

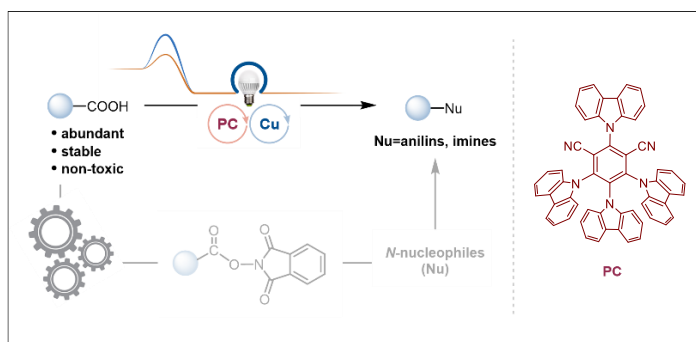
Tandem photoredox and copper-catalyzed decarboxylative C(sp³)-N coupling of anilines and imines using an organic photocatalyst

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Supporting Information Placeholder



ABSTRACT: An organic photoredox catalyst, 4CzIPN, was used in combination with a copper catalyst, CuCl, to effect decarboxylative C(sp³)-N coupling. The coupling worked with both anilines and imines as nitrogen sources and could be used to prepare a variety of alkyl amines from readily available alkyl carboxylic acids.

Alkyl amines are an important class of organic molecules with wide applications in materials and medicines.¹⁻⁴ C(sp³)-N coupling is potentially an efficient method to streamline the synthesis of alkyl amines, complementing traditional methods such as reductive amination⁵⁻⁷, direct N-alkylation,⁸⁻⁹ the Curtius rearrangement¹⁰ and the Mitsunobu reaction.¹¹ However, C(sp³)-N coupling remains challenging due to difficulty in C(sp³)-N reductive elimination as well as side reactions such as β -H elimination. We and others recently developed photoredox catalysis to effect decarboxylative C(sp³)-N coupling (Figure 1A-B).¹²⁻¹⁸ This approach employs readily available alkyl carboxylic acids as starting reagents, activating them via either N-hydroxyphthalimide esters (NHPI) (Figure 1A), or hyperiodide intermediates (Figure 1B), and resulting in wide substrate scope. However, the photocatalysts were all based on precious metals such as Ru and Ir. Herein we report a method for decarboxylative C(sp³)-N coupling using an organic photoredox catalyst in tandem with a Cu coupling catalyst (Figure 1C). The organic photocatalyst enabled the coupling of both aniline and imines, an

improvement over precious photocatalysts which worked for only one type of N coupling partners.^{13, 15}

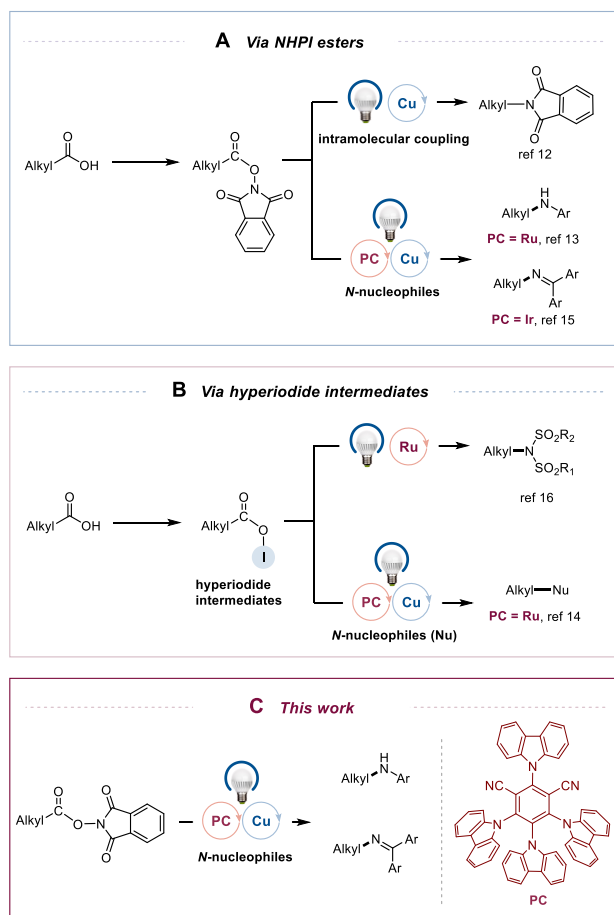
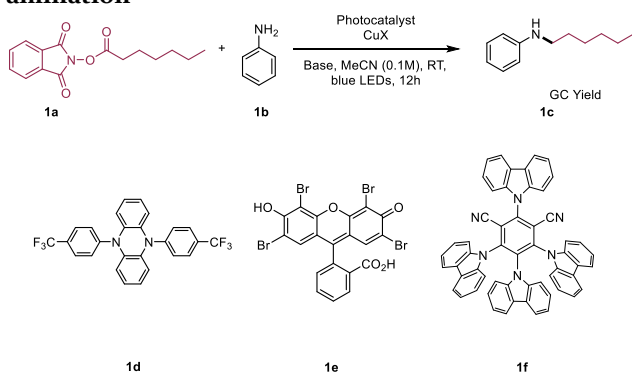


Figure 1. Photoredox-based decarboxylative C(sp³)-N coupling. (a) Via NHPI esters; (b) Via hyperiodide intermediates. (c) This work, using an organic photocatalyst.

Table 1. Optimization for decarboxylative amination



Entry	PC	Cu cat.	Base	Yield
1	1d 10%	CuBr 20%	Et ₃ N 5 eq.	28%
2	1d 1%	CuBr 20%	Et ₃ N 5 eq.	29%
3	1d 5%	CuCl 20%	Et ₃ N 5 eq.	34%
4	1d 5%	CuCl 5%	Et ₃ N 5 eq.	18%
5	4CzIPN 1%	CuCl 20%	Et ₃ N 5 eq.	56%

6	Eosin Y 1%	CuCl 20%	Et ₃ N 5 eq.	n.d.
7	4CzIPN 1%	CuCl 20%	Lutidine 5 eq.	n.d.
8	4CzIPN 1%	CuCl 20%	DIPEA 5 eq.	n.d.
9	4CzIPN 1%	CuCl 20%	DIPEA 5 eq.	20%
10	4CzIPN 1%	CuCl 20%	Et ₃ N 1 eq.	66%
11	4CzIPN 1% (No light)	CuCl 20%	Et ₃ N 1 eq.	n.d.
12	/	CuCl 20%	Et ₃ N 1 eq.	n.d.

General condition: NHPI ester (0.5 mmol), aniline (0.25 mmol), MeCN (2.5 mL), under N₂; yields calculated via GC with an internal standard. DIPEA = diisopropylamine; N.d. = not detected.

A representative C(sp³)-N coupling of heptanoic acid NHPI ester **1a** with aniline **1b** was chosen as the test reaction for optimization. Conditions previously applied for the analogous coupling using Ru(bpy)₃(PF₆)₂ as photocatalyst were first applied.¹³ When the commercially available organophotocatalyst, 5,10-bis(4-(trifluoromethyl)phenyl)-5,10-dihydrophenazine **1d** was used (10 mol %), together with 20 mol % of CuBr and 5 equiv of triethylamine (Table 1, entry 1), the reaction occurred (0.1 M acetonitrile, at room temperature, under the irradiation of blue LEDs, overnight) to give **1c** in a yield of 28%. Decreasing the loading of photocatalyst to 1% gave a similar yield (Table 1, entry 2). Replacing CuBr with CuCl increased the yield to 34% (Table 1, entry 3). Decreasing the loading of CuCl to 5 mol % decreases the yield to 18% (Table 1, entry 4). Different photocatalysts were then screened (Table S6, SI). While Eosin Y (**1e**) (1 mol%) gave no yield, 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (4CzIPN) **1f** gave a yield of 56%. Decarboxylative activation of NHPI esters using **1f** was previously reported.^{27,28} This catalyst can be easily synthesized from inexpensive precursors and requires no chromatographic purification. Several organic and inorganic bases were screened as bases, but only triethylamine and N,N-Diisopropylethylamine (DIPEA) were effective (Table 1, entries 1-5, 9, 10). Finally, the optimized conditions were: 1 mol % of **1f**, 20 mol % of CuCl, 1 equiv of triethylamine, in 0.1 M of acetonitrile at room temperature for 12h under the irradiation of blue LEDs. The yield of **1c** under these conditions was 66% (Table 1, entry 10). Control experiments showed that no coupling occurred when there was no light, or no photocatalyst (Table 1, entries 11-12).

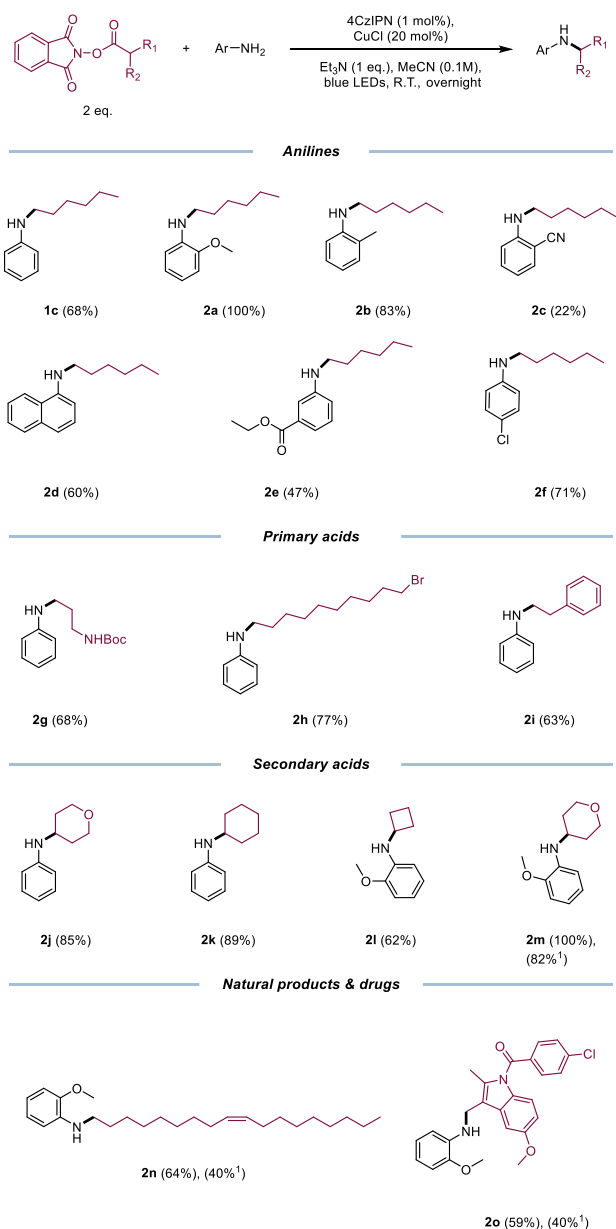


Figure 2. Scope of decarboxylative C(sp³)-N coupling of anilines. Isolated yields were reported. ¹Yields using a Ru photocatalyst as previously reported.¹³

These optimized conditions in Table 1 were applied to explore the scope of the coupling (Figure 2). The coupling worked well with different types of anilines (**1c**, **2a-2f**). *Ortho*- (**2a-2c**), *meta*- (**2e**), and *para*-substitution (**2f**) in the anilines were tolerated. High yields (> 80%) were obtained with electron-rich anilines (**2a**, **2b**, **2d**). Yields dropped when electron-poor anilines were used (**2c**, **2e**, **2f**). Coupling with electron-poor heterocycles, such as aminopyridine and aminoquinolines, was unsuccessful. Both primary (**1c**, **2g-2i**, **2n**) and secondary (**2j-2m**) alkyl carboxylic acid derivatives could be used as coupling partners. The coupling of tertiary alkyl carboxylic acid derivatives, as well as alkyl amines, was unsuccessful. Coupling was also unsuccessful if one of the partners bears a non-protected protic group (e.g., free alcohols and amines).

The coupling had high functional group tolerance, as aryl-Cl (**2f**), ester (**2e**), nitrile (**2c**), NHBoc (**2g**), alkyl-Br (**2h**) groups were compatible. Moreover, the coupling of NHPI esters derived from a natural fatty acid (**2n**) and a indometacin (**2o**) gave good yields, demonstrating the utility of the method for late-stage functionalization. Note that the yields using 4CzIPN as the photocatalyst were often higher than using Ru(bpy)₃(PF₆)₂ as the photocatalyst (e.g., **2m**, **2n**, **2o**).¹³

Benzophenone imine and its derivatives are useful ammonia equivalents, which allow rapid and selective synthesis of masked primary amines.²³ We previously reported that the conditions for the decarboxylative coupling of NHPI esters with anilines were not efficient for the analogous coupling of NHPI esters with imines, which provided access to alkylated primary amines upon hydrolysis of coupling products.¹⁵ A change of photocatalyst from Ru(bpy)₃(PF₆)₂ to Ir-[(dtbbpy)(ppy)₂]PF₆ was necessary for the latter coupling. To our delight, we found that the same organic photocatalyst **1f** catalyzed the coupling of NHPI esters with both anilines and imines. For the latter coupling, further optimization of conditions was necessary (Table S3, SI). We were able to use benzophenone imine (**3a**) as the imine partner. In the previous protocol using an Ir photocatalyst, **3a** was a poor coupling partner and 3,3'-bis-(trifluoromethyl)benzophenone imine had to be used. **3a** is a better imine partner than 3,3'-bis-(trifluoromethyl)benzophenone imine as it is less costly and even commercially available. The optimized conditions for the coupling with **1c** were: 1 mol % of 4CzIPN (**1f**), 20 mol % of CuCl, 1 equiv. of Cs₂CO₃, in 0.1 M DMA at room temperature overnight under blue LEDs light.

The conditions for the coupling of imines worked with primary, secondary, and tertiary alkyl NHPI esters (**3b-3l**, Figure 3), although the coupling of some tertiary substrates had modest yields (**3j** and **3k**). Coupling of NHPI esters derived from a complex natural product (**3m**), a fatty acid (**3n**), and a drug (**3o**) was also successful. Hydrolysis of the coupling product **3o** gave the corresponding primary amine derivative with negligible loss of yield (**3p**). Overall, the coupling was compatible with many functional groups, including ketones (**3m**), esters (**3b**), amides (**3o**, **3p**), halogen groups (**3e**, **3o**), olefins (**3n**), ethers (**3o**), protected amines (**3d**) and acetals (**3i**). A 1 mmol scale synthesis of **3e** was achieved in 51% yield.

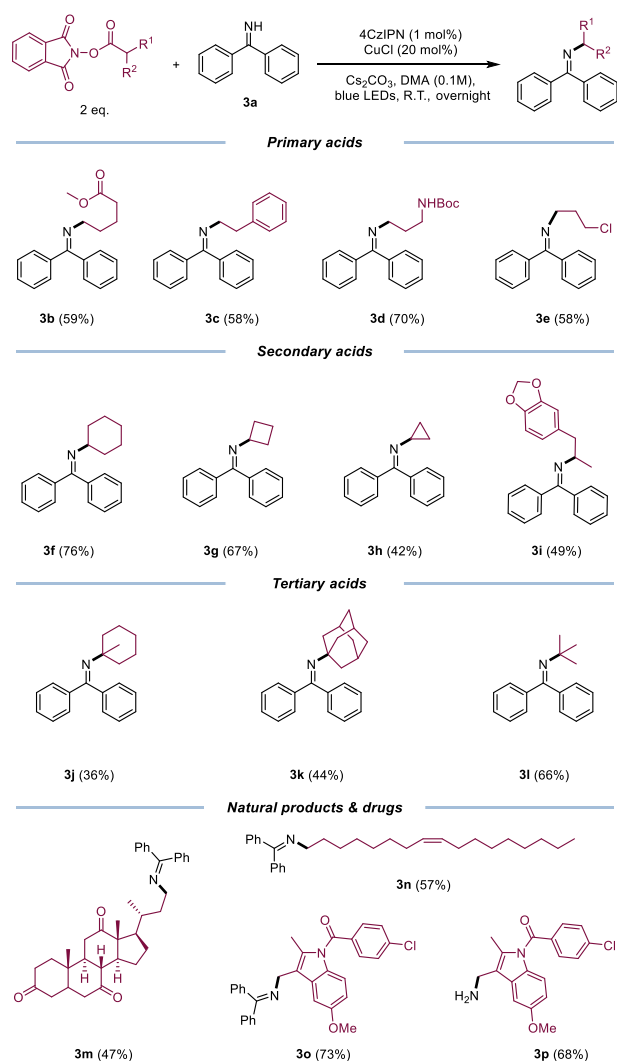


Figure 3. Scope of decarboxylative C(sp³)-N coupling of imines. General optimized conditions: NHPI ester (0.5 mmol), benzophenone imine (0.25 mmol), 4CzIPN (1 mol %), CuCl (20 mol %), DMA (2.5 mL), Cs₂CO₃ (0.5 mmol), under N₂, blue LEDs, overnight. **3o** was deprotected with 1M HCl in methanol for 1 hour to obtain **3p**.

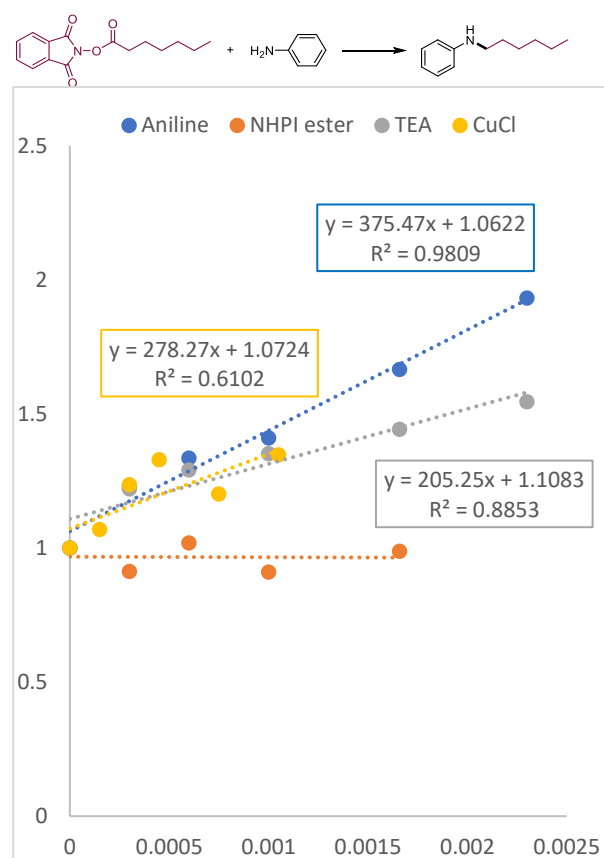


Figure 4. Stern-volmer plots of fluorescence quenching of 4CzIPN by aniline, NHPI ester (**1a**), TEA, or CuCl.

Fluorescence quenching experiments were conducted to probe the reaction mechanism. Aniline, CuCl, and TEA, but not the NHPI ester (**1a**), could quench the fluorescence of 4CzIPN (Figure 4). Because CuCl might bind to TEA, aniline, and **1a**, fluorescence quenching was monitored for a binary mixture of CuCl with another reaction component (Fig. S2-S4, SI). The quenching was nearly identical with CuCl alone and with a 1:5 mixture of CuCl:**1a** (Fig. S2, SI), further excluding the quenching of the excited photocatalyst by NHPI ester or its potential Cu complex, which is different to the Ru-based photocatalyst.¹³ The mixtures of Cu:aniline were less efficient than the sum of the two components alone to quench the fluorescence of 4CzIPN (Fig. S2). This result suggested the formation of Cu-aniline species that have distinct quenching properties from its individual components. For the mixtures of Cu:TEA, varying the ratios of the two components resulted in only small and non-linear changes of the quenching rates (Fig. S3). This result suggested the formation of Cu-TEA species, which is a poor quencher, showing a distinct quenching effect compared to Ir-based photocatalyst.³⁰ Together these results suggested that due to binding to aniline or TEA or both, there was no free CuCl available as a quencher in the solution. Both aniline and TEA (in a free or Cu-coordinated form) could engage in reductive quenching of the excited state of 4CzIPN. The coupling was successful only in the presence of TEA or DIPEA,

but not with other bases, suggesting that TEA served more than a simple base. The quantum yield of the coupling was estimated to be 5.4% (SI). This low quantum yield would be consistent with the scenario that the dominant reductive quenching of the

photocatalyst in the reaction was by aniline, but this quenching was non-productive probably because it was reversible. The productive quenching was via the oxidation of TEA.

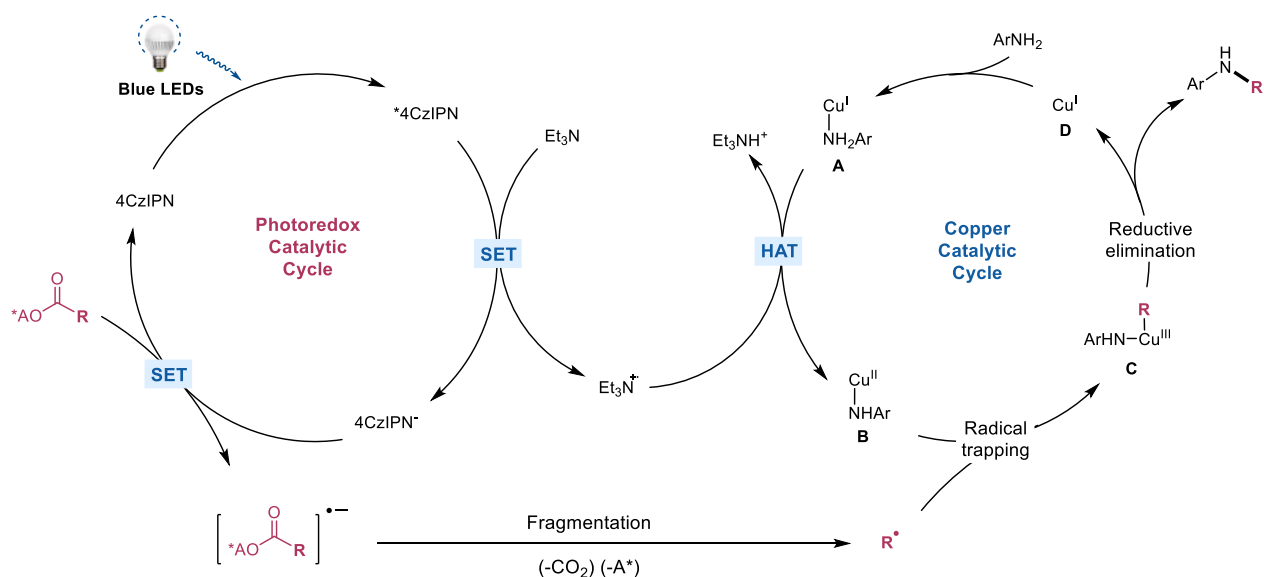


Figure 5. Proposed mechanism for decarboxylative C-N coupling with anilines

Based on the data and considerations above, we propose the following mechanism (Figure 5). Light excitation of 4CzIPN formed an excited 4CzIPN*, which was reductively quenched by TEA to form 4CzIPN^{•-} and a TEA radical cation. Reduction of an NHPI ester by 4CzIPN^{•-} regenerates the photocatalyst 4CzIPN and yields an NHPI ester radical anion. The latter quickly releases CO₂, a phthalimide anion, and an alkyl radical. Hydrogen atom transfer between a Cu^I-aniline species (A) with the TEA radical cation (see elaborations in SI) yields a protonated TEA cation and a Cu^{II}-anilido complex (B). The latter traps the alkyl radical to give a Cu^{III}-anilido species (C), which after C-N reductive elimination, delivers the coupling product and regenerates a Cu^I species (D) that can now bind aniline again.

The above mechanism is different from that of the analogous coupling using Ru(bpy)₃(PF₆)₂ as the photocatalyst. The difference might originate from the redox potentials of the excited state of the photocatalysts. 4CzIPN* (E_{1/2} 4CzIPN*/4CzIPN^{•-} = +1.35 V vs SCE)^{19-20, 23} is a more potent electron acceptor (oxidant) than Ru(bpy)₃(PF₆)₂* (E_{1/2} *Ru^{II}/Ru^I = +0.77 V vs SCE).³¹ Thus, unlike Ru(bpy)₃(PF₆)₂*, 4CzIPN* can oxidize triethylamine leading to a reductive quenching process. This reactivity differs from that of Ru-based photoredox catalysis, which involved an oxidative quenching pathway.¹³

In summary, we have developed tandem photoredox and Cu catalysis for decarboxylative C(sp³)-N coupling of anilines and imines using an inexpensive and easy to

make organic photocatalyst.²³ The method can be applied for the synthesis of a broad range of alkylated primary and secondary amines. The organic photocatalyst not only broadens the scope of the coupling compared to previously reported Ru or Ir photocatalyst, but also operates via a different mechanism. This work further demonstrates the potential of organic photoredox catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and characterization data (pdf).

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Notes

The authors declare no conflict of interest.

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