

# Synthesis of Cyclohexanones by a Tandem Photocatalyzed Annulation

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*Carbene, cyclization, photoredox, tandem catalysis*

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**ABSTRACT:** The rapid synthesis of cyclic scaffolds is of high importance to the chemistry community. Strategies for the convergent synthesis of substituted carbocycles and heterocycles remain underexplored despite the plethora of applications that these cyclic motifs have in the pharmaceutical and materials industries. Reported herein is a tandem carbene and photoredox-catalyzed process for the convergent synthesis of substituted cycloalkanones via a formal [5+1] cycloaddition. Featuring two distinct photoredox cycles and a novel  $\alpha$ -oxidation of benzylic ketones, this reaction offers a mild approach to construct two contiguous C–C bonds and eliminates the need for strong bases or expensive metal catalysts. The utility of this method is highlighted through various product diversification reactions that allow access to a range of important cyclic scaffolds.

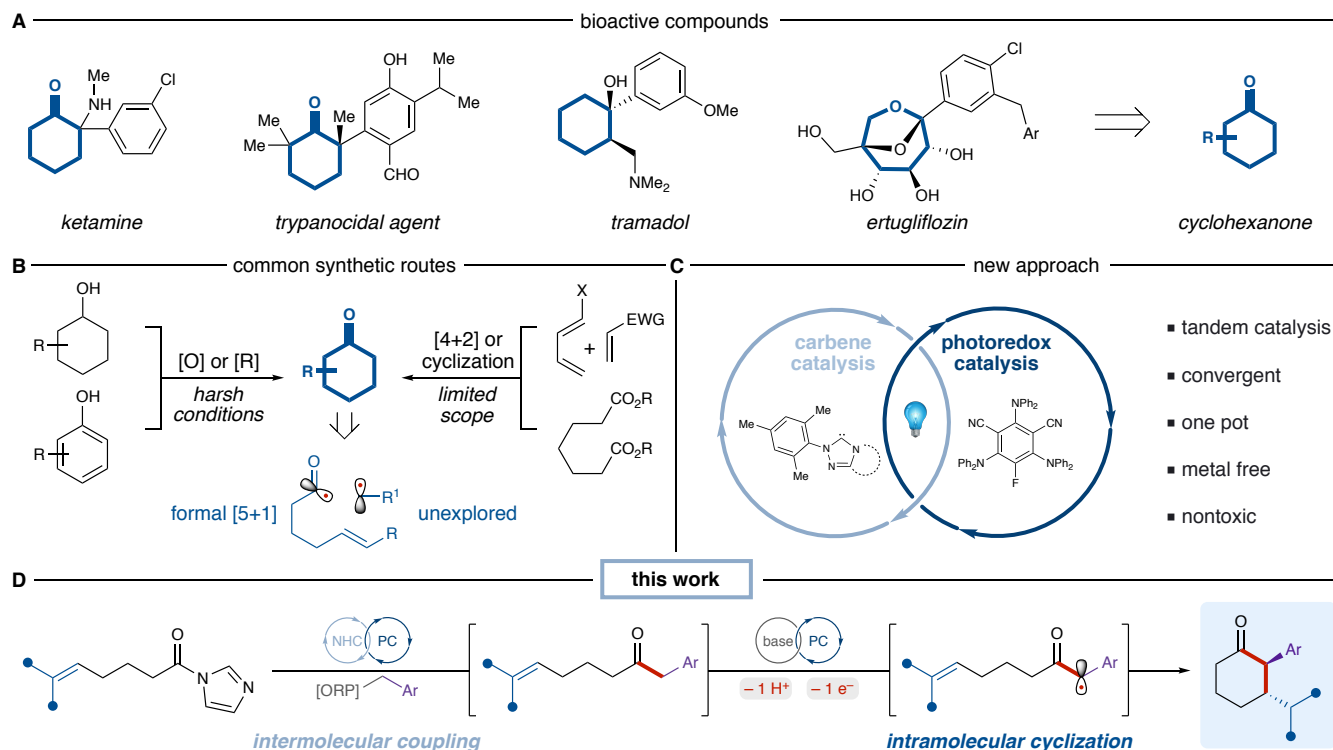
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The convergent synthesis of privileged small molecules remains a significant challenge among the organic and medicinal chemistry communities.<sup>1</sup> Of particular importance is the synthesis of carbocyclic and heterocyclic scaffolds, which are highly prevalent in FDA-approved drugs<sup>2</sup> as well as a multitude of bioactive compounds<sup>3</sup> and are common intermediates in the synthesis of various materials (**Figure 1A**).<sup>4</sup> These scaffolds can often be accessed from cycloalkanones, thus highlighting the need for methods that enable the convergent construction of cyclic ketones.<sup>5</sup> Cyclohexanones are most frequently synthesized in industry by reduction of the corresponding phenol<sup>6</sup> or oxidation of cyclohexane or cyclohexanol derivatives (e.g., Chapman-Stevens oxidation).<sup>7</sup> These processes often require elevated temperatures and strong redox agents or are plagued by over-reduction or over-oxidation. Cycloadditions (e.g., [4+2] reactions)<sup>8</sup> and various other cyclization processes (e.g., Dieckmann condensation,<sup>9</sup> Robinson annulation,<sup>10</sup> etc.) offer alternative routes for accessing cyclic scaffolds, but their applications in the synthesis of structurally complex cyclohexanones are limited due to electronic requirements or vigorous reaction conditions (**Figure 1B**).

The recent renaissance of radical chemistry through the emergence of photocatalysis<sup>11</sup> and electrocatalysis<sup>12</sup> has resulted in new approaches for the formation of C–C bonds, thus enabling non-traditional disconnections. While the versatile reactivity enabled by these radical redox strategies is unquestionable, significant limitations still exist. In particular, the majority of approaches in recent years for the photocatalytic synthesis of ketones concentrate on building acyclic products.<sup>13</sup> Apart from work focused on the synthesis of fused ring systems via radical cascade mechanisms, the synthesis of carbocyclic or heterocyclic rings via radical C–C bond formation remains underexplored.<sup>11a,14</sup> Moreover, structural complexity can be achieved efficiently by the formation of multiple bonds in a one-pot procedure, yet few protocols have been established for the construction of highly functionalized cyclic products. Recent advancements in metal catalysis (e.g., zinc, samarium, etc.) and photoredox strategies (e.g., iridium catalysis, single-electron carbene

catalysis, etc.) have enabled the facile construction of ketones via C–C bond formation,<sup>13e,15</sup> and these reactivity modes have been extended to radical relay processes for the formation of multiple bonds in a single reaction.<sup>14a,16</sup> While these strategies can afford highly functionalized products, they tend to feature 1,3-bond formation patterns, thus restricting their scope and overall utility. As a result, development of a new methodology for the synthesis of multi-functionalized cyclic scaffolds would allow for the exploration of new chemical space.

Given our recent investigations on the synthesis of ketones in combination with the rise in methods utilizing single-electron benzylic oxidations, we envisioned that oxidation of benzylic ketones might be possible. Benzylic C–H bonds are highly prevalent in many bioactive compounds (e.g., ~40% of the top 200 small molecule drugs by retail sales in 2020 contain benzylic or benzylic-like C–H bonds),<sup>17</sup> and their functionalization using single-electron catalysis has been of great interest in recent years.<sup>18</sup> Given that ketones are highly valuable functional groups that are often the center of reactivity and diversification, the efficient synthesis of benzylic ketones has also received significant attention; advancements in the construction of these prevalent motifs include the  $\alpha$ -arylation of ketones (e.g., via transition metal catalysis) and various radical coupling strategies (e.g., via an acyl/ketyl radical).<sup>18a,19</sup> We were surprised to identify few strategies for the mild  $\alpha$ -functionalization of benzylic ketones. We hypothesized that combined carbene and photoredox catalysis would allow for the construction of two contiguous C–C bonds via radical  $\alpha$ -functionalization of in-situ generated benzylic ketones under mild reaction conditions. Reported herein is the tandem carbene and organophotoredox-catalyzed convergent synthesis of  $\alpha,\beta$ -disubstituted cyclohexanones (**Figure 1C**). This process features consecutive photoredox cycles that facilitate two distinct transformations in one pot for the rapid generation of chemically complex cyclic scaffolds. Generation of a linear ketone occurs via a light-driven, carbene-catalyzed intermolecular radical-radical coupling, and subsequent oxidation of the corresponding enol in a second photoredox



**Figure 1.** A) Cyclohexanone-derived scaffolds found in bioactive compounds. B) Selected synthetic routes to prepare cyclohexanones. C) Combined light-driven carbene and photoredox catalyzed approach and its inherent advantages. D) A new strategy to build substituted cyclohexanones featuring an initial intermolecular radical-radical coupling followed by an intramolecular cyclization via oxidation of a benzylic enol.

cycle enables intramolecular cyclization to the  $\alpha,\beta$ -disubstituted cyclohexanone product (**Figure 1D**).

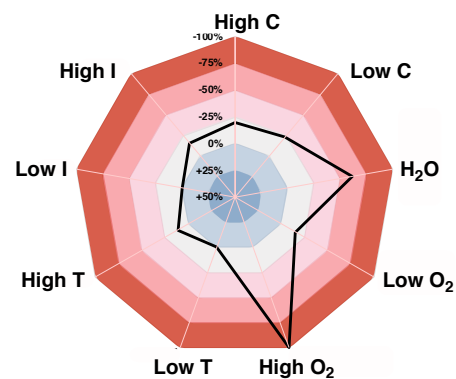
Using our previously optimized reaction conditions for the synthesis of aliphatic ketones as a starting point,<sup>19n</sup> it was quickly determined that further optimization of the solvent, *N*-heterocyclic carbene (NHC) precursor, and base was unnecessary. Given that this process features two distinct photoredox cycles by the same photocatalyst, choice of photocatalyst unsurprisingly was found to be critical in optimizing for the desired reactivity. Use of iridium photocatalyst [Ir(dF[CF<sub>3</sub>]ppy)<sub>2</sub>(dtbpy)]PF<sub>6</sub> led primarily to linear ketone **3a'** (**Table 1**, entry 2), confirming the feasibility of the first reaction step. Highly oxidizing or highly reducing photocatalysts were

not suitable for this process (**Table 1**, entries 3-4), as their range of redox potentials were not broad enough to enable the various oxidations and reductions. When organophotocatalyst 3DPAFIPN was employed, significant cyclized product was observed (**Table 1**, entry 1), suggesting that the necessary redox potentials fall near its redox range ( $E_{1/2}$  PC<sup>•+</sup>/PC<sup>•-</sup> to  $E_{1/2}$  PC/PC<sup>•-</sup> = +1.09 to -1.59 V vs. SCE).<sup>11h</sup> Although this process was optimized with Hantzsch esters,<sup>20</sup> use of organophotocatalyst 4CzIPN afforded product using benzyl potassium trifluoroborate salts (Bn-BF<sub>3</sub>Ks)<sup>21</sup> as an alternative oxidatively-generated radical precursor (ORP; **Table 1**, entry 5). Final optimization of the reaction concentration proved to be essential, as this one-pot transformation features both intermolecular

**Table 1. Optimization of reaction conditions and reaction sensitivity.<sup>a</sup>**

1a      Bn-HE (**2a**, 2.5 equiv)      5,5-Mes (30 mol %)      Cs<sub>2</sub>CO<sub>3</sub> (1 equiv)      3DPAFIPN (5 mol %)      456 nm LEDs      CH<sub>3</sub>CN (0.025 M)      3a      3a'

entry	deviation from standard	yield <b>3a</b> (%) <sup>b</sup>	yield <b>3a'</b> (%) <sup>b</sup>
1	none	55 (52) <sup>c</sup>	7
2	[Ir(dF[CF <sub>3</sub> ]ppy) <sub>2</sub> (dtbpy)]PF <sub>6</sub> instead of 3DPAFIPN	0	31
3	<i>fac</i> -Ir(ppy) <sub>3</sub> instead of 3DPAFIPN	trace	trace
4	Mes-Acr-Ph instead of 3DPAFIPN	0	0
5	Bn-BF <sub>3</sub> K + 4CzIPN instead of Bn-HE + 3DPAFIPN	35	7
6	0.01 M instead of 0.025 M	21	8
7	0.05 M instead of 0.025 M	26	5
8	0.1 M instead of 0.025 M	15	6



<sup>a</sup> See SI for details. <sup>b</sup> <sup>1</sup>H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> Isolated yield.

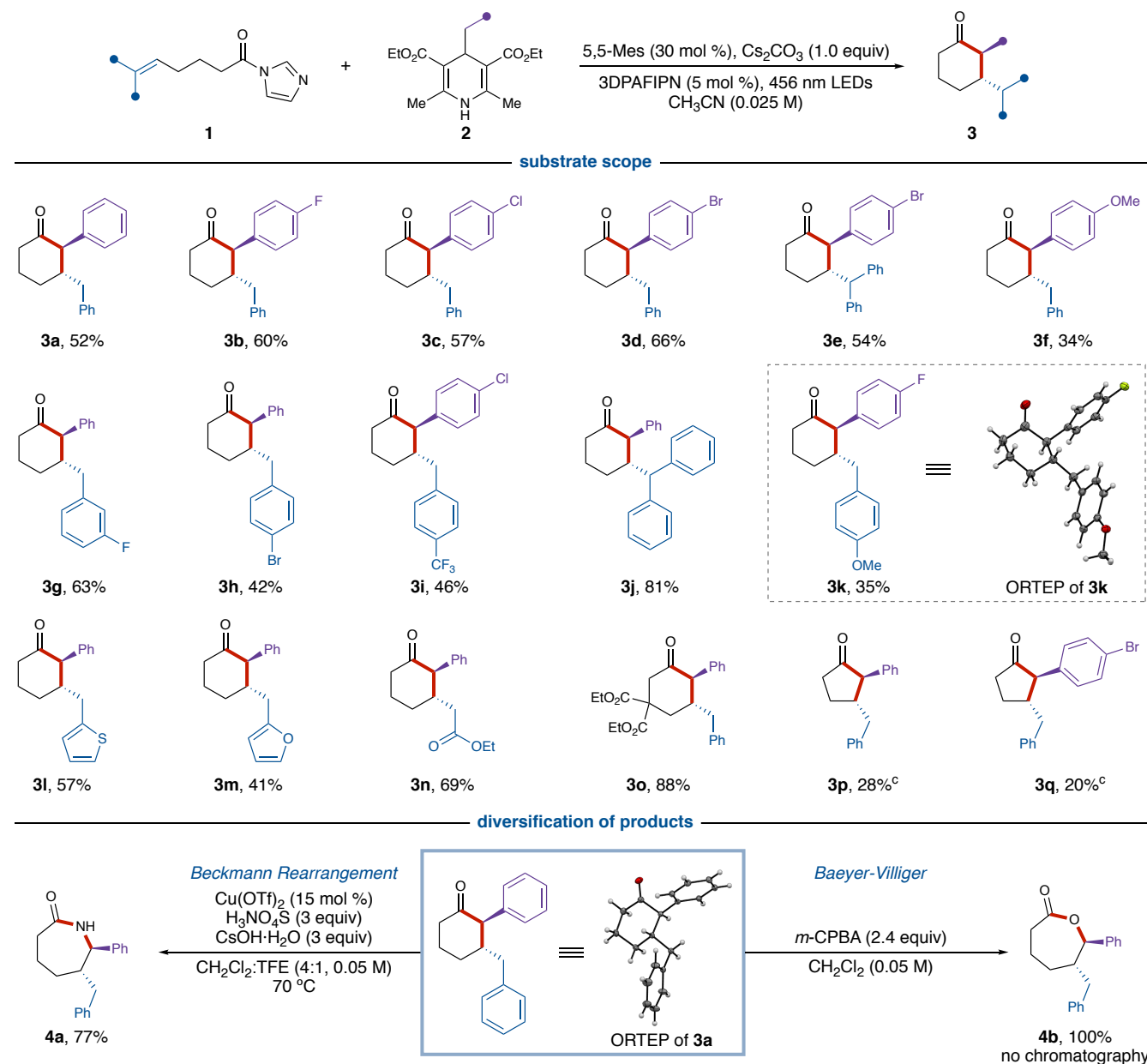
and intramolecular bond-forming steps. The screening of various reaction concentrations revealed that the cyclization occurred most readily under dilute reaction conditions (**Table 1**, entries 1,6-8).

The optimized reaction was evaluated for its sensitivity to demonstrate the practical nature of this protocol and ensure a high degree of reproducibility with differing reaction setups (**Table 1**, right, see SI for details).<sup>22</sup> Only minor deviations in yield were observed for small changes in concentration, light intensity, and temperature. As expected, it was found that high oxygen levels are detrimental to the reaction efficiency, with a dramatic change in yield (i.e., 0% yield) when air was bubbled through the reaction solution prior to irradiation. Similarly, addition of water decreased the reaction efficiency, but normal reactivity was restored using non-degassed acetonitrile without additional drying under inert atmosphere (i.e., low oxygen

and low water). The demonstrated overall robustness of this reaction suggests that little-to-no difficulty should be encountered when these reactions are run in other laboratories.

These reaction conditions were used to synthesize cycloalkanones with a variety of substituted  $\alpha$ -aryl substituents and a diverse array of  $\beta$ -substituents (**Table 2**). Substituted benzyl radical precursors featuring electron-withdrawing or electron-donating groups were found to be suitable coupling partners and allowed for significant conversion to the corresponding cyclohexanone product (**3b-3f**). Many benzylic oxidation strategies are inefficient or completely ineffective with electron-poor arenes, as these groups increase the oxidation potential of the arene ring significantly. The strategy reported herein, however, tolerates electron-withdrawing groups, with yields up to 66% (**3d**) over two C-C bond-forming steps in our one-

**Table 2. Substrate scope of reaction and application of the products to synthesize heterocyclic scaffolds in high yields.<sup>a,b</sup>**



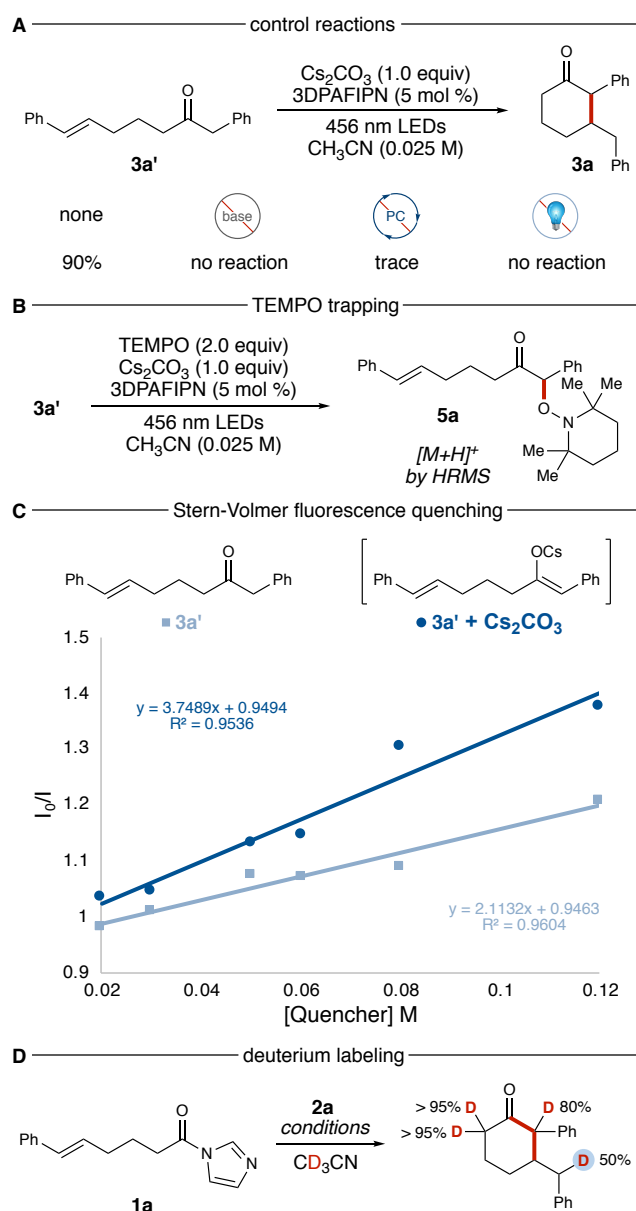
<sup>a</sup> See SI for details. <sup>b</sup> Diastereomers were assigned by analogy to ORTEPs of **3a** and **3k**. A single diastereomer was observed by <sup>1</sup>H NMR analysis for all reactions. <sup>c</sup> Isolated from the corresponding pentenyl imidazole **1**.

pot procedure. This difference in reactivity likely stems from the mechanism of oxidation, wherein deprotonation of the  $\alpha$ -position gives the enol, which can be oxidized at lower potentials.

A diverse array of  $\beta$ -substituted cycloalkanones was also accessed using this protocol. Various substituted  $\beta$ -benzyl cyclohexanone products were isolated in moderate-to-good yields (**3g-i,k**). Disubstituted alkenes were also tolerated, with isolation of **3j** in 81% yield. Cyclohexanones featuring heteroaromatic substitution were also constructed using this tandem cyclization process, with thiophene-substituted **3l** and furan-containing **3m** isolated in moderate-to-good yields. The diversity of products that may be synthesized under these reaction conditions was further showcased by isolation of  $\delta$ -ester **3n** in high yield, providing a functional group handle for diversification. Isolation of 4-geminal-diester **3o** in excellent yield suggests that highly functionalized cyclohexanones may be synthesized using this method by pre-functionalization of the linear starting material; moreover, the excellent yield obtained for **3o** demonstrates the potential utility of this method for the construction of key synthetic building blocks. Although these conditions were optimized for the synthesis of cyclohexanone derivatives, isolation of **3p** and **3q** suggests that this process may be employed for the synthesis of cyclopentanones and other cycloalkanones with additional optimization.

Reactions of cyclic ketones have been extensively reported in the literature (e.g., reduction to the corresponding cyclohexane, condensation with an amine, etc.), highlighting their versatility as synthetic intermediates.<sup>23</sup> As such, the utility of this process in synthesis was demonstrated through a brief series of product diversification reactions (**Table 2**). When **3a** was subjected to established modified Beckmann conditions, the corresponding caprolactam **4a** was isolated in 77% yield.<sup>24</sup> Similarly, subjecting **3a** to standard Baeyer-Villiger conditions enabled the corresponding lactone **4b** to be furnished in quantitative yield.<sup>25</sup> A multitude of additional diversification directions can be envisioned for these products given their synthetic utility.

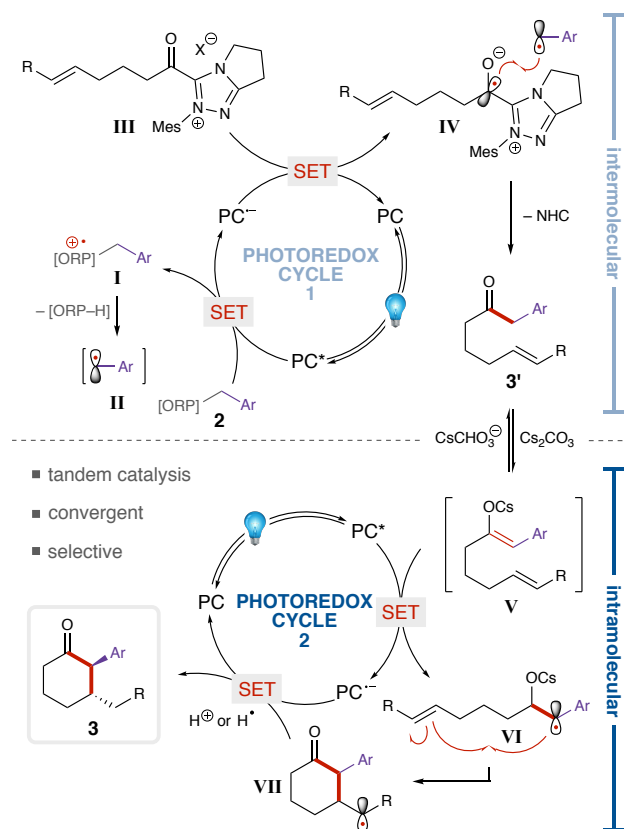
While the mechanism of the carbene-catalyzed radical-radical coupling has been studied previously,<sup>19n,26</sup> a series of key mechanistic experiments were employed to study the reaction mechanism of the benzylic oxidation. Subjecting linear ketone **3a'** to the organophotocatalyst and light under basic conditions yielded cyclic **3a** in 90% yield, supporting linear ketone **3a'** as an intermediate in this reaction (**Scheme 1A**) and offering an alternative route to access these products. Control experiments strongly support a photocatalytic transformation, as no reaction occurred in the absence of base, photocatalyst, or light (**Scheme 1A**). A TEMPO-trapping experiment further suggests production of an  $\alpha$ -benzylic radical, as the mass of TEMPO-adduct **5a** was observed by high-resolution mass spectrometry (HRMS; **Scheme 1B**). Stern-Volmer fluorescence quenching experiments reveal that both **3a'** and a basic mixture of **3a'** with cesium carbonate quench the photocatalyst, with the basic mixture being the more prominent quencher (**Scheme 1C**). Together with the requirement of basic reaction conditions as indicated by the control experiments (*vide infra*), these results suggest that the enol or enolate form of **3a'** likely undergoes single-electron oxidation by the photocatalyst. Lastly, the reaction was run under standard reaction conditions in deuterated acetonitrile to shed light on the final step of this reaction. Analysis of the isolated cyclized product revealed significant deuterium incorporation at the ketone  $\alpha$ -positions, an expected result given the acidity of these protons. Moreover, approximately 50% deuterium incorporation was identified at the  $\gamma$ -benzylic



**Scheme 1.** A) Control reactions for the benzylic oxidation. B) TEMPO-trapping experiment. C) Stern-Volmer fluorescence quenching experiment used to identify the species that is oxidized by the photocatalyst. D) Deuterium labeling experiment that reveals deuterium incorporation from the solvent terminates the reaction approximately 50% of the time (blue highlighted deuterium atom). TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl radical.

position of the cyclic product (blue highlight, **Scheme 1D**), suggesting that the mechanism terminates by hydrogen-atom abstraction<sup>27</sup> or reduction followed by protonation.<sup>28</sup>

Using our previous knowledge and the results of these mechanistic experiments, we propose a mechanism featuring two distinct photoredox cycles (**Scheme 2**; see SI p12 for detailed mechanism including NHC catalytic cycle). Single-electron oxidation of the oxidatively-generated radical precursor (ORP) yields radical cation **I**, which fragments to provide benzyl radical **II**. Single-electron reduction of acyl azolium **III**, derived in situ from acyl imidazole **1**, affords acyl azolium radical **IV**. Intermolecular radical-radical coupling and loss of the NHC gives linear ketone intermediate **3'**. Single-electron



**Scheme 2. Proposed mechanism for the tandem cyclization process.**

oxidation of the corresponding enol or cesium enolate **V** affords  $\alpha$ -benzylic radical **VI**, which engages in an intramolecular cyclization with the alkene. The resulting  $\gamma$ -benzylic radical **VII** may undergo hydrogen atom transfer (HAT) or be reduced by the photocatalyst to the corresponding anion, which deprotonates the solvent or bicarbonate to afford the desired cyclohexanone product **3**.

In summary, we have developed a tandem carbene and photocatalyzed strategy for the convergent synthesis of  $\alpha,\beta$ -disubstituted cyclic ketones. This process enables the construction of two contiguous C–C bonds via a formal [5+1] cycloaddition and highlights a novel method for the  $\alpha$ -functionalization of ketones under mild reaction conditions. Through the combination of two distinct processes in one pot, this reaction offers a route to synthesize complex cycloalkanone products that can be leveraged to access scaffolds relevant in both the pharmaceutical and materials industries.

## ASSOCIATED CONTENT

### Supporting Information

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

Experimental procedures and characterization data (PDF).

Crystallographic files (CIF).

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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### ABBREVIATIONS

HAT, hydrogen atom transfer; NHC, *N*-heterocyclic carbene; ORP, oxidatively-generated radical precursor; SET, single-electron transfer

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The convergent synthesis of highly functionalized carbocycles and heterocycles remains a high priority among organic chemists due to their numerous applications in the pharmaceutical and materials industries. Described herein is a tandem carbene and photoredox-catalyzed process for the synthesis of substituted cycloalkanones via a formal [5+1] cycloaddition that features a novel  $\alpha$ -oxidation of benzylic ketones.

