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Photoredox Decarboxylative C(sp^3)−N Coupling of α-Diazoacetates with Alkyl *N*-Hydroxyphthalimide Esters for Diversified Synthesis of Functionalized *N*-Alkyl Hydrazones

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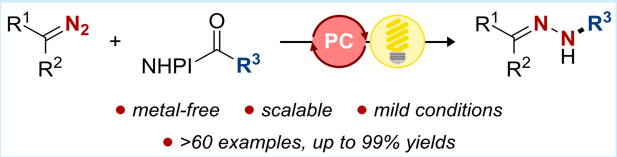
Supporting Information

ABSTRACT: Herein we report a metal-free photocatalytic coupling reaction for the synthesis of structurally and functionally diverse *N*-alkyl hydrazones from α-diazoacetates and *N*-alkyl hydroxyphthalimide esters. By employing Rose Bengal as a 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 an electron donor and proton source for the reaction. This strategy offers a simple retrosynthetic disconnection for conventionally inaccessible C(sp^3)-rich *N*-alkyl hydrazones.



The hydrazone (C═N−NH) functional group has found extensive applications in various disciplines including organic synthesis,[1] medicinal chemistry,[2] and supramolecular chemistry.[3] 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,[4] hole-transporting materials,[5] and molecular switches.[6] Notably, most studies were limited to libraries of (hetero)aryl-substituted hydrazones; few studies were designed to examine libraries of C(sp^3)-rich *N*-alkyl hydrazones.[7] 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,[8] we are attracted to some studies using diazo compounds for selective C−N bonds coupling reactions to afford hydrazones.[9] A classic example is the Japp−Klingemann reaction, in which aryldiazonium salts react with β-ketoesters or acids to form hydrazones.[10] The research groups of Takamura[11a,b] and Zhao[11c] 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 α-hydrazonation of ketones with diazoesters (Scheme 1b).[12] In 2016, Cui and co-workers reported an Fe-catalyzed alkene hydroamination with diazo esters to furnish *N*-alkyl hydrazones (Scheme 1c).[13] Likewise, Wang and co-workers developed a Cu(I)-catalyzed aminoborylation of alkenes with diazo esters to produce borylated hydrazones (Scheme 1d).[14] Recently, Nikolaev and co-workers reported photoactivated coupling of 2-diazocyclopentane-1,3-diones with THF to form *N*-alkyl hydrazones (Scheme 1e).[15] Despite these earlier achievements, direct *N*-alkylation of diazo compounds are largely limited in scope.

Pioneered by Baran's group,[16] alkyl *N*-hydroxyphthalimide esters (NHPI esters) are superior surrogates of carboradicals for decarboxylative C−C[17] and C−heteroatom[18−23] 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.[24] 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.

To begin, we treated α-(4-bromophenyl)diazoacetate **1a** (0.1 mmol) with *N*-cyclopentyl NHPI ester **2a** (0.15 mmol), Hantzsch ester (1.2 equiv), and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, 2.3 equiv) with Rose Bengal in CH_2Cl_2 (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). No desired product was obtained without Rose Bengal (entry 2). Performing the reaction using Fluorescein and Eosin Y was found to promote the hydrazone formation in 82−88% yields (entries 3−4). The analogous reactions employing $[Ru(bpy)_3]Cl_2$ and $[Ir(ppy)_2(bpy)]PF_6$ as photocatalysts also gave the desired *N*-cyclopentyl hydrazone **3a** in 95−99% yield (entries 5−6). For the solvent effect, common organic solvents such as CH_3OH, DMF, and toluene gave poor results (entries 7−9). Evidently, organic bases are critical for effective hydrazone

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

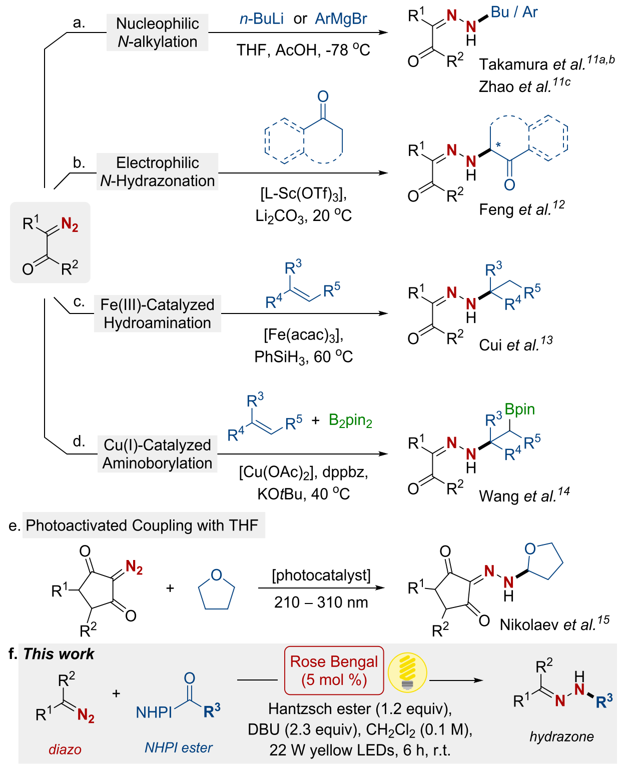
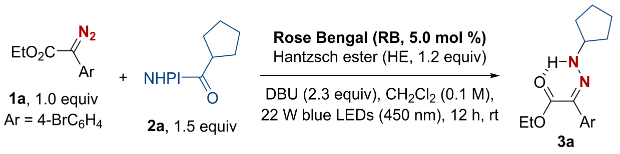


Table 1. Optimization of Reaction: Catalysts, Solvents and Additives[a–b]



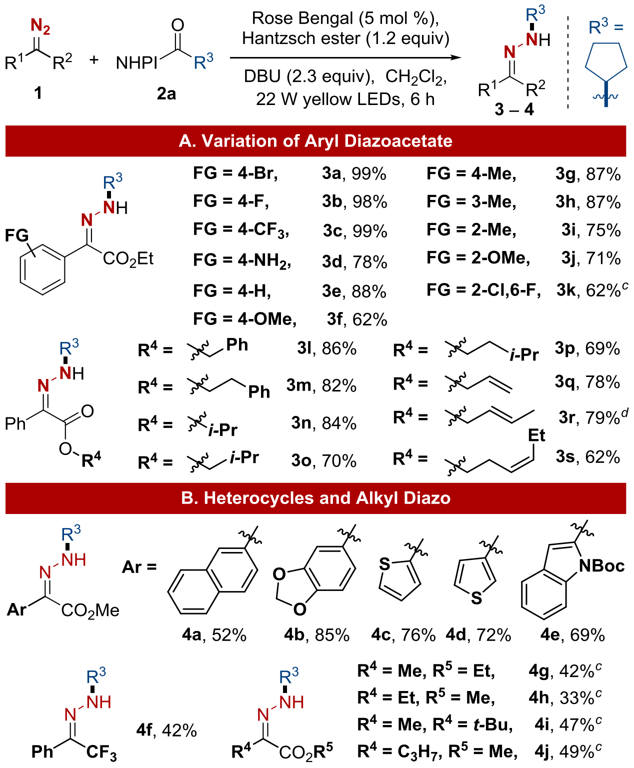
entry	variation from standard conditions	yield (%)[b]
1	none	99
2	without RB	<5
3	Eosin Y instead of RB	82
4	Fluorescein instead of RB	88
5	$[Ru(bpy)_3]Cl_2$ instead of RB	99
6	$[Ir(bpy)(ppy)_2]PF_6$ instead of RB	95
7	CH_3OH instead of CH_2Cl_2	22
8	DMF instead of CH_2Cl_2	36
9	toluene instead of CH_2Cl_2	<5
10	iPrNEt$_2$ instead of DBU	88
11	K_2CO_3 instead of DBU	<5
12	without base	<5
13	0.1 equiv of DBU	<5
14	1.0 equiv of DBU	22
15	0.1 equiv of HE	13
16	1.5 equiv of HE	99
17	**22 W yellow LED (585 nm) for 6 h**	**99**

[a]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_2 under 22 W blue LED irradiation (450 nm) at room temperature for 12 h unless otherwise specified. [b]NMR yield.

formation, and DBU (2.3 equiv)[25] seems to furnish the best results (**3a** in 99% yield) compared to those using iPrNEt$_2$ and K_2CO_3 as bases (entries 10–11). No **3a** formation was formed in the absence of bases (entry 12). Regarding the use of DBU, less effective coupling reactions (<5–22% product yield) were observed when DBU (0.1 and 1.0 equiv) was used (entries 13–14). It was found that a stoichiometric amount of Hantzsch ester is necessary for complete reaction (entries 15–16). To our delight, employing 22 W yellow LEDs (entry 17) produced the best results with 99% of **3a** formation being achieved in 6 h (see Supporting Information for details).

With the optimized conditions in hand, we next examined the scope of the diazo esters. Diazo esters with electron-donating (FG = 4-Me, −OMe, $-NH_2$) and -withdrawing (FG = 4-F, $-CF_3$, −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 (Scheme 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 α-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.

Scheme 2. Substrate Scope Study on Diazo Compounds[ad]

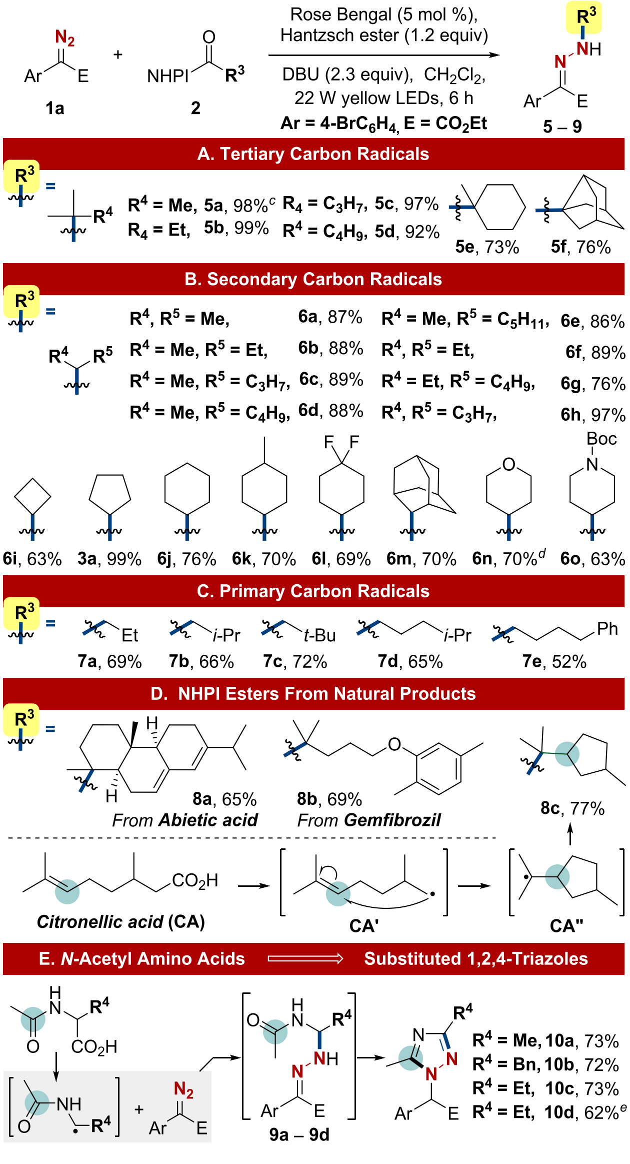


[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Rose Bengal (5.0 mol %), Hantzsch ester (1.2 equiv) and DBU (2.3 equiv), in CH_2Cl_2 (1.0 mL) under 22 W yellow LEDs (585 nm) at room temperature for 6 h. [b]Isolated yield. [c]NMR yields. [d]4-MeOC$_6$H$_4$ instead of Ph on diazo.

Heteroaromatic functions such as thiophenyl (**4c**: 76%; **4d**: 72%) and indolyl groups (**4e**: 69%) are compatible with the coupling reaction (Scheme 2B). The diazo substrates with a CF_3 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. An attempt to isolate **4g**−**4j** by column chromatography was futile, as the isolated compound readily decomposed.

The synthetic versatility of this reaction is further explored with the scope of the NHPI esters. With **1a** as substrate, we first examined the reactivity of tertiary alkyl radicals (Scheme 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.

Scheme 3. Substrate Scope Study on NHPI Esters[a,e]



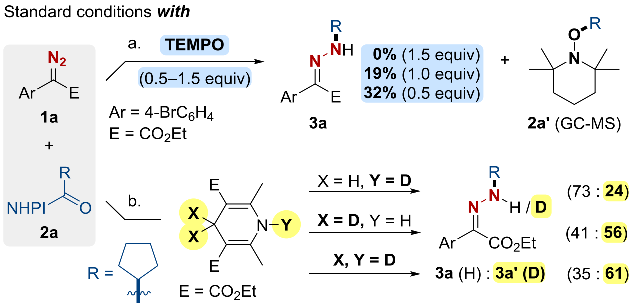
[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), Rose Bengal (5.0 mol %), Hantzsch ester (1.2 equiv) and DBU (2.3 equiv), in CH_2Cl_2 (1.0 mL) under 22 W yellow LEDs (585 nm) at room temperature for 6 h. [b]Isolated yield. [c]Gram scale: 83%, 1.4 g. [d]NMR yield. [e]Ar = Ph, E = CO_2Me.

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%) (Scheme 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 (Scheme 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 (Scheme 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% (Scheme 3E). 1,2,4-Triazoles are key skeletons of many applicational compounds,[26] which are conventionally prepared by intramolecular cyclization of *N*-acyl amidrazones and carboxylic acid derivatives. Several copper-catalyzed 1,2,4-triazoles synthesis are known in the literature.[27] Our protocol offers an alternative approach for direct access to this class of molecules under mild conditions.

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 of TEMPO was used, no **3a** formation was detected and the TEMPO-trapped radical **2a′** can be detected by GC-MS (Scheme 4a). The role of Hantzsch ester has been examined by deuterium incorporation experiments using a series of deuterated Hantzsch esters (Scheme 4b).[28] Under the standard reaction conditions with the 1-*d*-

Scheme 4. Radical Trap Experiments and Deuterium Isotope Studies[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Rose Bengal (5.0 mol %) and DBU (2.3 equiv), in CH_2Cl_2 (1.0 mL) under 22 W yellow LEDs (585 nm) at room temperature for 6 h. [b]NMR yield.

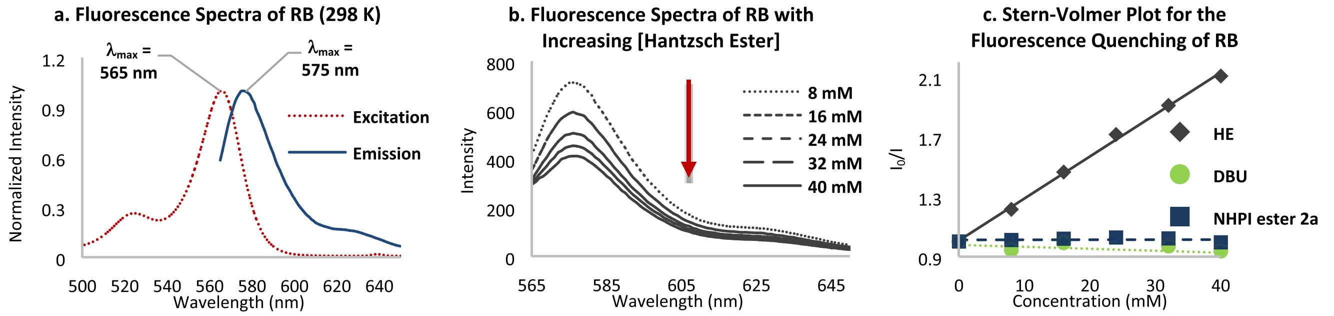


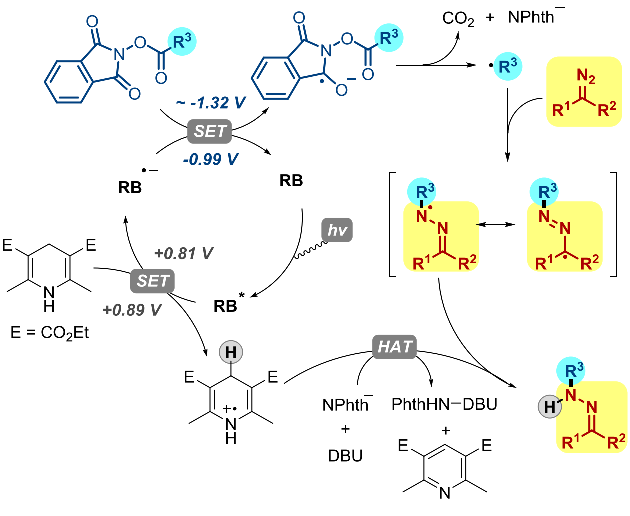
Figure 1. (a) Excitation of the Rose Bengal at wavelength 565 nm resulted in an emission band at λ_{max} = 575 nm. (b) The emission intensity of the 575 nm band is dependent only on the [Hantzsch Ester]. (c) The fluorescence quenching of RB by Hantzsch Ester display a linear Stern−Volmer plot.

Hantzsch ester (i.e., N−D labeled) as reagent, 24% (**3a′**) deuterium incorporation was observed on the corresponding hydrazone product. When the 4,4-d_2 Hantzsch ester and 1-*d*, 4,4-d_2 Hantzsch ester derivatives were employed, higher levels of deuteration of the hydrazones were observed [56% (for 4,4-d_2-HE) and 61% (for 1-*d*, 4,4-d_2-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 λ_{max} = 565 nm, the fluorescence intensity at λ_{max} = 575 nm was observed and monitored at various quencher concentrations (Figure 1a and 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.

Based on the above findings, a plausible mechanism is proposed (Scheme 5). Photoexcitation of the Rose Bengal (RB) should generate an excited state RB* [E(RB*/RB$^{•−}$) = +0.81 V vs SCE]; and the RB* would react with Hantzsch ester [E(HE$^{•+}$/HE) = +0.89 V vs SCE] by single-electron transfer (SET) to afford the Rose Bengal radical anion (RB$^{•−}$). The RB$^{•−}$ [E(RB/RB$^{•−}$) = −0.99 V vs SCE][29] should reduce the NHPI esters [E(NHPI/NHPI$^{•−}$) = −1.32 V vs SCE] by SET,[30] followed by C−C bond fragmentation to give alkyl radical R^3·. The alkyl radical would then couple to the terminal nitrogen of the diazo compound to give a C(sp^3)−N bond. To furnish the hydrazone product, the nitrogen-centered radical should undergo hydrogen-atom abstraction from the cationic radical Hantzsch ester.

Scheme 5. Proposed Mechanism



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

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03020.

> Experimental procedures, physical characterization data (^{1}H, ^{13}C, and ^{19}F NMR spectra) of the substrates and products, photochemical experiments, UV−vis titration studies, Stern−Volmer luminescence studies, and cyclic voltammetry studies (PDF)

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Notes

The authors declare no competing financial interest.

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