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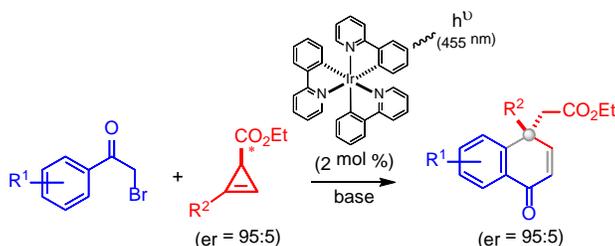
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# Visible-Light Mediated Addition of Phenacyl Bromides onto Cyclopropenes.

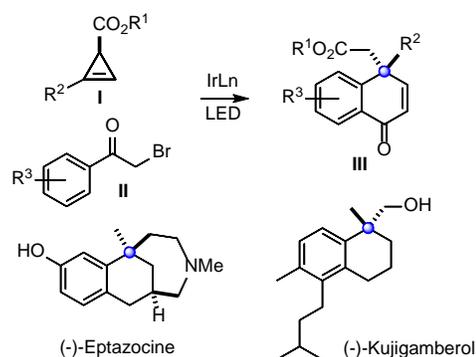
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**ABSTRACT:** Visible-light promoted addition of  $\alpha$ -bromoacetophenones onto the cyclopropene  $\pi$ -system in the presence of the *fac*-Ir(ppy)<sub>3</sub> catalyst was shown to afford the corresponding 1(4H)-naphthalenones. The *syn*-carbonylation of the cyclopropene is followed by a cyclopropane ring opening under the basic conditions, allowing the formation of two C-C bonds and the generation of 1(4H)-naphthalenones bearing an all-carbon benzylic quaternary stereocenter.

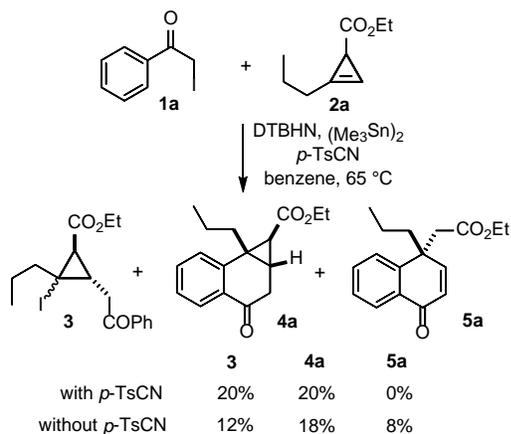
Cyclopropenes exhibit remarkable reactivity and behave both as electrophilic and nucleophilic species.<sup>1</sup> The high acidity of the olefinic protons, due to ring strain, allows their easy deprotonation and further functionalization with electrophiles, while their electrophilicity is revealed during addition of organometallic species, including hydrides, Grignard reagents, organocuprates, zinc and indium reagents. Cyclopropenes may be accessed by a number of methods and are readily available in enantiopure form through metal-catalyzed cyclopropanation of the corresponding alkynes.<sup>2</sup> These small ring systems thus continue to attract a great deal of interest, but surprisingly, few studies have been reported on their free-radical functionalization. Nakamura *et al.* first reported cyclopropene radical hydrostannation in 1994.<sup>3a</sup> Xanthate- but also bromine atom transfer processes were later described respectively by Saicic,<sup>3b</sup> Zard,<sup>3c</sup> Miyata, Ueda and co-workers.<sup>3d,e</sup> Recent work from our laboratory further enriched this field, with the development of a tin-mediated carbocyanation of cyclopropenes.<sup>4</sup> As a continuation of this work, we report here on the photoredox-catalyzed addition<sup>5</sup> of  $\alpha$ -bromoacetophenones **II** onto cyclopropenes **I** and the subsequent cyclopropane ring-opening, providing a straightforward access to naphthalenones **III** bearing a benzylic quaternary stereocenter, which stereochemistry is controlled early during the cyclopropene synthesis (Figure 1). Such a cyclopropene carbonylation should open an access to useful synthons for organic synthesis, the skeleton of which is found in natural products such as labdane terpenoid (-)-kujigamberol<sup>6a</sup> or the synthetic analgesic (-)-eptazocine.<sup>6b</sup>



**Figure 1.** Visible-light mediated addition of phenacyl bromides to cyclopropenes.

In contrast with our recent studies,<sup>4,7</sup> the carbocyanation of cyclopropene **2a**, using  $\alpha$ -iodoacetophenone **1a** in the presence of *p*-TsCN, (Me<sub>3</sub>Sn)<sub>2</sub> in benzene at 65 °C and di-*t*-butylhyponitrite (DTBHN) as an initiator, did not provide the carbocyanation product, but instead the atom-transfer product **3**, and unexpectedly the cyclized product **4a** in a 1:1 ratio (Scheme 1). Repeating the experiment without *p*-TsCN led to the same products along with the naphthalenone **5a**, which was shown to result from the cyclopropane ring-opening of **4a** under the reaction conditions.

**Scheme 1.** Addition of  $\alpha$ -iodoacetophenone **1a** to cyclopropene **2a**.



Intramolecular carboarylation of olefins has precedent in the literature but to our knowledge has not been reported with cyclopropenes.<sup>8</sup> Therefore, considering the synthetic value of compounds such as **5** (*vide supra*), we focused our attention on the development of their one-pot preparation from phenacyl halides and cyclopropenes, relying on an environmentally more benign initiation process than the one used above (Scheme 1). Pioneering studies by Stephenson *et al.*<sup>5b,8a,9</sup> have established that photoredox-catalyzed atom-transfer radical processes using  $\alpha$ -haloacetophenones were efficiently performed under mild conditions using Ru or Ir catalysts and simple LED irradiation. Optimization of the reaction was thus carried out using several photocatalysts, varying the nature of the base and solvents (Table 1).  $\alpha$ -Bromoacetophenone **1b** was used instead of **1a** to minimize the atom-transfer reaction. The transformation was first carried out using cheaper  $\text{Ru}(\text{bpy})_3\text{Cl}_2$  (2 mol %),  $\text{Et}_3\text{N}$  as a base and  $\text{LiBr}^9$  as an additive (Table 1, entry 1). This provided the desired naphthalenone **5a**, albeit in low yield. Better yield was observed when the reaction was performed in a DMF- $\text{H}_2\text{O}$  mixture (Table 1, entry 2). In the absence of  $\text{Et}_3\text{N}$ , **4a** was obtained without any trace of **5a**, indicating that the base was required for the ring-opening, but not for the photocatalyst turnover (Table 1, entry 3) (*vide infra*). *fac*- $\text{Ir}(\text{ppy})_3$  was then tested and displayed lower efficiency under these conditions (Table 1, entry 4). Higher amount of **5a** was however isolated with this catalyst, when  $\text{K}_2\text{CO}_3$  was used as a base (Table 1, entry 5). Interestingly, we noticed that **5a** was decomposed upon long exposure to the LED irradiation. Therefore, the carboarylation process was then performed during 12 h under irradiation, at which time **4a** was the major product formed. Then the lamp was switch-off and the ring-opening completed by a gentle heating at 60 °C (Table 1, entry 6). Slightly higher yields were also obtained at higher concentration (0.2 M) (Table 1, entry 7). An increase of the concentration (0.4 M) or a decrease (0.05 M) led to lower yields. Catalyst loading was also varied, indicating that 2 mol % was optimal for this reaction (Table 1, entries 8-9). Finally, the reaction was carried out in the absence of light and photocatalyst, leading in both cases to no product, thus demonstrating the crucial and cooperative role of the Ir complex and visible-light irradiation (*vide infra*).

The scope of the reaction was then established using optimized conditions (Table 1, entry 7) on a series of acetophenones **1b-k** and cyclopropenes **2a-j**, leading to naphthalenones **5a-t**, in moderate yields (Scheme 2). Higher yields are obtained with electron-donating substituents ( $\text{R}^2$ ) on the phenacyl moiety, illustrating the influence of electronic effects in the process. For instance, when a *p*-CN substituent was present on the acetophenone, the corresponding unsaturated ketone **5f** was not formed,

and large amount of *p*-cyanoacetophenone was recovered instead, indicating that reduction of the bromide was a competing pathway (*vide infra*).<sup>10</sup>

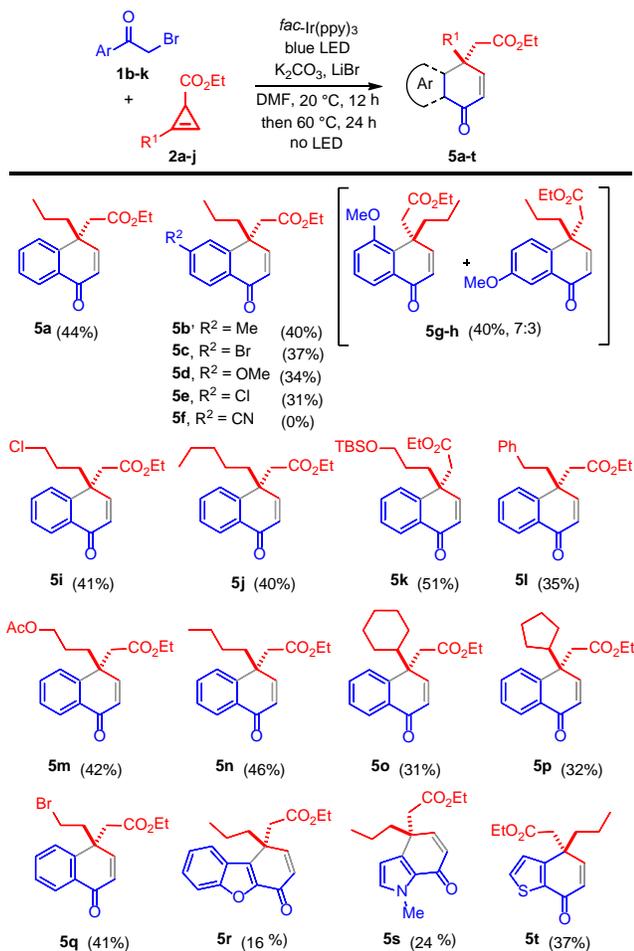
**Table 1.** Optimization of the carboarylation of cyclopropene **2a**.

entry	cat.	additive	solvent	Time (h)	yield% <sup>b</sup>
1	$\text{Ru}^{\text{II a}}$	$\text{Et}_3\text{N}$ , $\text{LiBr}$	DMF	72	10
2	$\text{Ru}^{\text{II a}}$	$\text{Et}_3\text{N}$ , $\text{LiBr}$	DMF- $\text{H}_2\text{O}^{\text{c}}$	72	30
3	$\text{Ru}^{\text{II a}}$	$\text{LiBr}$	DMF- $\text{H}_2\text{O}^{\text{c}}$	72	- <sup>d</sup>
4	$\text{Ir}^{\text{e}}$	$\text{Et}_3\text{N}$ , $\text{LiBr}$	DMF- $\text{H}_2\text{O}^{\text{c}}$	72	15
5	$\text{Ir}^{\text{e}}$	$\text{K}_2\text{CO}_3$	DMF	72	34
6	$\text{Ir}^{\text{e}}$	$\text{K}_2\text{CO}_3$ , $\text{LiBr}$	DMF	12 <sup>f</sup>	40
7	$\text{Ir}^{\text{e}}$	$\text{K}_2\text{CO}_3$ , $\text{LiBr}$	DMF <sup>g</sup>	12 <sup>f</sup>	44
8	$\text{Ir}^{\text{h}}$	$\text{K}_2\text{CO}_3$ , $\text{LiBr}$	DMF <sup>g</sup>	12 <sup>f</sup>	22
9	$\text{Ir}^{\text{i}}$	$\text{K}_2\text{CO}_3$ , $\text{LiBr}$	DMF <sup>g</sup>	12 <sup>f</sup>	39
10	$\text{Ir}^{\text{e}}$	$\text{K}_2\text{CO}_3$ , $\text{LiBr}$	DMF <sup>g</sup>	120 <sup>j</sup>	-
11	- <sup>k</sup>	$\text{K}_2\text{CO}_3$ , $\text{LiBr}$	DMF <sup>g</sup>	120	-

<sup>a</sup>  $\text{Ru}^{\text{II}}$ :  $\text{Ru}(\text{bpy})_3\text{Cl}_2$  (2 mol %). <sup>b</sup> Isolated yields. <sup>c</sup> DMF- $\text{H}_2\text{O}$  = 4:1. <sup>d</sup> **4a** was isolated (28%). <sup>e</sup> Ir: *fac*- $\text{Ir}(\text{ppy})_3$  (2 mol %). <sup>f</sup> The reaction mixture was stirred 12 h under LED irradiation, then heated 24 h at 60 °C without irradiation. <sup>g</sup> DMF (0.2 M). <sup>h</sup> *fac*- $\text{Ir}(\text{ppy})_3$  (1 mol %). <sup>i</sup> *fac*- $\text{Ir}(\text{ppy})_3$  (4 mol %). <sup>j</sup> Without LED irradiation. <sup>k</sup> Without photocatalyst.

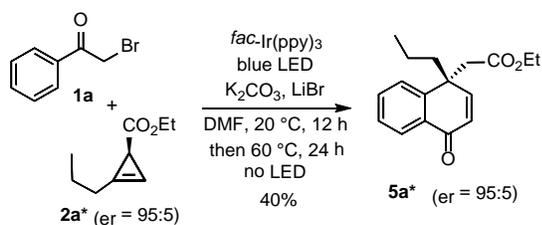
With *m*-substituted acetophenones, a mixture of regioisomers was isolated (**5g-h** Scheme 2). The size of the substituents on the cyclopropene ring has a slight influence on the process efficiency, with lower yields observed with cyclic substituents (**5o-p** Scheme 2). The reaction was compatible with the presence of silyl ethers, esters and halides as shown by the formation of **5i**, **5k** and **5m**. Interestingly, naphthalenone **5q** was formed from cyclopropene **2j** having a mesylate substituent ( $\text{R}^1 = (\text{CH}_2)_2\text{OMs}$ ), which was readily displaced *in situ* by  $\text{LiBr}$ . It is currently not established if the conversion of the mesylate into the bromide occurred before or after the photocatalyzed process. The reaction could also be performed with heteroarenes, leading to the desired compounds **5r-t**, albeit with modest yields. Finally, it is worth noticing that, although yields are generally moderate, final naphthalenones **5** are easily isolated through silica gel chromatography and obtained in only two synthetic operations from the corresponding commercially available alkenes.

**Scheme 2.** Scope of the intramolecular carboarylation of cyclopropenes **2a-j**.



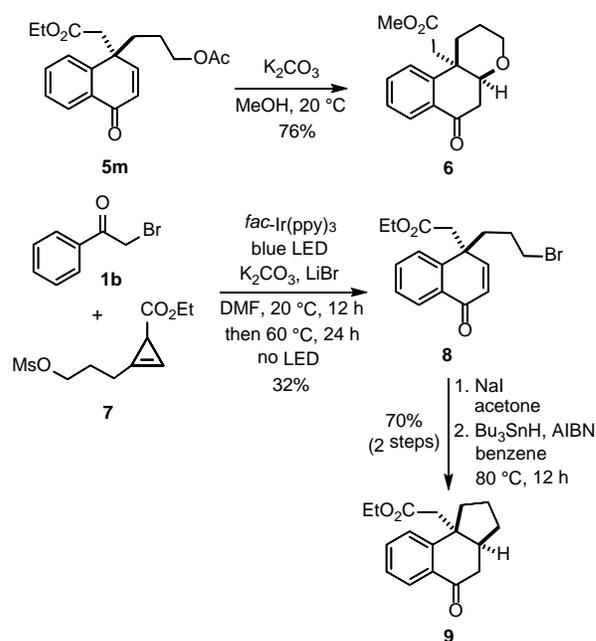
The stereochemical outcome of the carboarylation/cyclopropane ring-opening sequence was studied, applying the reaction to enantioenriched cyclopropene **2a\***, available through cyclopropanation of pent-1-yne using Corey's chiral rhodium catalyst (Scheme 3).<sup>2c</sup> **5a\*** was obtained with the same enantiomeric excess as that of the starting **2a\***, indicating that no erosion of the enantioselectivity occurred during the whole sequence.

**Scheme 3.** Intramolecular carboarylation of enantioenriched cyclopropene **2a\***.

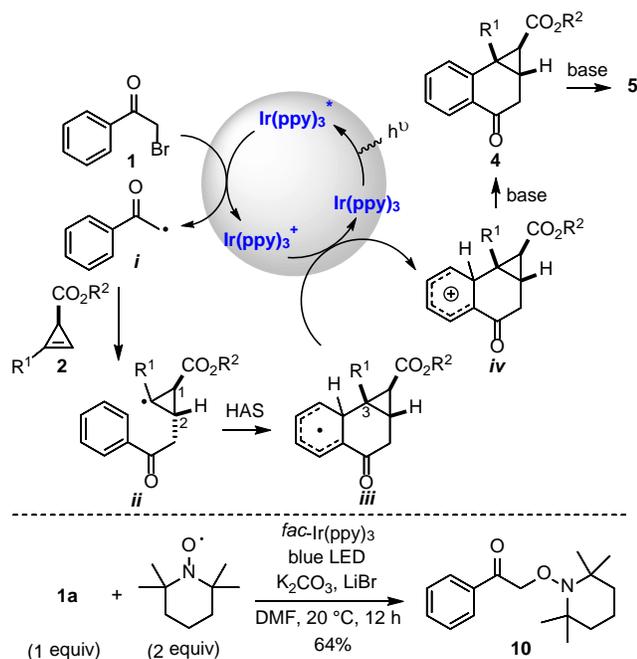


The naphthalenones obtained through this tandem process are useful precursors of polycyclic substrates, as demonstrated with the conversion of **5m** into the corresponding polysubstituted pyrane **6** through a simple treatment under basic conditions (Scheme 4). Carbocycles such as **9** may be reached in a straightforward manner starting from mesyl-cyclopropene **7** and **1b**, the conversion of which, under optimized conditions above led to the bromide **8**. Conversion of **8** into an iodide and then tin-mediated radical cyclization led to **9** as a single diastereomer.<sup>11</sup>

**Scheme 4.** Further elaboration of naphthalenones.



A mechanistic pathway was finally proposed to rationalize the course of the tandem process (Figure 2). This would involve, as a first step, a single electron transfer from the photocatalyst excited state ( $fac\text{-Ir(ppy)}_3^*$ ) to the bromide **1b**, affording the  $\alpha$ -phenacyl radical *i*.  $fac\text{-Ir(ppy)}_3^*$  exhibits a sufficiently strong reduction potential ( $E_{1/2} = -1.73\text{V vs SCE}$ )<sup>12a</sup> to convert **1b** (-0.49V vs SCE)<sup>12b</sup> into a radical-anion and then to *i*.<sup>8a,b</sup> The generation of the latter was shown by a radical trapping experiment using TEMPO, which led to the formation of **10**. When the same reaction was performed in the presence of cyclopropene **2**, **10** was also formed in 50% yield. *i* then adds onto the cyclopropene **2** to generate the highly reactive cyclopropyl radical *ii*,<sup>13</sup> which reacts intramolecularly with the arene moiety to afford the cyclohexadienyl radical *iii*. When using  $\alpha$ -iodoacetophenone, iodine atom transfer reaction was shown to compete with the intramolecular reaction (Scheme 1).<sup>14</sup> The homolytic aromatic substitution (HAS) is then completed through the oxidation of *iii* into *iv*, which rearomatizes through deprotonation under the basic conditions, to provide cyclopropane **4**. Oxidation of *iii* into *iv* is favored<sup>15</sup> due to the high oxidative power of  $\text{Ir}^+$  ( $E_{1/2} = +0.77\text{V vs SCE}$ ),<sup>5a</sup> which returns the iridium catalyst in its ground state. Single electron transfer from *iii* to **1** to generate *i* and *iv* is another option to sustain the radical chain (but not the Ir catalytic cycle).<sup>16</sup> **4** is finally converted *in situ* into naphthalenone **5** through deprotonation  $\alpha$ - to the ketone, followed by cyclopropane-ring opening.<sup>4</sup> This mechanism is consistent with the stereochemistry of **4a**, resulting from an addition of radical *i anti* relative to the ester group as in *ii*,<sup>4</sup> followed by the reaction of the cyclopropyl radical onto the arene from the same face. This *syn* addition (imposed by geometrical constraints) of the phenacyl radical across the cyclopropane  $\pi$ -system thus ensures a complete transfer of chirality from the stereocenter C1 to the newly created stereocenters at C2 and C3. Chirality at C3 is thus preserved upon base-promoted cyclopropane ring opening as shown in Scheme 3.



**Figure 2.** Proposed mechanism for the radical addition of phenacyl bromides to cyclopropenes.

In summary, we reported a straightforward synthesis of substituted 1(4)-naphthalenones, bearing a benzylic quaternary stereocenter, through a one pot visible light-mediated addition of  $\alpha$ -bromoacetophenones to cyclopropenes. Although the overall yield is moderate, this methodology offers an access to useful intermediates and constitutes a new way to generate synthons with quaternary stereocenter, still a challenging task in organic synthesis.<sup>4,17</sup> This methodology uses readily available enantiomer-enriched cyclopropenes as starting material, the stereospecific *syn* carboarylation of the cyclopropene  $\pi$ -system allowing the formation of two new C-C bonds and ensuring a perfect control of the stereochemistry of the quaternary stereocenter. Application of this methodology to the enantioselective synthesis of bioactive targets such as (-)-eptazocine is now underway and will be reported in due course.

## AUTHOR INFORMATION

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