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Visible Light-Promoted Magnesium, Iron, and Nickel Catalysis Enabling C(sp^3)−H Lactonization of 2-Alkylbenzoic Acids

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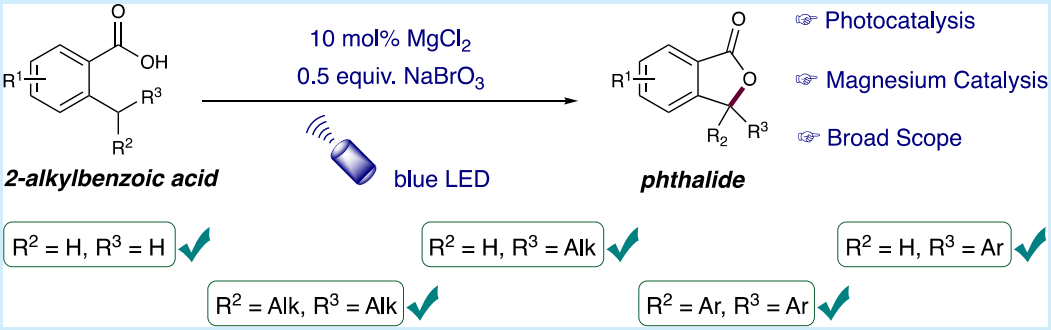

ABSTRACT: A mild and practical C(sp^3)−H lactonization protocol has been achieved by merging photocatalysis and magnesium (iron, nickel) catalysis. A diverse range of 2-alkylbenzoic acids with a variety of substitution patterns could be transformed into the corresponding phthalide products. Based on the mechanistic experimentation and reported prior studies, a possible mechanism for the benzylic oxidative lactonization reaction was proposed with the hypothetic photoactive ternary complex formed between the 2-alkylbenzoic acid substrate, magnesium ion, and bromate anion.

Phthalides are the bioactive constituents in several pharmaceutical agents, such as mycophenolic acid (immunosuppressive), noscapine (antitussive), and butylphthalide (neuroprotective).[1] Among the versatile strategies developed so far for the synthesis of phthalide scaffolds,[2] the direct C(sp^3)−H lactonization of 2-alkylbenzoic acids represents the most straightforward synthetic pathway. Along this line, a number of pioneering and elegant studies have been reported. Phthalides could be prepared effectively by platinum- and palladium-catalyzed C(sp^3)−H activation methods at 140−150 °C (Figure 1A).[3] However, only one example of 3-substituted phthalide product was prepared in 38% yield by these methods. Another feasible strategy to construct phthalides from 2-alkylbenzoic acids is through the radical C(sp^3)−H functionalization pathways (Figure 1B). A benzylic radical intermediate might be produced by an intermolecular hydrogen atom transfer (inter-HAT),[4] intramolecular hydrogen atom transfer (intra-HAT),[5] proton-coupled electron transfer (PCET),[6] or single-electron transfer/deprotonation (SET/DP)[7] process, followed by an oxidation/cyclization sequence to furnish the lactone product. In most cases, R^2/R^3 should be at least one aryl or two alkyl substituents in order to activate the *ortho* benzylic C(sp^3)−H bond of the benzoic acids and thus stabilize the corresponding benzylic radical intermediate. Although much progress has been made in the C(sp^3)−H lactonization recently, it remains a challenging task. The current methods typically suffer from moderate yields (mostly around 30−70%) and narrow scopes. Visible-light-promoted transition-metal catalysis has very recently emerged as a new paradigm in organic photocatalysis.[8] As part of our long-term interest in visible-light-promoted organic synthesis,[9] herein we report the merging of magnesium (iron, nickel) catalysis and visible-light photocatalysis at room temperature to deliver the phthalides from 2-alkylbenzoic acids with rich functionalities and substitution patterns both on the parent benzene ring and at the C3 position of phthalides (Figure 1C).

We began our exploration into the C(sp^3)−H lactonization by exposing an acetonitrile solution of 2-methylbenzoic acid, $MgCl_2$ (10 mol %), and $NaBrO_3$ (0.5 equiv) to the irradiation of 427 nm LEDs for 18 h. To our delight, the desired phthalide product was obtained in 78% yield under the standard conditions (Table 1). The control experiments demonstrated the critical roles of the light, magnesium catalyst, and oxidant (entries 1−3). No lactonization product was formed in the absence of light, $NaBrO_3$, or $MgCl_2$. The reaction did not occur even under the irradiation of 370 nm UV light without $MgCl_2$. We tried to achieve a higher conversion by increasing

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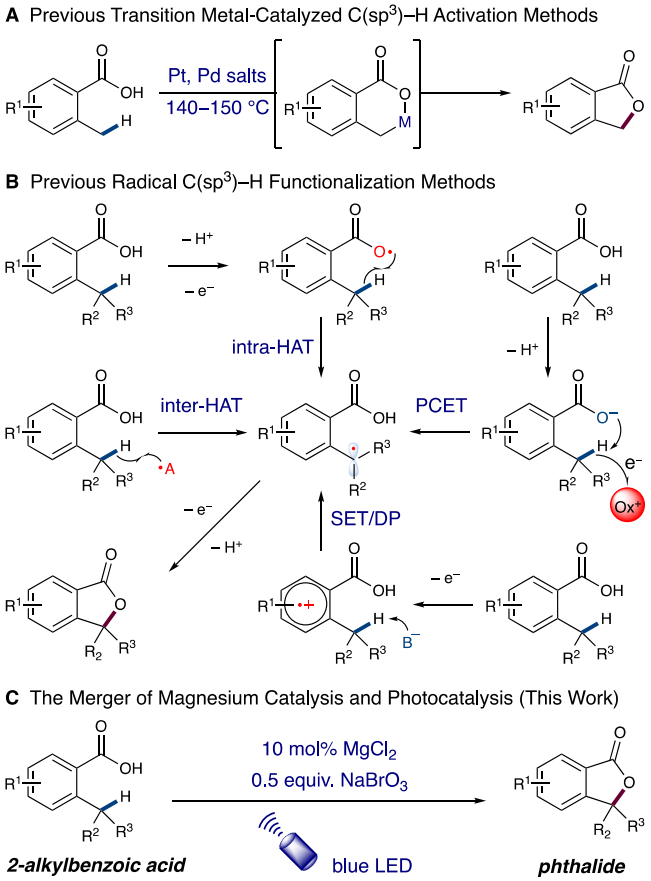
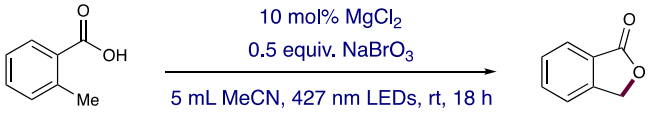


Figure 1. Synthetic approaches to phthalides.

Table 1. Optimization for the Lactonization Reaction[a]



entry	variation from standard conditions	yield (%)
1	no light	0
2	no $NaBrO_3$	0
3	no $MgCl_2$ (427 or 370 nm LED)	0
4	increase the amount of $MgCl_2$ to 100 mol %	61
5	$MgBr_2{\cdot}Et_2O$ instead of $MgCl_2$	73
6	$CaCl_2$ instead of $MgCl_2$	56
7	LiCl instead of $MgCl_2$	45
8	20 mol % LiCl instead of $MgCl_2$	64
9	NaCl or KCl instead of $MgCl_2$	0
10	$MnCl_2$ instead of $MgCl_2$	31
11	$FeCl_3{\cdot}6H_2O$ instead of $MgCl_2$	50
12	$Fe(NO_3)_3{\cdot}9H_2O$ instead of $MgCl_2$	41
13	$CoCl_2{\cdot}.6H_2O$ instead of $MgCl_2$	16
14	$NiCl_2{\cdot}6H_2O$ instead of $MgCl_2$	69
15	$CuCl_2$ instead of $MgCl_2$	34
16	reduce the amount of $NaBrO_3$ to 0.3 equiv	67
17	$NaClO_3$ instead of $NaBrO_3$	0
18	KIO_3 instead of $NaBrO_3$	0

[a]Yield determined by ^1H NMR using 1,3-benzodioxole as the internal standard in $CDCl_3$. LED = light-emitting diode.

the amount of $MgCl_2$ up to 100 mol %. However, it only led to a slightly lower yield (entry 4). This might be due to the poor solubility of too much magnesium salt. $MgCl_2$ could be displaced by a variety of magnesium salts with different anions, such as $MgBr_2{\cdot}Et_2O$, affording the lactone product in a 73% yield (entry 5). Alkaline and alkali metal salts, such as $CaCl_2$ and LiCl, could also render the transformation successfully, although NaCl and KCl failed (entries 6–9). It is worth mentioning that a positive effect was observed when the amount of LiCl was doubled (entry 8). Moreover, the first-row transition metal salts, including but not limited to $MnCl_2$, $FeCl_3{\cdot}6H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$, $CoCl_2{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$, and $CuCl_2$, showed good capability to catalyze the lactonization reaction (entries 10–15). These control experiments suggested that the metal salt might play a role as a Lewis acid. It is notable that the reaction furnished a 67% yield of the phthalide when only 0.3 equiv of the oxidant $NaBrO_3$ was used (entry 16). Finally, $NaClO_3$ and KIO_3 proved to be ineffective for this oxidative reaction (entries 17 and 18).

With the optimal reaction conditions in hand, we sought to evaluate the generality of this C(sp^3)–H lactonization

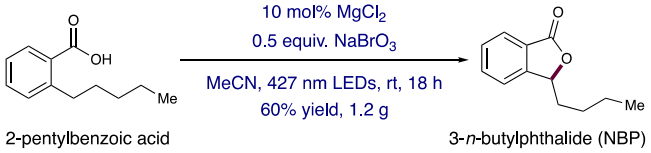


Figure 2. Gram-scale synthesis of the medicine NBP.

protocol. As illustrated in Scheme 1, $MgCl_2$ was applicable to a variety of 2-alkylbenzoic acid substrates with different functionalities and substitution patterns, while $NiCl_2{\cdot}6H_2O$ and $Fe(NO_3)_3{\cdot}9H_2O$ could afford higher yields for some substrates. First, 2-methylbenzoic acids with versatile substituents at the phenyl ring were examined, such as methyl, methoxy, acetoxy, fluoro, chloro, bromo, nitro, cyano, and trifluoromethyl groups, to provide the phthalides in 38–76% yields (**1**–**20**). Typically, $NiCl_2{\cdot}6H_2O$ was superior to $MgCl_2$ for the substrates with electron-donating groups (**2**–**5**). In addition, 2-methyl-1-naphthoic acid was converted into the lactonization product in 70% yield (**20**). However, it was found that 2-methylnicotinic acid did not work for the reaction. We then turned our attention to the benzoic acids with an extra alkyl or aryl group at the *ortho* benzylic position. 3-Substituted phthalides were formed smoothly by this protocol (**21**–**36**, 36–81% yields). Remarkably, the ester (**30**), ether (**31** and **32**), amide (**33**), and imide (**34** and **35**) functionalities attached to the side chain were tolerated well in the reaction. Furthermore, 2-benzylbenzoic acid performed quite well to give a 81% yield of **36** with the Fe(III) catalyst. Lastly, this lactonization protocol was applied to the benzoic acids with two alkyl or aryl groups at the *ortho* benzylic positions using $Fe(NO_3)_3{\cdot}9H_2O$ as the optimal catalyst to furnish the products **37**–**43** in 36–98% yields. Gratifyingly, spiro phthalides could be forged rapidly via this operationally simple cyclization method (**39**–**41**), while 3,3-bis(aryl)-phthalides were obtained in excellent yields (**42** and **43**, 95 and 98% yields).

The practical application of our C(sp^3)–H lactonization protocol was demonstrated by the gram-scale synthesis of 3-*n*-butylphthalide (NBP), a medicine for the treatment of cerebral ischemia (Figure 2).[1d] The lactonization of 2-pentylbenzoic

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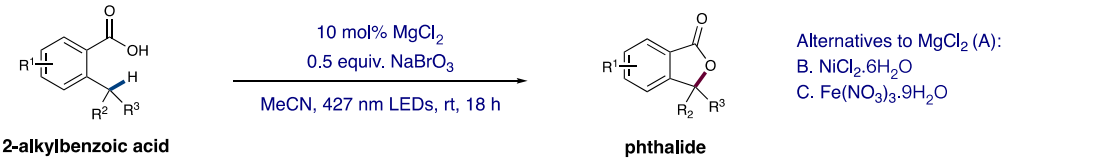
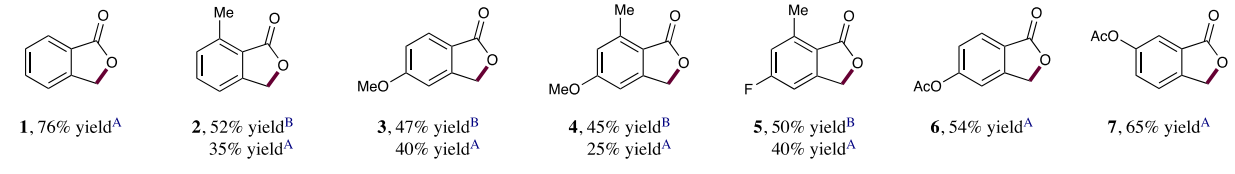
Org. Lett. 2021, 23, 5842–5847

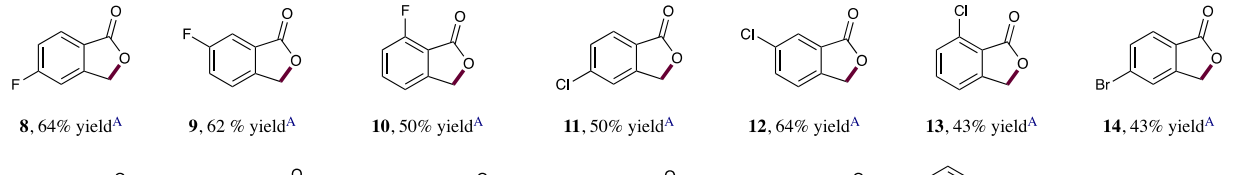
Scheme 1. Scope of the Lactonization Reaction[a]



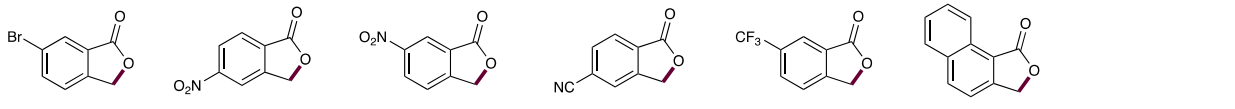
a R^2 = H; R^3 = H



1, 76% yield[A] | **2**, 52% yield[B] 35% yield[A] | **3**, 47% yield[B] 40% yield[A] | **4**, 45% yield[B] 25% yield[A] | **5**, 50% yield[B] 40% yield[A] | **6**, 54% yield[A] | **7**, 65% yield[A]

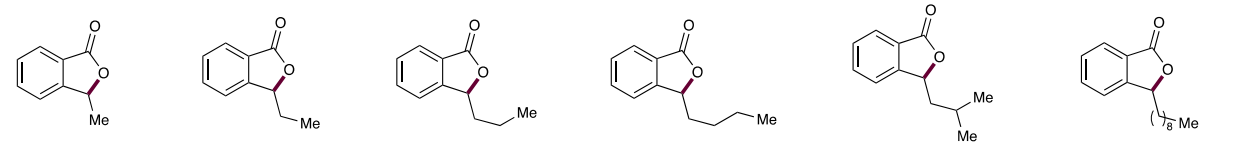


8, 64% yield[A] | **9**, 62 % yield[A] | **10**, 50% yield[A] | **11**, 50% yield[A] | **12**, 64% yield[A] | **13**, 43% yield[A] | **14**, 43% yield[A]

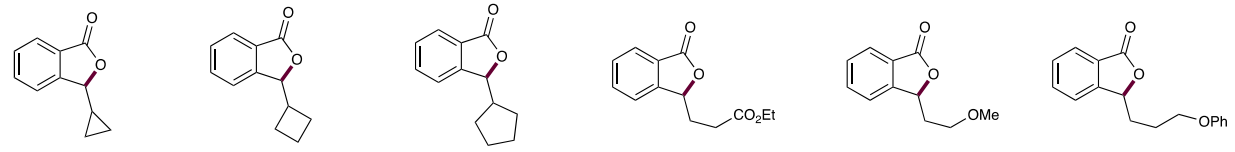


15, 55% yield[A] | **16**, 38% yield[A] | **17**, 41% yield[A] | **18**, 42% yield[A] | **19**, 48% yield[A] | **20**, 70% yield[A]

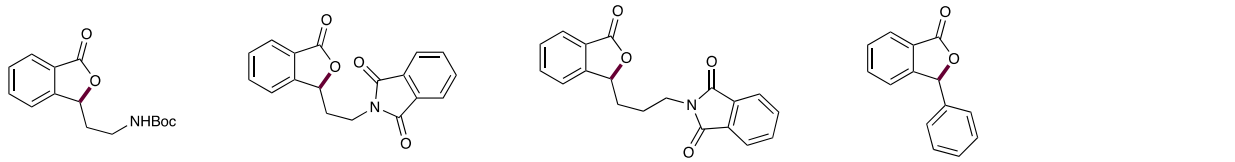
b R^2 = H; R^3 = alkyl, phenyl



21, 71% yield[A] | **22**, 52% yield[A] | **23**, 50% yield[A] | **24**, 60% yield[A] | **25**, 43% yield[A] | **26**, 49% yield[A]

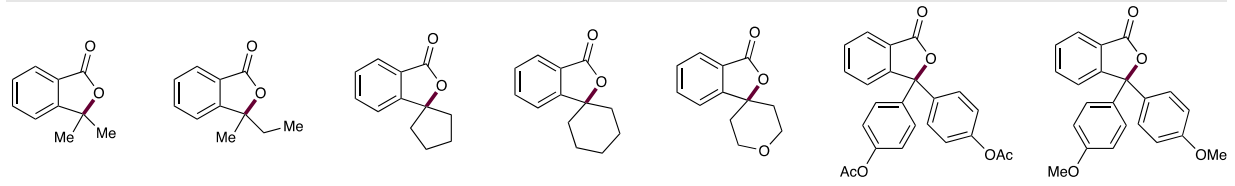


27, 56% yield[A] | **28**, 63% yield[A] | **29**, 40% yield[A] | **30**, 63% yield[A] | **31**, 53% yield[A] | **32**, 50% yield[A]



33, 36% yield[A] | **34**, 60% yield[B], 35% yield[A] | **35**, 62% yield[A] | **36**, 81% yield[C], 61% yield[A]

c R^2 = alkyl, aryl; R^3 = alkyl, aryl



37, 84% yield[C] 18% yield[A] | **38**, 70% yield[C] | **39**, 36% yield[C] | **40**, 54% yield[C] | **41**, 40% yield[C] | **42**, 95% yield[C] | **43**, 98% yield[C]

[a]Isolated yields.

acid under the standard conditions successfully provided 1.2 g of NBP in 60% yield in one step.

In order to gain an insight into the reaction mechanism, multiple experiments were carried out as shown in Figure 3. 2-Phenethylbenzoic acid was selected as a probe to check whether a carboxylate radical intermediate was involved in the benzylic C−H oxidative lactonization reaction (Figure 3A). According to the reported studies,[4b] if the carboxylate radical

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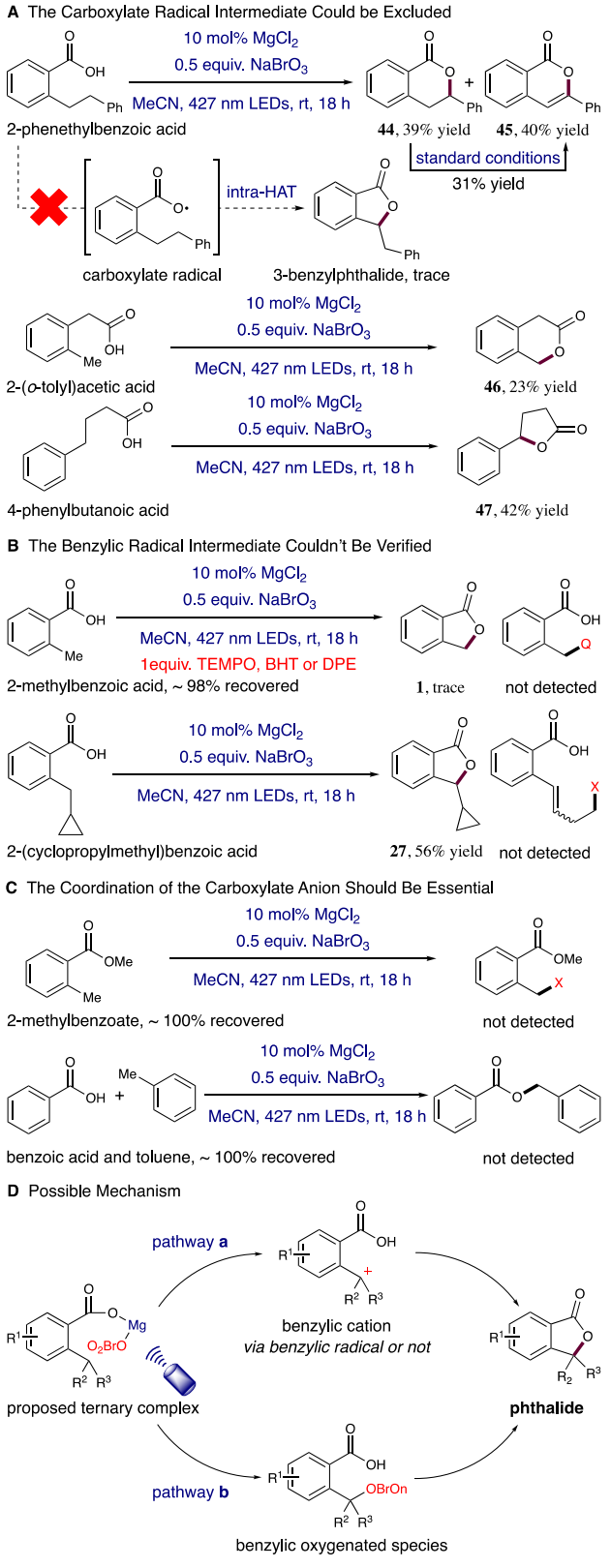

Figure 3. Mechanistic studies.

was generated from 2-phenethylbenzoic acid, a 1,5-hydrogen atom transfer event would occur preferentially to furnish the 5-membered lactone 3-benzylphthalide as the major product. In sharp contrast to those results from the carboxylate radical pathway, when 2-phenethylbenzoic acid was subjected to the standard conditions of our protocol, the oxidative cyclization happened at the more electron-rich benzylic position to form the six-membered lactone **44** and its overoxidized derivative **45** in a combined yield of 79%. The control experiment demonstrated that the product **44** could be oxidized further to the product **45** under the standard conditions. Moreover, it is well-known that alkyl carboxylate radicals are prone to undergo decarboxylative fragmentation.[9a] However, under the standard conditions of this protocol, 2-(*o*-tolyl)acetic acid and 4-phenylbutanoic acid yielded the lactonization products **46** and **47**, respectively, which were not likely formed through the alkyl carboxylate radical intermediates.[7b] In conclusion, the carboxylate radical mechanism should be not operative for our protocol. Next we tried to figure out if the benzylic radical intermediate was produced in the reaction (Figure 3B). Although the model reaction could be completely inhibited by the common radical quenchers, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), and 1,1-diphenylethylene (DPE), no benzylic radical−quencher adduct was detected. The reaction might be inhibited via a nonradical mechanism. The radical clock experiment with 2-(cyclopropylmethyl)benzoic acid only furnished the phthalide product **27** with a yield of 56%. No cyclopropyl ring-opened product was detected. At this stage, there is no conclusion whether the benzylic radical intermediate was involved in the transformation. Furthermore, in control experiments, no conversion of methyl 2-methylbenzoate was observed under the standard conditions for 18 h, indicating an essential role of coordination of the carboxylate anion to magnesium ion (Figure 3C). Also, no reaction occurred between benzoic acid and toluene, suggesting intermolecular direct oxidation of benzylic C(sp^3)−H bond was not feasible via this protocol. Finally, no carbocation rearrangement product in the case of **27**−**29** was observed. Therefore, it could not be confirmed whether the benzylic cation intermediate was involved in the reaction. Our speculation on the possible mechanism is outlined in Figure 3D. A ternary complex of the 2-alkylbenzoic acid, $MgCl_2$, and $NaBrO_3$ should be formed first. Upon the irradiation of visible light, the benzylic C(sp^3)−H bond would be oxidized by the bromate ion at close proximity. There might be two different pathways leading to the final product; in pathway a, a benzylic cation intermediate would be generated, while in pathway b a benzylic oxygenated species would be produced.

In summary, we have developed a mild and practical protocol for the C(sp^3)−H lactonization of 2-alkylbenzoic acids via the merger of photocatalysis and magnesium (iron, nickel) catalysis. A diverse array of substrates with rich substitution patterns were successfully converted into the valuable phthalide products. The practical application was demonstrated by the gram-scale synthesis of NBP. Moreover, a possible mechanism was proposed with the hypothesis of a photoactive ternary complex.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01984.

General experimental procedures, mechanistic studies, reaction setup, characterization data and spectra for all key compounds (PDF)

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Notes

The authors declare no competing financial interest.

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