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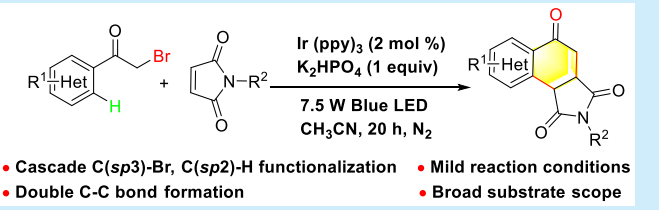
Cascade Functionalization of C(sp^3)−Br/C(sp^2)−H Bonds: Access to Fused Benzo[*e*]isoindole-1,3,5-trione via Visible-Light-Induced Reductive Radical Relay Strategy

Jia-Nan Zhu, Wen-Kang Wang, Yuan Zhu, Yin-Qiu Hu, and Sheng-Yin Zhao*

College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, People's Republic of China

Supporting Information

ABSTRACT: A reductive radical relay strategy for the construction of fused benzo[*e*]isoindole-1,3,5-trione through a reaction of α-bromo ketones with maleimides in the presence of Ir(ppy)$_3$ under visible-light irradiation is described. The protocol employs very mild reaction conditions and offers satisfactory yields. Moreover, the reaction proceeds through a cascade C(sp^3)−Br/C(sp^2)−H functionalization, double C−C bond formation, and oxidative aromatization sequence.



Generally, nitrogen-containing heterocycles were found in an array of bioactive molecules,[1] natural products,[2] and functional materials.[3] They thereby play a significant role in diverse research disciplines including drug discovery, chemical biology, and material science. They also represent a very important and fast-developing area in organic synthesis.[4] Among them, benzo[*e*]isoindole-1,3,5-trione derivatives show glycogen synthase kinase 3β inhibitors,[5] α1A adrenoceptor antagonistic activity,[6] and so on[7] (Figure 1). However, reports

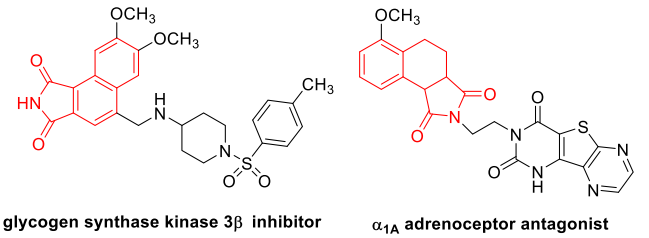
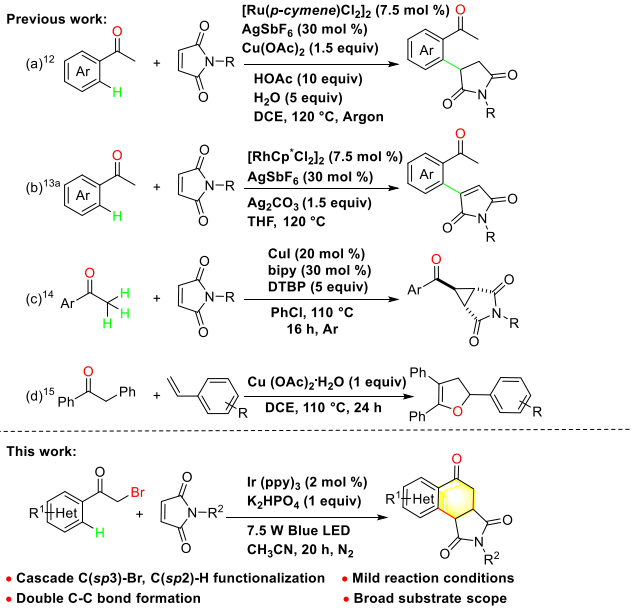


Figure 1. Representive examples of benzo[*e*]isoindoles.

on the synthesis of benzo[*e*]isoindole scaffolds are rarely seen in the literature[8] (Figure 1). Given the usefulness of benzo[*e*]isoindole-1,3,5-triones, development of a practical and efficient avenue to their synthesis is of great significance.

The maleimide frames are ubiquitously found in a large number of natural products and pharmaceutically active molecules[9] as well as functional materials.[10] As a consequence, the introduction of maleimide skeleton has drawn considerable attention for chemists. In recent years, transition-metal-catalyzed C−H bond activation of (hetero)arenes with maleimides has been the most efficient and convenient approach for the synthesis of structurally diverse compounds.[11] For example, in 2015, the Prabhu group[12] reported the 1,4-addition of ketone with maleimides via Ru(II)-catalyzed direct C−H bond activation and the succinimide scaffolds were obtained in moderate to excellent yields (Scheme 1a). Subsequently, they[13] successfully applied this transformation for the synthesis of 3-substituted maleimides through oxidative-Heck reaction of maleimides with ketones by Rh(III)-catalyzed C−H activation strategy (Scheme 1b).

Scheme 1. Functionalization of Different Positions of Acetophenones



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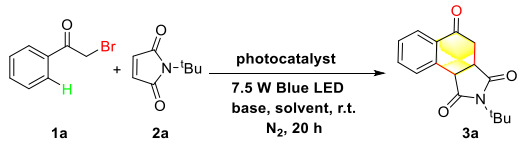
Furthermore, the Antonchick group[14] described a copper-catalyzed double C−H bond functionalization reaction at the α-position of acetophenones with maleimides for the direct synthesis of cyclopropanes (Scheme 1c). In addition, Maiti's group[15] developed a copper-catalyzed example with respect to dihydrofuran synthesis from aryl ketones and aromatic olefins via radical cyclization strategy (Scheme 1d). To the best of our knowledge, a cascade functionalization of $C(sp^3)-Br/C(sp^2)-H$ of α-bromo ketones with maleimides for the construction of fused benzo[*e*]isoindole-1,3,5-triones was not explored so far. Therefore, development of a direct avenue for the efficient construction of the benzo[*e*]isoindole-1,3,5-trione is highly desirable.

Visible-light-induced photoredox catalysis has achieved impetus in recent years for the development of nontraditional bond constructions in organic synthesis. A milestone was gained in this field on account of the pioneering research by MacMillan,[16] Stephenson,[17] Yoon,[18] and other groups.[19] Indeed, a series of covalent bonds such as C−C, C−X, and even C−H have been activated into corresponding radical intermediates,[20] and plentiful momentous synthetic transformations have been realized, including radical addition, cross-dehydrogenative coupling, and radical cyclic reaction.[21] Meanwhile, related photoredox catalysis reactions of maleimides have been investigated to some extent.[22] However, these reactions are mainly limited to tertiary anilines.[22] While significant advances have been made, the exploration of photoredox-catalyzed transformation via a radical relay strategy for the construction of privileged fused benzo[*e*]isoindole-1,3,5-triones is still promising and attractive. As part of our ongoing research on the development of maleimide chemistry,[23] herein we disclose a cascade functionalization of $C(sp^3)-Br/C(sp^2)-H$ bonds for the synthesis of fused benzo[*e*]isoindole-1,3,5-triones via visible-light-induced reductive radical relay.

To test this feasibility, we initiated our investigation by exploring diverse reaction conditions for this photoredox cascade protocol of 2-bromoacetophenone **1a** and *N*-*tert*-butylmaleimide **2a**, and screening results are summarized in Table 1. To our delight, the desired product **3a** was isolated in 32% yield when the reaction proceeded in the presence of 2 mol % of $Ir(ppy)_3$ and 1.0 equiv of $NaHCO_3$ in degassed DMF under blue LED irradiation, which showed this novel radical cyclic reaction strategy is feasible. Further screening of solvents suggested that CH_3CN was the best choice, affording the desired product in 67% yield (entries 2−10). Obviously, the base played a crucial role in neutralizing the byproduct HBr. Then a variety of bases were validated, and the results revealed that none of the other bases was superior to K_2HPO_4, with an up to 81% yield (entries 11−20). It should be noted that the target molecule **3a** was not observed because maleimides are unstable in the presence of strong bases and are subjected to polymerization and decomposition (entries 19 and 20).[24] The replacement of $Ir(ppy)_3$ with other photocatalysts, including eosine and $Ru(bpy)_3Cl_2·6H_2O$, led to no product detection, probably due to the unfavorable redox potential[25] with substrate **1a** (entries 21 and 22). Finally, control experiments indicated that the base, photocatalyst $Ir(ppy)_3$, and visible light were all necessary for this transformation (entries 23−25).

Having the optimal reaction conditions in hand (Table 1, entry 17), the scope and generality of this reductive radical relay reaction were then explored. The reaction revealed good functional group compatibility and proved to be a versatile

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	catalyst	solvent	base	**3a** yield[b] (%)
1	$Ir(ppy)_3$	DMF	$NaHCO_3$	32
2	$Ir(ppy)_3$	DMSO	$NaHCO_3$	trace
3	$Ir(ppy)_3$	dioxane	$NaHCO_3$	23
4[c]	$Ir(ppy)_3$	THF	$NaHCO_3$	0
5	$Ir(ppy)_3$	$CHCl_3$	$NaHCO_3$	26
6	$Ir(ppy)_3$	acetone	$NaHCO_3$	48
7	$Ir(ppy)_3$	CH_3CN	$NaHCO_3$	67
8	$Ir(ppy)_3$	DCE	$NaHCO_3$	39
9	$Ir(ppy)_3$	PhCl	$NaHCO_3$	21
10	$Ir(ppy)_3$	CH_3OH	$NaHCO_3$	0
11	$Ir(ppy)_3$	CH_3CN	Na_2CO_3	54
12	$Ir(ppy)_3$	CH_3CN	DBU	11
13	$Ir(ppy)_3$	CH_3CN	Et_3N	57
14	$Ir(ppy)_3$	CH_3CN	NaOAc	42
15	$Ir(ppy)_3$	CH_3CN	DABCO	56
16	$Ir(ppy)_3$	CH_3CN	Na_2HPO_4	74
17	**$Ir(ppy)_3$**	**CH_3CN**	**K_2HPO_4**	**81**
18	$Ir(ppy)_3$	CH_3CN	K_3PO_4	69
19	$Ir(ppy)_3$	CH_3CN	KOH	0
20	$Ir(ppy)_3$	CH_3CN	Cs_2CO_3	0
21	Eosine	CH_3CN	K_2HPO_4	0
22	$Ru(bpy)_3Cl·6H_2O$	CH_3CN	K_2HPO_4	0
23[c]	$Ir(ppy)_3$	CH_3CN		trace
24[d]		CH_3CN	K_2HPO_4	0
25[e]	$Ir(ppy)_3$	CH_3CN	K_2HPO_4	0

[a]Reactions were carried out with **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (2 mol %), and base (1 equiv) in a solvent (2.0 mL) upon irradiation with a 7.5 W blue LED under N_2 atmosphere at rt for 20 h. [b]Isolated yield. [c]No base was used. [d]No photocatalyst was used. [e]Performed in the dark.

approach for the construction of desired products (Scheme 2). First, a variety of N-protected maleimides can react smoothly under the standard conditions to furnish the products in 70−81% yield (**3a−e**). Noteworthily, this transformation was not confined to N-protected maleimides, but it could also be extended to the unprotected maleimides supplying the target products in 52−71% yield (**3f−h**). The structure of **3g** was confirmed by X-ray single-crystal diffraction. It should be noted that the reaction is completely selective toward cis configuration. Furthermore, either *trans*-dimethyl fumarate or *cis*-diethyl maleate was well compatible, affording the product in 65−74% yield (**3i,j**). Unfortunately, when maleic anhydride was utilized as the substrate, no product was detected. A possible reason is that maleic anhydride is unstable in the presence of base and is inclined to polymerize or decompose.

Next, we sought to examine the scope with respect to various 2-bromoacetophenone derivatives (Scheme 3). Both electron-withdrawing and electron-donating substituents readily underwent the desired radical relay cascade reactions, providing benzo[*e*]isoindole-1,3,5-triones in moderate to good yields (**3k−v**). The mild conditions can bear a variety of functional groups, including bromides, chlorides, trifluoromethyl, nitriles, ethers, and esters (**3k−r**, 51−77% yields). Fortunately, we unexpectedly delivered the target products

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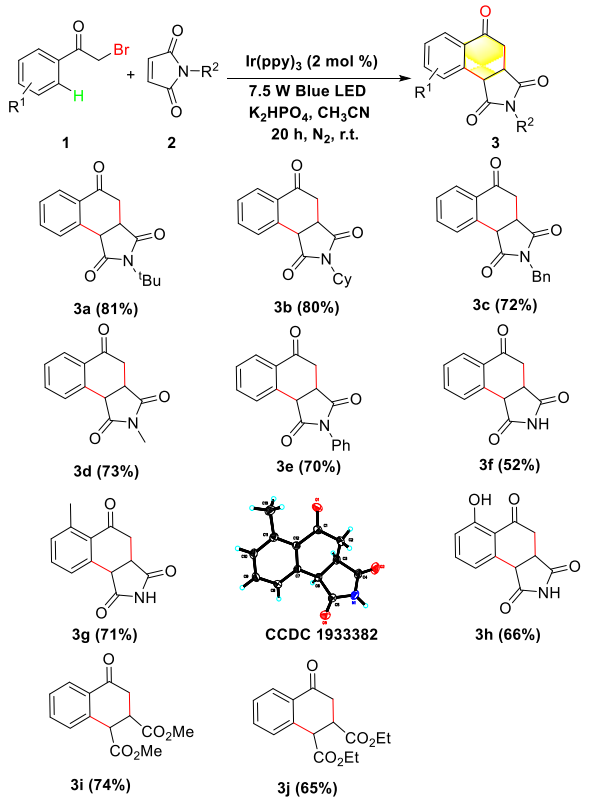
Scheme 2. Scope of Electron-Deficient Olefins[a,b]



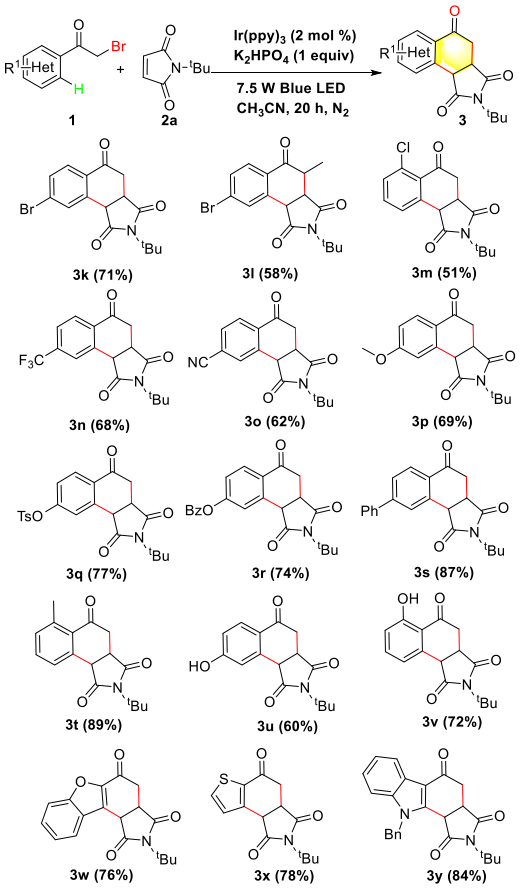
[a]Reactions were carried out with **1** (0.6 mmol), **2** (0.4 mmol), $Ir(ppy)_3$ (2 mol %), and K_2HPO_4 (1 equiv) in CH_3CN (4.0 mL) under N_2 conditions at rt for 20 h. [b]Isolated yield.

containing the free hydroxy group in moderate yields, which can offer the opportunity for further functionalization (**3u,v**). In addition, this radical relay protocol was also applicable to heteroaryl *α*-bromo ketones in the form of benzofuran, thiophene, and indole, affording the corresponding products in 76−84 yields (**3w−y**). Eventually, the regioselectivity of this reaction was further demonstrated with *meta*-functionalized substrates (Scheme 4). Regrettably, no regioselective products were achieved. When *m*-bromo-substituted substrate **1z** was implemented under the standard conditions, the proportion of $\mathbf{3z_1}$ and $\mathbf{3z_2}$ was 1.4:1. In contrast, *m*-methoxy-substituted substrate **1A** gave the isomers $\mathbf{3A_1}$ and $\mathbf{3A_2}$ in a ratio of 1.8:1. All of these isomers were confirmed by ^{1}H NMR (see the Supporting Information).

To further demonstrate the mechanism of this photocatalytic reaction, radical trapping experiments were performed (Scheme 5). The radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was directly introduced into *α*-bromoacetophenone under the standard conditions, and the intermediate TEMPO-adduct **4a** was isolated in 86% yield, confirmed by NMR and HRMS (Scheme 5A). Notably, when TEMPO was added to the reaction of *α*-bromoacetophenone **1a** and *N*-*tert*-butylmaleimide **2a** under the standard conditions, the desired radical relay reaction was completely shut down, with the formation of the TEMPO-adduct **4a** in 81% yield, explicitly indicating that a single-electron-transfer radical process was involved (Scheme 5B).

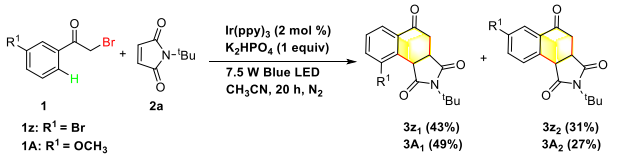
On the basis of these control experiments and literature precedent,[22a] a plausible mechanism for this reductive radical relay reaction is shown in Scheme 6. Under blue LED

Scheme 3. Scope of Various 2-Bromoacetophenones[a,b]

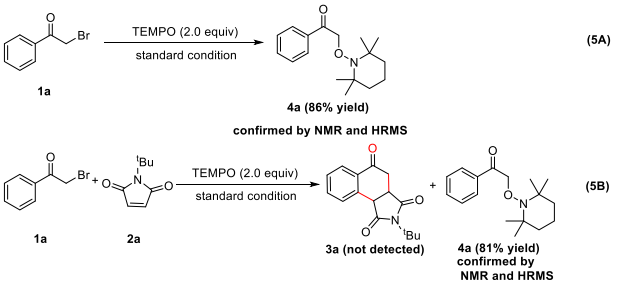


[a]Reactions were carried out with **1** (0.6 mmol), **2a** (0.4 mmol), $Ir(ppy)_3$ (2 mol %), and K_2HPO_4 (1 equiv) in CH_3CN (4.0 mL) under N_2 conditions at rt for 20 h. [b]Isolated yield.

Scheme 4. Examination of Regioselectivity



Scheme 5. Control Experiments



irradiation, the photocatalyst $Ir^{III}(ppy)_3$ is converted into the strongly reducing excited state $Ir^{III}*\{E_{1/2}^{red}$ $[*Ir^{III}/Ir^{IV}] = -1.73$ V vs SCE$\}$,[25a] which is oxidatively quenched by **1** with the formation of carbon-centered radical intermediate **4**[26] and Ir^{IV}. Subsequent C-centered radical inserts into the C═C of maleimides, and cyclization onto the aromatic ring produces the corresponding cyclohexadienyl radical **5**, which undergoes

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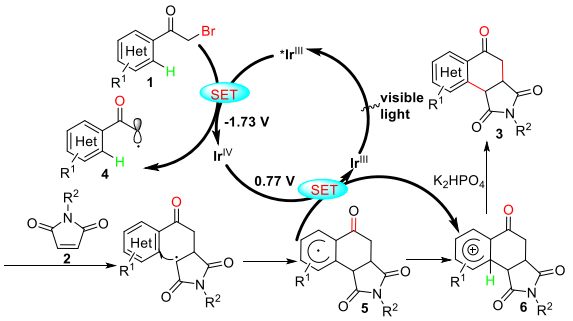
Scheme 6. Proposed Reaction Mechanism



a stepwise single-electron oxidation to achieve the carbocation **6** with the regeneration of the photocatalyst $Ir^{III}(ppy)_3$. Further deprotonation of **6** offers the eventual product **3** in the presence of base.

In conclusion, we have successfully developed an efficient and practical strategy for the synthesis of fused benzo[*e*]-isoindole-1,3,5-trione from α-bromo ketones and maleimides via visible-light-induced reductive radical relay. This versatile protocol proceeds through a cascade $C(sp^3)-Br/C(sp^2)-H$ functionalization, double C−C bond formation, and oxidative aromatization sequence under mild conditions. Further activity tests of these privileged structures are ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02153.

Experimental details, characterization data of all compounds, and copies of ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1933382 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail:syzhao8@dhu.edu.cn.

ORCID

Sheng-Yin Zhao: 0000-0002-5778-8068

Notes

The authors declare no competing financial interest.

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