

# Visible-Light-Induced C–O Bond Formation for the Construction of Five- and Six-Membered Cyclic Ethers and Lactones

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Supporting Information

ABSTRACT: Visible-light-induced intramolecular C-O bond formation was developed using 2,4,6-triphenylpyrylium tetrafluoroborate (TPT), which allows the regiocontrolled construction of cyclic ethers and lactones. The reaction is likely to proceed through the single-electron oxidation of the phenyl group, followed by the formation of a benzylic radical, thus



preventing a competing 1,5-hydrogen abstraction pathway. Detailed mechanistic studies suggest that molecular oxygen is used to trap the radical intermediate to form benzyl alcohol, which undergoes cyclization. This new approach serves as a powerful platform by providing efficient access to valuable five- and six-membered cyclic ethers and lactones with a unified protocol.

vclic ethers and lactones are the basic structural unit of numerous naturally occurring compounds and privileged motifs in the areas of pharmaceuticals, agrichemicals, materials, and polymers.<sup>1,2</sup> Accordingly, a number of synthetic strategies have been investigated to enable the rapid construction of these skeletons.<sup>3</sup> One such convenient and attractive route for the synthesis of these scaffolds is direct intramolecular C-O bond-forming reactions starting from the corresponding carboxylic acids or alcohols.<sup>4</sup>

In Hofmann-Loffler-type reactions, the O-I bond undergoes light-induced homolysis to form the O-centered radicals, which enable a subsequent 1,5-hydrogen atom transfer (1,5-HAT) event. In the process, the selectivity is governed by kinetically controlled C–H functionalization at the  $\delta$  position, which would result in the construction of five-membered ether rings. For substrates containing benzylic sites, the formation of benzylic radicals can compete with this kinetically preferred 1,5-HAT, eventually providing a mixture of five- and six-membered rings (Scheme 1a).<sup>5</sup> Moreover, for substrates bearing acidic functional groups, the generated acyloxy radical species can induce nonproductive decarboxylation.<sup>6</sup> Driven by the need for an efficient and unified synthetic route to five- and six-membered cyclic ethers and lactones, we were intrigued by the possibility of visible-light-promoted, site-selective C-O bond formation occurring through direct benzylic C-H activation. Herein, we report an efficient photocatalytic system for the selective construction of benzyl cyclic ethers and lactones.

To test the feasibility of our envisioned approach, we initially aimed to identify a suitable photocatalyst (PC) by screening the oxidative quenching abilities of widely employed PCs." For this purpose, we carried out quenching experiments by measuring the luminescence spectra of nine different PCs (PC1-9) with 1a (Table 1). Photocatalysts PC2 (TPT) and PC3 were greater than 50% in quenching fractions; TPT was





the most effective in this evaluation (>90%) and was chosen for further exploration.

By carrying out a series of competitive luminescence quenching experiments,<sup>8</sup> we observed that 5-phenylpentan-1ol (1a) acts as an efficient reductive quencher of excited TPT (see the Supporting Information (SI) for details). Based on these results, we investigated the proposed transformation using 1a and TPT under irradiation with visible light from blue LEDs (Table 2). A substantial amount of the hemiacetal product 4 was obtained (entries 1-3). Interestingly, when TPT was used without any additives, 4 was formed in 10% yield along with large amounts of decomposition products. We rationalized that, upon single-electron oxidation of 1a by excited TPT\*, the resulting benzylic radical would react with molecular oxygen to generate benzylic hydroperoxide. There-

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<sup>*a*</sup>Fluorescence was measured under 415 nm irradiation (0.001 mmol of PC and 0.2 mmol of **1a** in 20 mL of MeCN),  $F = 100 (1 - I/I_0)$ .



| Ph                | OH 5% TPT<br>additive<br>blue LED<br>1a rt | Ph O + Ph OH<br>2a 3  | OH Ph |                      | н он |
|-------------------|--|-----------------------|-------|----------------------|------|
|                   |  |                       | 9     | % yield <sup>1</sup> | ,    |
| entr              | y additive (equiv)                         | solvent               | 2a    | 3                    | 4    |
| 1                 | _  | MeCN                  | 0     | 0                    | 10   |
| 2                 | $I_2(0.1)$                                 | MeCN                  | 0     | 0                    | 34   |
| 3                 | $ZnI_{2}(0.1)$                             | MeCN                  | 0     | 0                    | 50   |
| 4                 | $I_2(0.1)$                                 | HFIP                  | 21    | 0                    | 12   |
| 5                 | $ZnI_{2}(0.1)$                             | HFIP                  | 27    | 29                   | 17   |
| 6                 | $ZnI_{2}(0.1)$                             | $CH_2Cl_2$            | 11    | 23                   | 2    |
| 7                 | $ZnI_{2}(0.1)$                             | $CH_2Cl_2/HFIP$ (1:1) | 31    | 34                   | 4    |
| 8 <sup>c</sup>    | $ZnI_{2}(0.1)$                             | $CH_2Cl_2/HFIP$ (1:1) | 57    | 8                    | 0    |
| 9 <sup>c</sup>    | $ZnI_{2}(0.2)$                             | $CH_2Cl_2/HFIP$ (1:1) | 61    | 5                    | 0    |
| 10 <sup>c</sup>   | $ZnI_{2}(0.3)$                             | $CH_2Cl_2/HFIP$ (1:1) | 74    | 4                    | 0    |
| 11 <sup>c</sup> , | d ZnI <sub>2</sub> (0.3)                   | $CH_2Cl_2/HFIP$ (1:1) | 10    | -                    | -    |

"Reactions were performed with mixtures of 1 (0.1 mmol), additives, and TPT (5 mol %) in solvent (2 mL) at rt under irradiation by a 15 W blue LED for 24 h under an  $O_2$  atmosphere. <sup>b</sup>Yield was analyzed by <sup>1</sup>H NMR. <sup>c</sup>1 equiv of AcOH was added. <sup>d</sup>Under a  $N_2$  atmosphere.

fore, it is conceivable that 4 is derived from the Hock rearrangement of benzylic hydroperoxide.<sup>10</sup> Remarkably, if the same reaction was carried out in the presence of a catalytic amount of  $I_2$  in hexafluoroisopropanol (HFIP), tetrahydropyran 2a was, indeed, formed along with 4, indicating that the desired reaction is operative and competes with the Hock rearrangement (entry 4). More promising results were obtained using ZnI<sub>2</sub>, presumably because the coordination of Zn(II) with the hydroxyl group promoted the intramolecular C–O cyclization (entry 5). Notably, 1-phenylpentane-1,5-diol (3), which is thought to be a potential reaction intermediate for an intramolecular C–O cyclization, was isolated in a substantial yield.<sup>11</sup> After extensive screening of various solvents, the use of a mixture of CH<sub>2</sub>Cl<sub>2</sub><sup>12</sup> and HFIP in the presence of AcOH gave the best performance. Under the optimized reaction conditions, tetrahydropyran product **2a** was formed in 74% yield without producing Hock rearrangement product **4** (entry 10). Subsequent control experiments confirmed the essential roles of visible light and TPT in this reaction (see the SI for details). Furthermore, a significant turnover was observed when the reaction was attempted under an atmosphere of N<sub>2</sub> instead (entry 11), indicating that molecular oxygen serves as an indispensable reagent. Next, we carried out stoichiometric control experiments under reaction conditions similar to those of the NIS-mediated Hofmann– Loffler-type reaction.<sup>13</sup> As a result, the five-membered cyclized product was obtained as a major product (Table S1 and Scheme S1d in the SI) via a 1,5-HAT process.

As illustrated in Scheme 2, we next investigated the substrate scope with respect to phenyl alcohol substrates to extend the



<sup>*a*</sup>Reactions were performed with mixtures of 1 (0.1 mmol), ZnI<sub>2</sub> (0.3 equiv), AcOH (1.0 equiv), and TPT (5 mol %) in CH<sub>2</sub>Cl<sub>2</sub> + HFIP (1:1) at rt under irradiation by a 15 W blue LED for 24 h under O<sub>2</sub> atmosphere. Isolated yields of products. <sup>*b*</sup>Under air atmosphere. <sup>*c*</sup>The reaction was conducted at 34 W Kessil LED under an air atmosphere.

utility and generality of this method. The reaction was tolerant of halogen-substituted substrates including fluoro, chloro, and bromo substituents at the *para*-position, and products **2c**, **2d**, and **2e** were formed, thus enabling further synthetic functionalizations at this position. Pentanols bearing *meta*substituents on the phenyl rings also underwent the intramolecular C–O cyclization reaction to provide the corresponding cyclic ethers **2f** and **2g**. The reactions of substrates possessing *ortho*-substituents worked well and provided **2h** and

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2i. Substrates containing no substituent at the  $\alpha$ -carbon performed well (2j and 2k), which indicates that the Thorpe-Ingold effect is not a prerequisite for the cyclization. Tricyclic indanofuran 21 was successfully synthesized from the corresponding alcohol precursor in good yield. In addition, the scope could be expanded to a secondary alcohol, which afforded the desired cyclic ether product 2m. Next, we turned our attention to the reactivity of 5-phenylpentanol substrates to construct tetrahydropyran scaffolds. The employment of substrates with or without dimethyl groups were efficiently converted to desired products 2n and 2a. The present C-O bond formation with substituted pentanols containing methyl (20), fluoro (2p, 2r, and 2s), and chloro (2q) groups proceeded smoothly. It is worth noting that substrates bearing cyclic motifs, as exemplified by cyclohexyl, cyclopentyl, and triflate-protected piperidine groups were well tolerated in the reaction and provided oxaspirocycles 2t, 2u, and 2v in good yields. The utility of the present method was further demonstrated by conveniently accessing prominent isochromane scaffold 2z. In addition, 6-phenylhexan-1-ol was tested, and seven-membered cyclic ether 2aa was formed, albeit in a low 17% yield. When the reaction was carried out with a tosylprotected amine substrate, C-N bond formation proceeded to afford the corresponding six-membered piperidine 2ab.<sup>14</sup>

Importantly, the scope of the C-H etherification reaction could be expanded to the selective formation of  $\gamma$ - and  $\delta$ lactones (Scheme 3). First, the scope of this transformation was studied with respect to butyric acids for the synthesis of  $\gamma$ lactones in a slightly modified solvent system  $(CH_2Cl_2/HFIP =$ 6:1). Phenylbutanoic acid with geminal methyl groups at the  $\alpha$ -carbon underwent C-O bond formation to provide the corresponding  $\gamma$ -lactone product **6a** in good yield. An array of butyric acids bearing methyl, tert-butyl, fluoro, chloro, bromo, or trimethylsilyl groups on the phenyl ring were readily transformed into the cyclized products under the reaction conditions (6b-6i, 6l, and 6m). 4-Phenylbutyric acid containing no substituent at the  $\alpha$ -carbon also performed well (6j, 77% yield). Expanding the scope to a 2-benzylbenzoic acid was also possible, and isobenzofuran 6n was generated in excellent yield. We subsequently assessed the applicability of our method with respect to indanyl carboxylic acid 50. Indeed, the utility of the present method was further demonstrated by providing convenient access to prominent structural motifs featuring lactone units fused to 2,3-dihydro-1H-indene (60). Further exploration demonstrated that heterocyclic acids that are typically incompatible with strong oxidative conditions, as exemplified by thiophene, can undergo the present reaction to afford 5p. Next, we explored the substrate scope of sixmembered lactone formation. A series of 5-phenylpentanoic acid substrates possessing different substitution patterns were subjected to the reaction, and the benzylic positions were exclusively functionalized to afford the corresponding  $\delta$ lactones **6q–6ad**. Substrates bearing sterically hindered groups at the  $\alpha$ -position generally led to reasonable yields (6w, 63%) and 6x, 61%). We applied the present reaction to 2phenethylbenzoic acid and isochromanone derivatives. Diverse isochromanone and isohydrocoumarin scaffolds<sup>15</sup> were successfully constructed (6z-6ad), highlighting the attractiveness of this method and its potential applications in the construction of compound libraries.

To elucidate the mechanism, we conducted a series of control experiments (see the SI for details). First, in an attempt to identify the plausible reaction intermediates, benzyl alcohol





<sup>*a*</sup>Reactions were performed with mixtures of **1** (0.1 mmol), ZnI<sub>2</sub> (0.3 equiv), AcOH (1.0 equiv), and TPT (5 mol %) in CH<sub>2</sub>Cl<sub>2</sub> + HFIP (6:1) at rt under irradiation by a 15 W blue LED for 72 h under an O<sub>2</sub> atmosphere. Isolated yields of products. <sup>*b*</sup>The reaction performed in CH<sub>2</sub>Cl<sub>2</sub> + HFIP (1:1). <sup>*c*</sup>The reaction was conducted for 24 h at 45 °C and 34 W Kessil LED under an air atmosphere.

3 and benzyl iodide 8 were employed for the intramolecular cyclization reaction (Scheme S2a). In both cases, desired cyclic ether 2a was produced. Next, to clarify the role of a hydroxyl group in the reaction, methyl ether 9 was subjected to the standard reaction conditions. In this case, we were able to detect three benzylic-functionalized products bearing hydroxyl, hexafluoroisopropyl, or acetoxyl groups (Scheme S2b).<sup>1</sup> Intriguingly, the use of ZnI<sub>2</sub> under the irradiation of visible light is critical for the cyclization of 3, whereas 8 was readily cyclized without requiring the above-mentioned reagents. Because benzylic C-H activation could be achieved in the absence of hydroxyl groups in the substrate, the involvement of an alkoxy radical-engaging 1,5 HAT pathway could be excluded. These results are in good agreement with our mechanistic hypothesis that a benzylic radical intermediate is generated by the direct benzylic C-H oxidation.

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To understand the iodine-catalyzed cyclization of benzyl alcohol 3, we carried out a DFT study (Figure 1).



Figure 1. Free energy profile for the intramolecular cyclization.

Unsurprisingly, coordination of  $I_2^*$  to the benzylic hydroxyl group is an energetically downhill process by -7.8 kcal/mol (Int1). Interestingly, the bond length of  $I_2$  in the excited state is considerably longer (3.155 Å) than in the ground state (2.660 Å). Furthermore, we found that the bond length of  $I_2$  in Int1 is extended to 3.304 Å, and the I-I bond can be cleaved to generate the corresponding cationic intermediate Int2 with a barrier of only 4.9 kcal/mol. Next, intramolecular cyclization traversing the transition state Int2-TS at 17.0 kcal/mol liberates IOH and affords Int3, which readily undergoes nearly barrierless acetate-mediated deprotonation to form the desired product 2a at -44.7 kcal kcal/mol. In the presence of  $ZnI_2$  as a Lewis acid (Int4), the energy barrier for intramolecular cyclization from Int4 is only 7.9 kcal/mol.<sup>17</sup> The alternative reaction pathway associated with direct activation and cyclization by I2\* demands a much higher energy barrier of 40.0 kcal/mol (Int2-TS'), as shown in blue.<sup>18</sup> Based on these observations, a proposed mechanistic pathway is shown in Scheme 4 (see the SI for details and discussions).

In summary, we have developed a visible-light-induced photocatalytic reaction for the expedient synthesis of cyclic ethers and lactones from alcohols and carboxylic acids in a

#### Scheme 4. Proposed Mechanistic Pathway



controllable and selective manner. TPT enables the generation of benzylic radicals and subsequent intramolecular C–O cyclization through the intermediacy of benzyl alcohols. The direct substrate oxidation that was rationalized by control experiments offers predictable control over product selectivity by avoiding complications from the 1,5-HAT. A variety of value-added five- and six-membered cyclic ether and lactone derivatives were successfully synthesized with the present protocol, which provides a straightforward route to the bioactive scaffolds.

# ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b03166.

Experimental procedures and characterization of new compounds (<sup>1</sup>H and <sup>13</sup>C NMR spectra) (PDF)

#### **Accession Codes**

CCDC 1871380 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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(16) We observed that 10b and 10c could be obtained from 10a, which indicates that 10a could be an initial reaction intermediate (see the SI).

(17) Int4 was redefined as a standard point, 0.00 kcal/mol.

(18) The formation of benzyl cation species via direct dissociation of IOH from Int2 appears to be less feasible, and the nucleophilic attack by the hydroxyl group is required for the C–O bond cleavage (see the SI for details).

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