Communication

Intermolecular Radical Addition to Carbonyls Enabled by Visible Light Photoredox Initiated Hole Catalysis

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Intermolecular Radical Addition to Carbonyls Enabled by Visible Light Photoredox Initiated Hole Catalysis

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Supporting Information Placeholder

ABSTRACT: Herein, we present a novel strategy for the utilization of simple carbonyl compounds, aldehydes and ketones, as intermolecular radical acceptors. The reaction is enabled by visible light photoredox initiated hole catalysis and the *in situ* Brønsted acid activation of the carbonyl compound. This regioselective alkyl radical addition reaction does not require metals, ligands or additives and proceeds with a high degree of atom economy under mild conditions. The proposed mechanism is supported by both experimental and theoretical studies.

Over the last decade photo(redox) catalysis has emerged as a powerful platform for organic chemists to develop valuable transformations proceeding via radical pathways.[1,2] Concomitant with the rapid growth of the field is an ever-present need for the continued expansion of the scope of amenable radical precursors and acceptors. Addressing this, our group recently developed a screening method for the identification of new quenchers.[3] However, the scope of radical acceptors is still limited and exploration of a broader acceptor pool remains an ongoing challenge.[4] In general, C–C double bonds represent the most commonly used radical π-acceptors. C–N double bonds have also been shown to act as acceptors, but generally activation via electron deficient substituents on the nitrogen is required.[5] Notably, C–O double bonds, specifically substituted aldehydes or ketones, have to the best of our knowledge, only been used once as intermolecular radical acceptors.[6-8]

The intermolecular addition of radicals to alkenes is known to proceed irreversibly to yield carbon centered radicals. In contrast, addition to carbonyls is a reversible process due to the formation of a thermodynamically unfavorable alkoxy radical.[9] Upon formation, these radicals preferably decay via homolytic cleavage, i.e. C–C β-scission, to form a more stable radical species.[10] Therefore, successful radical addition is only possible if the alkoxy radical can be intercepted via a subsequently fast event, e.g. electron transfer (ET). As Studer and Curran recently emphasized, electron or hole catalysis can offer such possibilities by controlling the selectivity of competing radical reactions.[11] In this context, C–C β-scission could be suppressed by using Brønsted or Lewis acid coordination to form an alkoxy radical cation, which allows for hole catalysis. This coordination would concurrently provide a greater thermodynamic driving force for the desired forward reaction while kinetically enhancing the rate of the ET step (see Figure 1).
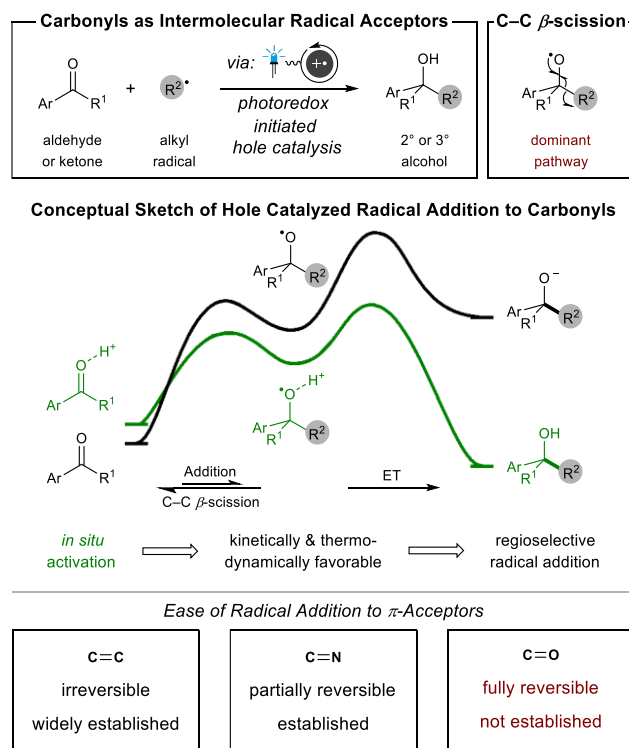

Figure 1. Concept of applying carbonyls as radical π-acceptors. *In situ* Brønsted acid activation facilitates ET to an alkoxy radical.

Considering this, we sought to develop a process based on hole catalysis induced by a combination of common photoredox chemistry with Brønsted or Lewis acid coordination.[12] We hypothesized the formation of an alkyl radical via quenching of a photoredox catalyst with a suitable substrate. This alkyl radical could then add to an activated, e.g. protonated, carbonyl. The formed alkoxy radical cation would be able to engage in ET due to its enhanced oxidation potential, contrary to an alkoxy radical (see Figure 1).

Inspired by Nicewicz's work, we became interested in alkenes as alkyl radical precursors.[15] The oxidation of an alkene to form a radical cation, followed by trapping of the cation with a protic nucleophile, would not only generate the alkyl radical, but also liberate a proton for the required activation of the carbonyl. The highly oxidizing and poorly reducing photoredox catalyst 9-mesityl-10-methylacridinium tetrafluoroborate (**1**) ($E_{1/2}^{red}$ = -0.57 V vs SCE)[2b], which has already been applied in such

oxidations, would furthermore ensure the exclusion of a contrary reaction pathway proceeding via reduction of the carbonyl. Interestingly, carbonyls in photoredox catalysis have only ever been used as radical donors even though they possess a largely negative reduction potential (e.g. $E_{1/2}^{red} = -1.93$ V vs SCE for benzaldehyde)[13]).[14]
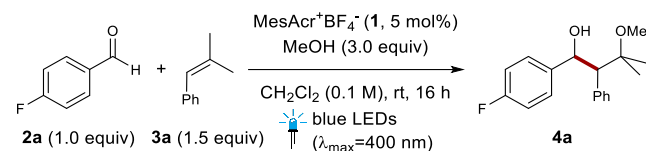

Figure 2. Standard reaction conditions.

Studies began by irradiating a mixture containing photocatalyst **1**, the inexpensive and easily available starting materials 4-fluorobenzaldehyde (**2a**) and alkene **3a** in the presence of methanol as a nucleophile in dichloromethane (see Figure 2) with blue LEDs ($\lambda_{max} = 455$ nm). Pleasingly, under these conditions we observed the formation of the desired product **4a** in 20% yield.[16] As reported in other reactions performed with **1**, we also

recognized immediate bleaching of the solution, which is proposed to be caused by catalyst decomposition.[17] Isolation of a modified catalyst species and submission to the standard conditions without **1** still resulted in moderate product formation.[16] Furthermore, the UV-visible absorption spectrum of this species revealed significant absorption only until 410 nm. Consequently, the light source was changed to blue LEDs with a λ_{max} of 400 nm, which increased the yield of the product to 73%. Control experiments also showed the necessity of using both light and the photocatalyst. Performing the reaction under air resulted in only a slight decrease in yield. The regioselectivity of the addition reaction was fully confirmed by X-ray analysis of products **4g** and **4h**.[16]

This reaction is proposed to proceed via the photoexcitation of **1**, followed by reductive quenching with **3a** to form radical cation **I** (see Figure 3A). Nucleophilic trapping of the cation by methanol and proton transfer to the carbonyl delivers **II** as a hydrogen-bonded adduct consisting of the alkyl radical and the activated carbonyl.[16] Subsequent radical addition via a six-membered transition state forms radical cation **III**. ET with **3a**
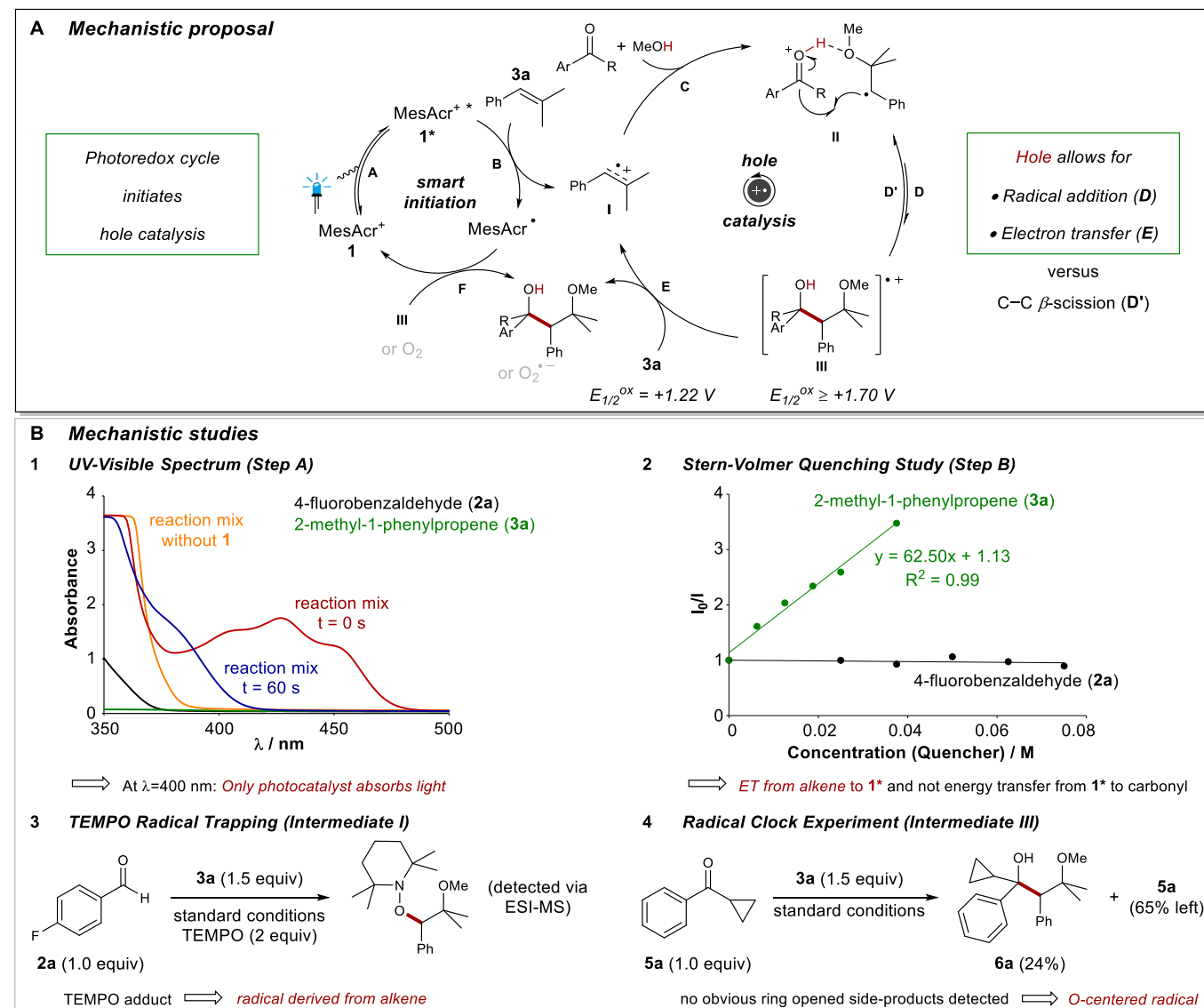
Figure 3. A. Mechanistic proposal. B. Mechanistic studies: 1) UV-vis spectra of **2a** (green), **3a** (pink), reaction mixture without **1** (orange), reaction mixture (red), reaction mixture after 60 s of irradiation (blue), 2) Stern-Volmer quenching study with **3a** (red) and **2a** (blue), 3) Radical trapping experiment adding TEMPO to standard conditions, 4) Radical clock experiment using benzoylcyclopropane **5a** as radical acceptor (yields determined via ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard).

generates the product and the initial radical cation **I**, thus completing the hole catalysis cycle. The product can also potentially be formed via oxidation of the reduced photocatalyst by **III**.

This mechanistic proposal is based on several experimental and theoretical studies (see Figure 3B and SI), which support the different steps or intermediates. UV-visible spectroscopy ensured that only **1** absorbs light at $\lambda = 400$ nm. Therefore, a direct excitation of the carbonyl compound is unlikely. Furthermore, Stern-Volmer quenching studies support ET from the styrene to **1***. An alternative pathway, proceeding via energy transfer from **1*** to the carbonyl as an indirect excitation of the carbonyl is also unlikely, due to no observable quenching of **1*** by the carbonyl. Radical trapping with TEMPO provided evidence for the formation of the alkyl radical derived from the alkene after nucleophilic trapping with methanol. Thus, the formation of a theoretical radical anion derived from the aldehyde could be dismissed. Moreover, kinetic isotope experiments suggested that proton transfer to the carbonyl is not the rate determining step.[16] It is however of high importance, as no reactivity was observed in the presence of a base (e.g. 2,6-lutidine) or in the presence of a non-protic nucleophile, e.g. when using NaOMe instead of methanol as a nucleophile.[16] A radical clock experiment using benzoylcyclopropane (**5a**) as radical acceptor provided evidence for the regioselective addition to the C-terminus of the C–O double bond, as no obvious ring opened side products could be detected. Thus, we assume that a C-centered radical (derived from **5a**) is not formed and an alternative pathway, proceeding via reduction of the protonated carbonyl and subsequent radical coupling with the alkyl radical, is unlikely. Additionally, experiments to determine the reaction quantum yield and chain length suggest the possibility of the ET between **III** and **3a** and further oppose the probability of a radical coupling

through carbonyl reduction.[16] Given that the lower limit approximation of the chain length was determined to be 7, the photoredox initiation cycle should be completed and performed more than once to account for the yield of >70% (**4a**, Figure 3). Lastly, DFT calculations suggest the formation of the six-membered transition state following **II**.[16] The key ET between **III** and **3a** should also be thermodynamically favorable according to calculated redox potentials ($E(\textbf{III})_{1/2}^{ox} \geq +1.70$ V vs SCE and $E(\textbf{3a})_{1/2}^{ox} = +1.22$ V vs SCE)[16]. Without proton coordination, this ET would not be feasible ($E(\textbf{III}_{deprotonated})_{1/2}^{ox} \leq -0.25$ V vs SCE (calculated).[16]

Scope and limitation studies were then performed with a variety of aromatic aldehydes, ketones, alkenes and alcohols (Figure 3). In general, aldehydes provided higher yields of the respective products than ketones. For both carbonyl classes we detected increased yields when electron withdrawing substituents at the aromatic ring were present compared to electron donating substituents (e.g. 79%, **4h** vs 63%, **4m**). Apart from monoaryl ketones, diaryl ketones and electron deficient aliphatic ketones were also found to be viable radical acceptors (e.g. **6i**, 43%, **6h**, 31%). Regarding the alkene scope, no specific order of reactivity can be attributed to the electronic influence based on the performed examples. Aliphatic alkenes also gave the corresponding products in acceptable yields (**4q**, 52%). Variation of the alcohol was well tolerated (74%, **4w**, 86%, **4u**), though more steric hindrance resulted in lower yields (**4v**, 51%). Scaling up the reaction to 2.5 mmol did not cause any decrease in yield (**4c**, 90%). An additive-based robustness screen was also performed, showing in average minimal adverse effects of different additives on the reaction yield, indicating high functional group tolerance;[18] good functional group preservation was also observed.[16]

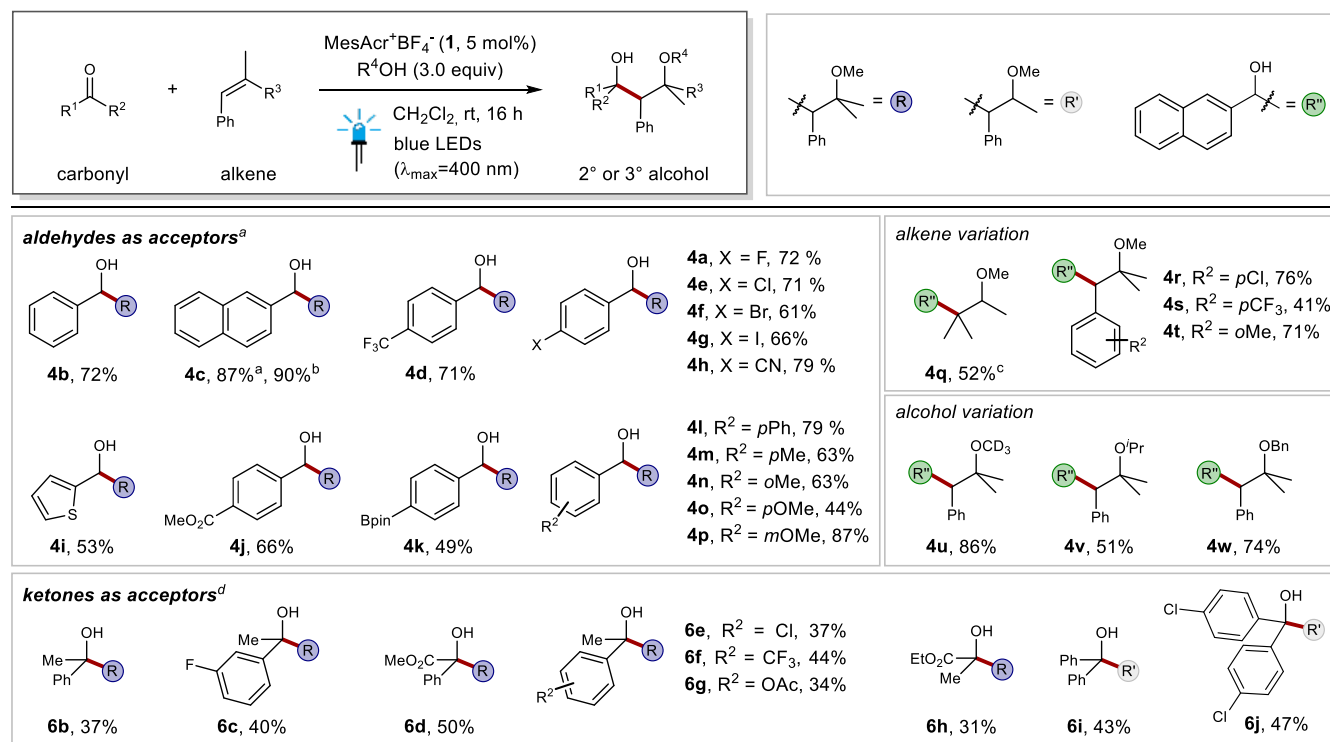**Figure 4. Scope of the intermolecular radical addition to carbonyls.** Standard conditions: Aldehyde (0.3 mmol), alkene (0.45 mmol), **1** (0.015 mmol), ROH (0.9 mmol), CH$_2$Cl$_2$, isolated yields given as a sum of the two separated diastereomeres, d.r. generally 1:1.2. a) 0.1 M (3.0 mL CH$_2$Cl$_2$) b) Reaction performed on a 2.5 mmol scale. c) 0.75 mmol of alkene + 1.5 mmol of MeOH used. d) 0.2 M (1.5 mL CH$_2$Cl$_2$).

In conclusion, a strategy for the intermolecular trapping of alkyl radicals with simple carbonyl compounds, including substituted aldehydes and ketones, has been developed. The reaction utilizes visible light photoredox smart initiated hole catalysis to facilitate the key *in situ* Brønsted acid activation of the carbonyl. The mechanistic proposal is based on several experimental and theoretical studies. In future work it is hoped that this Brønsted acid coordination strategy will enable the stereochemically controlled formation of C–C bonds. No metals, ligands or additives were necessary, leading to a high degree of atom economy. The reactions displayed high functional group tolerance, were performed with inexpensive starting materials and under mild conditions. Overall, this work constitutes a powerful new strategy for the longstanding challenge of using carbonyls as intermolecular radical acceptors.

ASSOCIATED CONTENT

Supporting Information

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

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Notes
The authors declare no competing financial interests.

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Carbonyls as Intermolecular Radical Acceptors

aldehyde or ketone + alkyl radical → *via:* photoredox initiated hole catalysis → 2° or 3° alcohol

via: in situ activation by Brønsted acid

experimental and computational studies included

additive-based screen applied

⊕ high atom economy   ⊕ regioselective radical addition   ⊕ repression of C–C β-scission