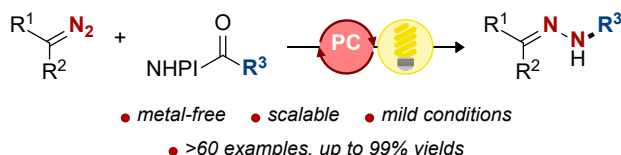


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# Photoredox Decarboxylative C(sp<sup>3</sup>)–N Coupling of $\alpha$ -Diazoacetates with Alkyl *N*-Hydroxyphthalimide Esters for Diversified Synthesis of Functionalized *N*-Alkyl Hydrazones

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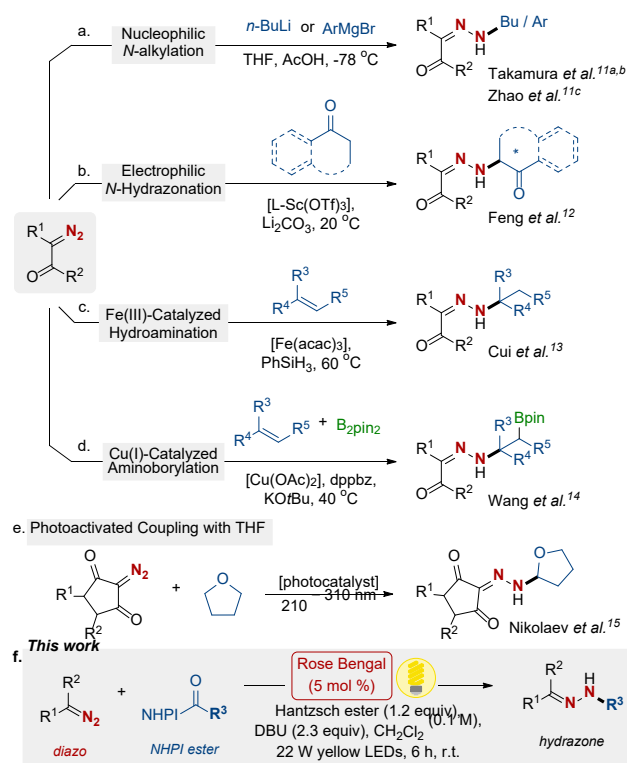


**ABSTRACT:** Herein we report a metal-free photocatalytic coupling reaction for the synthesis of structurally and functionally diverse *N*-alkyl hydrazones from  $\alpha$ -diazoacetates and *N*-alkyl hydroxyphthalimide esters. Employing Rose Bengal as photocatalyst with yellow LEDs irradiation, over 60 *N*-alkyl hydrazones were synthesized. Fluorescence quenching analysis and deuterium incorporation experiments reveal that Hantzsch ester serves as both electron donor and proton source for the reaction. This strategy offers a simple retrosynthetic disconnection for conventionally inaccessible C(sp<sup>3</sup>)-rich *N*-alkyl hydrazones.

The hydrazone (C=N–NH) functional group has found extensive applications in various disciplines including organic synthesis,<sup>1</sup> medicinal chemistry<sup>2</sup> and supramolecular chemistry.<sup>3</sup> The unique azomethine motif containing a nucleophilic imine / amino group and an electrophilic imine carbon center has endowed distinctive physical and chemical properties crucial for designing new materials such as covalent organic frameworks,<sup>4</sup> hole-transporting materials<sup>5</sup> and molecular switches<sup>6</sup>. Notably, most studies were limited to libraries of (hetero)aryl-substituted hydrazones; few studies were designed to examine libraries of C(sp<sup>3</sup>)-rich *N*-alkyl hydrazones.<sup>7</sup> The current lack of synthetic routes to access functionally and structurally diverse *N*-alkyl hydrazones severely limits the realization of the full potential of this class of molecules.

While diazo compounds are versatile reagents for metal-carbene mediated C–C bond formations,<sup>8</sup> we are attracted to some studies on the use of diazo compounds for selective C–N bond coupling reactions to afford hydrazones.<sup>9</sup> A classic example is the Japp-Klingemann reaction, in which aryldiazonium salts react with  $\beta$ -ketoesters or acids to form hydrazones.<sup>10</sup> The research groups of Takamura<sup>11a,b</sup> and Zhao<sup>11c</sup> independently reported nucleophilic *N*-alkylation of diazoesters by organolithium and Grignard reagents to afford *N*-alkyl hydrazones (Scheme 1a). Notably, Feng and co-workers developed the catalytic asymmetric  $\alpha$ -hydrazone of ketones with diazoesters (Scheme 1b).<sup>12</sup> In 2016, Cui and co-workers reported a Fe-catalyzed alkene hydroamination with diazo esters to furnish *N*-alkyl hydrazones (Scheme 1c).<sup>13</sup> Likewise, Wang and co-workers developed a Cu(I)-catalyzed aminoborylation of alkenes

## Scheme 1. *N*-Alkyl Hydrazones Synthesis by *N*-Alkylation of Diazo Compounds

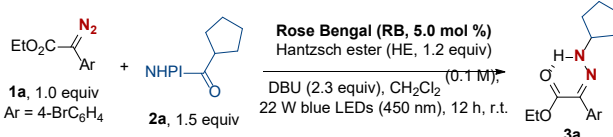


with diazo esters to produce borylated hydrazones (Scheme 1d).<sup>14</sup> Recently, Nikolaev and co-workers reported

photoactivated coupling of 2-diazocyclopentane-1,3-diones with THF to form *N*-alkyl hydrazones (Scheme 1e).<sup>15</sup> Despite these earlier achievements, direct *N*-alkylation of diazo compounds are largely limited in its scope.

Pioneered by Baran's group,<sup>16</sup> alkyl *N*-hydroxyphthalimide esters (NHPI esters) are superior surrogates of carbonyl radicals for decarboxylative C–C<sup>17</sup> and C–heteroatom<sup>18–23</sup> cross coupling reactions. NHPI Esters would undergo single-electron reduction to form radical anions under thermal or photochemical conditions, followed by decarboxylative fragmentation to generate alkyl radicals.<sup>24</sup> Here we describe a photocatalytic decarboxylative radical cross coupling of alkyl *N*-hydroxyphthalimide ester with diazoacetates for the synthesis of skeletal and functionally diverse *N*-alkyl hydrazones (Scheme 1f). This photoredox cross coupling reaction is highly modular by independently varying the diazo esters and the NHPI ester structures under metal-free conditions.

**Table 1. Optimization of Reaction: Catalysts, Solvents and Additives<sup>a,b</sup>**



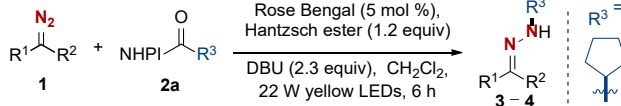
entry	variation from standard conditions	yield <sup>b</sup>
1	none	99
2	Eosin Y instead of RB	82
3	Fluorescein instead of RB	88
4	[Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> instead of RB	99
5	[Ir(bpy)(ppy) <sub>2</sub> ]PF <sub>6</sub> instead of RB	95
6	CH <sub>3</sub> OH instead of CH <sub>2</sub> Cl <sub>2</sub>	22
7	DMF instead of CH <sub>2</sub> Cl <sub>2</sub>	36
8	toluene instead of CH <sub>2</sub> Cl <sub>2</sub>	<5
9	<i>i</i> PrNEt <sub>2</sub> instead of DBU	88
10	K <sub>2</sub> CO <sub>3</sub> instead of DBU	<5
11	without base	<5
12	0.1 equiv DBU	<5
13	1.0 equiv DBU	22
14	0.1 equiv HE	13
15	1.2 equiv HE	99
<b>16</b>	<b>22 W yellow LED (585 nm) for 6 h</b>	<b>99</b>

<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (5.0 mol %), solvent (1.0 mL), additives (2.3 equiv), and Hantzsch ester, N<sub>2</sub> under 22 W blue (450 nm) at room temperature for 12 h unless otherwise specified. <sup>b</sup>NMR yield.

To begin, we treated  $\alpha$ -(4-bromophenyl)diazoacetate **1a** (0.1 mmol) with *N*-cyclopentyl NHPI ester **2a** (0.15 mmol), Hantzsch ester (1.2 equiv), 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, 2.3 equiv) with Rose Bengal in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) at room temperature under illumination by 22 W blue LEDs (450 nm) for 12 h, and *N*-cyclopentyl hydrazone **3a** was obtained in 99% yield (Table 1, entry 1). Performing the reaction using Fluorescein and Eosin Y were found to promote the hydrazone formation in 82 – 88% yields (entries 2–3). The analogous reactions employing [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> and [Ir(ppy)(bpy)<sub>2</sub>]PF<sub>6</sub> as photocatalysts also gave the desired *N*-cyclopentyl hydrazone **3a** in 95 – 99% yield (entry 4–5). For the solvent effect, common organic solvents such as CH<sub>3</sub>CN, DMF and toluene gave poor

results (entries 6–8). Evidently, organic bases are critical for effective hydrazone formation, and DBU (2.3 equiv)<sup>25</sup> seems to furnish the best results (**3a** in 99% yield) compared to those using *i*PrNEt<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> as bases (entries 9–10). No **3a** formation was formed in the absence of bases (entry 11). Regarding to the use of DBU; less effective coupling reactions (<5 – 22% product yield) were observed when DBU (0.1 and 1.0 equiv) were used (entries 12–13). It was found that a stoichiometric amount of Hantzsch ester is necessary for complete reaction (entries 14–15). To our delight, employing a 22 W yellow LEDs produced the best results with 99% of **3a** formation being achieved in 6 h (see Supporting Information for details).

**Table 2. Substrate Scope Study on Diazo Compounds<sup>a-d</sup>**



A. Variation of Aryl Diazoacetate			
FG = 4-Br,	<b>3a</b> , 99%	FG = 4-Me,	<b>3g</b> , 87%
FG = 4-F,	<b>3b</b> , 98%	FG = 3-Me,	<b>3h</b> , 87%
FG = 4-CF <sub>3</sub> ,	<b>3c</b> , 99%	FG = 2-Me,	<b>3i</b> , 75%
FG = 4-NH <sub>2</sub> ,	<b>3d</b> , 78%	FG = 2-OMe,	<b>3j</b> , 71%
FG = 4-H,	<b>3e</b> , 88%	FG = 2-Cl,6-F,	<b>3k</b> , 62% <sup>c</sup>
FG = 4-OMe,	<b>3f</b> , 62%		
R <sup>4</sup> = Ph,	<b>3l</b> , 86%	R <sup>4</sup> = <i>i</i> Pr,	<b>3p</b> , 69%
R <sup>4</sup> = Ph,	<b>3m</b> , 82%	R <sup>4</sup> = allyl,	<b>3q</b> , 78%
R <sup>4</sup> = <i>i</i> Pr,	<b>3n</b> , 84%	R <sup>4</sup> = 2-pentenyl,	<b>3r</b> , 79% <sup>d</sup>
R <sup>4</sup> = <i>i</i> Pr,	<b>3o</b> , 70%	R <sup>4</sup> = 3-pentenyl,	<b>3s</b> , 62%
B. Heterocycles and Alkyl Diazo			
Ar =	<b>4a</b> , 52%	<b>4b</b> , 85%	<b>4c</b> , 76%
	<b>4d</b> , 72%	<b>4e</b> , 69%	
R <sup>4</sup> = Me, R <sub>5</sub> = Et,	<b>4g</b> , 42% <sup>c</sup>	R <sup>4</sup> = Et, R <sub>5</sub> = Me,	<b>4h</b> , 33% <sup>c</sup>
R <sup>4</sup> = Me, R <sub>4</sub> = <i>t</i> Bu,	<b>4i</b> , 47% <sup>c</sup>	R <sup>4</sup> = C <sub>3</sub> H <sub>7</sub> , R <sub>5</sub> = Me,	<b>4j</b> , 49% <sup>c</sup>

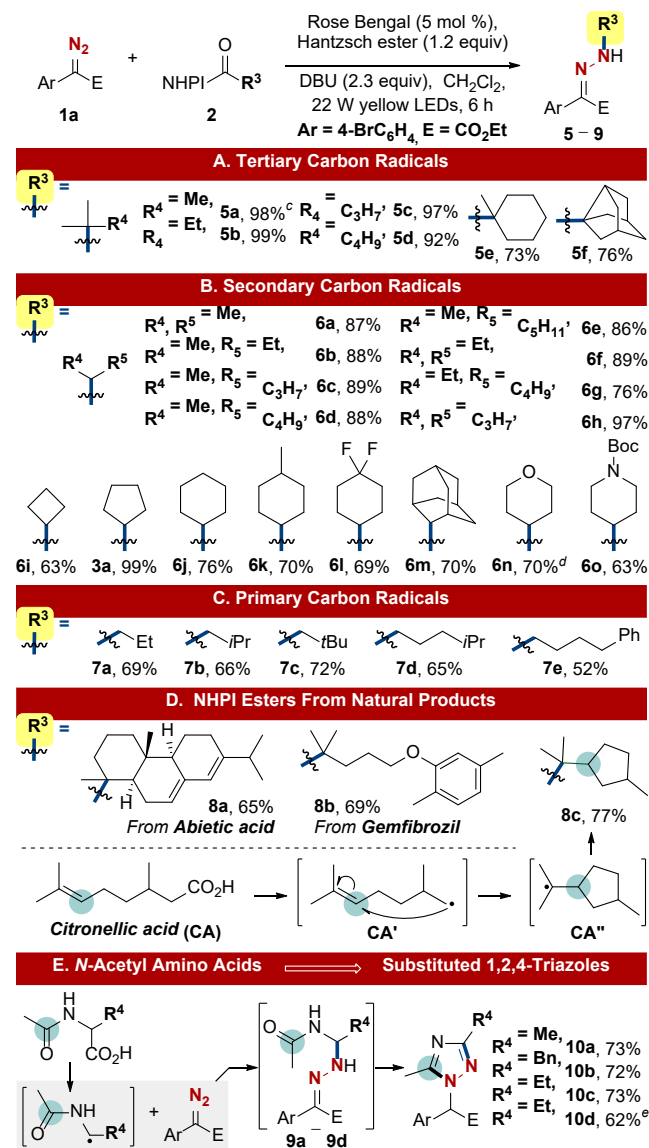
<sup>a</sup>Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Rose Bengal (5.0 mol %), Hantzsch ester (1.2 equiv) and DBU (2.3 equiv), in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) under 22 W yellow LEDs (585 nm) at room temperature for 6 h. <sup>b</sup>Isolated yield. <sup>c</sup>NMR yields. <sup>d</sup>4-MeOC<sub>6</sub>H<sub>4</sub> instead of Ph on diazo.

With the optimized conditions in hand, we turned to examine the scope of the diazo esters. Diazo esters with electron-donating (FG = 4-Me, -OMe, -NH<sub>2</sub>) and -withdrawing (FG = 4-F, -CF<sub>3</sub>, -Cl) substituents on the para-position of the aryl groups are equally effective coupling partners, and the corresponding hydrazones **3a** – **3f** were obtained in 62 – 99% yields (Table 2A). Diazo esters bearing functional groups on other positions such as 2-Me (**3i**), 2-MeO (**3j**) and 2,6-disubstituted (FG = 2-Cl, 6-F) (**3k**) diazo ester reacted successfully to give hydrazones in comparable yields (62 – 75%). A series of  $\alpha$ -phenyldiazoacetates derived from simple aliphatic alcohols reacted with **2a** to afford **3l** – **3p** in 69 – 86% yields. Notably, diazoesters bearing reactive C=C bonds are also compatible with this reaction furnishing **3q** (78%), **3r** (79%) and **3s** (62%) in good yields.

Heteroaromatic functions such as thiophenyl (**4c**: 76%; **4d**: 72%) and indolyl groups (**4e**: 69%) are compatible with the

coupling reaction (Table 2B). The diazo substrates with a CF<sub>3</sub> group was also found to be effective coupling partners, and the corresponding hydrazone **4f** was formed in 42% yield. For alkyl-substituted diazo derivatives, the corresponding hydrazones **4g** – **4j** were formed in ca. 45% yields based on NMR analysis of the crude reaction mixture. Attempt to isolate **4g** – **4j** by column chromatography was futile as the isolated compound readily decomposed.

**Table 3. Substrate Scope Study on NHPI Esters<sup>a-e</sup>**



<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), Rose Bengal (5.0 mol %), Hantzsch ester (1.2 equiv) and DBU (2.3 equiv), in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) under 22 W yellow LEDs (585 nm) at room temperature for 6 h. <sup>b</sup>Isolated yield. <sup>c</sup>Gram scale: 83%, 1.4 g. <sup>d</sup>NMR yield. <sup>e</sup>Ar = Ph, E = CO<sub>2</sub>Me.

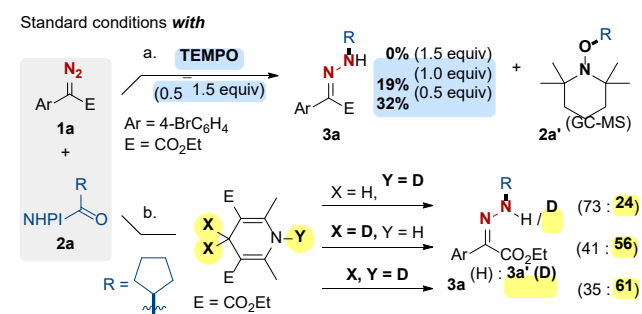
The synthetic versatility of this reaction is further explored with the scope of the NHPI esters (Table 3). With **1a** as substrate, we first examined the reactivity of tertiary alkyl radicals (Table 3A). Trisubstituted carbon radicals such as *tert*-butyl and 2-methylalkyl radicals are effectively coupled to the diazo, and

the corresponding hydrazones **5a** – **5d** were furnished in 92 – 99% yields. A gram-scale reaction has been performed with 1.4 g of **5a** being obtained in 83% yield. The coupling reactions with 1-methylcyclohexyl (**5e**) and 3-noradamantyl (**5f**) radicals are also achieved to afford the corresponding hydrazones in 73% and 76% yield respectively.

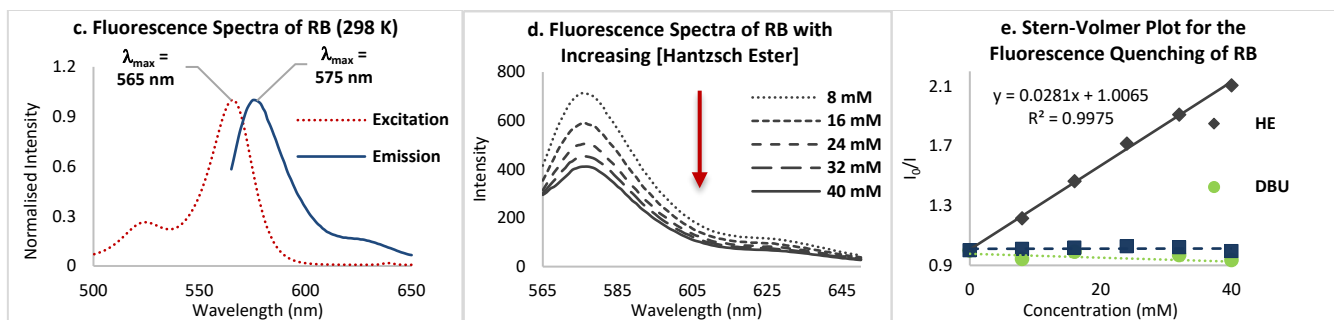
The coupling reactions employing secondary alkyl radicals involving 2-propyl, 2-butyl, 2-pentyl, 2-hexyl, 2-heptyl, 3-pentyl, 3-heptyl and 4-heptyl radicals gave excellent product yields (**6a** – **6h**, 76 – 97%) (Table 3B). The desired cyclobutyl- (**6i**) and cyclohexyl- (**6j**) hydrazones were also formed in 63 – 76% yields. 4-Methyl- (**6k**) and 4-difluoro- (**6l**) substituents on the cyclohexyl- ring are excellent coupling partners for the transformation, and up to 70% yields of the desired hydrazones were obtained. 1-Adamantyl- (**6m**), pyranyl- (**6n**) and piperidinyl- (**6o**) type radicals are effective for the hydrazones formation (63 – 70% yields). It is well accepted that primary radicals are less accessible than those secondary and tertiary radicals. To our pleasure, successful coupling reactions were achieved for the primary alkyl radicals (**7a** – **7e**) to give the corresponding hydrazones in 52 – 72% yields (Table 3C).

Coupling reactions of **1a** with NHPI esters derived from some natural products such as abietic acid (**8a**) and gemfibrozil (**8b**) gave the corresponding hydrazones in 65 – 69% yields (Table 3D). Interestingly, the coupling reaction employing NHPI ester derived from citronellic acid produced **8c** in 77% yield. Presumably, the primary radical (**CA'**) undergoes spontaneous radical addition to the C=C bond to generate a tertiary radical (**CA''**) prior to the *N*-alkylation of the **1a**. For the reactions with *N*-acetyl amino acids-derived NHPI esters, the expected hydrazone products were found to undergo further transformation to afford 1,2,4-triazoles **10a** – **10d** in 62 – 73% (Table 3E). 1,2,4-Triazoles are key skeletons of many applicational compounds,<sup>26</sup> which are conventionally prepared by intramolecular cyclization of *N*-acetyl amidrazones and carboxylic acid derivatives. Several copper-catalyzed 1,2,4-triazoles synthesis are known in the literature.<sup>27</sup> Our protocol offers an alternative approach for direct access to this class of molecules under mild conditions.

### Scheme 2. Radical Trap Experiments and Deuterium Isotope Studies<sup>a-b</sup>



<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Rose Bengal (5.0 mol %) and DBU (2.3 equiv), in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) under 22 W yellow LEDs (585 nm) at room temperature for 6 h. <sup>b</sup>NMR yield.

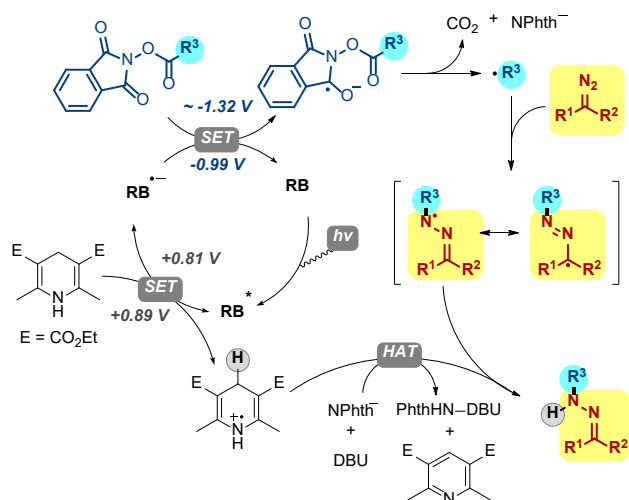


**Figure 1.** (a) Excitation of the Rose Bengal at wavelength 565 nm resulted in an emission band at  $\lambda_{\text{max}} = 575$  nm. (b) The emission intensity of the 575 nm band is dependent only on the [Hantzsch Ester]. (c) The fluorescence quenching of RB by Hantzsch Ester display a linear Stern-Volmer plot.

Regarding the mechanism, addition of TEMPO suppressed the **3a** formation in a concentration dependent manner consistent with a radical-mediated transformation. For instance, when 1.5 equiv TEMPO was used, no **3a** formation was detected and the TEMPO-trapped radical **2a'** can be detected by GC-MS (Scheme 2a). The role of Hantzsch ester has been examined by deuterium incorporation experiments using a series of deuterated Hantzsch esters (Scheme 2b).<sup>28</sup> Under the standard reaction conditions with the 1-*d*-Hantzsch ester (i.e. N-D labelled) as reagent, 24% (**3a'**) deuterium incorporation was observed on the corresponding hydrazone product. When the 4,4-*d*<sub>2</sub> Hantzsch ester and 1-*d*, 4,4-*d*<sub>2</sub> Hantzsch ester derivatives were employed, higher levels of deuteration of the hydrazones were observed [56% (for 4,4-*d*<sub>2</sub>-HE); and 61% (for 1-*d*, 4,4-*d*<sub>2</sub>-HE)]. This result implies that the Hantzsch ester is involved in the N-H bond formation for product turnovers.

Moreover, we performed luminescence quenching experiments of Rose Bengal with NHPI ester **2a**, DBU and Hantzsch ester. Upon excitation at  $\lambda_{\text{max}} = 565$  nm, the fluorescence intensity at  $\lambda_{\text{max}} = 575$  nm was observed and monitored at various quencher concentrations (Figures 1a & 1b). Apparently, only Hantzsch ester showed effective luminescence quenching of the Rose Bengal in a concentration-dependent manner (Figure 1c). This result clearly suggests that the excited state of the Rose Bengal is quenched selectively by the Hantzsch ester.

### Scheme 3. Proposed Mechanism



Based on the above findings, a plausible mechanism is proposed (Scheme 3). Photoexcitation of the Rose Bengal (RB) should generate an excited state  $\text{RB}^*$  [ $E(\text{RB}^*/\text{RB}^*) = +0.81$  V

vs SCE]; and the  $\text{RB}^*$  would react with Hantzsch ester [ $E(\text{HE}^+/\text{HE}) = +0.89$  V vs SCE] by single-electron transfer (SET) to afford the Rose Bengal radical anion ( $\text{RB}^{\bullet-}$ ). The  $\text{RB}^{\bullet-}$  [ $E(\text{RB}/\text{RB}^{\bullet-}) = -0.99$  V vs SCE]<sup>29</sup> should reduce the NHPI esters [ $E(\text{NHPI}/\text{NHPI}^{\bullet-}) = -1.32$  V vs SCE] by SET,<sup>30</sup> followed by C-C bond fragmentation to give alkyl radical  $\text{R}^{\bullet}$ . The alkyl radical would then couple to the terminal nitrogen of the diazo compound to give a  $\text{C}(\text{sp}^3)\text{-N}$  bond. To furnish the hydrazone product, the nitrogen-centered radical should undergo hydrogen-atom abstraction from the cationic radical Hantzsch ester.

In summary, we have developed a metal-free photocatalytic synthesis of structurally and functionally diverse *N*-alkyl hydrazones from  $\alpha$ -diazoacetates and alkyl *N*-hydroxyphthalimide esters. This photoredox strategy offers a simple retrosynthetic disconnection for conventionally inaccessible  $\text{C}(\text{sp}^3)$ -rich *N*-alkyl hydrazones that may be of interest for designing advanced materials and drug discovery.

### ASSOCIATED CONTENT

#### Supporting Information

The following files are available free of charge. Experimental procedures, physical characterization data (<sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra) of the substrates and products, photochemical experiments, UV-vis titration studies, Stern-Volmer luminescence studies, and cyclic voltammetry studies.

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#### Author Contributions

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#### Notes

The authors declare no competing financial interest.

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