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Oxidative lactonization of C(sp^3)–H bond in methyl aromatic alcohols enabled by proton-coupled electron transfer

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Direct functionalization of inert C(sp^3)–H bonds in pharmaceutically significant compounds is very important in modern synthetic organic chemistry. In this article, we disclose a practical and efficient method for the oxidative lactonization of benzylic C(sp^3)–H bonds enabled by the synergistic interactions of organic dye-type rose bengal, *n*-Bu_4N•Br, O_2 and Na_2HPO_4 under visible light irradiation. This reaction does not require transition metal catalysts or strong oxidants. A range of structurally diverse phthalides has been synthesized with excellent selectivity and high functional group compatibility. The late-stage application of this reaction to the preparation of structurally complex phthalides demonstrates its synthetic utility.

photoredox catalyst, metal free, singlet oxygen, bromine radical, dehydrogenated lactonization

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Lactones are privileged structural units in many biologically active and pharmaceutically significant substances [1]. For example, dermacozine D, which has been found to be cytotoxic against the K562 cancer cell line, a human chronic myelogenous leukemia, contains a lactone moiety [2a]. Other lactone-based active molecules, including sinaspirolide, 3-oxo citalopram, and danshen-spiro-ketallactone are shown in Scheme 1 [2]. The demonstrated biological and pharmaceutical significance of lactones has fueled a strong interest in the development of more general, practical and efficient strategies for their facile preparation [3a–3e]. In addition to biosynthetic protocols, traditionally employed methods involving readily available carboxylic acids usually require either reagents that can activate carboxylic acids or generation of active intermediates, such as acyl chlorides and anhydrides, for subsequent lactonization with alcohols [3f–3g]. Strategies that have attempted to overcome these drawbacks include the use of direct C–H bond functionalizations through transition-metal catalysis.

Radical chemistry has emerged in recent years as a powerful synthetic technology for the rapid preparation of valuable organic molecules due to the development of versatile open-shell reactive species [4]. A number of methods, involving photolysis [5], thermolysis [6], and electrolysis [7] can be employed to easily produce the active radical species. In this context, one of the most important transformations is the conversion of petroleum by-products into fine chemicals or pharmaceutically useful substances. For instance, toluene derivatives can be directly oxidized to corresponding aromatic carboxylic acids through visible light-enabled photoredox catalysis, in which molecular oxygen serves as the terminal oxidant [8a]. König and coworkers [8b] recently reported a practical method for the conversion of methylarenes to the corresponding aromatic nitriles in the presence of

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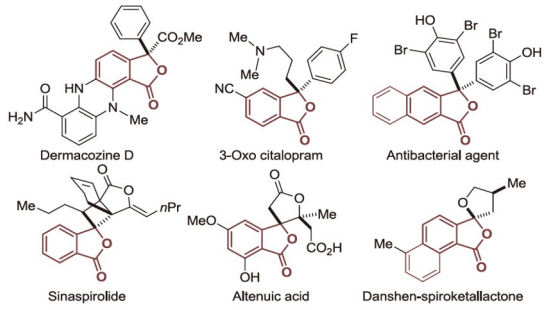
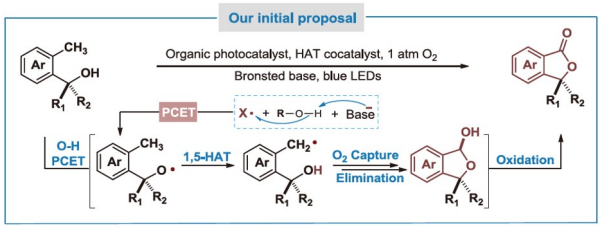


Scheme 1 Lactone moieties in representative biologically active molecules (color online).

a catalytic amount of an organic dye, 2,4,6-triphenylpyrylium tetrafluoro-borate (TPP) under visible light irradiation. However, to date, no catalytic method has been reported for the conversion of methyl aromatic alcohols into phthalides and this is the subject of this paper.

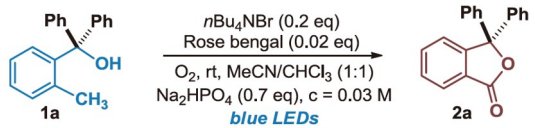
On the basis of the aforementioned studies on photoenabled oxidation of toluene derivatives, we attempted to determine if it is possible to employ a photoredox catalyst [9] with an appropriate hydrogen atom transfer (HAT) cocatalyst and a weak Brønsted base to develop a conceptually novel protocol for phthalide synthesis enabled by proton-coupled electron transfer (PCET) [10]. Our design concept is depicted in Scheme 2. We postulated that, in the presence of photoexcited catalysts, the *in-situ* generated catalytic open-shell HAT radicals, *e.g.*, halogen radicals ($X^{\cdot}$), with the assistance of the Brønsted base, can jointly mediate the homolysis of a substrate alcohol O–H bond to give a key alkoxy radical species [11]. The alkoxy radical will selectively abstract a hydrogen atom from the benzylic position *via* a 1,5-hydrogen atom transfer process to yield a benzyl radical, and this is followed by a sequence of oxygen capture, acylation and oxidation, thus affording the final phthalide product.

Our initial investigations began with an exploration of the oxidative lactonization of the model substrate diphenyl(*o*-tolyl)methanol (**1a**) at room temperature (Table 1). After careful optimization of the reaction conditions, 89% yield of the phthalide (**2a**) was obtained in a mixed solvent of MeCN/$CHCl_3$ (1:1) after 8 h of blue-light irradiation (450 nm) with an organic rose bengal as a photocatalyst in the presence of tetrabutylammonium bromide (TBAB) (0.2 equiv.) and Na_2HPO_4 (0.7 equiv.) (Table 1, entry 1). When other frequently encountered agents, including tetrabutylammonium iodide (TBAI), tetrabutylammonium chloride (TBAC), *N*-hydroxyphthalimide (NHPI), tetrachloro-*N*-hydroxy-phthalimide (Cl_4NHPI) or ethyl 2-mercaptoacetate, were utilized as hydrogen atom transfer (HAT) cocatalysts, all the reactions completely failed (entries 2–5). The photocatalyst, rose bengal was shown to play a significant role in this reaction since a significantly decreased yield of the desired product



Scheme 2 Concept of visible-light-promoted photocatalytic dehydrogenated lactonization by proton-coupled electron transfer (color online).

Table 1 Optimization of the oxidative lactonization of diphenyl(*o*-tolyl) methanol

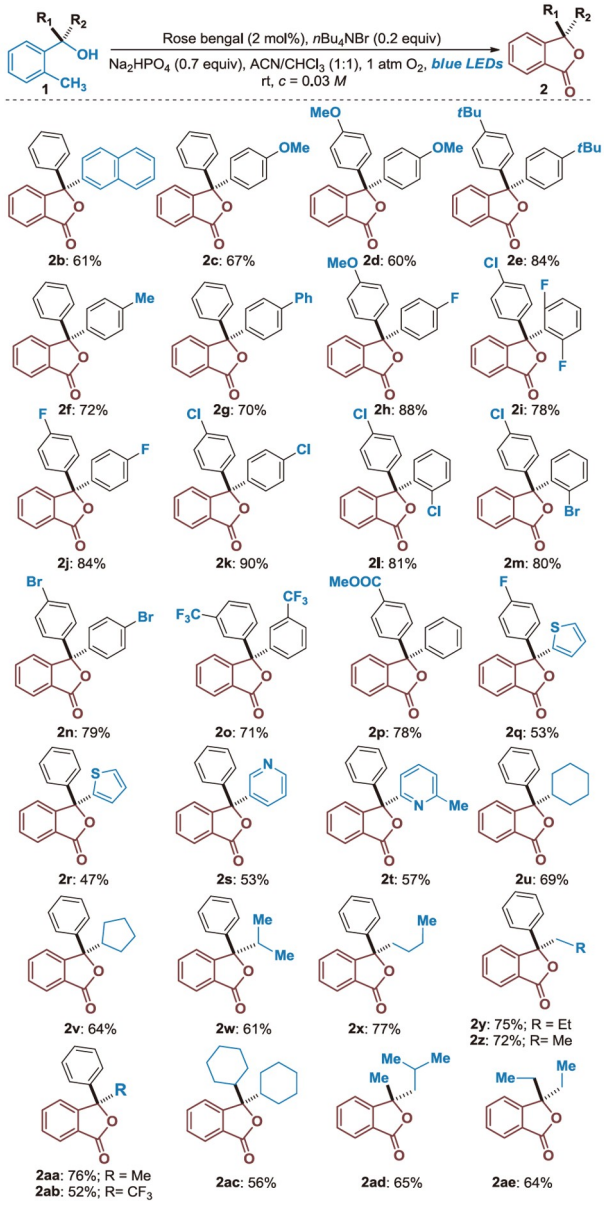


Entry	Variation to standard conditions[a)]	Yield (%)[b)]
1	none	89
2	nBu$_4$NCl instead of nBu$_4$NBr	NR
3	nBu$_4$NI instead of nBu$_4$NBr	NR
4	NHPI or Cl_4NHPI instead of nBu$_4$NBr	NR
5	EtO_2CCH_2SH instead of nBu$_4$NBr	NR
6	Eosin Y instead of Rose bengal	45
7	4CzIPN instead of Rose bengal	43
8	$Ru(bpy)_3Cl_2$ instead of Rose bengal	21
9	MeCN as solvent	46
10	MeCN/(DCM or DCE) (1:1) as solvent	trace
11	MeCN/TFE (1:1) as solvent	trace
12	Na_2CO_3 instead of Na_2HPO_4	NR
13	Cs_2CO_3 instead of Na_2HPO_4	31
14	without nBu$_4$NBr	NR
15	without light	NR
16	without Rose bengal	trace

a) 4CzIPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; NHPI = 2-hydroxyisoindoline-1,3-dione; TFE = 2,2,2-trifluoroethanol. b) Yield of isolated product.

was furnished when eosin Y, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN), or $Ru(bpy)_3Cl_2$ was used in place of rose bengal (entries 6–8). The solvent effect was also confirmed to be fairly critical during this transformation. Replacing $CHCl_3$ with dichloromethane (DCM), dichloroethane (DCE), or tetrafluoroethylene (TFE) completely shut down the oxidative lactonization (entries 10–11) and the yield of **2a** decreased to 53% when MeCN was used as the only solvent (entry 11). Attempts using Na_2CO_3 or Cs_2CO_3 as an alternative base were also found to be disadvantageous, resulting in either no product or a yield of only 31%, respectively (entries 12–13). Finally, control experiments showed that the photocatalyst, irradiation and TBAB were all essentials (entries 14–16).

With the optimized conditions identified, we explored the substrate scope of the transformation (Scheme 3). In addition to diphenyl(*o*-tolyl)methanol (**1a**), a broad array of structurally varied benzylic alcohols were well tolerated and furnished the corresponding phthalide products (**2**) in good yields



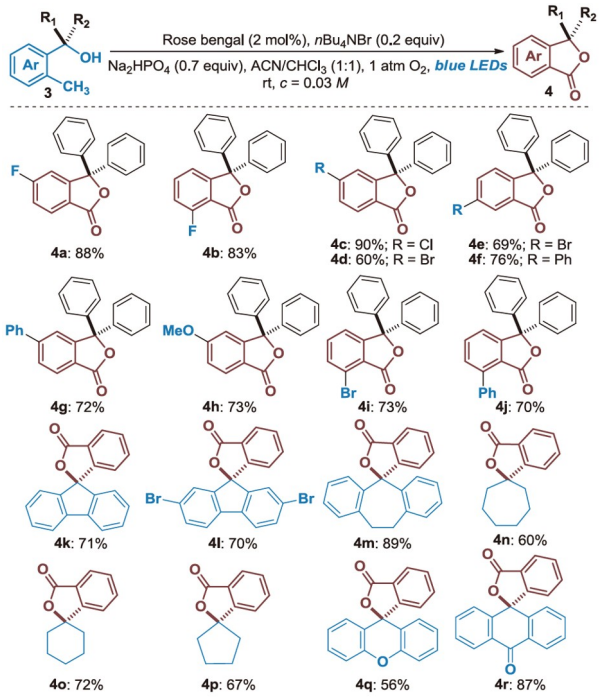
Scheme 3 Substrate scope for photocatalytic oxidative lactonization (color online).

(47%–90%). Neither further conjugation (**2b**) or electron-donating properties (**2c**–**2g**) had any obvious effect on the reaction efficiency. Alcohols bearing a halogen atom (**2h**–**2n**) on the aryl ring served as competent substrates, leaving carbon-halogen bonds intact and available for further structural modification. These mild conditions were also compatible with different electron-withdrawing groups, such as the trifluoromethyl (**2o**) and ester (**2p**) groups. Notably, the wide scope of this method was further demonstrated by employing a series of heteroaromatic ring-containing benzylic alcohols. Thiophenes (**2q**, **2r**) and pyridines (**2s**, **2t**) underwent dehydrogenated lactonization smoothly and with good yields, a remarkable feature with respect to preparations and applications of pharmaceutical agents. Alkyl (**2u**-**2aa**, **2ac**–**2ae**) or perfluoroalkyl (**2ab**) substrates also performed with comparable efficiency in oxidative lactonization.

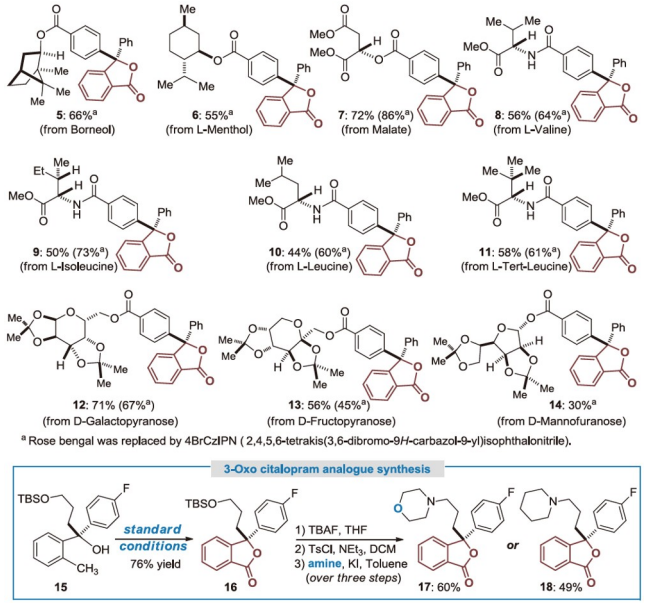
To extend the substrate scope of this method, other diverse benzylic alcohols (**3**) were exposed to the optimal reaction conditions. As shown in Scheme 4, benzylic alcohols with either electron-withdrawing (**4a**–**4e**) or electron-donating (**4f**–**4h**) substituents on the aromatic ring could afford the corresponding phthalides smoothly and in high yields (60%–90%). We utilized this new activation mode to form products with an *ortho*-substituent (**4l**, **4j**) and it was found that a range of spiro-phthalides (**4k**–**4r**) could be readily obtained in good yields (56%–89%), thus greatly enhancing the synthetic value of the method.

The synthetic robustness of this oxidative dehydrogenated lactonization was further highlighted by its application in the late-stage functionalization of complex bioactive-molecules (Scheme 5). This new technology is compatible with substrates such as borneol (**5**), menthol (**6**), malate (**7**) and amino acid derivatives (**8**–**11**). Complex substrates derived from galacto-pyranose (**12**), fructopyranose (**13**) and mannofuranose (**14**) were all readily transformed into the corresponding products. Notably, under the optimized conditions, the alcohol (**15**) primarily undergoes dehydrogenated lactonization, followed by consecutive tris buffered saline (TBS) deprotection, esterification and amine substitution, giving the 3-oxo citalopram analogues (**17**, **18**).

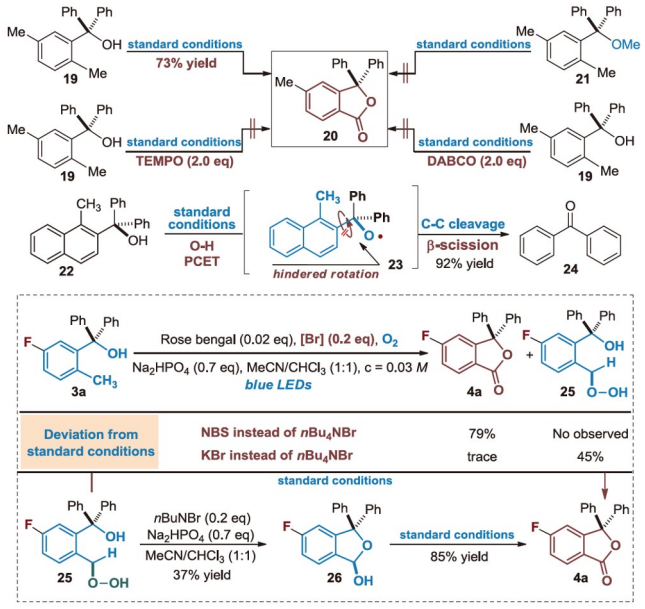
Encouraged by the generality of this dehydrogenated lactonization, we investigated the possible reaction pathways. As described in Scheme 6, dehydrogenated lactoni-



Scheme 4 Reactivity screening on different methyl aromatic alcohols (color online).



Scheme 5 Late-stage functionalization of substances derived from natural products and drugs (color online).

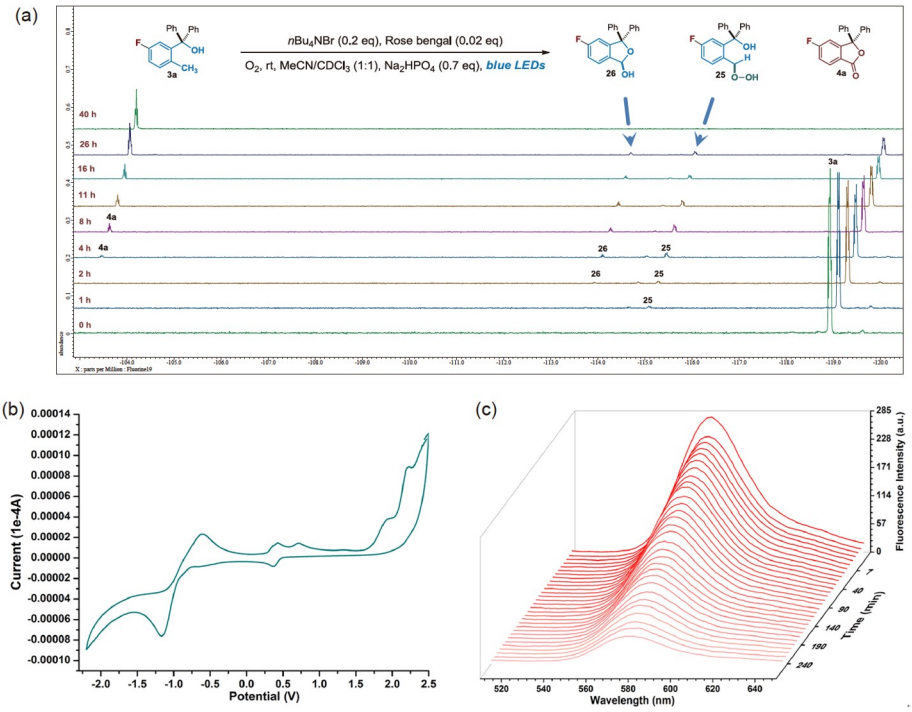


Scheme 6 Experimental investigation of the reaction mechanism (color online).

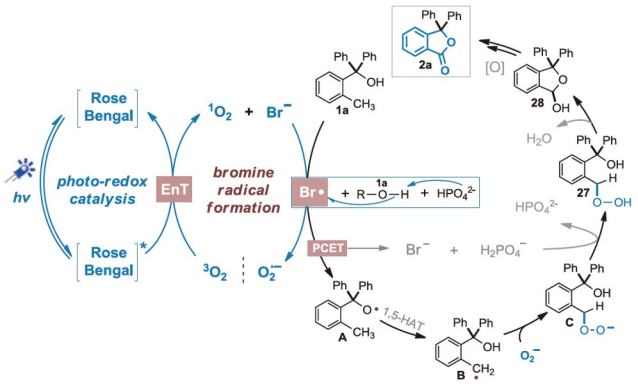
zation selectively occurs on the methyl at the β-position relative to the hydroxyl side-chain on the substrate (**19**) without interacting with the remote methyl group, indicating that oxygen-centered radicals might be involved in this transformation. For comparison, no desired product was observed when the hydroxyl group on the substrate **19** was protected with methyl group, and the use of the well-known radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or the singlet oxygen quencher 1,4-diazabicyclo-[2.2.2]octane (DABCO, $E_{ox(DABCO)}$ = +0.69 V *vs*. SCE) [12] resulted in complete inhibition of the reaction, suggesting the involvement of radical intermediates and singlet oxygen in the reaction. Remarkably, because of hindered rotation about the C–C bond in the substrate (**22**), benzophenone (**24**) was generated in high yield through the β-scission of a vicinal C–C bond, which further confirmed the formation of alkoxy radicals. Interestingly, *n*-Bu_4N•Br could be replaced by *N*-bromosuccinimide (NBS) or KBr:NBS displayed comparable reactivity while KBr gave a new key product peroxide (**25**), which could be transformed into the phthalide (**4a**) under the standard conditions. In alkaline conditions, the peroxide (**25**) underwent H_2O elimination to afford the hemiacetal (**26**), which could also serve as a viable substrate for the synthesis of the phthalide (**4a**). Taken together, these findings support the notion that bromine radical and peroxide, as well as hemiacetal, could be the key intermediates in this reaction.

Monitoring the oxidative lactonization of **3a** by *in-situ* ^{19}F-NMR showed that a peroxide (**25**) (δ = −114.9 ppm) was first produced and then further converted into the hemiacetal (**26**) (δ = −113.6 ppm) under the standard conditions (Scheme 7a). To confirm which reactant quenched the excited photocatalyst in this reaction, a fluorescence emission quenching investigation was conducted (for details, see the Supporting Information online). The results showed that, in strong contrast to the substrate benzylic alcohol (**1a**) and *n*-Bu_4N•Br, the concentration of molecular oxygen had a notable effect on the emission intensity of the excited rose bengal, and the quenching effect increased with the increase of oxygen concentration in the solution (Scheme 7c). Therefore, it was concluded that the oxygen rather than benzylic alcohol or *n*-Bu_4N•Br reacted with the excited rose bengal, and furnished the active singlet oxygen through an energy transfer (EnT) process. Another result which could further preclude the possibility of a single electron transfer (SET) process is the redox potential of substrate (**1a**) measured by cyclic voltammetry (CV) (Scheme 7b). The oxidation potential of the photoexcited rose bengal (E_{RB*/RB^-} = +1.18 V *vs*. SCE) [5i] is significantly lower than that of the substrate (**1a**) ($E_{\mathbf{1a}/\mathbf{1a}^{+\cdot}}$ = +1.92 V *vs*. SCE), and this supports that the generation of singlet O_2 by energy transfer is the dominant reaction pathway.

Based on the above observations and published literatures [13,14] on the behaviors of rose bengal and oxygen, a plausible mechanism network for accessing phthalides is depicted in Scheme 8. Irradiation of reaction mixtures with blue LEDs first gives the excited state rose bengal, which subsequently proceeds through an energy transfer (EnT) process with oxygen to deliver the reactive singlet oxygen ($^1O_2$) [15]. Then, the $^1O_2$ ($E_{1/2}$ ~ +0.16 V *vs*. SCE) [15a] undergoes a single electron transfer (SET) with Br^- ($E_{Br^-/Br^{\cdot}}$ = +0.80 V *vs*. SCE) [13], producing a Br radical $Br^{\bullet}$ [14]. With the synergistic interactions of the alkoxy radical intermediate (**A**) and HPO_4^{2-}, the substrate (**1a**) can be converted to the



Scheme 7 Mechanistic studies. (a) Reaction progress of **3a** monitored by *in-situ* ^{19}F-NMR; (b) CV curve of the substrate **1a**; (c) fluorescence quenching of rose bengal by molecular oxygen (color online).



Scheme 8 Proposed mechanism of the oxidative lactonization (color online).

alkoxy radical intermediate (**A**) through a proton-coupled electron transfer (PCET) process. Subsequently, the alkoxy radical intermediate (**A**) may participate in two possible pathways, *i.e.*, coupled with the Br$^{\bullet}$ to afford hypobromite [16] or abstract a hydrogen atom from the benzylic position *via* a 1,5-hydrogen atom transfer process to give the key benzylic radical (**B**), which subsequently undergoes a sequence of oxygen capture, oxidation, protonation and H_2O elimination to afford the hemiacetal (**27**). Finally, the hemiacetal (**27**), generated *in-situ* is capable of engaging in further oxidation resulting in the formation of the final phthalide product (**2a**).

In summary, an efficient and practical visible light-induced photocatalytic strategy has been applied to the oxidative dehydrogenated lactonization of *o*-tolylmethanols without the need for strong oxidants or transition metal catalysts. A detailed mechanistic investigation involving electrochemical and spectroscopic techniques was performed to support the proposed, plausible mechanism. This established methodology was demonstrated to be general in terms of substrate scope, and its high synthetic value is reflected by the synthetic versatility of the achieved functionalized phthalides. In view of the operational simplicity and mild conditions of this new protocol, as well as the widely appreciated significance of phthalide-type substances in the chemical and pharmaceutical context, we envision that this discovery will find broad applications in organic synthesis.

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Conflict of interest The authors declare no conflict of interest

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