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Letter

Visible-Light-Induced Metal-/Photocatalyst-Free C−H Bond Imidation of Arenes

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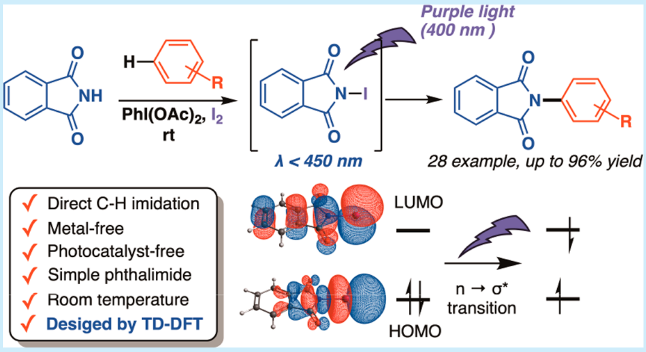
ABSTRACT: In this study, a visible-light-induced intermolecular C−H bond imidation of arenes was achieved at ambient condition. By using simple phthalimide with (diacetoxyiodo)benzene and molecular iodine, direct metal-/photocatalyst-free C−N bond formation was achieved. The imidation protocol was designed by using time-dependent density functional theory calculations and experimentally demonstrated for 28 substrates with as high as 96% yield. Mechanistic studies indicated that radical-mediated aromatic substitution occurred via photolysis of *N*-iodophthalimide under visible-light irradiation

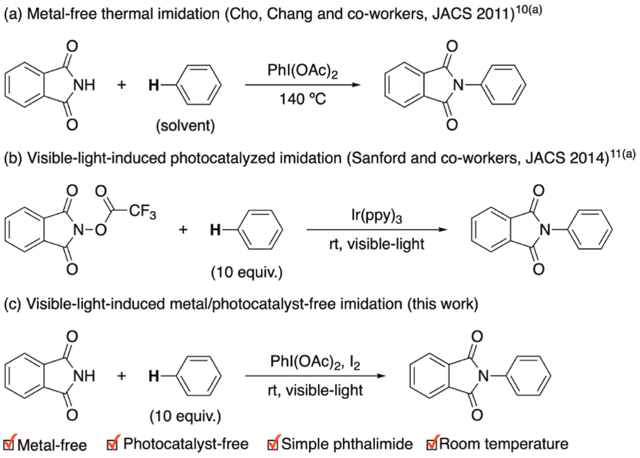


Arylamines are one of the most fundamental structural motifs found widely in pharmaceuticals, bioactive molecules, agrochemicals, reagents, and functional materials.[1] These molecules are typically prepared by nitration, followed by reduction[2] or transition-metal-catalyzed cross-coupling reactions.[3] Although the latter methods, including Buchwald−Hartwig amination, Goldberg amination, and Chan−Lam coupling, are efficient, the requirement of (pseudo)halide for the reaction represents one of the disadvantages. Therefore, direct inactive C−H bond aminations have been increasingly reported.[4] Because these reactions do not require arene prefunctionalization, they are advantageous in terms of ease of preparation, waste of material, and cost effectiveness; late-stage amination is also applicable.

Because the *N*-phthaloyl group can be efficiently cleaved with an acid, base, or hydrazine, phthalimide is often used as a nitrogen source for C−H bond imidation. Several attractive direct phthalimidation methods have been reported, specifically phthalimidation using Pd,[5] Rh,[6] Cu,[7] Au,[8] UV irradiation,[9] hypervalent iodine,[10] and visible-light photoredox catalysis.[11] However, these methods require transition metals, high temperatures, high pressures, photocatalysts, or prefunctionalized phthalimides (Schemes 1a and b). Therefore, the aim of this study was to develop a new C−H imidation methodology avoiding these disadvantages. In this article, we report a method for metal- and photocatalyst-free C−H imidation under mild conditions using simple phthalimide (Scheme 1c).

We hypothesized that the generation of phthalimidyl radicals is the key to the imidation under room temperature and metal-free conditions. Therefore, we performed a calculation to design a phthalimide derivative that absorbs visible light and generates phthalimidyl radicals under low-energy light: time-dependent density functional theory (TD-DFT) calculation of the $S_0 \rightarrow S_1$ absorption and bond dissociation energy (BDE) of the N−R bond in phthalimide derivatives (Figure 1a). All calculations were performed using the Gaussian 16 program.

Scheme 1. (a, b) Reported C−H Bond Phthalimidation of Arenes and (c) This Work



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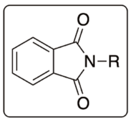
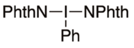
(a) Screening for $S_0 \rightarrow S_1$ absorption wavelength and BDE of N–R bond

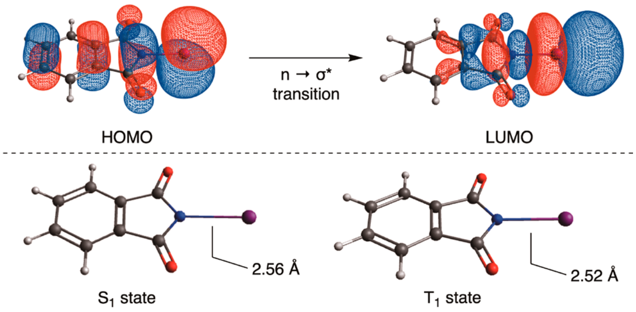




1i

R	$S_0 \rightarrow S_1$ (nm)	BDE $_{(N–R)}$ (kcal/mol)
H (**1a**)	326.0	117.3
NPhth (**1b**)	328.2	89.0
NH_2 (**1c**)	334.7	78.3
OH (**1d**)	351.4	68.7
Cl (**1e**)	319.7	63.4
Br (**1f**)	327.3	57.9
$OCOCF_3$ (**1g**)	319.3	57.1
I (**1h**)	371.9	51.8
PhI(NPhth) (**1i**)	329.1	46.0

(b) Computational analysis of **1h**



(c) Initial trial of the **1h** photolysis

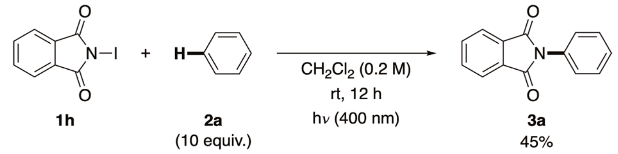


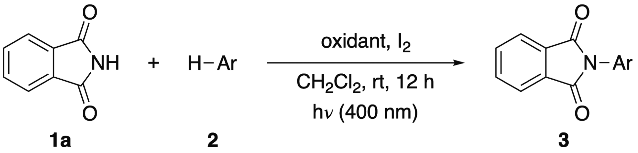
Figure 1. (a) *In silico* screening of the phthalimidyl radical precursor; (b) computational analysis of the orbital and structure; (c) preliminary experiment for the direct C−H imidation.

The B3LYP functional[12] was used in combination with SDD[13] (for iodine) and 6-311++G(d,p)[14] (for the other atoms) basis sets. Based on the *in silico* screening, *N*-iodophthalimide (**1h**) has the longest $S_0 \rightarrow S_1$ absorption wavelength at 371.9 nm and the second smallest BDE of 51.8 kcal/mol, suggesting that the irradiation with black light (365 nm, 78.3 kcal/mol) or purple light (400 nm, 71.5 kcal/mol) triggers the cleavage of the N−I bond. Although λ^3-iodane (**1i**) has the smallest BDE (46.0 kcal/mol), the calculated $S_0 \rightarrow S_1$ absorption is 329.1 nm, indicating that the absorption of visible light is difficult. Hence, we set **1h** as the precursor for the phthalimidyl radical by irradiation with 365 nm black or 400 nm purple light. The calculated molecular orbital contributing to the $S_0 \rightarrow S_1$ excitation is the n → σ^* transition, and the N−I bond length in the optimized S_1 and T_1 states is 2.56 and 2.52 Å, respectively, indicating that the N−I bond weakened and was almost cleaved in the excited state (Figure 1b). Therefore, we conducted an initial C−H bond imidation trial on benzene using **1h** under the irradiation with 400 nm purple light. We successfully obtained *N*-phenylphthalimide (**3a**) with a yield of 45% (Figure 1c).

Because **1h** is not resistant to moisture and light, we planned to prepare **1h** *in situ* using phthalimide **1a**, molecular iodine, and (diacetoxyiodo)benzene (Table 1).[15] We started the optimization studies of the C−H bond imidation with **1a** in the presence of benzene (10 equiv), (diacetoxyiodo)benzene (2 equiv), and molecular iodine (1 equiv) in dichloromethane under irradiation with a 400 nm light emitting diode (LED) light. The desired product, **3a**, was obtained with a 62% yield (Table 1, entry 1). An inert atmosphere, such as an argon atmosphere, was not essential for this reaction (entries 1 and 2). The increase in the amount of oxidant improved the yield, and 4 equiv of (diacetoxyiodo)benzene generated **3a** with the highest yield (96%, entry 4). Although a half equivalent of iodine also led to high yields in the case of benzene (entry 5), these reaction conditions were not suitable for other substrates such as mesitylene (entry 7) as it decreases the product yield. Importantly, the imidation did not proceed under light-shielding conditions (entry 8), and the yield decreased under irradiation with 365 nm black light and 450 nm blue LED light (entries 9 and 10). Other oxidants, such as bis(trifluoroacetoxyiodo)benzene and para-substituted (diacetoxyiodo)benzene, did not improve the yield (entries 11−13). When the amount of benzene was decreased to 5 equiv, the yield was decreased to 81% (entry 14). The phthalimidation of iodobenzene produced from $PhI(OAc)_2$ mainly proceeded with one equivalent of benzene; thus, excess amount of arene would be necessary for this reaction.

We investigated the substrate generality for the aryl imidation reaction under optimal conditions (Scheme 2). Benzene and mono/di/trimethyl-substituted benzene transformed into the corresponding *N*-aryl phthalimide products; high yields were obtained (**2a−g**), and no kinetic isotope effect was observed (**2b**). Notably, ethylbenzene (**2h**) with a benzylic position that can be reacted based on Muñiz's recent report[16] is also capable of chemoselective imidation of the $C(sp^2)$−H bond of aryl with excellent yields. Electron-donating substituents such as methoxy, acetoxy, and *tert*-butyldimethylsilyloxy led to the formation of phthalimide-arene (**2i−k**), and

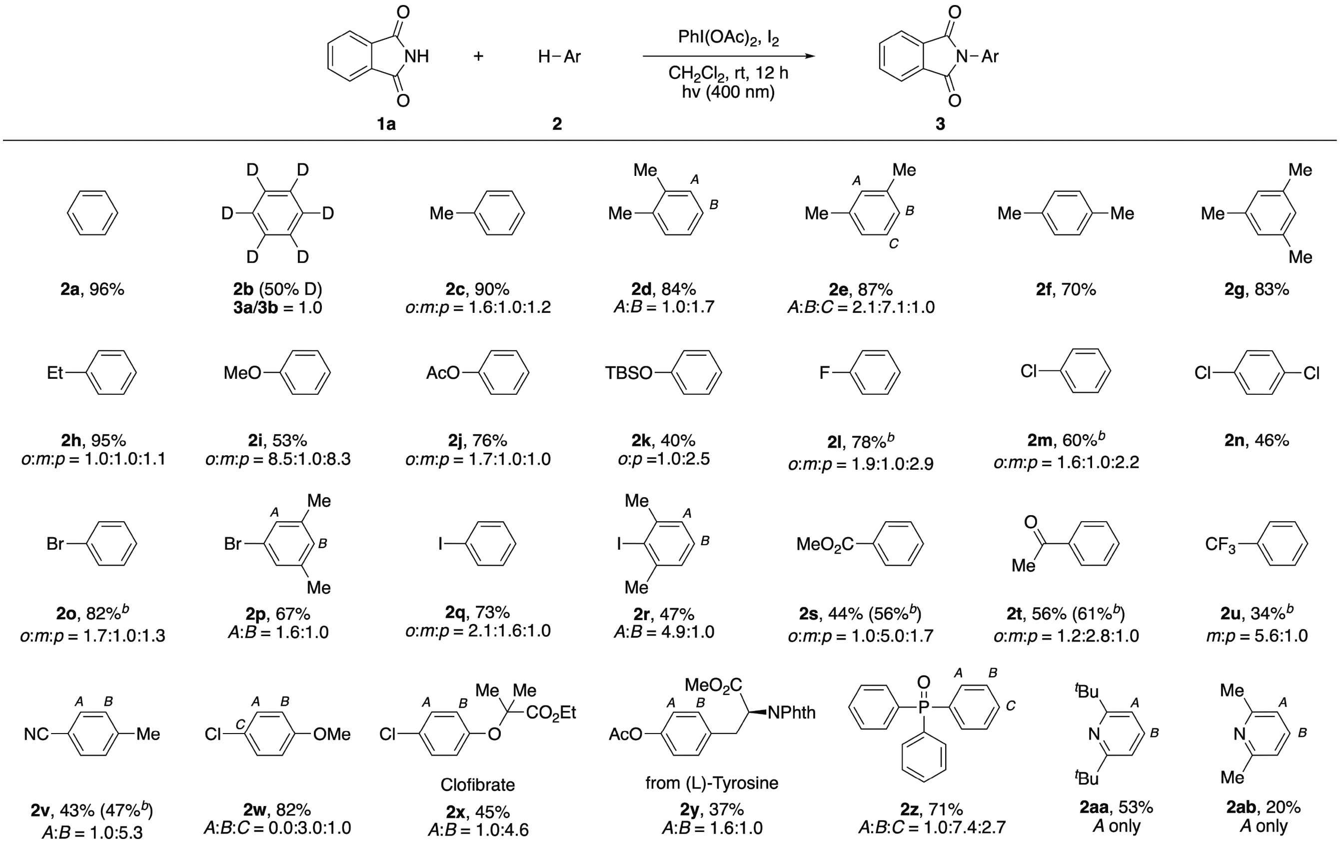
Table 1. Optimization Studies for the Direct C−H Imidation[a]



entry	H−Ar	oxidant (equiv)	I_2 (equiv)	yield (%)
1	benzene	$PhI(OAc)_2$	1.0	62
2[b]	benzene	$PhI(OAc)_2$	1.0	62
3	benzene	$PhI(OAc)_2$	1.0	86
4	benzene	$PhI(OAc)_2$	1.0	96[c]
5	benzene	$PhI(OAc)_2$	0.5	93
6	mesitylene	$PhI(OAc)_2$	1.0	83[c]
7	mesitylene	$PhI(OAc)_2$	0.5	49
8[d]	benzene	$PhI(OAc)_2$	1.0	n.d.[e]
9[f]	benzene	$PhI(OAc)_2$	1.0	65
10[g]	benzene	$PhI(OAc)_2$	1.0	60
11	benzene	$PhI(TFA)_2$	1.0	15
12	benzene	$(4\text{-}F)PhI(OAc)_2$	1.0	82
13	benzene	$(4\text{-}Cl)PhI(OAc)_2$	1.0	85
14[h]	benzene	$PhI(OAc)_2$	1.0	81

[a] General conditions: 0.2 mmol scale of phthalimide (1.0 equiv), arene (10.0 equiv), oxidant (2.0−4.0 equiv), I_2 (0.5−1.0 equiv), CH_2Cl_2 (0.2 M), rt, 12 h, *hν* (400 nm), under ambient air. Yields were determined by ^1H NMR analysis. [b] Reaction performed under argon. [c] Isolated yield. [d] Reaction performed in the dark. [e] n.d. = not detected. [f] *hν* (365 nm) was used instead of *hν* (400 nm). [g] *hν* (450 nm) was used instead of *hν* (400 nm). [h] 5 equiv of benzene was used.

Scheme 2. Substrate Scope for the Visible-Light-Induced Metal-/Photocatalyst-Free C−H Bond Imidation of Arenes[a]



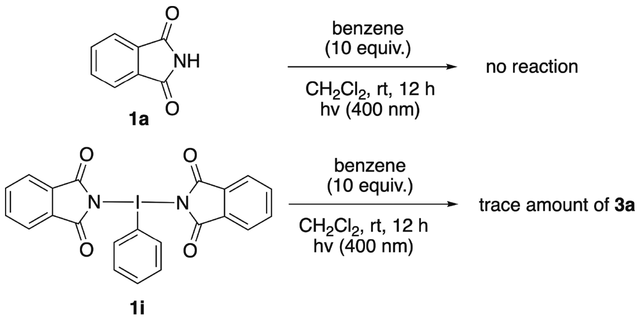
[a]Reaction conditions: 0.2 mmol scale of **1a** (1.0 equiv), arene (10.0 equiv), PhI(OAc)$_2$ (4.0 equiv), I$_2$ (1.0 equiv), CH$_2$Cl$_2$ (0.2 M), rt, 12 h, *hν* (400 nm), under ambient air. Isolated yields. [b](4-Cl)PhI(OAc)$_2$ was used instead of PhI(OAc)$_2$.

the trace amount of iodinated arene was observed only with the methoxy substrate **2i**. Moreover, electron-withdrawing substrates such as halogen, ester, acetyl, trifluoromethyl, and cyano-substituted arenes were also tolerated based on this protocol and generated the corresponding products (**2l−w**). The *ipso*-substitution was observed when chloro- and methoxyl-substituted arene **2w** was used. In some electron-withdrawing substrates, (1-diacetoxyiodo)-4-chloro-benzene [(4-Cl)PhI(OAc)$_2$] was used instead of (diacetoxyiodo)-benzene because the phthalimidyl radicals reacted faster with iodobenzene that was produced *in situ* from (diacetoxyiodo)-benzene (**2l−m**, **2o**, **2s−v**). The site selectivity of these reactions is consistent with a previously reported radical C−H imidation reaction.[11]

To further explore the substrates, C−N bond formation necessary for the generation of more complex molecules was investigated. Clofibrate, which is a lipid-regulating agent that belongs to the class of fibrates, led to the formation of *N*-aryl phthalimide products with a yield of 45% (**2x**). An (L)-tyrosine derivative and triphenylphosphine oxide also yielded 37 and 71% of products, respectively (**2y** and **z**). Furthermore, our conditions were suitable for heteroarenes; 2,6-difunctionalized-pyridine selectively underwent C−H imidation at C3-position, written as A (**2aa** and **ab**).

Subsequently, mechanistic studies and control experiments were carried out to determine the active species. Compared with *N*-iodophthalimide (**1h**), which generated **3a** with a 45% yield (Figure 1c), phthalimide (**1a**) and λ^3-iodane (**1i**)[17] yielded no or only trace amounts of **3a**, respectively (Scheme 3), indicating that *N*-iodophthalimide (**1h**) is the key molecule absorbing 400 nm purple light.

Scheme 3. Control Experiments to Determine the Active Species



Thus, we next measured the ultraviolet−visible (UV−vis) spectra of **1h** and benzene (**2a**; Figure 2). As expected from the DFT calculation (Figure 1a), **1h** exhibits broad absorption in the UV−vis region including 400 nm. Furthermore, the addition of 10 equiv of benzene did not affect the waveform nor strength of the spectra, suggesting that **1h** did not form a complex with arene. Therefore, **1h** absorbs the 400 nm light and photolysis occurs, leading to the generation of phthalimidyl radicals.

The proposed imidation mechanism is shown in Figure 3. The reaction starts with the photolysis of *in situ* generated **1h** using 400 nm visible light to generate a long-lasting T$_1$ state via

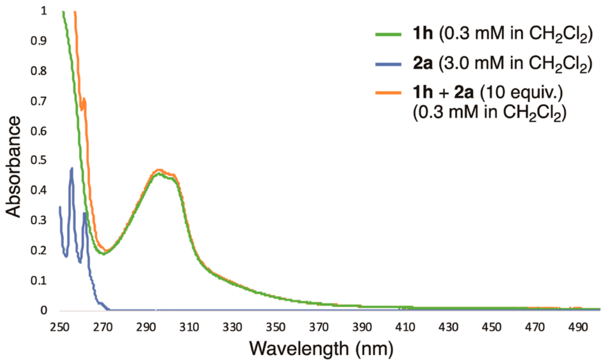


Figure 2. Absorption spectra of **1h** and **2a**.

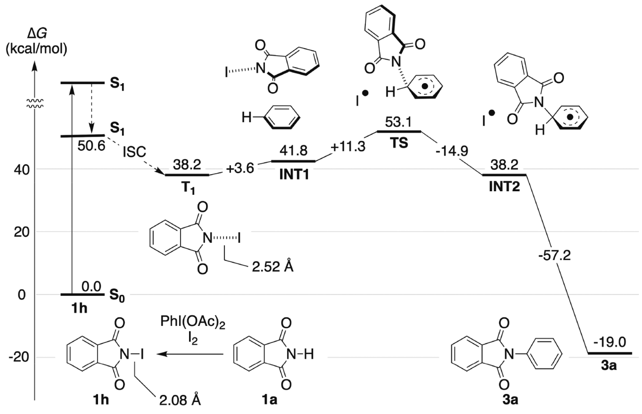


Figure 3. Proposed reaction mechanism by DFT calculation

intersystem crossing from the S_1 state. The DFT calculation shows that the length of the N−I bond in the triplet excited state is 2.52 Å, which is 0.44 Å longer than that in the ground state. Thus, the N−I bond almost dissociates in the triplet excited state. The phthalimidyl radical-mediated aromatic substitution to benzene proceeds with a low activation energy of 11.3 kcal/mol. Finally, the aromatization of INT2 provides the thermodynamically stable product **3a**.

In conclusion, we describe a metal- and photocatalyst-free method for the C−H imidation of various arenes. Based on the molecular and reaction design derived from DFT calculations, simple phthalimide and visible light can be used. This methodology, which requires neither prefunctionalized phthalimide nor arene, is meaningful for both academic and industrial research. Further progress with respect to its application to the synthesis of various arylamines is anticipated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00433.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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