

## Photoredox Catalysis

## Activation of C–H Bonds through Oxidant-Free Photoredox Catalysis: Cross-Coupling Hydrogen-Evolution Transformation of Isochromans and $\beta$ -Keto Esters

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Abstract: The direct and controlled activation of a C(sp<sup>3</sup>)-H bond adjacent to an O atom is of particular synthetic value for the conventional derivatization of ethers or alcohols. In general, stoichiometric amounts of an oxidant are required to remove an electron and a hydrogen atom of the ether for subsequent transformations. Herein, we demonstrate that the activation of a C-H bond next to an O atom could be achieved under oxidant-free conditions through photoredox-neutral catalysis. By using a commercial dyad photosensitizer (Acr<sup>+</sup>-Mes ClO<sub>4</sub><sup>-</sup>, 9-mesityl-10methylacridinium perchlorate) and an easily available cobaloxime complex (Co(dmgBF<sub>2</sub>)<sub>2</sub>·2 MeCN, dmg = dimethylglyoxime), the nucleophilic addition of  $\beta$ -keto esters to oxonium species, which is rarely observed in photocatalysis, leads to the corresponding coupling products and H<sub>2</sub> in moderate to good yields under visible-light irradiation. Mechanistic studies suggest that both isochroman and the cobaloxime complex quench the electron-transfer state of this dyad photosensitizer and that benzylic C-H bond cleavage is probably the rate-determining step of this cross-coupling hydrogen-evolution transformation.

The formation of C–C bonds through controlled activation of  $C(sp^3)$ –H bonds has become one of the most active research fields in modern synthetic organic chemistry.<sup>[1]</sup> The direct functionalization of a  $C(sp^3)$ –H bond adjacent to an O atom is a powerful tool for the conventional synthesis of O-containing compounds.<sup>[2]</sup> However, this activation is much more challenging than the well-established activation of a C–H bond adjacent to an N atom owing to its higher oxidation potential.<sup>[3]</sup> To realize this type of C–H bond activation, stoichiometric

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201503361. amounts of an oxidant, such as 2,3-dichloro-5,6-dicyano-1,4benzoquinone (DDQ) or a peroxide, are always required to remove an electron and a hydrogen atom of the ether, thereby leading to the formation of an  $\alpha$ -oxy radical or an oxonium intermediate for subsequent transformations under thermal synthetic conditions (Scheme 1).<sup>[2-4]</sup>



Scheme 1. C–H bond activation of  $\alpha$ -CH<sub>2</sub>-O systems.

Recently, the use of visible-light catalysis as a complementary strategy for the functionalization of C(sp<sup>3</sup>)-H bonds has achieved a broad range of bond-forming reactions.<sup>[5]</sup> The photocatalytic generation of  $\alpha$ -oxy radicals by hydrogen-atom-transfer pathways and transformations by conjugate addition and radical coupling have been realized for the efficient derivatization of ethers or alcohols.<sup>[6]</sup> However, successful photo-mediated examples for the use of oxonium species, formed by two-electron oxidation, as reactive intermediates are very limited. Since the oxidation of an aromatic ring is easier than that of an oxygen atom, oxonium species ought to be obtained by single-electron oxidation of electron-rich aromatic rings and, thereafter, hydrogen-atom abstraction (or electron and proton abstraction in a stepwise manner) from the benzylic position in the case of benzylic ethers (Scheme 2).<sup>[7]</sup> To the best of our knowledge, so far there are only very few reports on the formation of oxocarbenium ions that are quenched by water to yield the hydrolysis products. In these cases,  $BrCCl_3$  or  $H_2O_2$ were used as the terminal oxidant.<sup>[7,8]</sup> Herein, we apply this oxi-

Oxidation of Aromatic Ring instead of Oxygen Atom



Scheme 2. Photoredox-catalyzed utilization of oxonium species.

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dative strategy to the transformation of oxonium species by the addition of appropriate nucleophiles to form new C–C bonds under oxidant-free conditions.

It is generally accepted that for the functionalization of C-H bonds with other C-H bonds stoichiometric oxidants are needed.<sup>[3]</sup> Our group recently proposed a novel protocol for the formation of a C–C bond by two different C–H bonds with concomitant emission of hydrogen (H<sub>2</sub>) in the absence of stoichiometric oxidants.<sup>[9]</sup> A series of amines have been converted to imine (or iminium-ion) intermediates and, subsequently, cross-coupling products and H<sub>2</sub> have been obtained by the coupling of two catalytic cycles.<sup>[10]</sup> Based on these results, we questioned whether oxonium species could be obtained from benzylic ethers with H<sub>2</sub> emission by using an appropriate photosensitizer and a cooperative catalyst. More specifically, we focused our attention on 9-mesityl-10-methylacridinium perchlorate (Acr<sup>+</sup>-Mes ClO<sub>4</sub><sup>-</sup>), one of the strongest oxidizing photosensitizers ( $E_{1/2}^{red}$  = + 2.06 V vs. SCE), which can oxidize alkyl aromatic compounds to produce the radical cation of the aromatic ring.<sup>[11]</sup> For the cooperative catalyst, we chose a cobaloxime complex, which can efficiently accept electrons and thereafter reduce protons to H<sub>2</sub>.<sup>[12]</sup> We envisioned that the benzylic C-H oxidation step would be electronically balanced by a photocatalyst-mediated reduction of the cobaloxime complex. The successful application of this strategy for the activation of a C(sp<sup>3</sup>)–H bond adjacent to an O atom is described as follows (Scheme 3).



Scheme 3. Cross-coupling hydrogen-evolution transformation of isochromans and  $\beta$ -keto esters by visible-light catalysis.

To begin this study, isochroman (**1a**) and ethyl acetoacetate (**2a**) were chosen as the standard substrates for the desired coupling reaction. As shown in Table 1, 5 mol% of Acr<sup>+</sup>-Mes  $ClO_4^-$  and 10 mol% of Co(dmgBF<sub>2</sub>)<sub>2</sub>·2 MeCN (dmg=dimethyl-glyoxime) were added to a solution of **1a** and **2a** in an organic solvent under ambient argon atmosphere. After 24 h of irradiation with blue LEDs ( $\lambda = 450 \pm 10$  nm), 64% and 57% yield of the desired crossing-coupling product **3a** and H<sub>2</sub> were obtained, respectively, with 70% conversion of **2a** in CH<sub>2</sub>Cl<sub>2</sub> (Table 1, entry 1). A comparative experiment revealed that the generated amount of H<sub>2</sub> actually contains two parts: one results from isochroman deprotonation (Table S1), because part of isochroman plays the role of sacrificial electron donor and proton source for the generation of H<sub>2</sub>, and the other is due to



[a] Isochroman **1a** (0.4 mmol), ethyl acetoacetate **2a** (0.2 mmol), Acr<sup>+</sup> -Mes (0.01 mmol, 5 mol%), Co(dmgBF<sub>2</sub>)<sub>2</sub>·2MeCN (0.02 mmol, 10 mol%), and metal salt (0.02 mmol, 10 mol%) in solvent (1 mL) were irradiated by blue LEDs for 24 h under argon atmosphere. [b] Determined by <sup>1</sup>HNMR spectroscopy using an internal standard. [c] Determined by gas chromatography using an internal standard. [d] The amount of H<sub>2</sub> that was generated by isochroman deprotonation has been deducted. [e] Co(dmgH)<sub>2</sub>pyCl instead of Co(dmgBF<sub>2</sub>)<sub>2</sub>·2MeCN, or light. n.d.=not determined.

the pseudo-cross-coupling  $H_2$  evolution. For clarity, we subtracted the amount of  $H_2$  from isochroman itself and would present the yield of  $H_2$  only for the cross-coupling reaction throughout this work.

Next, a few common solvents were examined, with MeCN providing the optimal medium and being selected for further optimizations (Table 1, entry 2). Then, we aimed at improving the yield of H<sub>2</sub>; we expected that H<sub>2</sub> emission could be facilitated by the presence of certain transition-metal salts, which have the ability of activating the nucleophile and the benzylic C-H bonds.<sup>[3]</sup> Several readily accessible and inexpensive copper and iron salts, such as CuBr<sub>2</sub>, CuCl<sub>2</sub>, Cu(OTf)<sub>2</sub>, and FeCl<sub>3</sub>, were then screened. Most of them proved unsuccessful, except for a catalytic amount of Cu(OTf)<sub>2</sub>. It is important to note that under this conditions almost complete conversion of 2a (95%) and good yields for 3a (89%) and H<sub>2</sub> (88%) were achieved (Table 1, entry 6). Additionally, replacing Co(dmgBF<sub>2</sub>)<sub>2</sub>·2 MeCN with Co(dmgH)<sub>2</sub>pyCl (py = pyridine)diminished the reaction efficiency (Table 1, entry 8). A control experiment proved the requirement of light, a cobaloxime complex  $(Co(dmgBF_2)_2 \cdot 2 MeCN)$ , and a photosensitizer (Acr<sup>+</sup>-Mes ClO<sub>4</sub><sup>-</sup>), since the reaction did not proceed in the absence of these components (Table 1, entry 9).

Under the optimized conditions, various active  $\beta$ -keto esters were then treated in the nucleophilic addition with isochroman variants; representative results are listed in Table 2. Both aliphatic and electronically varied aromatic  $\beta$ -keto esters were effective in the reaction. There was no evident difference in the reactivity among them, and the desired cross-coupling products and H<sub>2</sub> were obtained in moderate to good yields with a diastereomeric ratio of 1:1 to 1:2. Owing to the impor-

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Table 2. Cross-coupling hydrogen-evolution transformation of isochromans and  $\beta$ -

Co(angls/ $_{2/2}$  MeCN (0.02 mmol, 10 mol%), and Cu(O17)<sub>2</sub> (0.02 mmol, 10 mol%) in MeCN (1 mL) were irradiated by blue LEDs for 24 h under argon atmosphere. [b] Yields of isolated products. The ratio of the two diastereomers is reported in parentheses. [c] Determined by gas chromatography using an internal standard. [d] The amount of H<sub>2</sub> that was generated by isochroman deprotonation has been deducted. [e] The amount of H<sub>2</sub> caused by isochroman decomposition was higher than that of the reaction evolution.

tance of the chloro-functionality in organic synthesis, we were delighted to find that product **3g** was obtained in a relatively high yield. However, the use of butyl acetoacetate provided  $H_2$  and the desired product in small amounts, which could hardly be separated from undesired side products. In addition, we at-

tempted to utilize other types of nucleophiles, such as 1,3-dicarbonyl compounds (2,4-pentanedione), and the coupling product was obtained in a reasonable yield while the corresponding H<sub>2</sub> was not observed. Subsequently, the substituent effect of isochroman was investigated. Alkyl substituents, such as a methyl group at C5 or C7 and a tert-butyl group at C7 of the isochroman, resulted in slightly reduced yields compared with the model reaction, probably owing to the increased steric hindrance. In sharp contrast, a methoxy substituent at the C7 position and 4-methoxymethyl anisole afforded no reaction. This observation was consistent with the mechanistic studies of DDQ-mediated ether functionalizations by Floreancig.<sup>[13]</sup> Although attaching an electron-donating group to the substrate would lower its oxidation potential, it would form a stabilized aromatic radical cation upon single-electron oxidation and increase the bond-dissociation energy of the benzylic C-H bond. It also demonstrated that the formation of an aromatic radical cation prior to benzylic C-H bond cleavage was not rate determining. Therefore, a similar key intermediate (aromatic radical cation) probably exists in our reaction pathway. Given the relatively high oxidation potential of the electron-poor aromatic moiety, a very low cross-coupling yield (< 20%) was obtained when a chloro-substituent was placed at the C7 position. This partly indicates that the isochroman derivative initially loses the electron of the aromatic group to form the aromatic radical cation. When using an acylic substrate (1-(methoxymethyl)-4-methylbenzene), no cross-coupling product was observed, while 4-methylbenzaldehyde was the main identifiable product through analyzing the <sup>1</sup>H NMR spectra of the reaction mixture.

To obtain further information on the reaction pathway, we investigated the reaction of [D2]-1a with [D<sub>2</sub>]-2a under the same conditions (Scheme 4a). After purification, the corresponding cross-coupling product  $[D_2]$ -**3 a**<sup>[14]</sup> was obtained in 75% yield and  $D_2$ (instead of H<sub>2</sub>) was detected. Furthermore, no deuterium incorporation of 3a or D<sub>2</sub> was observed in the reaction of 1a with 2a in CD<sub>3</sub>CN (Scheme 4b). These results indicate that the source of H atoms in the product H<sub>2</sub> derives from the  $\alpha$ -proton of **1a** and the activated methylene proton of 2a. Subsequently, as shown in Scheme 4c, we investigated the kinetic isotopic effect (KIE) by competition experiments. The intermolecular  $k_{\rm H}/k_{\rm D}$  was determined to be 2.3 based on <sup>1</sup>H NMR spectroscopic analysis of the isolated products. This isotopic effect implies that benzylic C-H bond cleavage is probably involved in the rate-de-

termining step of the reaction.

Furthermore, we conducted a series of time-resolved transient absorption spectrum measurements with  $Acr^+-Mes\ ClO_4^-$ , **1 a**, and  $Co(dmgBF_2)_2\cdot 2MeCN$ . Considering the transient absorption of electron-transfer state of  $Acr^+-Mes\ (Acr^--Mes^{++})$  at

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Scheme 4. Deuterium experiments.

500 nm,<sup>[11a]</sup> this kinetic decay of transient absorption clearly demonstrates that both isochroman and the cobaloxime complex indeed decrease the lifetime of Acr<sup>-</sup>Mes<sup>++</sup> with increasing concentration of either (Figure 1 a and c). In addition, the rate constant for the addition of **1 a** was determined from the slope of the liner plot of  $k_{decay}$  versus [**1 a**] to be  $3.5 \times 10^8 \text{ m}^{-1} \text{ s}^{-1}$ , and Co(dmgBF<sub>2</sub>)<sub>2</sub>·2 MeCN had a comparative quenching rate constant of  $9.0 \times 10^8 \text{ m}^{-1} \text{ s}^{-1}$  (Figure 1 b and d). These observations collectively support that the oxidative and reductive quench-



ing proceed simultaneously in this new photoredox coupling reaction. In other words, the single-electron transfer (SET) process occurs not only between Acr<sup>-</sup>-Mes<sup>++</sup> and **1** a, but also between Acr<sup>-</sup>-Mes<sup>++</sup> and Co(dmgBF<sub>2</sub>)<sub>2</sub>·2 MeCN.

In view of these experimental results, a possible mechanistic rationale of this transformation is outlined in Scheme 5. The initial step involves an intramolecular photoinduced electron transfer from the mesitylene moiety to the singlet excited state of the acridinium ion, resulting in the formation of an extremely long-lived (e.g., 2 h at 203 K)<sup>[11a]</sup> electron-transfer state (Acri-

Mes<sup>++</sup>). The acridinyl radical moiety delivers an electron to  $Co(dmgBF_2)_2 \cdot 2$  MeCN, whereas the Mes<sup>++</sup> moiety accepts an electron from isochroman (**1 a**). After that, the photosensitizer (Acr<sup>+</sup>-Mes) is regenerated. Subsequently, the produced radical cation **4** leads to the corresponding oxocarbenium intermediate **6** through deprotonation, followed by a second electron transfer. When two equivalents of 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) or 2,6-di-tert-butyl-4-methylphenol (BHT) were added into the reaction system, nearly no product was gener-

ated. This observation suggests that a radical intermediate **5** might be involved in the reaction pathway. Meanwhile, the one-electron-reduced form of the cobaloxime complex, which then accepts a proton, is responsible for the evolution of  $H_2$ . Finally, the attack of nucleophile (**2a**), activated by a Cu<sup>II</sup> salt, onto the oxonium species furnishes the C–C coupling product (**3a**).

In conclusion, we have developed an efficient method for the visible-light-promoted utilization of oxocarbenium ions. Although to date the scope of ethers is limited to a certain extent, we were able to realize the addition of a variety of  $\beta$ -keto esters to oxonium species, which are generated by photocatalytic C–H bond oxidation. We also found that this photocatalytic reaction requires no sacrificial oxidants as it proceeds via a redox neutral pathway. Remarkably, the results



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d) Plot of k<sub>decay</sub> versus [Co(dmgBF<sub>2</sub>)<sub>2</sub>·2 MeCN] for the reaction of Acr<sup>-</sup>-Mes<sup>++</sup> with Co(dmgBF<sub>2</sub>)<sub>2</sub>·2 MeCN.



Scheme 5. Plausible mechanism.

described herein provide a generic catalytic approach to the direct photoredox-mediated functionalization of  $C(sp^3)$ –H bonds adjacent to the O atom of ethers at room temperature. Further work to broaden the synthetic application of the oxonium species under visible-light irradiation is in process.

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