

N-Heterocycles

 Photochemical C(sp²)-H Pyridination via Arene-Pyridinium
 Electron Donor-Acceptor Complexes

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Abstract: This report describes the development of a photochemical method for C(sp²)-H pyridination that leverages the photoexcitation of electron donor-acceptor (EDA) complexes. Experimental and DFT studies show that black light ($\lambda_{\text{max}} \approx 350$ nm) irradiation of solutions of protonated pyridines (acceptors) and aromatic C-H substrates (donors) results in single electron transfer to form aryl radical cation intermediates that can be trapped with pyridine nucleophiles under aerobic conditions. With some modification of the reaction conditions, this EDA activation mode is also effective for promoting the oxidatively triggered S_NAr pyridination of aryl halides. Overall, this report represents an inexpensive and atom-economical approach to photochemical pyridination reactions that eliminates the requirement of an exogenous photocatalyst.

The photochemical C(sp²)-H amination of aromatic substrates offers an attractive route to arylamine products, which are of high value in pharmaceutical, agrochemical, and materials chemistry applications.^[1,2] In 2015, Nicewicz and co-workers developed a method for arene C(sp²)-H amination via visible light photoredox catalysis.^[3] Since then, there have been numerous reports of C(sp²)-H amination utilizing a range of photocatalysts (PC) and nitrogen nucleophiles (Figure 1a).^[4,5] A general mechanism for these sequences is shown in Figure 1a and involves: excitation of the photocatalyst (PC) to generate PC⁺⁺, single electron transfer (SET) between the PC⁺⁺ and the arene substrate to form an arene radical cation intermediate (I), and capture of I by a nitrogen nucleophile under oxidative conditions to yield the aminated product.^[2,3,6] In this report, we demonstrate that

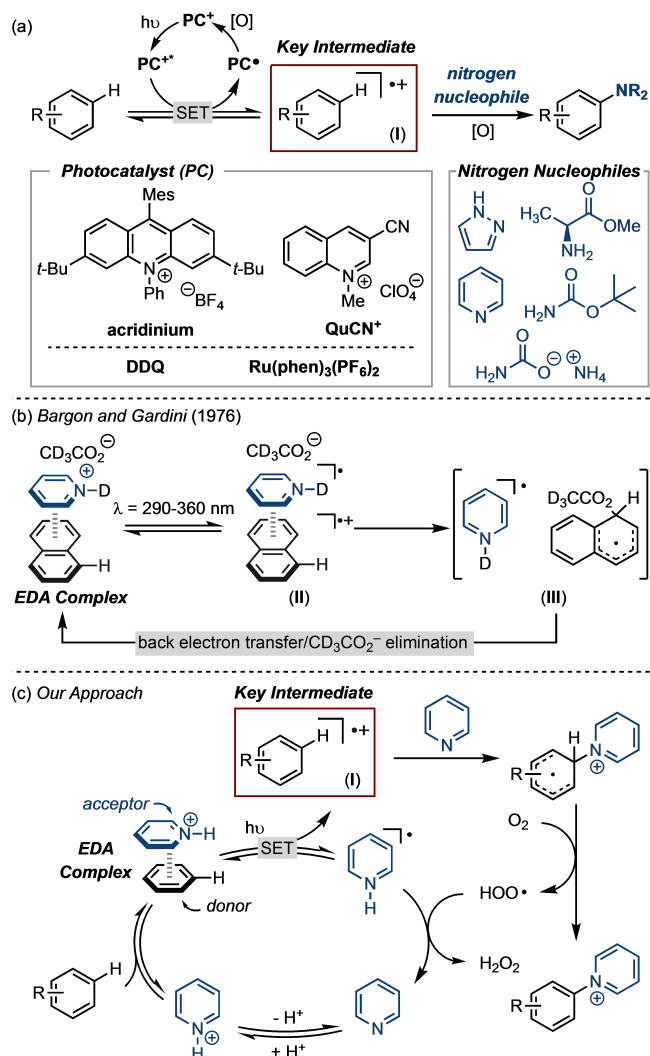


Figure 1. a) Photocatalytic C-H amination of arenes, including common photocatalysts and nitrogen nucleophiles. b) Generation of radical ion pairs II and III via photoexcitation of EDA complex.^[11] c) Plausible mechanism for our approach. Anion omitted for clarity.

analogous C(sp²)-H amination reactions can be achieved without the requirement for an exogenous photocatalyst. Instead, photoexcitation of an arene-pyridinium electron donor-acceptor (EDA) complex^[7-10] is leveraged to access the key radical cation intermediate (I) that is then trapped with pyridine and an oxidant.

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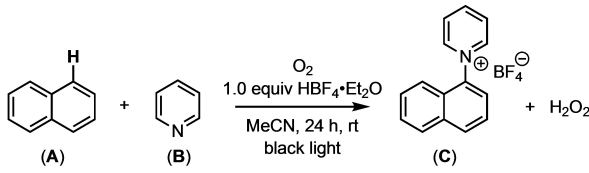
Our approach was inspired by early work of Bargon and Gardini, who studied the EDA complex between naphthalene (electron donor) and pyridinium-1-*d* acetate-*d*₃ (electron acceptor).^[11–14] As shown in Figure 1b, exposure of this EDA adduct to black light ($\lambda=290\text{--}360\text{ nm}$) resulted in charge transfer from naphthalene to the pyridinium to generate first the radical ion pair **II** and then the diradical **III**, which was detected by CIDNP NMR spectroscopy. Notably, **II** bears strong resemblance to the radical cation intermediate formed during photocatalytic C–H amination (**I**, Figure 1a). However, under these conditions (which lacked a strong nucleophile and a terminal oxidant), no arene C–H functionalization products were detected. Instead, **III** decayed to the starting materials via back electron transfer and elimination of acetate-*d*₃.

We noted that pyridine (the conjugate base of the electron acceptor in Figure 1b) is known to react with arene radical cations in the presence of oxidants.^[5,15,16] As shown in Figure 1c, reversible protonation of pyridine could enable this reagent to serve a dual role in photochemical arene C–H pyridination: (1) as an electron acceptor (to form an EDA complex) and (2) as a nitrogen nucleophile (to functionalize the arene radical cation intermediate). We demonstrate herein that black light irradiation of the simple combination of arene substrate, pyridine, acid (to generate a pyridinium acceptor in situ), and O₂ (to serve as a terminal oxidant) yields *N*-arylpiperidinium products.^[17] These products are valuable synthetic intermediates that are readily converted to anilines (via reactions with amine bases)^[15,17a,b] and piperidine derivatives (via hydrogenation).^[17a,18] DFT calculations and UV/Vis studies are consistent with a mechanism involving photo-induced charge transfer at an arene-pyridinium EDA complex in the parallel displaced geometry. Overall, this transformation represents a complementary approach to photochemical pyridination reactions that eliminates the need for an exogenous photocatalyst.

Initial studies targeted the reaction of naphthalene (**A**) and pyridine (**B**) to form pyridinium product **C** (Table 1).^[11] With O₂ as the terminal oxidant, a balanced equation for the proposed transformation is shown above Table 1. Using black light (UVA compact fluorescent lamp (CFL) with $\lambda_{\text{max}} \approx 350\text{ nm}$, analogous to that used by Bargon and Gardini), a 1.05:1.0:1.0 molar mixture of pyridine : HBF₄ : naphthalene in MeCN was irradiated for 24 h at room temperature under an atmosphere of O₂. A slight excess of pyridine relative to HBF₄ was used to maintain a reservoir of the nitrogen nucleophile to react with the putative radical cation intermediate.^[19] Under these conditions, the C–H pyridination product **C** was formed in 5% yield (Table 1, entry 1). Notably, using a 1:1 ratio of pyridine to HBF₄ (such that no free pyridine is present in solution) resulted in <1% yield under otherwise analogous conditions (entry 2).

The reaction was further optimized with respect to concentration, equiv. of naphthalene and pyridine, and solvent (see Tables 1 and S2 for details). One key finding is that the reaction is sensitive to concentration, with higher yields at lower concentrations (compare entries 3, 5, and 6). Furthermore, the addition of O₂ is important (compare entries 3 and 4), consistent with the oxidant driving the

Table 1: C(sp²)–H Pyridination of Naphthalene.



Entry	A [equiv]	B [equiv]	[HBF ₄ ·Et ₂ O]	C [%] ^[a]
1	1.0	1.05	0.1 M	5
2	1.0	1.0	0.1 M	< 1
3	2.5	1.05	0.1 M	6
4 ^[b]	2.5	1.05	0.1 M	< 1
5	2.5	1.05	0.05 M	18
6 ^[c]	2.5	1.05	0.02 M	23
7	1.0	2.0	0.02 M	20

[a] Crude yields determined by ¹H NMR spectroscopy. [b] Reaction was not sparged with an O₂ balloon before light irradiation (conducted under ambient air). [c] Compound **C** was isolated in 17% yield.

trapping and re-aromatization sequence.^[3,6c,20,21] A peroxide strip test of the crude reaction mixture was positive, consistent with the formation of H₂O₂. Ultimately, under the best identified conditions (1.05 equiv pyridine, 1.0 equiv HBF₄, 2.5 equiv naphthalene), product **C** was obtained in 23% yield (entry 6). The mass balance was a complex mixture of products that appear to be derived from competing oxidation reactions of naphthalene (see Figure S3).^[22–24]

Literature precedent suggests that the extended π -system of naphthalene renders it susceptible to competing oxidation and other side reactions.^[21–23] To circumvent this issue, we next conducted a computational screen to identify other aromatic substrates that could form EDA complexes with pyridinium salts and undergo photochemical excitation. Density functional theory (DFT) calculations were used to compare the energetics of the naphthalene–pyridinium EDA complex to that with other arenes. The calculations (using the B3LYP functional^[25] and 6–311+G** basis set including empirical dispersion effects in an acetonitrile dielectric) indicate that EDA complexation with the pyridinium cation (PyH⁺) is energetically accessible for a variety of aromatic substrates, including biphenyl, anisole, *tert*-butylbenzene, and benzene. As summarized in Figure 2 and Table S5, the binding energy (BE) for the EDA adduct in the parallel displaced (PD) geometry ranges from $-9.1\text{ kcal mol}^{-1}$ (naphthalene) to $-5.4\text{ kcal mol}^{-1}$ (benzene). Furthermore, in all cases DFT predicts a charge transfer band with λ_{max} ranging from 399 nm (anisole) to 324 nm (benzene). Overall, biphenyl is predicted to have the most similar properties to naphthalene. Consistent with these calculations, experimental UV/Vis spectroscopic analysis of solutions of PyH⁺–naphthalene and PyH⁺–biphenyl show similar bathochromic shifts (Figures S7 and S8 in Supporting Information). Furthermore, a Job plot for the PyH⁺–biphenyl system shows a 1:1 stoichiometry between the donor and acceptor.^[26]

Based on the computational and experimental UV/Vis results, we next explored biphenyl as a substrate. Under

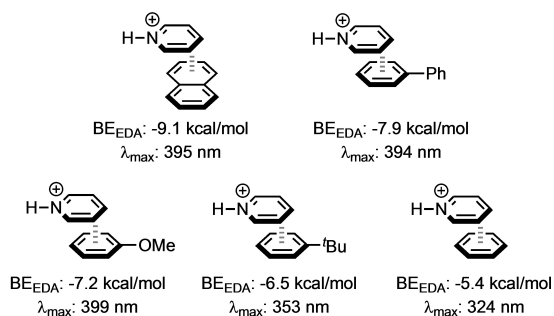


Figure 2. Comparison of the binding energy (BE) and excitation wavelength (λ_{\max}) of arene-pyridinium EDA complexes in the parallel-displaced (PD) geometry. Values from DFT calculations (B3LYP functional and 6-311 + G** basis set including empirical dispersion effects in an acetonitrile dielectric). As detailed in the Supporting Information (p. S12), this method captures trends, but overestimates binding energy and excitation wavelength.

analogous conditions to Table 1, entry 6, biphenyl reacts with pyridine to form **1** in 72 % yield as determined by ^1H NMR spectroscopy (Table 2, entry 1). Product **1** was isolated in 70 % yield under these conditions (entry 1).^[19] Unlike the reaction of naphthalene, the C–H pyridination of biphenyl to form **1** proceeds cleanly, with unreacted starting material accounting for the mass balance (compare Figure S3 to S4). Control experiments demonstrate that the reaction requires both the light source (black light) and acid ($\text{HBF}_4 \cdot \text{Et}_2\text{O}$) to afford more than trace yield of **1** (entries 3 and 4).^[27] Additionally, when the reaction mixture was not sparged with O_2 the yield of **1** decreased to 14 % (entry 2). As discussed above, we propose that O_2 serves as the terminal oxidant to promote rearomatization and generate the product.^[3,6c,20,21] Finally, the reaction afforded **1** in comparable (70 %) yield when biphenyl was used as the limiting reagent, along with 2 equiv. of pyridine (entry 7). Under these conditions, the mass balance was primarily the dipyridinated product (18 % yield) along with traces of unreacted starting material.

A variety of pyridine derivatives were next evaluated for the reaction with biphenyl. Importantly, the substituted pyridinium products serve as precursors to piperidines (via

Table 2: C(sp^2)–H Pyridination of Biphenyl.

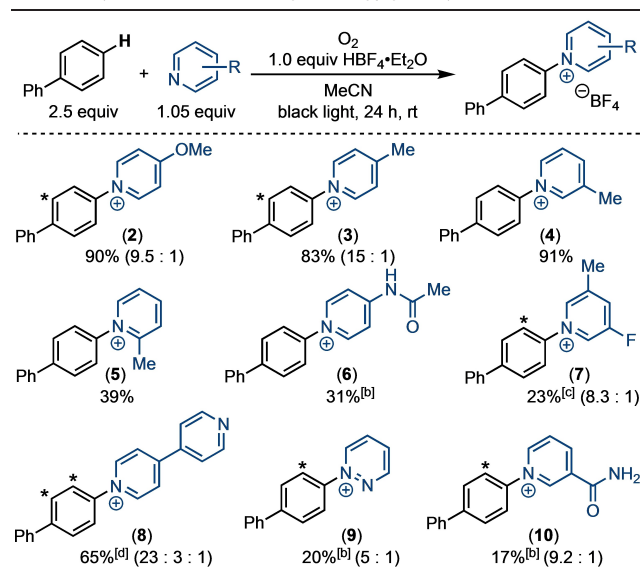
Entry	Modification	Yield ^[a]
1	none	72 %, (70 %) ^[b]
2	no O_2 sparge (ambient air)	14 %
3	no light	0 %
4	no $\text{HBF}_4 \cdot \text{Et}_2\text{O}$	1 %
5	390 nm Kessil LED	39 %
6	440 nm Kessil LED	0 %
7	1 equiv biphenyl, 2 equiv pyridine	70 % ^[c]

[a] Crude yields determined by ^1H NMR spectroscopy. [b] Isolated yield. [c] The 4,4'-dipyridinated product was also formed in 18 % yield.

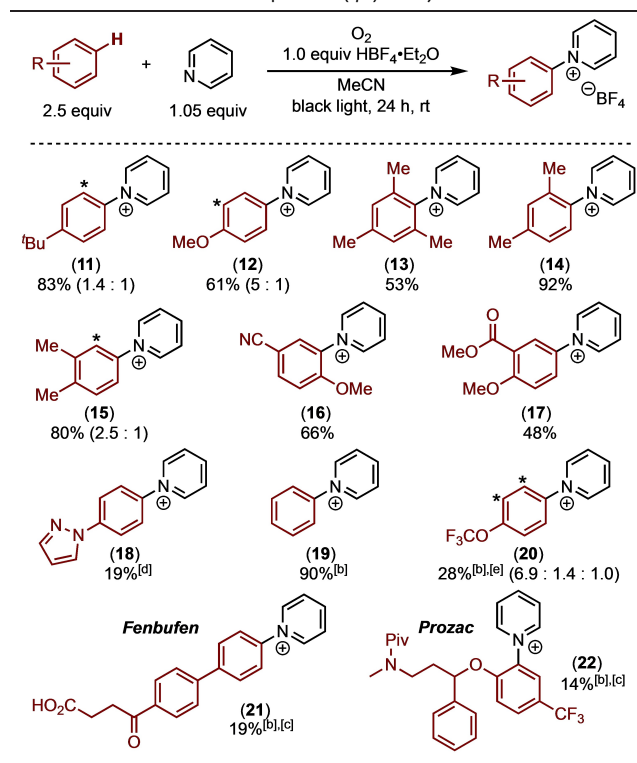
hydrogenation).^[17a,18] Since the pyridine is proposed to serve as both the nucleophile and the acceptor (as the conjugate acid), a key question was how sensitive this transformation would be to pyridine substitution. As summarized in Table 3, pyridines bearing electron donating methyl- and methoxy- substituents at the 3- and 4-positions reacted to afford high yields (83–91 %) of pyridinium products **2–4**. With 2-methylpyridine, the pyridinium product **5** was also formed, albeit in significantly lower yield (39 %). Yields were also modest with pyridines bearing moderately electron-withdrawing fluorine (**7**) or amide substituents (**10**) or when using less nucleophilic nitrogen heterocycles such as pyridazine (**9**).^[28] Furthermore, pyridines bearing stronger electron withdrawing groups (e.g., 2- or 4- CF_3 or CN) afforded $\leq 5\%$ yield of the pyridinium product. These results indicate that the nucleophilicity of the pyridine derivative is a key driver in this transformation. In all cases, the *para*-isomer was favored with good to excellent selectivity (presumably due to steric effects), but the minor regioisomer varied depending on the electronics of the pyridine. With electron rich pyridine nucleophiles the minor isomer was *ortho*-, while with more electron deficient derivatives the minor isomer was *meta*-substituted.^[29]

The scope of photochemical C–H pyridination was also evaluated with respect to the arene substrate (Table 4). As predicted by DFT (Figure 2), anisole showed high reactivity under the standard conditions, affording the pyridinium product **12** in 61 % isolated yield as a 5:1 mixture of the *para* and *ortho* isomers. The observed *para* selectivity is

Table 3: Pyridine Substrate Scope for C(sp^2)–H Pyridination.^[a]



[a] Reactions run under black light ($\lambda_{\max} \approx 350$ nm) for 24 h in MeCN. All products isolated as BF_4^- salts. See Supporting Information for additional details. [b] 2 equiv of pyridine relative to 1 equiv of arene and $\text{HBF}_4 \cdot \text{Et}_2\text{O}$. [c] 3 equiv. of pyridine relative to 1 equiv of arene and $\text{HBF}_4 \cdot \text{Et}_2\text{O}$. [d] Ratio refers to *para:meta:ortho* (*p:m:o*) selectivity. Ratios represent ratio of crude products between major (pictured) and minor (*) isomers. All yields are isolated and represent mixtures of inseparable regioisomers unless otherwise noted. BF_4^- counterion omitted for clarity.

Table 4: Arene Substrate Scope for C(sp²)-H Pyridination.^[a]

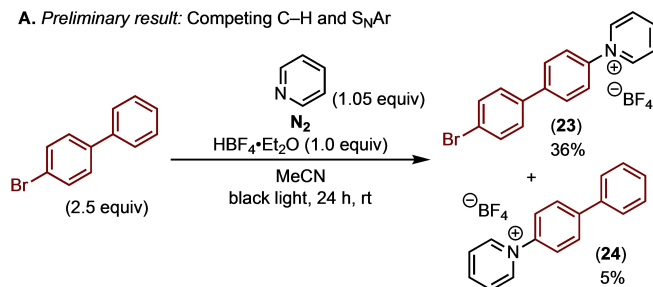
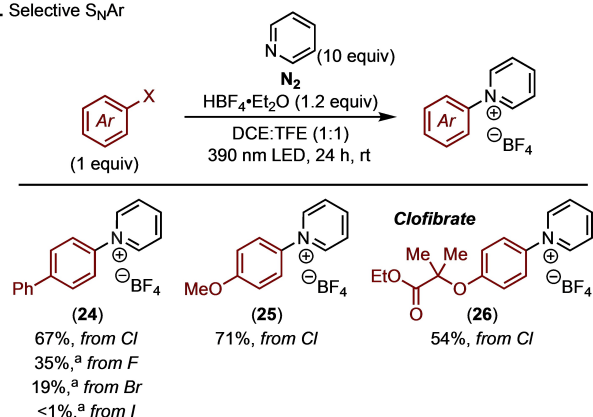
[a] Reactions run under black light ($\lambda_{\text{max}} \approx 350 \text{ nm}$) for 24 h in MeCN. All products isolated as BF₄⁻ salts. See Supporting Information for additional details. [b] Reactions run using a UVB CFL ($\lambda_{\text{max}} \approx 300 \text{ nm}$). [c] 2 equiv of pyridine relative to 1 equiv of arene and HBF₄·Et₂O. [d] 3 equiv of pyridine relative to 1 equiv of arene and HBF₄·Et₂O. [e] Ratio refers to *para:ortho:meta* (*p:o:m*) selectivity. Ratios represent ratio of crude products between major (pictured) and minor (*) isomers. All yields are isolated and represent mixtures of inseparable regioisomers unless otherwise noted. BF₄⁻ counterion omitted for clarity.

analogous with that reported by Yoshida^[15] for electrochemical C(sp²)-H pyridination of anisole via an analogous radical cation intermediate, and it is likely driven by sterics.^[30] Under the same conditions *tert*-butylbenzene reacted to form **11** in 83% yield as a 1.4:1 mixture of the *para* and *meta* isomers. Other alkyl-substituted aromatic substrates, including mesitylene, *meta*-xylene, and *ortho*-xylene, afforded comparable yields of the corresponding pyridinium products **13**–**15**. Anisole derivatives bearing electron withdrawing cyano and ester substituents reacted to afford **16** and **17** in 66% and 48% yield, respectively, under the standard conditions. Benzene and trifluoromethoxybenzene gave <1% yield of the corresponding C(sp²)-H pyridination products upon irradiation with black light. However, switching to a higher energy light source (UVB CFL) with these less electron rich substrates led to the pyridinated products **19** and **20**. These results are consistent with the DFT calculations showing that higher energy is required for charge transfer in the benzene-pyridinium EDA complex compared to that with more electron rich arenes (Figure 2).

While the reactions in Table 4 were conducted using a 2.5:1 ratio of arene to pyridine, the arene can also be used as the limiting reagent with minimal impact on the yield. For example, with anisole, mesitylene, and anisonitrile as the limiting reagent (along with 2 equiv. of pyridine), products **12**, **13**, and **16** were isolated in 56%, 49%, and 52%, respectively. The mass balance in these reactions was primarily unreacted starting material.

The drug molecules Fenbufen and Prozac underwent C(sp²)-H pyridination to form **21** and **22** in modest yields utilizing a UVB CFL. With these substrates the arene was used as the limiting reagent, and the mass balance was unreacted starting material.^[31] Notably, the reaction of Prozac was conducted with the HBF₄ salt of the amine, and the product was subsequently converted to the pivoyl amide to facilitate isolation.^[32] Prozac presents two aromatic rings that could undergo C-H pyridination, and the reaction is selective for the ring bearing ether and CF₃ substituents. These examples demonstrate compatibility with ketones, carboxylic acids, and protonated amines.

Finally, we sought to expand this EDA activation mode to aromatic functionalization reactions beyond just C-H pyridination. We initially targeted S_NAr pyridination based on a preliminary result showing that 4-bromobiphenyl reacts under the standard conditions to afford traces ($\approx 5\%$) of the S_NAr product **24** along with the expected C(sp²)-H pyridination product **23** (36%; Scheme 1A).^[33] Optimization of the S_NAr reaction, including switching to an N₂ atmosphere with DCE:TFE (1:1) as the solvent^[5,34] and using a

A. Preliminary result: Competing C-H and S_NAr**B. Selective S_NAr**

Scheme 1. A) Mixture of C(sp²)-H pyridination and S_NAr pyridination with 4-bromobiphenyl. B) Selective S_NAr pyridination. [a] Crude yield determined by ¹H NMR spectroscopy.

Kessil LED (390 nm) light source, resulted in enhanced yield and selectivity for **24** (19% yield; >20:1 selectivity; Scheme 1B).^[35] Furthermore, changing the leaving group from bromide to chloride under otherwise identical conditions, led to a 67% isolated yield of **24**, along with <1% of the C–H pyridination product.^[36] Similar results were obtained with 4-chloroanisole and Clofibrate as substrates, affording exclusively S_NAr products **25** and **26** in 71% and 54% isolated yield, respectively.

In conclusion, this paper demonstrates the photochemical C(sp²)–H pyridination of electron rich and -neutral arenes using pyridine as a nucleophile and protonated pyridine as an acceptor for EDA complex formation and photoactivation. These transformations use O₂ as the terminal oxidant and proceed without an exogenous photocatalyst. DFT studies of the proposed EDA intermediates guided the selection of arene substrates. This activation mode enables C(sp²)–H pyridination of both electron rich and electron-neutral arenes, which complements the scope of analogous transformations using visible light and acridinium photocatalysts.^[5] Furthermore, with substrates bearing aryl halide functional groups, this activation mode also enables S_NAr reactivity. Ongoing work is focused on detailed studies of the scope of arene functionalization reactions enabled by this approach.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: C–H Functionalization · N-Heterocycles · Photochemistry · Radical Intermediates · Reaction Mechanisms

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- [26] See Figure S10 for the Job plot and Figure S12 for NMR spectra of biphenyl, pyridinium tetrafluoroborate and a 1:1 mixture of these compounds.
- [27] The time course for the formation of **1** was nearly identical under the standard conditions and upon the addition of 25 mol % of **3** at the outset of the reaction (Figure S13). This result provides evidence against an autocatalysis scenario in which the *N*-arylpyridinium products accelerate the C(sp²)–H pyridination reaction.
- [28] With electron deficient pyridines, higher yields were obtained using biphenyl as the limiting reagent in the presence of an excess of the pyridine, potentially due to slow capture of the radical cation intermediate with these nucleophiles.
- [29] We hypothesize that the *ortho* selectivity observed with stronger pyridine nucleophiles may reflect a kinetic preference, while the *meta* selectivity with weaker nucleophiles may be a thermodynamic effect. Ongoing work is focused on gaining further mechanistic insights.
- [30] We are actively investigating the unusual *ortho*-selectivity observed in our previous report of acridinium-catalyzed C(sp²)–H pyridination, ref. [5].
- [31] The crude yield of **21** was 52 %, and 40 % unreacted Fenbufen starting material remained. Similarly, the crude yield of **22** was 20 %, and 70 % unreacted Prozac remained.
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