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Visible light sensitization of benzoyl azides: cascade cyclization toward oxindoles via a non-nitrene pathway

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Visible light sensitization of benzoyl azides was examined in reaction with N-phenylmethacrylamides to afford biologically important oxindoles and spirooxindoles via a cascade cyclization under mild reaction conditions. Mechansitic studies suggested a non-nitrene pathway, where triplet benzoyl azides act as the reactive intermediate.

Ubiquity of aminated molecules in natural products and synthetic materials allured generations of organic chemists to develop efficient amination methodologies.¹ Utilizing acyl azides as an efficient and environment-friendly amino source has long been pursued because the only stoichiometric by-product is N₂. However, thermal or photochemical activation of acyl azides often leads to unwanted by-products such as isocyanates (via the Curtius rearrangement)² and solvent adducts of acyl nitrenes (via N₂ dissociation of activated acyl azides).

Recently, mild and selective activation of carbonyl azides was achieved by the visible light triplet sensitization. In 2015, König and coworkers reported amidation of electron-rich heteroarenes in reaction with benzoyl azides (Scheme 1a).³ Importantly, undesired reactions of neutral acyl nitrene were effectively inhibited by generating nitrenium species through the combined transfer of triplet energy and proton. Yoon and coworkers' study of olefin aziridination with triplet carbethoxynitrenes is also a compelling illustration of the efficacy of visible light triplet sensitization for the mild and selective activation of carbonyl azides (Scheme 1b).⁴ However, in both studies, photosensitization of benzoyl azide still gave rise to either undesired products (König's study without H₃PO₄)³ or

much diminished reaction efficiency (Yoon's study with benzoyl azide).⁴

Continuing our efforts on the C-H amidation reactions,⁵ we envisioned that the diradical character of triplet acyl azides could be deployed for developing a versatile synthetic methodology. Considerably long lifetime⁶ and low quantum yields in the decomposition of triplet benzoyl azide7 were especially noteworthy for realizing our hypothesis. Visible light photocatalysis⁸ was chosen as a tool for the mild and selective energy transfer. For the reaction substrate. Nphenylmethacrylamides were selected based on their welldocumented reactivity as an excellent radical acceptor, thus furnishing biologically relevant oxindole products (Scheme 1c).9

(a) via acyl nitrenium (König (2015))



(b) via triplet carbethoxynitrene (Yoon (2016))



(c) via triplet acyl azide (this work)



Scheme 1 Visible light activation of carbonyl azideS

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⁺ Electronic Supplementary Information (ESI) available: Detailed experimental procedures, characterization of new compounds, details of computational studies and X-ray analysis. CCDC 1505485 and 1505486. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

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The prospective photocatalytic reaction of 1a and 2a were scrutinized with visible light irradiation applied by 20 W household compact fluorescent lamp (CFL) (Table 1). Photocatalyst optimization unveiled the highest reactivity with [Ir{dF(CF3)ppy}2(dtbbpy)]PF6 which has the highest singlettriplet energy difference ($E_{ST} = 60.8$ kcal/mol) and the longest triplet excited-state lifetime (τ = 2300 ns) among those tested.^{8a} From the solvent screening, acetonitrile turned out to be most effective. The most notable observation with various solvents was the absence of by-products typically derived from isocyanate or acyl nitrene. In fact, no ylides were detected from reactions in DMSO,¹⁰ and pyridine.¹¹ Likewise, 1,3,4-oxadiazole was not formed in acetonitrile.7a, 12 In addition, no O-H insertion product was observed in a reaction using methanol solvent,^{7c, 13} while a significant amount (47%) of benzamide by-product was attributed to the hydrogen atom abstraction by triplet benzoyl azide7c from methanol.14 All of these results clearly indicate that the generation of benzoyl nitrene as the reactive intermediate can be excluded at the present stage.



| Entry | Photocatalyst | Solvent | Yield (%) ^{a,b} |
|-----------------|---|----------------------------------|--------------------------|
| 1 | [Cu(dap)₂]Cl | CH₃CN | 0 |
| 2 | [Ru(bpy)₃]Cl₂ | CH₃CN | 0 |
| 3 | [lr(dtbbpy)(ppy)2]PF6 | CH₃CN | 11 |
| 4 | <i>fac</i> -Ir(ppy)₃ | CH₃CN | 42 |
| 5 | [lr{dF(CF3)ppy}2(dtbbpy)]PF6 | CH₃CN | 79 |
| 6 | [Ir{dF(CF ₃)ppy} ₂ (dtbbpy)]PF ₆ | DMSO | 69 |
| 7 | [Ir{dF(CF ₃)ppy} ₂ (dtbbpy)]PF ₆ | DMF | 42 |
| 8 ^c | [Ir{dF(CF ₃)ppy} ₂ (dtbbpy)]PF ₆ | MeOH | 50 |
| 9 | [Ir{dF(CF ₃)ppy} ₂ (dtbbpy)]PF ₆ | pyridine | 56 |
| 10 | [Ir{dF(CF ₃)ppy} ₂ (dtbbpy)]PF ₆ | CH ₂ Cl ₂ | 74 |
| 11 ^d | [Ir{dF(CF ₃)ppy} ₂ (dtbbpy)]PF ₆ | CH ₃ CN | 96 |
| | Changes from entry 11 | | |
| 12 | No photocatalyst or light at 25 °C | | 0 |
| 13 | No light at 60 °C | | 0 |
| 14 | with NEt ₃ or EtN(<i>i</i> -Pr) ₂ (3 equiv.) | | 0 |
| 15 | with Hantzsch ester (3 equiv.) | | 0 |
| 16 | with TEMPO (3 equiv.) or O_2 (1 atm) | | 0 |

^a **1a** (0.2 mmol), **2a** (0.3 mmol), photocatalyst (2.5 mol %), solvent (1.5 mL), Ar atmosphere, visible light irradiation with 20 W CFL at 25 °C for 24 h. ^b Determined by ¹H-NMR analysis using 1,1,2,2,-tetrachloroethane as an internal standard. ^c 47% of 4-methoxybenzamide was obtained as side product. ^d Reaction for 36 h at 25 °C.

Under the optimized reaction conditions, we explored the scope of N-arylmethacrylamides (1) and benzow azides (2) (Table 2). Both electron-donating and electron-withdrawing groups on the benzoyl azides were compatible, thus furnishing the corresponding oxindole products equally in good to excellent yields (**3a–3j**).¹⁵ Importantly, a broad range of functional groups such as halo (3d-3e), ester (3f), or cyano (3h) were well tolerated. Benzoyl azides bearing multiple substituents at sites other than the para-position were also highly facile in the current transformation (3i-3j). Electronic and steric effects of substituents on the N-arylmethacrylamides were also studied. For N-substituents, ethyl (3k), benzyl (3l) and phenyl (3m) were tested to reveal good reactivity. Also, methacrylamides with various phenyl ring substituents underwent the current cyclization without difficulty to afford the desired products in good to moderate yields (3n-3v).

While a molecular scaffold of spirooxindoles is embedded in a number of biologically active natural alkaloids, its straightforward synthesis has been a highly challenging task.¹⁶ We envisioned that our present method can be extended to the synthesis of spirooxindoles by using cyclic α , β -unsaturated amides (4, Table 3). Indeed, various substituted benzoyl azides (2) were readily reacted with 4 to furnish spirooxindoles (5a– 5k).¹⁵ Surprisingly, all spirooxindoles products were obtained as single diastereomers and this stereoselectivity is attributed to the sterically much favoured reaction on the convex-face of 4 (Figure 1).



^a **1** (0.2 mmol), **2** (0.3 mmol), photocatalyst (2.5 mol %), CH₃CN (1.5 mL), Ar atmosphere, visible light irradiation with 20 W CFL at 25 °C for 36 h. All yields refer to isolated products (**3a-3v**) by column chromatography.

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Table 3 Substrate scope for aminated spirooxindoles^a



^a 4 (0.2 mmol), 2 (0.3 mmol), photocatalyst (2.5 mol %), CH₃CN (1.5 mL), Ar atmosphere, visible light irradiation with 20 W CFL at 25 °C for 36 h. All yields refer to isolated products (5a-5k) by column chromatography.





Based on the observations in Table 1 and Scheme 2b-2c, we proposed the reaction pathway as illustrated in Scheme 2a. The first step would be the triplet energy transfer from the excited photocatalyst to benzoyl azide to generate the triplet benzoyl azide (IM1). Next, bimolecular reaction between IM1 and 1 must precede N₂ dissociation (path A) because none of the benzoyl nitrene-derived side products (oxadiazole7a, 12 and aziridine^{6, 7c}) was detected. The resulting diradical intermediate¹⁷ (IM2) may undergo N2 release and cascade cyclization leading to a cyclohexadienyl radical intermediate9 (IM4). Finally, an intramolecular 1,4-hydrogen atom transfer (1,4-HAT)¹⁸ will bring out the product (3) with concomitant rearomatization.¹⁹





The energy transfer to benzoyl azide was supported by the Stern-Volmer quenching experiment²⁰ and photocatalytic reactions with the hydrogen atom donor (Scheme 2b). While Narylmethacrylamide remained completely unreacted under the optimized photocatalytic conditions with and without the hydrogen atom donor, 4-chlorobenzoyl azide efficiently reacted with the hydrogen atom donor to afford the corresponding benzamide in quantitative yield. The reversibility of triplet sensitization and deactivation of benzoyl azide (Scheme 2a) could be inferred from the complete recovery of unreacted benzoyl azide in the reaction without the hydrogen atom donor (Scheme 2b).

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While the stability of the excited azide might be seen counterintuitive, there are multiple previous studies implying the stability of triplet-sensitized azides. In many cases, quantum yields for the decomposition of triplet-sensitized azides were very low and the non-zero conversion had been attributed to the inadvertent direct irradiation from high energy UV light sources.^{7, 21} Also, non-nitrene reaction mechanism had been proposed for the intermolecular reactions of triplet-sensitized azides with molecular oxygen²² or hydrogen atom donors.^{7c}

The final step, hydrogen atom transfer, had been examined with a 1:1 mixture of deuterated and non-deuterated *N*arylmethacrylamide subjected to the photocatalytic reaction with benzoyl azide (Scheme 2c). As a result, no H/D scrambling was observed, indicating an intramolecular hydrogen atom transfer in the last step. In an experiment with repeated on-off cycling of visible light irradiation, a complete quenching of reactivity was observed in the absence of light.²⁰ Although this result may not be a definitive evidence in excluding a radical chain pathway, any chain propagation process, if there is, must be short-lived.²³

In conclusion, we have developed a mild and efficient synthetic route to biologically important oxindole and spirooxindole scaffolds enabled by the visible light of benzoyl photocatalytic reaction azides and N_{-} arylmethacrylamides. A triplet energy transfer process was proposed to operate by visible light photocatalysis with $[Ir{dF(CF_3)ppy}_2(dtbbpy)]PF_6.$ The cyclization proceeds smoothly over a broad range of substrates and reactants without involving a competitive decomposition side pathway. The observed stability and reactivity of the presumed reactive intermediate, triplet benzoyl azides, would be a promise for further synthetic studies of acyl azides.

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