-CI (*m/z*) $[M + NH_4]^+$ calculated for $C_{20}H_{24}O_2NH_4$ 314.2120, found 314.2130.

Data for **46**: R_f 0.72 (100% hexanes); mp 39–41 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.1, 2H), 7.30 (t, *J* = 7.4, 2H), 7.25–7.21 (m, 1H), 5.26 (d, *J* = 2.0, 1H), 4.97 (s, 1H), 2.34 (s, 2H), 1.86 (s, 3H), 1.62 (d, *J* = 12.1, 3H), 1.53 (d, *J* = 13.3, 3H), 1.38 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 144.0, 128.2, 127.0, 126.6, 116.3, 49.9, 43.1, 37.1, 33.8, 28.9; IR (thin film): 2901, 2846, 1450 cm^{-1}; HRMS-CI (*m/z*) $[M]^+$ calculated for $C_{19}H_{24}$ 252.1878, found 252.1870.

3,5,5-Trimethyl-3-(3-phenylbut-3-en-1-yl)dihydrofuran-2(3H)-one (47). In an identical fashion, oxalate **3k** (50 mg, 0.15 mmol, 1.5 equiv) was coupled with α-(bromomethyl)styrene (**32**, 15 μL, 0.10 mmol, 1 equiv). After 18 h, the reaction mixture was diluted with CH_2Cl_2. The

resulting organic phase was washed with 4 M HCl (3 x 10 mL) and 2 N NaOH (3 x 10 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography (10% acetone/hexanes) to provide **47** (12 mg, 0.047 mmol, 47%) as a colorless oil. R_f 0.53 (10% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.1, 2H), 7.33 (t, *J* = 7.5, 2H), 7.29–7.27 (m, 1H), 5.29 (s, 1H), 5.09 (s, 1H), 2.67–2.60 (m, 1H), 2.48-2.41 (m, 1H), 2.15 (d, *J* = 13.3, 1H),1.95 (d, *J* = 13.5, 1H), 1.77–1.72 (m, 2H), 1.46 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.3, 147.8, 140.9, 128.6, 127.7, 126.2, 112.9, 81.1, 46.7, 45.1, 38.4, 30.6, 30.3, 30.2, 25.9; IR (thin film): 2974, 2934, 2874, 1758, 1455, 1376, 1268, 1187, 1090 cm^{-1}; HRMS-CI (*m/z*) [M + NH_4]$^+$ calculated for $C_{17}H_{22}O_2NH_4$ 276.1964, found 276.1962.

General procedure for coupling reactions in the absence of a photocatalyst (Tables 8 and 9). Preparation of 5. A 1-dram vial was charged with oxalate **3a** (100 mg, 0.30 mmol, 1.5 equiv), Hantzsch ester **4** (76 mg, 0.30 mmol, 1.5 equiv), *i*-Pr_2NEt•HBF_4 (44 mg, 0.20 mmol, 1 equiv) and a magnetic stir bar under argon. After sequential addition of CH_2Cl_2, (1 mL, sparged with Ar for 5 min), THF (1 mL, sparged with Ar for 5 min), and methyl vinyl ketone (17 μL, 0.20 mmol, 1 equiv), the vial was capped and placed in the center of a 30 cm loop of blue LEDs. The reaction mixture was stirred for 18 h, after which time it was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (3% EtOAc/hexanes) to yield ketone **5** (23 mg, 0.14 mmol, 67%) as a colorless oil. Characterization data for **5** matched those previously reported.[3b]

Deuterium incorporation in product 5 using 4,4-*d*$_2$-Hantzsch ester 48. A 1-dram vial was charged with oxalate **3a** (100 mg, 0.30 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (3 mg, 3.0 μmol, 0.015 equiv), 4,4-*d*$_2$-Hantzsch ester **48** (77 mg, 0.30 mmol, 1.5 equiv), *i*-Pr_2NEt•HBF_4 (44 mg,

0.20 mmol, 1 equiv) and a magnetic stir bar under argon. After sequential addition of CH_2Cl_2, (1 mL, sparged with Ar for 5 min), THF (1 mL, sparged with Ar for 5 min), and methyl vinyl ketone (17 μL, 0.20 mmol, 1 equiv), the vial was capped and placed in the center of a 30 cm loop of blue LEDs. The reaction mixture was stirred for 18 h, after which time it was concentrated under reduced pressure. Purification of the crude residue by silica gel chromatography (2.5% EtOAc/hexanes) provided ketone **5** (13 mg, 0.070 mmol, 37%)[46] as a colorless oil. Integration of all ^{1}H NMR signals determined the deuterium incorporation to be >95%. R_f 0.43 (10% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.39–2.30 (m, 1H), 2.15 (s, 3H), 1.49 (d, J = 8.4, 2 H), 1.46–1.38 (m, 5H), 1.33–1.20 (m, 5H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.2, 38.1 (t, J = 20.2), 37.7, 32.3, 30.0, 29.8, 26.5, 24.7, 22.1; IR (thin film): 2925, 2853, 1716, 1356 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{11}H_{19}DONa$ 192.1475, found 192.1484.

2-Cyanocyclopent-2-en-1-yl benzoate (49a). A round bottom flask was charged with 5-hydroxycyclopent1-ene 1-carbonitrile[47] (500 mg, 4.58 mmol, 1 equiv) and Et_3N (1.3 mL, 9.17 mmol, 2 equiv), DMAP (56 mg, 0.45 mmol, 0.1 equiv) and THF (15 mL) were added sequentially under argon. The solution was cooled to 0 °C and benzoyl chloride (1.1 mL, 9.17 mmol, 2 equiv) was added dropwise. The cloudy suspension was stirred while warming to rt over 18 h. After this time, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl solution (10 mL). The contents of the flask were transferred to a separatory funnel, diluted with Et_2O (50 mL) and the layers separated. The organic layer was washed with saturated aqueous NH_4Cl solution (3 x 40 mL), aqueous 1 N NaOH (3 x 40 mL), and brine (2 x 40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10-20% EtOAc/hexanes) to provide **49a** (862 mg, 4.04 mmol, 88%) as a colorless oil that solidified after storage at –20

°C. R_f 0.14 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.9, 2H), 7.57 (t, *J* = 7.9, 1 H), 7.44 (t, *J*= 7.9, 2H), 7.03–7.00 (m, 1H), 6.08–6.04 (m, 1H), 2.81–2.73 (m, 1H), 2.64–2.56 (m, 2H), 2.09–2.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 154.3, 133.3, 129.7, 129.5, 128.4, 115.1, 114.9, 79.3, 32.1, 30.6; IR (thin film): 3069, 2950, 2226, 1972, 1915, 1720 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{13}H_{11}NO_2Na$ 236.0687, found 236.0678.

Preparation of reductive-coupling product 50. A 1-dram vial was charged with oxalate **3a** (100 mg, 0.30 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (3 mg, 3.0 μmol, 0.015 equiv), Hantzsch ester **4** (76 mg, 0.30 mmol, 1.5 equiv), *i*-$Pr_2NEt•HBF_4$ (44 mg, 0.20 mmol, 1 equiv) and a magnetic stir bar under argon. After sequential addition of CH_2Cl_2 (1 mL, sparged with Ar for 5 min), THF (1 mL, sparged with Ar for 5 min), and acceptor **49a** (43 mg, 0.20 mmol, 1 equiv), the vial was capped and placed in the center of a 30 cm loop of blue LEDs. The reaction mixture was stirred for 18 h, after which time it was diluted with Et_2O (30 mL) and transferred to a separatory funnel. The ether layer was washed with aqueous 4 N HCl (4 x 20 mL) and aqueous 2 N NaOH (3 x 20 mL) and was dried over $MgSO_4$. The organic layer was filtered and concentrated under reduced pressure. The crude residue was subjected to silica gel chromatography (4% acetone/hexanes) to provide **50** (34 mg, 0.11 mmol, 55%, dr 8:2:1:1) as a colorless oil.

Data for **50** (major diastereomer, **8**:2:1:1): R_f 0.40 (10% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.0, 2 H), 7.58 (t, *J* = 7.4, 1 H), 7.45 (t, *J* = 8.0, 2H), 5.30 (app. q, *J* = 7.6, 1H), 3.42–3.39 (m, 1H), 2.31–2.24 (m, 1H), 2.10–1.96 (m, 3H), 1.82–1.76 (m, 1H), 1.60–1.55 (m, 2H), 1.53–1.45 (m, 6H), 1.31–1.22 (m, 2H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 133.5, 130.0, 129.6, 128.6, 118.6, 74.4, 37.01, 37.0, 35.3, 34.5, 28.2, 26.2, 21.9, 21.62, 21.61; IR (thin film): 2925, 2853, 1722, 1271 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{20}H_{25}NO_2Na$ 334.1783, found 334.1789.

Data for **50** (minor diastereomer, 8:**2**:1:1): R_f 0.44 (10% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.1, 2H), 7.6 (t, *J* = 7.6, 1H), 7.46 (t, *J* = 7.6, 2H), 5.52–5.50 (m, 1H), 3.08–3.05 (m, 1H), 2.53–2.46 (m, 1H), 2.25–2.19 (m, 1H), 1.96–1.78 (m, 3H), 1.60–1.45 (m, 8H), 1.34–1.23 (m, 2H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 133.5, 129.8, 129.7, 128.6, 119.9, 78.5, 37.5, 37.1, 36.9, 34.1, 30.6, 26.3, 23.1, 22.0, 21.7.

5-Bromocyclopent-1-enecarbonitrile (49b). A round-bottom flask was charged with 5-hydroxycyclopent1-ene 1-carbonitrile[47] (500 mg, 4.58 mmol, 1 equiv) and Et_2O (20 mL) and CBr_4 (3.04 g, 9.17 mmol, 2 equiv) were added sequentially under argon. The solution was cooled to 0 °C and PPh_3 (2.40 g, 9.17 mmol, 2 equiv) was added in one portion. The resulting heterogeneous mixture was warmed to rt and stirred for 2 h. After this time, the reaction mixture was filtered through a plug of Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10-15% EtOAc/hexanes) to yield **49b** (481 mg, 2.81 mmol, 61%) as a colorless oil. R_f 0.26 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87–6.82 (m, 1H), 5.09–5.04 (m, 1H), 2.86–2.75 (m, 1H), 2.63–2.52 (m, 2H), 2.50–2.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.9, 119.1, 114.7, 53.1, 35.5, 32.3; IR (thin film): 2927, 2227, 1607, 1189, 1010 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for C_6H_6BrNNa 193.9581, found 193.9582.

Preparation of allylated product 51. A 1-dram vial was charged with oxalate **3a** (100 mg, 0.30 mmol, 1.5 equiv), $Ru(bpy)_3(PF_6)_2$ (3 mg, 3.0 μmol, 0.015 equiv), Hantzsch ester **4** (76 mg, 0.30 mmol, 1.5 equiv), *i*-Pr_2NEt•HBF_4 (44 mg, 0.20 mmol, 1 equiv) and a magnetic stir bar under argon. After sequential addition of CH_2Cl_2 (1 mL, sparged with Ar for 5 min), THF (1 mL, sparged with Ar for 5 min), and acceptor **49b** (43 mg, 0.20 mmol, 1 equiv), the vial was capped and placed in the center of a 30 cm loop of blue LEDs. The reaction mixture was stirred for 18 h,

after which time it was concentrated under reduced pressure. The crude residue was subjected to silica gel chromatography (4% acetone/hexanes) to provide **51** (22 mg, 0.11 mmol, 57%) as a colorless oil: R_f 0.47 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79–6.76 (m, 1H), 2.89–2.83 (m, 1H), 2.50–2.34 (m, 2H), 2.01–1.92 (m, 1H), 1.87–1.79 (m, 1H), 1.64–1.38 (m, 7H), 1.36–1.18 (m, 3H), 0.88 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4, 118.7, 116.7, 36.7, 36.1, 36.0, 33.0, 26.3, 25.2, 22.0, 21.8 ; IR (thin film): 2926, 2853, 2215, 1459 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calculated for $C_{13}H_{19}NNa$ 212.1415, found 212.1405.

ASSOCIATED CONTENT

Supporting Information. Image of a typical photocatalysis reaction setup, copies of ^{1}H and ^{13}C NMR spectra of new compounds, nOe data for compound **50**, and and cyclic voltammetry data. 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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Dedication

Dedicated to Stephen Hanessian, a friend and leader in the practice and pedagogy of organic synthesis.

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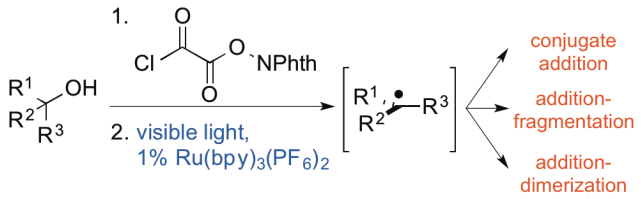
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2. visible light,
1% Ru(bpy)3(PF6)2
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conjugate addition
addition-fragmentation
addition-dimerization