Photoredox Catalysis

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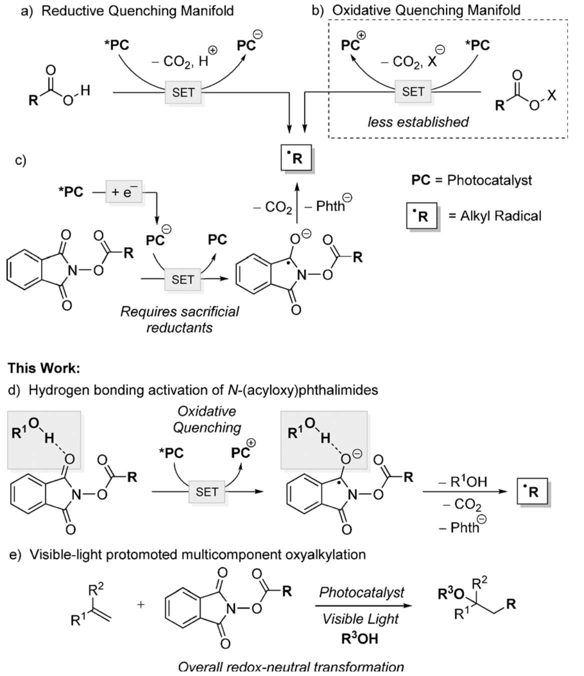
Multicomponent Oxyalkylation of Styrenes Enabled by Hydrogen-Bond-Assisted Photoinduced Electron Transfer

*Adrian Tlahuext-Aca, R. Aleyda Garza-Sanchez, and Frank Glorius**

Abstract: *Herein, we disclose a strategy for the activation of N-(acyloxy)phthalimides towards photoinduced electron transfer through hydrogen bonding. This activation mode enables efficient access to C(sp^3)-centered radicals upon decarboxylation from bench-stable and readily available substrates. Moreover, we demonstrate that the formed alkyl radicals can be successfully employed in a novel redox-neutral method for constructing sp^3–sp^3 bonds across styrene moieties that gives straightforward access to complex alcohol and ether scaffolds.*

Visible-light-mediated radical decarboxylation of aliphatic acids has emerged in recent years as a powerful tool to access C(sp^3)-centered radical intermediates.[1] The formation of these species under mild conditions has led to the development of impressive C–C and C–X bond forming transformations using cheap, abundant, and synthetically versatile carboxylic functionalities.[2] From a fundamental point of view, these strategies rely on photoinduced electron transfer (PET) processes between carboxylic acids and strongly oxidizing photoexcited catalysts, leading to the formation of alkyl radicals after CO_2 extrusion (Scheme 1 a). Whereas this PET event has been extensively explored in the vast majority of photoredox-catalyzed transformations involving carboxylic acids, electronically reversed light-driven electron transfers where the carboxylic acid derivative is reduced before undergoing radical decarboxylation have been less explored (Scheme 1 b).[3] If feasible, these new mechanistic pathways would expand the scope of synthetic applications amenable to visible-light-mediated decarboxylative methods, while taking advantage of the efficiency of this radical generation strategy.



Scheme 1. a–c) Visible-light-mediated radical decarboxylative methods. d, e) Development of an oxyalkylation method.

Motivated by the desire to investigate such an intriguing mechanistic scenario and its potential applications in visible-light-mediated organic synthesis, we were drawn to the pioneering work of Okada on the use of *N*-(acyloxy)phthalimides as electrophilic substrates for radical decarboxylation.[4] Interestingly, despite to their ability to generate alkyl radicals under visible-light-mediated conditions, their highly negative reduction potentials ($E^{\text{red}}_{1/2} < -1.28$ V vs. SCE in MeCN)[5] hamper direct photoinduced electron transfers with photoexcited catalysts. For these substrates, therefore, reductive conditions must be employed where the photoexcited catalyst is converted into a highly reducing species prior to engaging in SET with the corresponding *N*-(acyloxy)phthalimide (Scheme 1 c).[6,7] This dramatically limits the scope of accessible transformations to net reductive couplings. To overcome these limitations and provide efficient access to novel oxidative quenching processes for radical decarboxylation, we asked whether the ground-state redox properties of *N*-(acyloxy)phthalimides could be tuned to provide a thermodynamically feasible PET. Herein, we demonstrate that hydrogen bonding, one of the most important intermolecular interactions in biology, molecular self-assembly and non-covalent synthesis, can be suitable to drive a direct PET process using *N*-(acyloxy)phthalimides by means of increasing their electron-acceptor strength (Scheme 1 d).[8,9]

Moreover, we applied this strategy to the efficient generation of a variety of alkyl radicals upon decarboxylation from bench-stable and readily accessible substrates without the need for sacrificial reductants. Under mild redox-neutral conditions, we show that the formed alkyl radicals can be further manipulated to achieve the oxyalkylation of styrenes. These transformations are synthetically powerful since they install two single bonds across an olefin, giving straightforward access to molecular complexity from simple materials (Scheme 1 e). Moreover, in contrast to other radical difunc-

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[*] A. Tlahuext-Aca, R. A. Garza-Sanchez, Prof. F. Glorius
NRW Graduate School of Chemistry, Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Correnstrasse 40, 48149 Münster (Germany)
E-mail: glorius@uni-muenster.de

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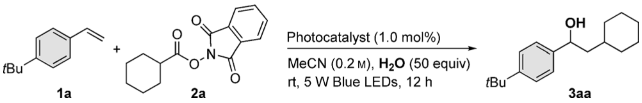
tionalization reactions such as oxytrifluoromethylation[10] or oxyarylation,[11] oxyalkylation remains challenging and only a limited number of methods are available for constructing these important and versatile carbooxygenated building blocks.[12]

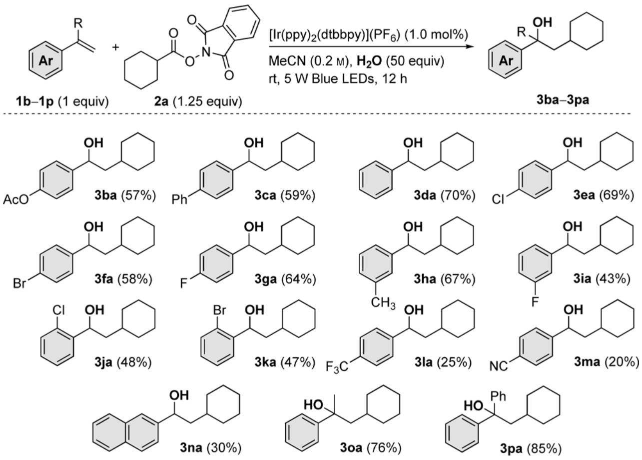
We started our investigation by identifying conditions to perform the radical hydroxyalkylation of 4-*tert*-butylstyrene (**1a**) with **2a** in the presence of water as a nucleophile and hydrogen-bond donor. We screened five commonly employed transition-metal-based photocatalysts (Table 1). To our delight, **3aa** was observed upon irradiation with 5 W blue LEDs ($\lambda_{max} = 455$ nm) in acetonitrile for 12 h when using 1 mol% of *fac*-Ir(ppy)$_3$ or [Ir(ppy)$_2$(dtbbpy)](PF$_6$) in 26 and 80% yield as determined by NMR, respectively. These reactivities are in agreement with the more reducing excited states of these two iridium complexes compared to the other photocatalysts tested. Following a short screen, conditions were identified under which alcohol **3aa** could be isolated in 75% yield when using [Ir(ppy)$_2$(dtbbpy)](PF$_6$) as a photocatalyst. Control experiments were then performed to demonstrate the visible-light-mediated nature of this process and the key role of water as an activator. Alcohol **3aa** was not observed in the absence of [Ir(ppy)$_2$(dtbbpy)](PF$_6$) or light irradiation. Moreover, when performed in the absence of water, no reactivity was observed and both **1a** and **2a** could be recovered. Consistent with the radical nature of the developed oxyalkylation, the presence of TEMPO as a radical scavenger completely inhibited the formation of **3aa**, and the corresponding 1-(cyclohexyloxy)-2,2,6,6-tetramethylpiperidine adduct was characterized by mass spectrometry from these assays (see the Supporting Information for details). With the optimized conditions in hand, the substrate scope for the hydroxyalkylation was assessed with a variety of styrenes and **2a** as a radical source. The reaction tolerates a variety of electron-donating and -withdrawing groups at the *para* position of the arene moiety (Scheme 2). Moreover, as shown for **3ha–3ka**, the reaction performs with similar efficiency with substituents at the *meta* and *ortho* positions. Styrenes featuring electron-withdrawing groups such as trifluoromethyl or cyano groups, however, reacted sluggishly, giving **3la** and **3ma** in moderate yields. While the 2-vinyl-substituted naphthalene afforded moderate yield, other alkenes such as α-substituted styrenes gave straightforward access to the tertiary alcohols **3oa–3pa** in good yields.

Table 1: Visible-light-mediated oxyalkylation of **1a**.



Entry[a]	Photocatalyst	$E_{1/2}$ (M$^+$/M*)[b]	Yield [%][c]
1	*fac*-Ir(ppy)$_3$	−1.73	26
2	[Ir(ppy)$_2$(dtbbpy)](PF$_6$)	−0.96	80 (75)
3	[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)](PF$_6$)	−0.89	–
4	[Ru(phen)$_3$](PF$_6$)$_2$	−0.87	–
5	[Ru(bpy)$_3$](PF$_6$)$_2$	−0.81	–
6[d]	[Ir(ppy)$_2$(dtbbpy)](PF$_6$)	−0.96	52
7[e]	[Ir(ppy)$_2$(dtbbpy)](PF$_6$)	−0.96	76
8[f]	[Ir(ppy)$_2$(dtbbpy)](PF$_6$)	−0.96	–

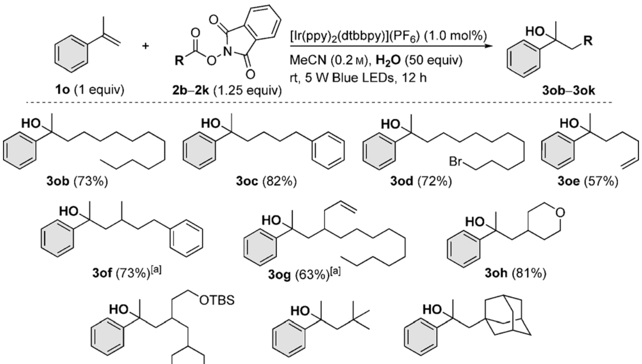
[a] Conditions: **1a** (0.10 mmol), **2a** (0.125 mmol), photocatalyst (1.0 mol%), water (5.0 mmol) and MeCN (0.5 mL) under argon. [b] All potentials are given in volts versus the saturated calomel electrode (Ref. [1d]). [c] NMR yields using CH$_2$Br$_2$ as internal standard. [d] Water (1.0 mmol). [e] **2a** (0.10 mmol). [f] TEMPO (1.5 equiv). See the Supporting Information for details. Yields of isolated product are given in parentheses.



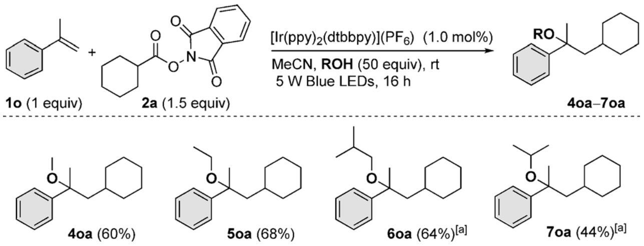
Scheme 2. Scope with respect to the styrenes. Yields of isolated product are given. See the Supporting Information for details.

We next turned our attention to investigate whether other *N*-(acyloxy)phthalimides can be employed as radical sources using **1o** as a substrate (Scheme 3). To our delight, a range of primary, secondary, and tertiary alkyl moieties can be successfully installed across the styrene unit with high yields and good functional group tolerance. Moreover, as shown for **3od**, **3oe**, **3og**, and **3oi**, C(sp^3)−X and aliphatic alkene moieties can easily be incorporated and can serve as reactive centers for further functionalization processes.

As the next stage of our investigation, we sought to demonstrate the generality of our approach in terms of the use of other hydrogen-bond donors that can also be used as nucleophiles in our oxyalkylation strategy (Scheme 4). Gratifyingly, a variety of primary alcohols reacted smoothly to



Scheme 3. Scope with respect to the *N*-(acyloxy)phthalimides. [a] Isolated as a 1:1 d.r. mixture. Yields of isolated product are given. See the Supporting Information for details.



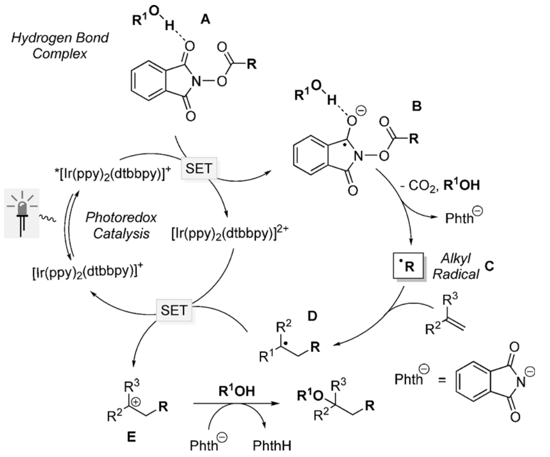
Scheme 4. Scope with respect to the alcohols. [a] **2a** (2.0 equiv), [Ir(ppy)$_2$(dtbbpy)](PF$_6$) (2.5 mol%). Isolated yields. See the Supporting Information for details.

afford the tertiary ethers **4oa–6oa** when employing **1o** and **2a** as model substrates. 2-Propanol, however, gave only a moderate yield of **7oa**, even under higher loadings of photocatalyst and coupling partner.

To gain insight into the mechanism of the visible-light-mediated oxyalkylation of **1a** with **2a** and water, we studied the kinetics of the photoexcited *[Ir(ppy)$_2$(dtbbpy)]$^+$ by fluorescence techniques. A Stern–Volmer analysis revealed that **2a** does not quench the excited state of [Ir(ppy)$_2$(dtbbpy)]$^+$ in pure acetonitrile at room temperature. Consistent with our proposed activation of **2a** by hydrogen bonding, however, the same assay in the presence of water (2.8 M) showed a marked decrease in the measured fluorescence of *[Ir(ppy)$_2$(dtbbpy)]$^+$. Under these conditions, a Stern–Volmer constant (K_{sv}) of 60.8 M^{-1} was measured. Moreover, variation of the concentration of **2a** and water showed that the quenching processes exhibit a first-order dependence on each component. Interestingly, a similar first-order concentration dependence on other protic species such as methanol was observed, however, due to its weaker ability to engage in hydrogen bonding, the PET between *[Ir(ppy)$_2$(dtbbpy)]$^+$ and **2a** is kinetically less favored when methanol is used instead of water.[13] Finally, to provide further evidence on the role of hydrogen bonding in the activation of **2a** towards PET, we performed a Stern–Volmer analysis using *N*,*N*-dimethylformamide (DMF) as the solvent. Due to the strong hydrogen-bond acceptor properties of DMF,[14] different concentrations of **2a** did not lead to any decrease in the *[Ir(ppy)$_2$(dtbbpy)]$^+$ fluorescence in this solvent in the presence of water (2.8 M).

A proposed mechanism for the oxyalkylation of alkenes is depicted in Scheme 5. Upon visible-light irradiation, the excited *[Ir(ppy)$_2$(dtbbpy)]$^+$ engages in single-electron transfer with the hydrogen bond complex **A** to give the radical anion **B**, which then undergoes N−O bond cleavage followed by decarboxylation to afford the alkyl radical **C**. This reactive species then adds to the olefin to deliver **D**. The photoredox cycle is then closed by SET between **D** and [Ir(ppy)$_2$(dtbbpy)]$^{2+}$ to afford the cation **E**, which is trapped by the nucleophile to afford the oxyalkylated product.

In conclusion, we have developed a mild and overall redox-neutral method for the oxyalkylation of styrenes using visible light as the source of energy. We have demonstrated that hydrogen-bonding interactions can drive otherwise inaccessible direct photoinduced electron transfer between N-(acyloxy)phthalimides and photoexcited catalysts. This novel oxidative quenching manifold serves as a platform to access a variety of alkyl radicals from bench-stable and readily accessible carboxylic acid derivatives, and we hope it will find further applications in visible-light-mediated organic synthesis.



Scheme 5. Proposed mechanism.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkyl radicals · decarboxylation · hydrogen bonding · oxyalkylation · photoredox catalysis

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[14] The hydrogen-bond acceptor basicity (β) of DMF and MeCN is 0.69 and 0.40, respectively. See Ref. [13].

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Communications

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A. Tlahuext-Aca, R. A. Garza-Sanchez, F. Glorius* ■■■■–■■■■

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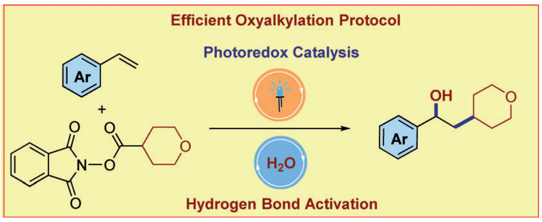

OH, I see: An efficient strategy to activate *N*-(acyloxy)phthalimides towards direct photoinduced electron transfer with photoexcited catalysts was developed. This strategy enables efficient visible-light-mediated formation of alkyl radicals that can be used to achieve the challenging oxyalkylation of styrenes under mild redox-neutral conditions.