

# Boronic Acid-Mediated Photocatalysis Enables the Intramolecular Hydroacylation of Olefins Using Carboxylic Acids

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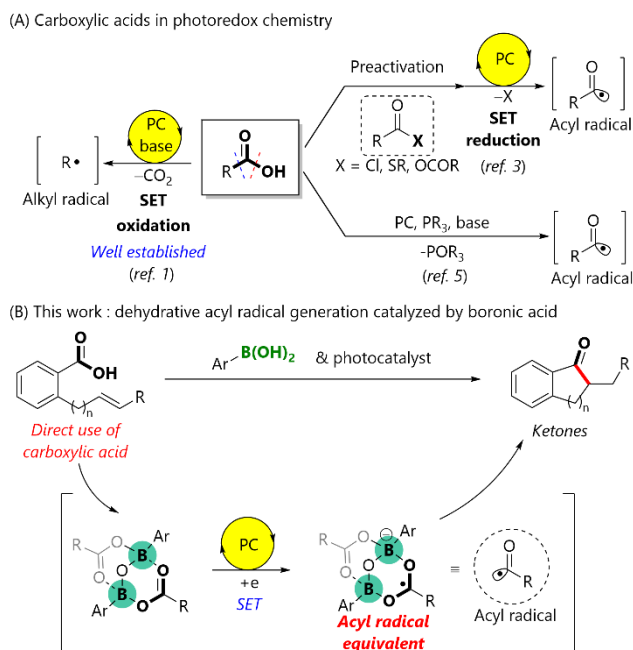
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**Abstract:** An intramolecular hydroacylation of olefins using carboxylic acids (CAs) has been developed. With the aid of a boronic acid, CAs can be used as acyl-radical precursors in catalytic photoredox reactions driven by visible light. The CAs are easily converted into their corresponding cyclic ketones without the need to use any stoichiometric activating reagents. Mechanistic studies implied that the formation of an “ate” complex from the CA and boronic acid is crucial for the generation of the acyl radical equivalent from the unreactive carboxy group.

## Introduction

Carboxylic acids (CAs) are abundant and inexpensive feedstock chemicals that can be easily accessed and exhibit great structural diversity. Therefore, much research effort has been dedicated to a wide variety of transformations that employ CAs, including radical reactions. Recently, visible-light-driven photoredox catalysis has emerged as a powerful tool in organic synthesis, which has further promoted the use of CAs, in this case as radical precursors (Scheme 1A).<sup>[1]</sup> It is well established that carboxy groups may be converted into alkyl radical intermediates via CO<sub>2</sub> extrusion following single-electron oxidation. However, the generation of acyl radicals from CAs is also a potentially attractive synthetic approach when one considers the ubiquity of the carbonyl group in organic synthesis.<sup>[2]</sup> To afford an acyl radical, the carboxy group must be transformed into a reactive CA derivative such as an acyl chloride,<sup>[3a,b]</sup> a carboxylic anhydride,<sup>[3c]</sup> or a thioester.<sup>[3d,e]</sup> This is due to the difficulty of single-electron reductions of CAs. These transformations of the carboxy group require stoichiometric activating reagents. In this context, an approach for the direct generation of acyl radicals from CAs has been developed, which is based on the reaction of a phosphine radical cation with a carboxylate to form a phosphoranyl radical while subsequent  $\beta$ -scission generates an acyl radical.<sup>[4,5]</sup> However, this method requires the use of a stoichiometric quantity of a phosphine to activate the CA. Despite the current high demand for environmentally friendly synthetic methods, a catalytic method for the generation of an acyl radical from CAs has not been reported. We envisaged that boronic acid would be able to catalyze the dehydrative generation of an acyl radical directly from a CA. Boronic acids have recently been used for catalytic dehydrative condensations,<sup>[6,7]</sup> whilst Whiting and co-workers

have reported that boronic acids form a dimer complex with CAs to accelerate the nucleophilic attack of an amine.<sup>[8]</sup> We anticipated that the formation of such a complex would also accelerate the single-electron reduction of CAs by lowering the LUMO and provide an acyl radical equivalent (Scheme 1B).<sup>[9]</sup> Herein, we demonstrate the intramolecular hydroacylation of olefins with CAs promoted by dual catalytic cycles that employ an arylboronic acid and a photocatalyst.



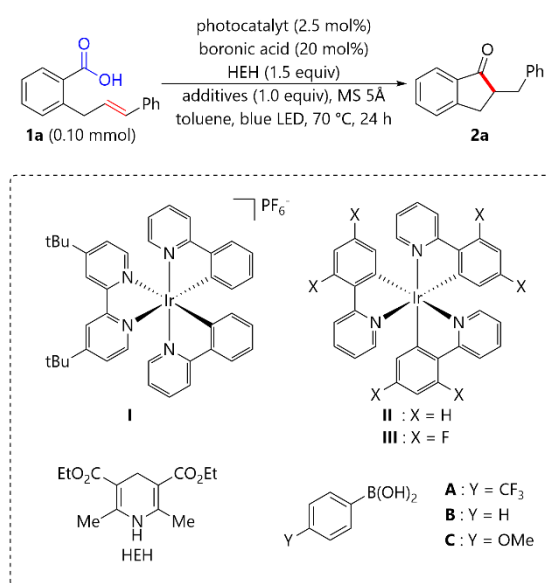
**Scheme 1.** Generation of radicals from carboxylic acids.

## Results and Discussion

Initially, we investigated the reaction conditions required to achieve the intramolecular cyclization of CA **1** using a photocatalyst (**PC**) and a boronic acid catalyst (Table 1). The screening of the **PCs** revealed that all three photocatalysts could afford the desired cyclization product **2a** (entries 1-3), and that *fac*-Ir(dFppy)<sub>3</sub> (**PC III**;  $E_{1/2}[\text{Ir}^{\text{III}*}/\text{Ir}^{\text{II}}] = +0.75 \text{ V vs SCE}$ ;  $E_{1/2}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -2.0 \text{ V vs SCE}$ )<sup>[10]</sup> provided the highest yield (44%) in the presence of Hantzsch ester (HEH) and 5 Å molecular sieves (MS) in toluene under blue LED irradiation (entry 3). Next, we screened a series of aryl boronic acids and found that one substituted with an electron-withdrawing group was most effective, probably due to the increased electrophilicity of boronic acid **A** (for details, see the Supporting Information). Considering that, as observed via <sup>1</sup>H NMR spectroscopy, HEH was consumed faster than **2a** was produced (for details, see the Supporting Information), we then investigated an additional electron or hydrogen-atom source in order to improve the yield. While increasing the amount of HEH used did not affect the yield (entry 6), the addition of *i*-Pr<sub>2</sub>Net, which is often used as a sacrificial reductant in photoredox reactions, significantly inhibited the reaction. This is probably because the CA is

deprotonated and thus, the complexation of the boronic acid and CA is inhibited (entry 7). The addition of a hydrogen-atom donor such as a thiol or silane was ineffective (entries 8 and 9). On the other hand,  $\gamma$ -terpinene improved the yield of **2a** to 57% (entry 10). Finally, cyclized **2a** was obtained in 66% yield by adding the photocatalyst and HEH in two portions (entry 11). Importantly, control experiments showed that each component of the reaction, i.e., the photocatalyst, boronic acid, HEH, 5Å MS, and blue LED irradiation were all essential for this transformation to proceed (see entry 12 and details in the Supporting Information).

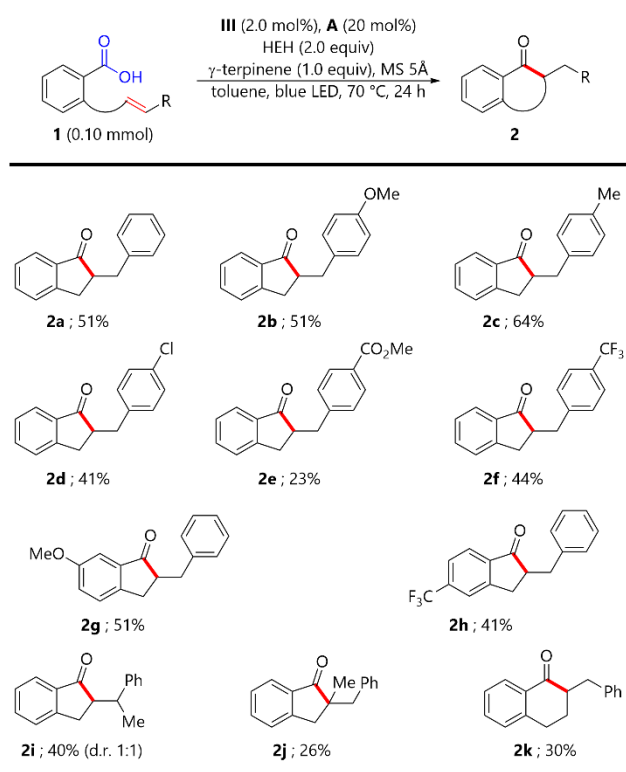
**Table 1.** Optimization of the reaction conditions.



Entry	Photocatalyst	ArB(OH) <sub>2</sub>	Additives	Yield (%) <sup>[a]</sup>
1	<b>I</b>	<b>A</b>	none	7
2	<b>II</b>	<b>A</b>	none	26
3	<b>III</b>	<b>A</b>	none	44
4	<b>III</b>	<b>B</b>	none	21
5	<b>III</b>	<b>C</b>	none	9
6 <sup>[b]</sup>	<b>III</b>	<b>A</b>	none	46
7	<b>III</b>	<b>A</b>	<i>i</i> -Pr <sub>2</sub> NEt	7
8 <sup>[c]</sup>	<b>III</b>	<b>A</b>	4-MeOC <sub>6</sub> H <sub>4</sub> SH	0
9 <sup>[c]</sup>	<b>III</b>	<b>A</b>	Ph <sub>3</sub> SiH	32
10 <sup>[c]</sup>	<b>III</b>	<b>A</b>	$\gamma$ -terpinene	57
11 <sup>[d]</sup>	<b>III</b>	<b>A</b>	$\gamma$ -terpinene	66
12 <sup>[c]</sup>	<b>III</b>	none	$\gamma$ -terpinene	0

[a] Yields were determined using <sup>1</sup>H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard. [b] 3.0 equiv. of HEH were employed. [c] 12 hours. [d] **III** (2 mol%) and HEH (2.0 equiv.) were added in two portions, i.e., at the start of the reaction and after 12 hours.

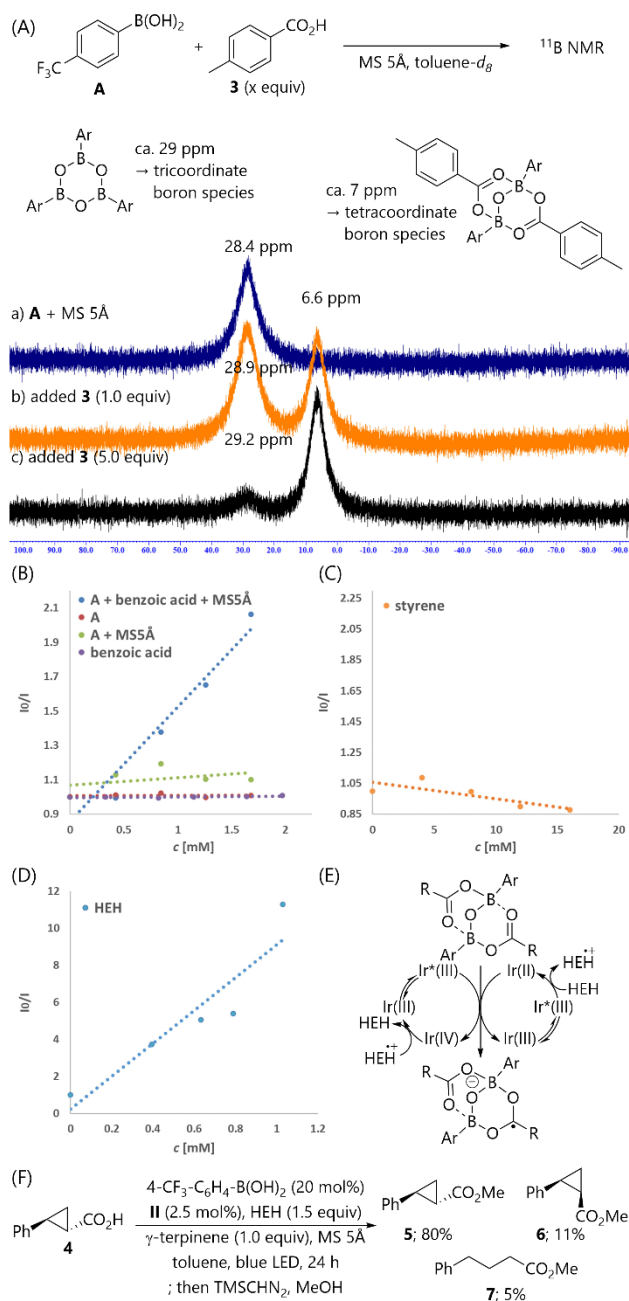
With the optimal reaction conditions in hand, we investigated the substrate scope of the intramolecular hydroacylation (Scheme 2).<sup>[11]</sup> Styrene motifs that bear both electron-donating (e.g., -Me or -OMe) and -withdrawing (e.g., -Cl, -CO<sub>2</sub>Me, or -CF<sub>3</sub>) substituents at the *para* position of the aromatic ring were well tolerated under the applied conditions, albeit that electron-withdrawing groups tend to slightly decrease the yield (**2a–f**). Methoxy-substituted and trifluoromethyl-substituted benzoic acids also afforded cyclization products **2g** and **2h** in moderate yield. Methyl substitution of the styrene was also compatible with the reaction conditions (**2i**, **2j**). However, the yield decreased when a  $\beta$ -substituted styrene was used, probably due to increased steric hinderance during the cyclization step (**2j**). This transformation may also be used to furnish a 6-*exo* cyclization that produces an  $\alpha$ -tetralone structure (**2k**).



**Scheme 2.** Substrate scope of the reaction. Isolated yields are shown.

To obtain mechanistic insights into this intramolecular hydroacylation reaction, we conducted several experiments (Figure 1). Firstly, we confirmed the formation of a dimer complex, as reported by Whiting's group,<sup>[8]</sup> under the applied reaction conditions. When boronic acid **A** was premixed with 5Å molecular sieves, only one peak was observed in the <sup>11</sup>B NMR spectrum (Figure 1A, a)). This peak ( $\delta$  ca. 29 ppm) was assigned to a tricoordinate boron species and is likely to be a boroxine derived from boronic acid **A**.<sup>[8]</sup> Upon addition of 1 equivalent of *p*-toluic acid (**3**), another <sup>11</sup>B NMR peak ( $\delta$  ca. 7 ppm) emerged and the addition of 5 equivalents of **3** resulted in almost full conversion of the peak in the <sup>11</sup>B NMR spectrum (Figure 1A, b) and c)). The new peak is located in the region

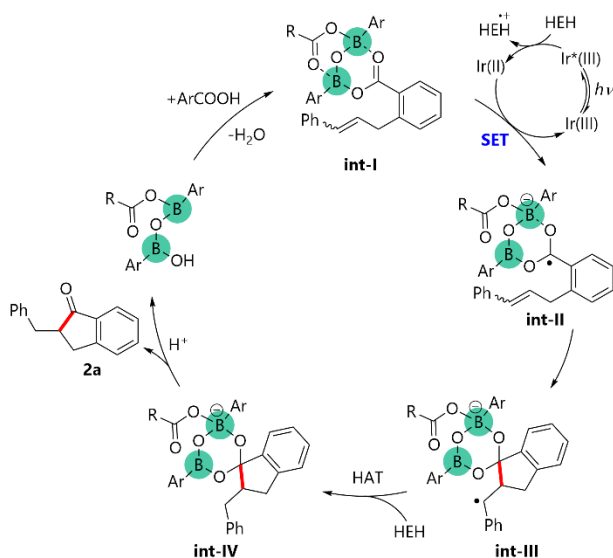
where tetracoordinate “ate” complexes of boronic acid are found and is similar to the peak of a dimer complex reported by Whiting and co-workers.<sup>[8]</sup> Moreover, the tetracoordinate complex predominantly forms in the presence of an excess of CA **3**; therefore, we speculate at this point that the tetracoordinate boron species, which is most likely the dimer complex, may be an active species in this catalytic photoredox reaction.



**Figure 1.** Mechanistic investigations. (A)  $^{11}\text{B}$  NMR spectra of mixtures of *p*-toluic acid (**3**), boronic acid **A** in the presence of  $5\text{\AA}$  MS. (B) Stern-Volmer quenching of  $\text{Ir}(\text{dFppy})_3$  vs. only boronic acid **A**, benzoic acid or boronic acid **A** in the presence of benzoic acid (13.48 mM) and  $5\text{\AA}$  MS in toluene. (C) Stern-Volmer quenching of  $\text{Ir}(\text{dFppy})_3$  vs. styrene in toluene. (D) Stern-Volmer quenching of  $\text{Ir}(\text{dFppy})_3$  vs. Hantzsch ester in  $\text{CH}_2\text{Cl}_2$ . (E) Two possible photocatalytic cycles. (F) Radical clock experiment.

Next, we performed luminescence-quenching experiments on the iridium photocatalyst in order to determine which species undergo single-electron reduction. The Stern-Volmer plots revealed that an excited state of photocatalyst **III** is quenched by a benzoic acid and boronic acid complex that is formed *in situ*. No remarkable luminescence quenching was observed when only benzoic acid was used (Figure 1B). Additionally, boronic acid **A** was not quenched, regardless of whether the 5Å molecular sieves were present or not. These results suggest that the boronic acid and its boroxine form are not involved in the redox processes and that a CA can become the redox-active species by forming the afore-mentioned tetracoordinate complex. Styrene did not undergo luminescence quenching either. This result indicates that the styrene moiety only functions as a radical acceptor (Figure 1C). On the other hand, HEH quenched the excited state of photocatalyst **III** (Figure 1D). The quenching of **III** by HEH produced an Ir(II) species ( $E_{1/2}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -2.0 \text{ V vs SCE}$ ) that is a stronger reductant than Ir\*(III) ( $E_{1/2}[\text{Ir}^{\text{III}*}/\text{Ir}^{\text{IV}}] = -1.46 \text{ V vs SCE}$ ),<sup>[10]</sup> and that can also undergo single-electron transfer to the tetracoordinate boron complex. Thus, both an Ir(II/III) and Ir(III/IV) photocatalytic cycle are possible in this reaction (Figure 1E).<sup>[12]</sup> In any case, these experiments showed that, as initially expected, boronic acid plays an important role in the single-electron reduction of CAs.

Finally, we conducted a radical-clock experiment to confirm the generation of a radical on the carbonyl carbon atom (Figure 1F). The reaction of cyclopropane CA **4** provided the ring-opened product **7** and *syn*-isomer **6**, although at a low conversion. Thus, this result supports the generation of a radical on the carbonyl carbon atom, where  $\beta$ -scission is promoted in order to release the ring strain of the cyclopropane.



**Figure 2.** A plausible catalytic cycle.

Based on the experiments described above, a plausible reaction mechanism is shown in Figure 2. Firstly, the CA and boronic acid would form complex **int-I** in the presence of the molecular sieves.

Next, a single-electron transfer to **int-I** from either a photoexcited Ir(III) or Ir(II) species would occur, resulting in the generation of acyl radical equivalent **int-II**. This radical would undergo addition to the pendant olefin and form a cyclic intermediate **int-III** with a benzyl radical. Hydrogen atom transfer from HEH or  $\gamma$ -terpinene to this benzyl radical intermediate and successive protonation would result in the formation of a cyclic ketone with concomitant recovery of the boronic acid catalyst.

## Conclusions

In summary, we have developed an intramolecular hydroacylation reaction of olefins using carboxylic acids (CAs) based on a dual-catalyst system that employs boronic acid and an iridium complex. This system effectively promotes the radical cyclization and the cyclic ketones were obtained without any preactivation of the unreactive carboxy group. A mechanistic analysis implied that the tetracoordinate boron complex derived from the boronic-acid catalyst and the CA plays a crucial role in the photocatalyzed radical reaction. We are currently exploring applications of this strategy and further mechanistic details of this transformation.

## Experimental Section

General procedure for the hydroacylation. A borosilicate tube was charged with a stirrer bar, benzoic acid (0.10 mmol, 1.0 equiv.), diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (25.3 mg, 0.10 mmol, 1.0 equiv.), photocatalyst **III** (0.8 mg, 0.001 mmol, 1 mol%), boronic acid **A** (3.8 mg, 0.020 mmol, 20 mol%), and 5Å molecular sieves (100 mg). The reaction vessel was then placed into a glove box.  $\alpha$ -Terpinene (16.0  $\mu$ L, 0.10 mmol, 1.0 equiv.) and toluene (2.0 mL) were added to the mixture. The tube was capped, removed from the glove box, and placed in a photoreactor. After stirring for 12 h under blue LED irradiation at 70 °C, the tube was placed in a glove box, where further **III** (0.8 mg, 0.0010 mmol, 1.0 mol%) and diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (25.3 mg, 0.10 mmol, 1.0 equiv.) were added to the mixture. The tube was capped, removed from the glove box, and placed in the photoreactor. After stirring for 12 h under blue LED irradiation at 70 °C, the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was purified using column chromatography to afford the desired ketone.

## Acknowledgements

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**Keywords:** Acyl radical • Boronic acid • Carboxylic acids • Dual catalysis • Photocatalysis

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