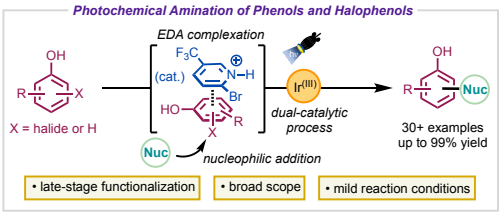
Amination of Phenols and Halophenols via Pyridinium–Iridium Dual Photocatalysis

Matthew C. Carson, Cindy R. Liu, Yaning Liu, Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States; *email: marisa@sas.upenn.edu

Supporting Information Placeholder



ABSTRACT: In this study, we present a photochemical method for the amination of phenols (C–H) and halophenols (S_NAr), facilitated by dual catalytic pathways involving both Ir(III) photocatalysis and phenol–pyridinium EDA complexation. By incorporating a pyridinium additive, we achieved efficient C–N coupling between phenols and diverse aromatic nitrogen nucleophiles, delivering high yields (up to 99%) across a wide range of substrates, including pharmaceuticals and natural products. We investigate reaction selectivity and substrate compatibility/limitations through a combination of experimental and computational techniques. Moreover, we highlight the synthetic versatility of the amination products through various late-stage functionalizations including the grafting of two different heteroarenes onto one phenol scaffold.

INTRODUCTION

The utilization of free phenols in organic synthesis has allowed for diverse C–H functionalization with excellent control of regio- and chemoselectivity. These methods leverage the innate reactivity of the free phenols, specifically their facile oxidation, and afford new C–C, C–O, C–N, and C–S bonds.[1–3] In particular, the construction of C–N bonds has been pivotal in the synthetic development of pharmaceuticals, agrochemicals, and materials chemistry.[4,5] The assembly of new C(sp^2)–N bonds typically requires transition-metal catalysts, high temperatures, and the prefunctionalization of the carbon fragment, often as boronic acids, aryl halides, and other electrophilic groups.[6,7]

Over the last two decades, photochemistry has proven to be a powerful method in the synthetic toolbox to reach diverse chemical space with mild conditions and the employment of commercial light sources.[8,9] Electrochemistry and photoredox catalysis has allowed for the diverse functionalization of electron-rich arenes (aryl ethers, etc.), often through radical cation and radical-radical mechanisms.[10–21] The recent emergence of electron donor-acceptor (EDA) photocatalysis has also enabled chemistries involving single-electron transfer (SET) events with low energy visible light and without the need for photoredox catalysts.[22,23] This avenue of radical generation has largely been biased toward activation of an electron-poor component (acceptor) where an electron-rich component (donor) that acts as a catalyst/reagent is optimized.

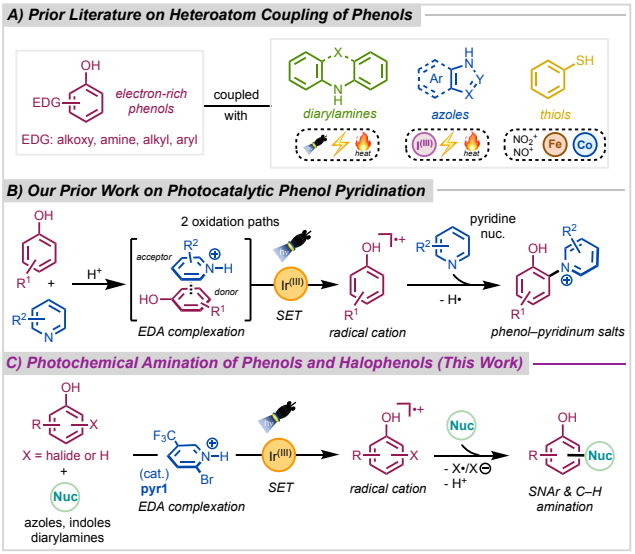


Figure 1. A) Previous synthetic approaches for amination of phenols. B) Previous work on pyridination of phenols. C) This current work.

With electron-rich phenols, several research groups have found success in coupling diarylamines, azoles, and thiols via C–N and C–S bond formation (**Figure 1A**). These reactions are typically proposed to proceed through a radical-radical mechanism. For example, the coupling of diarylamines and phenols has been achieved via photochemistry,[24–26] electrochemistry,[27–29] and thermal oxidative conditions.[30–36] Hypervalent iodine reagents,[37]

electrochemistry,[38] and thermal oxidative conditions[39] have enabled C–H amination with azoles (radical-radical coupling). By employing nitronium/nitrosonoium ions[40] or Co/Fe catalysts,[41,42] the C–S coupling between thiols and phenols has resulted in the formation of phenolic thiol ethers. The majority of the aforementioned methods afford *ortho*-C–H functionalized phenolic products, although a few *para*-functionalized products are present. Knowles and coworkers have reported Fe- and base-mediated S_NAr of halophenols with benzoates/carboxylates.[43]

Recently, we disclosed the photochemical C–H and S_NAr pyridination of electron-rich phenols to furnish a variety of phenol–pyridinium salts (**Figure 1B**).[44] The reaction proceeded via EDA complexation between the phenol and the protonated pyridine (pyridinium) to form reactive phenoxyl radical cations upon light irradiation. Pyridine also serves as a nucleophile to form the C–N bond. The addition of an $Ir^{(III)}$ photocatalyst boosted the yields, aiding in the phenol oxidation.

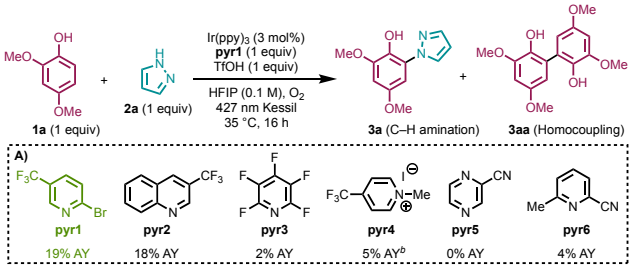
From this chemistry, we postulated that a pyridinium acceptor could act as a catalyst that would allow for interception of the phenoxyl radical cation by a different nucleophile (**Figure 1C**). This approach requires a delicate balance wherein the pyridine must satisfy several criteria: 1) is sufficiently basic to protonate, 2) is less nucleophilic than the exogenous nucleophile, 3) is sufficiently electron-poor to participate in EDA complexation, and 4) is not subject to direct reduction by the photocatalyst.

RESULTS AND DISCUSSION

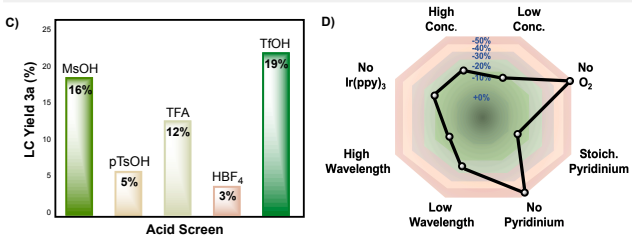
Reaction Design. Using our prior pyridination conditions,[44] the initial reaction discovery focused on the coupling of 2,4-dimethoxyphenol (**1a**) and pyrazole (**2a**) using $Ir(ppy)_3$ in HFIP (**Scheme 1**). We first screened several pyridine and alkyl pyridinium additives of varying steric and electronic nature (**Scheme 1A**). C–H amination product **3a** was obtained in the highest LC assay yield (AY) using 2-bromo-5-(trifluoromethyl)pyridine (**pyr1**) and TfOH (19%). **Pyr1** was strategically selected to fulfill the criteria discussed above. Namely, pyridines bearing C2 substituents were unreactive as nucleophiles in our pyridination work.[44] The CF_3 group ensures that **pyr1** is a good acceptor for the phenols while not being too electron-poor as to be deactivated by direct reduction with the photocatalyst or to preclude protonation. Phenol homocoupling product **3aa** was observed as a major reaction byproduct, as is commonly seen in photochemical phenol oxidation.[45,46]

A range of solvents, acids, oxidants, photocatalysts, light sources, stoichiometries, and concentrations were analyzed for the desired reaction (see the Supporting Information for full optimization). The acid screen shown in **Scheme 1C** illustrates the importance of pyridine protonation for reaction success with TfOH outperforming the other strong acids, for which counterion stability is likely important. An excess of pyrazole (**2a**) and catalytic pyridinium (30 mol%) in dilute conditions (0.08 M) achieved the highest yield (52% AY, 51% IY) and greatest selectivity for amination : homocoupling (15.9 : 1) (**Scheme 1**, **entry 5**). Removing the photocatalyst, $Ir(ppy)_3$, from the reaction mixture lowered the yield (35%), but not drastically, indicating that the reaction can be promoted by the pyridinium itself (**entry 7**). In contrast, the use of only $Ir(ppy)_3$, without any pyridinium additive, resulted in no desired product (**entry 10**). As this substrate is well within the oxidation window of $Ir(ppy)_3$ (E_{ox} = +0.31 V vs SCE),[8] it appears that back electron transfer (BET) prevents the forward reaction.[47,48] Together, these results support the EDA complex as a key intermediate that can both undergo productive direct excitation with light and stabilize the phenoxyl radical cations. Overall, the reaction sensitivity plot summarizes the significant dependence on the presence of pyridinium and an O_2 atmosphere to achieve optimal reactivity (**Scheme 1D**).

Scheme 1. Reaction Discovery and Optimization



Entry	Deviations from Above Conditions	LC Yield **3a** (%)	LC **3a**:**3aa**
1	2 equiv **1a**	11	0.3 : 1
2	3.5 equiv **2a**	43	4.0 : 1
3	3.5 equiv **2a** + 10 mol% **pyr1** & TfOH	35	3.6 : 1
4	3.5 equiv **2a** + 30 mol% **pyr1** & TfOH	44	4.2 : 1
5	3.5 equiv **2a** + 30 mol% **pyr1** & TfOH + 0.08 M HFIP	52 (51)	15.9 :1
6	3.5 equiv **2a** + 390 nm Kessil	31	5.4 : 1
7	3.5 equiv **2a** + No $Ir(ppy)_3$	35	5.7 : 1
8	3.5 equiv **2a** + No light	0	–
9	3.5 equiv **2a** + Under Ar	0	–
10	3.5 equiv **2a** + No **pyr1** & TfOH	0	–
11	3.5 equiv **2a** + No TfOH	trace	–

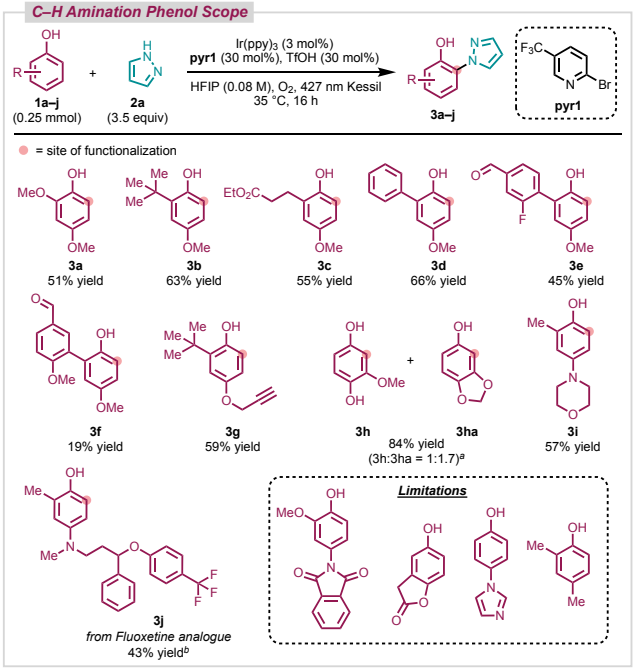


[a]Screen of pyridinium additives. AY is relative LC assay yields of **3a** and **3aa** with 4,4'-di-tert-butylbiphenyl internal standard (254 nm). [b]No TfOH was used with **pyr4**. Yield shown in parentheses is the isolated yield after column chromatography. [c]Screen of acid additives. [d]Sensitivity analysis of reaction based on percent difference from optimized condition for each respective change.

C–H Amination Phenol Scope. With the optimized C–H amination conditions, we explored the scope using a variety of electron-rich phenols (**Scheme 2**). *ortho*-C–H amination was facilitated in high yields (up to 84% yield) with good functional group tolerance (aldehydes, alkynes, esters, and halides) for eleven substrates (**3a–j**). Electron-rich (alkoxy and amine) substituents were needed at the *para*-position for sufficient yields. The amination of 2-methoxyhydroquinone (**1h**) resulted in a 1 : 1.7 mixture of **3h** : **3ha** (84% yield overall). We hypothesize that a 1,5-hydrogen atom transfer (HAT) with the phenoxyl radical and adjacent methoxy group resulted in the ketal cyclization product

3ha. Amination of a phenolic analogue of the selective serotonin reuptake inhibitor (SSRI) fluoxetine (**3j**) proceeded in a 43% yield after only 4 h. Electron-neutral phenols were found to be largely unreactive to the C–H amination, potentially due to a lack of sufficiently electrophilic sites in the radical cation[14] (see Supporting Information for substrate limitations).

Scheme 2. Phenol Scope of C–H Amination



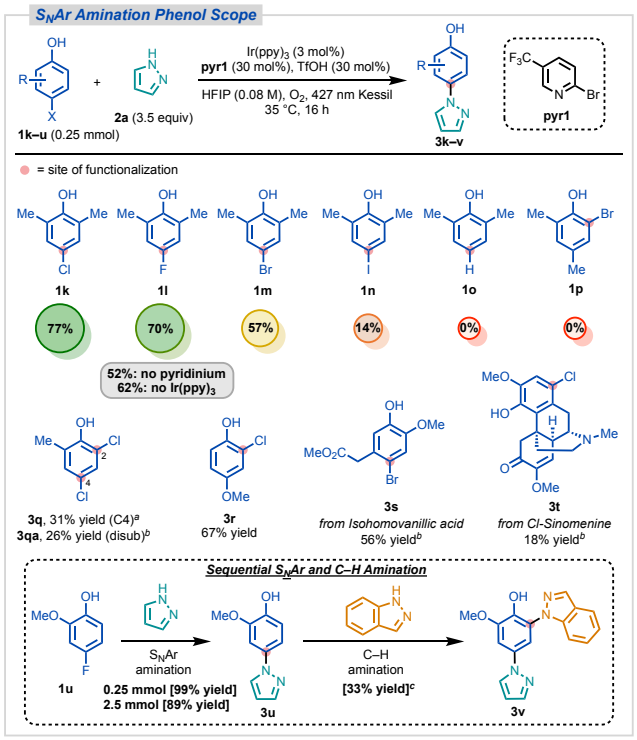
Yields shown are isolated yields after column chromatography. [a]Obtained as a mixture of separable isomers. [b]4 h reaction time.

S_NAr Amination Phenol Scope. Building upon our successful photocatalytic S_NAr pyridination involving 4-(trifluoromethyl)pyridine and 2,6-dimethyl-4-fluorophenol (**1l**),[44] the amination of a range of halophenols (**1k–u**) was explored via activation of C–X bonds (**Scheme 3**). Using the optimized C–H amination conditions, *ortho*- and *para*-S_NAr amination with pyrazole **2a** occurred in excellent yields (up to 99%) and with an increased tolerance for phenol electronics. For the 2,6-dimethylphenol backbone, amination occurred for 4-chloro (**1k**), 4-fluoro (**1l**), 4-bromo (**1m**), and 4-iodo (**1n**) derivatives (in this order of reactivity). Without the pyridinium additive (**pyr1** & TfOH), a reduced isolated yield of 52% was observed for fluorophenol **1l**. The pyridinium yield enhancement for S_NAr was not as profound as it was for C–H amination (0% without vs 51% with pyridinium) as BET is likely not as detrimental for these halogenated phenols.[47] The S_NAr of **1l** occurred in a comparable yield (62% IY) with the removal of $Ir(ppy)_3$, highlighting the organocatalytic capabilities of **pyr1** and acid. This suggests that the photocatalyst may not be necessary for adequate S_NAr reactivity.

Regioselective C4 amination product **3q** was obtained in a 31% yield and the disubstitution product **3qa** was isolated in a 26% yield when using organophotocatalyst 4CzIPN (E_{ox} = +1.43 V vs SCE).[49] Despite the poor performance of 2-bromophenol **1p**, *ortho*-S_NAr could be achieved with other phenols such as 2-chlorophenol **1r** in a 67% yield. A bromo catecholamine analogue **1s** and plant alkaloid **1t** were selectively aminated in 56% and 18% yields, respectively.

The S_NAr proved to be scalable; for the amination of **1u**, a 99% yield was obtained on a 0.25 mmol scale and an 89% yield on a 2.5 mmol scale (using only one Kessil lamp). The amination product **3u** was then subjected to sequential C–H amination to furnish tetra-substituted **3v** in 33% yield using $MesAcrBF_4$ (E_{ox} = +2.06 V vs SCE)[8] in TFE. High-throughput experimentation (HTE) was utilized to optimize the reactions conditions for this particular reaction as poor conversion was seen with $Ir(ppy)_3$ (see the Supporting Information).

Scheme 3. Phenol Scope of S_NAr Amination



Yields shown are isolated yields after column chromatography. [a]2.0 equiv **2a**. [b]4CzIPN instead of $Ir(ppy)_3$. [c]$MesAcrBF_4$ instead of $Ir(ppy)_3$ and TFE instead of HFIP.

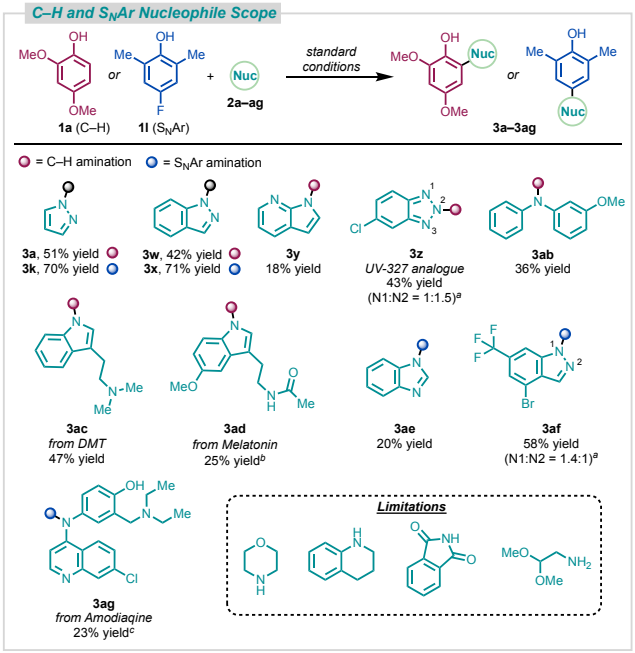
Nucleophile Scope. While pyrazole (**2a**) served as the primary nucleophile during the phenol exploration, the diverse chemical landscape and complexity inherent to the nucleophile was also surveyed. We achieved mild C–N functionalization using various aromatic nitrogen nucleophiles for both C–H and S_NAr amination, resulting in satisfactory yields of up to 70% (**Scheme 4**). As previously observed, the S_NAr was typically higher yielding than the C–H amination for the same nucleophile (**3a**/**k** and **3w**/**x**). Various azoles, including both fused and unfused (**3a**, **3k**, **3w**, **3x**, **3ae**, **3af**), indoles (**3y**, **3ac**, **3ad**), triazoles (**3z**), and diarylamines (**3ab**, **3ag**) were competent nucleophiles in this reaction. Notably, indoles have never previously been used in a C–N coupling reaction with a free phenol.

The mild nature of the reaction conditions enabled the use of natural product and pharmaceutical substrates. Of note, the amination of *N,N*-dimethyltryptamine (DMT) (**2ac**) and melatonin (**2ad**) proceeded in 47% and 25% yields,

respectively. A novel UV-327 analogue (**3z**) as obtained as a mixture of N1 : N2 regioisomers (1 : 1.5) in a 43% overall yield. Remarkably, the antimalarial drug amodiaquine (**2ag**), which contains a 2,4-substituted phenol, was aminated in a 23% yield with only 1.1 equiv of the nucleophile.

This transformation was unsuccessful with aliphatic amines or amides. (For successful use of the nucleophiles in non-phenolic arene couplings, see refs 10–21) Other heteroatom-based nucleophiles (thiols, alcohols, carboxylates, etc.) also did not lead to any desired products (see Supporting Information).

Scheme 4. Scope of Nucleophiles in Amination

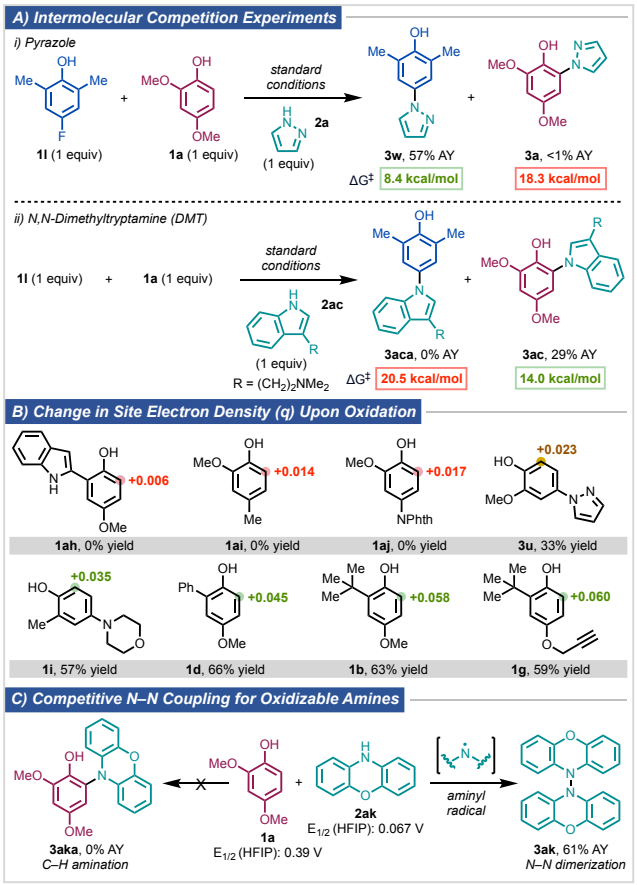


Same conditions as **Scheme 3**. Yields shown are isolated yields after column chromatography. [a]Obtained as a mixture of inseparable regioisomers. [b]2.0 equiv **2ad**. [c]1.1 equiv **2ag**.

Reaction Mechanism. To probe the reaction selectivity for C–H and SNAr amination, intermolecular competition experiments were performed using phenols **1l** and **1a** with nitrogen nucleophiles **2a** (pyrazole) and **2ac** (indole) (**Scheme 5A**). With a pyrazole (**2a**) nucleophile, the SNAr predominates with a 57% AY of **3w** and a <1% AY of the C–H amination product **3a**. Conversely, an indole nucleophile (**2ac**) gives rise to no SNAr amination (**3aca**) with only C–H amination product **3ac** being observed in 29% AY.

To understand this selectivity, DFT studies was conducted using UM06-2X/6-311++G(d,p)-CPCM(HFIP)//UB3LYP/6-31+G(d,p)-CPCM(HFIP). A comprehensive experimental and computational study by Nicewicz and co-workers on a similar arene amination reaction determined that nucleophilic addition to the arene radical cation was the rate-determining step.[18] With this in mind, we calculated the transition state energies for addition of each nucleophile to the respective phenol radical cations. The barriers matched the experimental observations, with the observed major products having lower transition-state energies (>6 kcal/mol). For azoles, the neutral adjacent nitrogen can serve as the nucleophilic center, but for indoles, the π-system must act as the nucleophile. Addition with nucleophiles of the latter type favors C–H bond activation whereas the former favors SNAr reaction.

Scheme 5. Experimental and Computational Mechanism Investigation



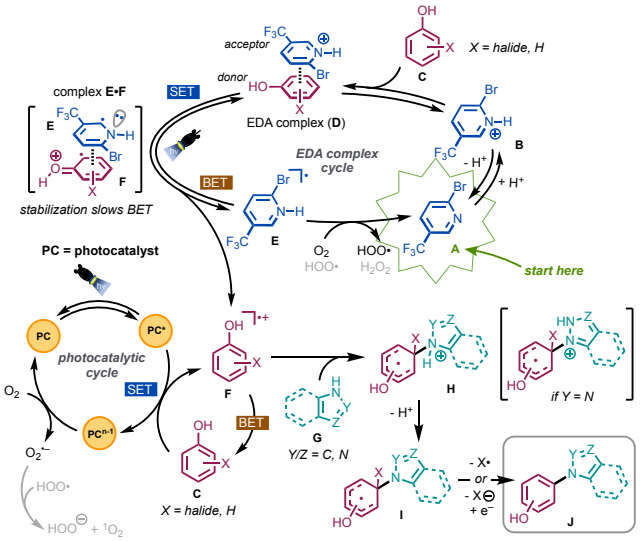
[a]AY is relative LC assay yields of with 4,4'-di-tert-butylbiphenyl internal standard (254 nm). Free energies were computed using UM06-2X/6-311++G(d,p)-CPCM(HFIP)//UB3LYP/6-31+G(d,p)-CPCM(HFIP). [b]Change in site electron density (q) for highlighted positions from neutral to radical cation species. Electron density values were obtained with NBO formalism using 6-31+G(d,p)-CPCM(HFIP). [c]Oxidation potentials measured with degassed HFIP, vs Ag/AgCl. (See Supporting Information for more details.)

Also inspired from work by Nicewicz *et al.*,[14] we calculated the natural population analysis (NPA) values or site electron densities for the reactive sites (*ortho*) of neutral phenols vs their radical cations (**Scheme 5B**). One would anticipate a shift towards greater positivity in these values as SET of a free phenol results in the formation of the electrophilic radical cation. We observed a good correlation (R^2 = 0.83) between the amination yield and the increase in NPA value (Δq) from neutral phenol to radical cation. When Δq exceeds 0.023, reactivity is seen. To forecast the reactivity of unidentified phenols, one could compute this value to determine if it is above this critical threshold.

When exploring the reaction scope, we observed N–N dimerization (**3ak**) in a 61% AY when attempting the amination reaction with phenoxazine **2ak** and **1a** (**Scheme 5C**). Utilizing cyclic voltammetry (CV) in HFIP, we determined the oxidation potentials ($E_{1/2}$) for the two substrates and noted a significant disparity, with **2ak** exhibiting a notably

lower potential (0.067 V) compared to **1a** (0.39 V). This transformation therefore likely occurs through aminyl radical formation followed by subsequent radical-radical coupling. We observed no C–H amination product with phenoxazine **2ak**, indicating that a radical-radical coupling mechanism is improbable for our reaction. This sets the current work apart from previous phenol aminations and suggests the probable involvement of the phenoxyl radical cation pathway (**Scheme 6**).

Scheme 6. Proposed Amination Mechanism

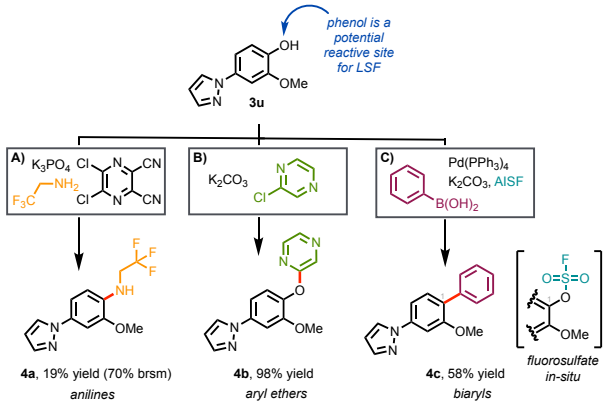


In the proposed mechanism depicted in **Scheme 6**, the catalytic formation of phenol–pyridinium EDA complex **D** leads to single-electron transfer (SET) to form complex **E•F**. The stabilization of the phenoxyl radical cation **F** by the pyridinyl radical **E** prevents/slows down back electron transfer (BET) of **F**. Simultaneously, a parallel photocatalytic cycle generates an additional supply of **F**. Addition of nucleophile **G** to **E•F** or **F** leads to **H**. Subsequent proton loss and re-aromatization culminates in the formation of the amination product **J**.

Utilization of Amination Products. To highlight the synthetic utility of the obtained amination products and the potential of the phenol functional group for further reactivity, we explored late-stage modifications of phenol **3u** (**Scheme 7**). From a 2.5 mmol scale reaction, we obtained ~500 mg of **3u** to use for additional transformations. In **Scheme 7A**, we utilized recent conditions from Fier and co-workers at Merck using a transition metal-free approach to turn phenols into anilines with sequential S_NAr.[50] Using trifluoroethylamine as a nucleophile aniline **4a** formed in a 19% yield (70% brsm). We leveraged the nucleophilic potential of the phenol upon deprotonation (phenolate) in a conventional S_NAr reaction with a (hetero)aryl chloride to form aryl ether **4b** in a 98% yield (**Scheme 7B**).

Finally, researchers at Pfizer have pioneered the use of 4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF) for *in-situ* activation of phenols in a variety of cross-coupling reactions.[51] We successfully facilitated a net C–C bond formation employing this reagent under typical Suzuki-Miyaura conditions, yielding biaryl **4c** in a one-pot manner with a satisfactory 58% yield (**Scheme 7C**). Overall, the phenol functional group can be seen as a directing/activating group to install three groups sequentially to rapidly increase molecular complexity. Since this transformation is applicable to both *ortho*- and *para*-amination, a large diversity of regiochemical space can be scanned.

Scheme 7. Late-Stage Diversification of Phenol 3u



Reaction conditions: (A) *i*) K_3PO_4 (7.0 equiv), 2,2,2-trifluoroethylamine hydrochloride (1.3 equiv), 5,6-dichloropyrazine-2,3-dicarbonitrile (1.2 equiv), 1,4-dioxane, 50 °C, 2 h *ii*) **3u** (0.25 mmol), DMSO, 100 °C, 16 h *iii*) Zn (10 equiv), AcOH, 80 °C, 30 min (B) **3u** (0.25 mmol), K_2CO_3 (3.0 equiv), 2-chloropyrazine (1.0 equiv), DMF, 110 °C, 16 h (C) **3u** (0.26 mmol), $PhB(OH)_2$ (1.5 equiv), $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3.0 equiv), AISF (1.2 equiv), 5:1 1,4-dioxane:H_2O, 100 °C, 1 h.

CONCLUDING REMARKS

In summary, we have developed a mild method utilizing pyridinium EDA complexation and photocatalytic cycles for the formation of C–N bonds between phenols/halophenols and a diverse range of nitrogen nucleophiles (azoles, indoles, diarylamines). Selective C–H amination ensues for electron-rich phenols while S_NAr is seen with halogenated phenols. Selective sequenced reactions are also possible as amines that react via an sp^2 lone pair undergo S_NAr reactions while amine that react via a p-system undergo oxidative C-H amination. Calculations and mechanistic experiments support a reaction pathway featuring oxidation to a phenoxyl radical cation followed by nucleophilic addition. The pyridinium catalyst aids phenol oxidation by formation of an EDA complex and also stabilizes the radical cation preventing back electron transfer.

The versatility of the resulting products, as well as phenols in general, is showcased through their applications in late-stage functionalizations. With this work, up to three hetero(arene) bonds can be forged from phenol starting materials to rapidly explore chemical space. Future aspirations involve the development of an efficient one-pot system for halogenation-amination, targeting difficult-to-activate C(sp^2)–H bonds.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental and computational procedures, product characterization, HRMS, and NMR spectral data (PDF).
FAIR data, includes the primary NMR FID files for compounds [**1c–g**, **1i**, **1j**, **1s**, **1t**, **2ac**, **3a–ag**, **4a–c**] (ZIP) and computational coordinates (XYZ).

AUTHOR INFORMATION

Corresponding Author

***Marisa C. Kozlowski** – *Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6223, United States*; orcid.org/0000-0002-4225-7125; Email: marisa@sas.upenn.edu

Authors

Matthew C. Carson – *Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6223, United States*; orcid.org/0000-0002-5821-8681

Cindy R. Liu – *Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6223, United States*; orcid.org/0009-0008-1367-473X

Yaning Liu – *Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6223, United States*; orcid.org/0009-0009-2555-6236

Notes

The authors declare no competing financial interest.

Acknowledgment

We are grateful to the NSF (CHE2102626) and the NIH (R35 GM131902) for financial support of this research. Partial instrumentation support was provided by the NIH and NSF (1S10RR023444, CHE-1827457, 3R01GM118510-03S1, 3R01GM087605-06S1), as well as the Vagelos Institute for Energy Science and Technology. We thank Dr. Charles W. Ross III (UPenn) for chromatographic and mass spectral method development, training, analyses, and data interpretation.

REFERENCES

(1) Li, Y.; Huang, Y.; Li, Z.; Sun, J. Recent Advances in Regioselective C–H Bond Functionalization of Free Phenols. *Molecules* **2023**, *28* (8), 3397.

(2) Tang, S.; Zeng, L.; Lei, A. Oxidative R^1–H/R^2–H Cross-Coupling with Hydrogen Evolution. *J. Am. Chem. Soc.* **2018**, *140* (41), 13128–13135.

(3) Kumar, R.; Taily, I. M.; Banerjee, P. Electrochemical Sulfinylation of Phenols with Sulfides: A Metal- and Oxidant-free Cross-coupling for the Synthesis of Aromatic Sulfoxides. *Chem. Commun.* **2023**, *59* (3), 310–313.

(4) Afanasyev, O. I.; Kuchuk, E.; Usanov, D. L.; Chusov, D. Reductive Amination in the Synthesis of Pharmaceuticals. *Chem. Rev.* **2019**, *119* (23), 11857–11911.

(5) Bariwal, J.; Van Der Eycken, E. C–N bond forming cross-coupling reactions: an overview. *Chem. Soc. Rev.* **2013**, *42* (24), 9283–9303.

(6) Rayadurgam, J.; Sana, S.; Sasikumar, M.; Gu, Q. Palladium Catalyzed C–C and C–N Bond Forming Reactions: An Update on the Synthesis of Pharmaceuticals from 2015–2020. *Org. Chem. Front.* **2021**, *8* (2), 384–414.

(7) Louillat, M.-L.; Patureau, F. W. Oxidative C–H amination reactions. *Chem. Soc. Rev.* **2014**, *43* (3), 901–910.

(8) Prier, C. K.; Rankic, D. A.; Macmillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113* (7), 5322–5363.

(9) Moschetta, E. G.; Cook, G. C.; Edwards, L. J.; Ischay, M. A.; Lei, Z.; Buono, F.; Lévesque, F.; Garber, J. A. O.; MacTaggart, M.; Sezen-Edmonds, M.; Cole, K. P.; Beaver, M. G.; Doerfler, J.; Opalka, S. M.; Liang, W.; Morse, P. D.; Miyake, N. Photochemistry in Pharmaceutical Development: A Survey of Strategies and Approaches to Industry-wide Implementation. *Org. Process Res. Dev.* **2024**, *ASAP*, 10.1021/acs.oprd.3c00499.

(10) Hu, K.; Niyazymbetov, M. E.; Evans, D. H. Nucleophilic aromatic substitution by paired electrosynthesis: Reactions of methoxy arenes with 1H-tetrazoles. *Tett. Lett.* **1995**, *36* (39), 7027–7030.

(11) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. Site-selective arene C-H amination via photoredox catalysis. *Science* **2015**, *349* (6254), 1326–1330.

(12) Zheng, Y.-W.; Chen, B.; Ye, P.; Feng, K.; Wang, W.; Meng, Q.-Y.; Wu, L.-Z.; Tung, C.-H. Photocatalytic Hydrogen-Evolution Cross-Couplings: Benzene C–H Amination and Hydroxylation. *J. Am. Chem. Soc*. **2016**, *138* (32), 10080–10083.

(13) Kokorekin, V. A.; Solomatin, Y. A.; Gening, M. L.; Petrosyan, V. A. Electrochemical $S_N{}^H$(An) functionalization of 1,2- and 1,4-dihydroxybenzenes. *Mendeleev Commun.* **2016**, *26* (6), 540–542.

(14) Margrey, K. A.; Mcmanus, J. B.; Bonazzi, S.; Zecri, F.; Nicewicz, D. A.. Predictive Model for Site-selective Aryl and Heteroaryl C–H Functionalization via Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139* (32), 11288–11299.

(15) Niu, L.; Yi, H,; Wang, S.; Liu, T.; Liu, J.; Lei, A. Photoinduced oxidant-free oxidative C–H/N–H cross-coupling between arenes and azoles. *Nat. Commun.* **2017**, 8, 14226.

(16) Zhang, L.; Liardet, L.; Luo, J.; Ren, D.; Grätzel, M.; Hu, X. Photoelectrocatalytic arene C–H amination. *Nat. Catal.* **2019**, 2, 366–373.

(17) Ruffoni, A.; Juliá, F.; Svejstrup, T. D.; Mcmillan, A. J.; Douglas, J. J.; Leonori, D. Practical and regioselective amination of arenes using alkyl amines. *Nat. Chem.* **2019**, *11* (5), 426–433.

(18) Pistritto, V. A.; Liu, S.; Nicewicz, D. A. Mechanistic Investigations into Amination of Unactivated Arenes via Cation Radical Accelerated Nucleophilic Aromatic Substitution. *J. Am. Chem. Soc.* **2022**, *144* (33), 15118–15131.

(19) Pistritto, V. A.; Schutzbach-Horton, M. E.; Nicewicz, D. A. Nucleophilic Aromatic Substitution of Unactivated Fluoroarenes Enabled by Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2020**, *142* (40), 17187–17194.

(20) Targos, K.; Williams, O. P.; Wickens, Z. K. Unveiling Potent Photooxidation Behavior of Catalytic Photoreductants. *J. Am. Chem. Soc.* **2021**, *143* (11), 4125–4132.

(21) Buglioni, L.; Beslać, M.; Noël, T. Dehydrogenative Azolation of Arenes in a Microflow Electrochemical Reactor. *J. Org. Chem.* **2021**, *86* (22), 16195–16203.

(22) Wortman, A. K.; Stephenson, C. R. EDA photochemistry: Mechanistic investigations and future opportunities. *Chem* **2023**, *9* (14), 2390–2415.

(23) a) Lasky, M. R.; Salvador, T. K.; Mukhopadhyay, S.; Remy, M. S.; Vaid, T. P.; Sanford, M. S. Photochemical C(sp^2)–H Pyridination via Arene–Pyridinium Electron Donor–Acceptor Complexes. *Angew. Chem. Int. Ed.* **2022**, *61* (46), e202208741. b) Fuks, E.; Huber, L.; Schinkel, T.; Trapp, O. Investigation of Straightforward, Photoinduced Alkylations of Electron-rich Heterocompounds with Electron-deficient Alkyl Bromides in the Sole Presence of 2,6-lutidine. *Eur. J. Org. Chem.* **2020**, *2020* (39), 6192–6198. c) Mcclain, E. J.; Monos, T. M.; Mori, M.; Beatty, J. W.; Stephenson, C. R. J. Design and Implementation of a Catalytic Electron Donor–acceptor Complex Platform for Radical Trifluoromethylation and Alkylation. *ACS Catal.* **2020**, *10* (21), 12636–12641.

(24) Zhao, Y.; Huang, B.; Yang, C.; Xia, W. Visible-Light-Promoted Direct Amination of Phenols via Oxidative Cross-Dehydrogenative Coupling Reaction. *Org. Lett.* **2016**, *18* (14), 3326–3329.

(25) Zhao, Y.; Huang, B.; Yang, C.; Li, B.; Gou, B.; Xia, W. Photocatalytic Cross-Dehydrogenative Amination Reactions between Phenols and Diarylamines. *ACS Catal.* **2017**, *7* (4), 2446–2451.

(26) Li, B. X.; Kim, D. K.; Bloom, S.; Huang, R. Y.-C.; Qiao, J. X.; Ewing, W. R.; Oblinsky, D. G.; Scholes, G. D.; Macmillan, D. W. C. Site-selective Tyrosine Bioconjugation via Photoredox Catalysis for Native-to-bioorthogonal Protein Transformation. *Nat. Chem.* **2021**, *13* (9), 902–908.

(27) Tang, S.; Wang, S.; Liu, Y.; Cong, H.; Lei, A. Electrochemical Oxidative C–H Amination of Phenols: Access to Triarylamine Derivatives. *Angew. Chem. Int. Ed.* **2018**, *57* (17), 4737–4741.

(28) Song, C.; Liu, K.; Wang, Z.; Ding, B.; Wang, S.; Weng, Y.; Chiang, C.-W.; Lei, A. Electrochemical Oxidation Induced Selective Tyrosine Bioconjugation for the Modification of Biomolecules. *Chem. Sci.* **2019**, *10* (34), 7982–7987.

(29) Wu, Y.-C.; Jiang, S.-S.; Song, R.-J.; Li, J.-H. A Metal- and Oxidizing-reagent-free Anodic Para-selective Amination of Anilines with Phenothiazines. *Chem. Commun.* **2019**, *55* (30), 4371–4374.

(30) Yu, J.; Moon, H. R.; Kim, S. Y.; Kim, J. N. Cross-Coupling of Phenothiazines with Phenols: *Para*-Selective Molecular Oxygen-assisted C(sp^2)–H/N–H Cross-Coupling. *Bull. Korean Chem. Soc.* **2015**, *36* (11), 2765–2768.

(31) Louillat-Habermeyer, M.; Jin, R.; Patureau, F. W. O_2-mediated Dehydrogenative Amination of Phenols. *Angew. Chem. Int. Ed.* **2015**, *54* (13), 4102–4104.

(32) Jin, R.; Patureau, F. W. Mild, Periodate-Mediated, Dehydrogenative C–N Bond Formation with Phenothiazines and Phenols. *Org. Lett.* **2016**, *18* (18), 4491–4493.

(33) Goswami, M.; Konkel, A.; Rahimi, M.; Louillat-Habermeyer, M.; Kelm, H.; Jin, R.; De Bruin, B.; Patureau, F. W. Mechanism of the Dehydrogenative Phenothiazination of Phenols. *Chem. Eur. J.* **2018**, *24* (46), 11936–11943.

(34) Jin, R.; Bub, C. L.; Patureau, F. W. Phenothiazinimides: Atom-efficient Electrophilic Amination Reagents. *Org. Lett.* **2018**, *20* (10), 2884–2887.

(35) Yang, Y.; Zhang, D.; Vessally, E. Direct Amination of Aromatic C–H Bonds with Free Amines. *Top. Curr. Chem.* **2020**, 378, 37.

(36) Cremer, C.; Eltester, M. A.; Bourakhouadar, H.; Atodiresei, I. L.; Patureau, F. W. Dehydrogenative C–H Phenochalcogenazination. *Org. Lett.* **2021**, *23* (9), 3243–3247.

(37) He, Y.; Li, Y.; Ma, X.; Zhou, X.; Huang, Y.; Sun, J. Aryliodonium Salt-Induced Regioselective Access to *meta*-Substituted Anilines by Arylation of Azoles. *J. Org. Chem.* **2024**, *ASAP*, 10.1021/acs.joc.3c02417.

(38) Feng, P.; Ma, G.; Chen, X.; Wu, X.; Lin, L.; Liu, P.; Chen, T. Electrooxidative and Regioselective C–H Azolation of Phenol and Aniline Derivatives. *Angew. Chem. Int. Ed.* **2019**, *58* (25), 8400–8404.

(39) Wang, X.; Wang, S.; Gao, Y.; Sun, H.; Liang, X.; Bu, F.; Abdelilah, T.; Lei, A. Oxidant-Induced Azolation of Electron-Rich Phenol Derivatives. *Org. Lett.* **2020**, *22* (14), 5429–5433.

(40) Bering, L.; D'Ottavio, L.; Sirvinskaite, G.; Antonchick, A. P. Nitrosonium Ion Catalysis: Aerobic, Metal-free Cross-dehydrogenative Carbon–heteroatom Bond Formation. *Chem. Commun.* **2018**, *54* (92), 13022–13025.

(41) Rostami, A.; Khakyzadeh, V.; Zolfigol, M. A.; Rostami, A. Co(II)-catalyzed regioselective clean and smooth synthesis of 2-(aryl/alkyl-thio)phenols *via* sp^2 C–H bond activation. *Mol. Catal.* **2018**, 452, 260–263.

(42) Khaef, S.; Rostami, A.; Khakyzadeh, V.; Zolfigol, M. A.; Taherpour, A. A.; Yarie, M. Regioselective *Ortho*-C–H sulfenylation of free phenols catalyzed by Co(II)-immobilized on silica-coated magnetic nanoparticles. *Mol. Catal.* **2020**, 484, 110772.

(43) Shin, N. Y.; Tsui, E.; Reinhold, A.; Scholes, G. D.; Bird, M. J.; Knowles, R. R. Radicals as Exceptional Electron-Withdrawing Groups: Nucleophilic Aromatic Substitution of Halophenols Via Homolysis-Enabled Electronic Activation. *J. Am. Chem. Soc.* **2022**, *144* (47), 21783–21790.

(44) Carson, M. C.; Liu, C. R.; Kozlowski, M. C. Synthesis of Phenol–Pyridinium Salts Enabled by Tandem Electron Donor–Acceptor Complexation and Iridium Photocatalysis. *J. Org. Chem.* **2024**, *89* (5), 3419–3429.

(45) Niederer, K. A.; Gilmartin, P. H.; Kozlowski, M. C. Oxidative Photocatalytic Homo- and Cross-coupling of Phenols: Nonenzymatic, Catalytic Method for Coupling Tyrosine. *ACS Catal.* **2020**, *10* (24), 14615–14623.

(46) Wu, J.; Kozlowski, M. C. Visible-Light-Induced Oxidative Coupling of Phenols and Alkenylphenols with a Recyclable, Solid Photocatalyst. *Org. Lett.* **2023**, *25* (6), 907–911.

(47) Ohkubo, K.; Fujimoto, A.; Fukuzumi, S. Visible-Light-Induced Oxygenation of Benzene by the Triplet Excited State of 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone. *J. Am. Chem. Soc.* **2013**, *135* (14), 5368–5371.

(48) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116* (17), 10075–10166.

(49) Engle, S. M.; Kirkner, T. R.; Kelly, C. B. Preparation of 2,4,5,6-Tetra(9H-carbazol-9-yl)isophthalonitrile. *Org. Synth.* **2019**, 96, 455–473.
(50) Fier, P. S.; Kim, S. Transition-Metal-Free C–N Cross-Coupling Enabled by a Multifunctional Reagent. *J. Am. Chem. Soc.* **2024**, *146* (10), 6476–6480.
(51) Zhou, H.; Mukherjee, P.; Liu, R.; Evrard, E.; Wang, D.; Humphrey, J. M.; Butler, T. W.; Hoth, L. R.; Sperry, J. B.; Sakata, S. K.; Helal, C. J.; am Ende, C. W. Introduction of a Crystalline, Shelf-Stable Reagent for the Synthesis of Sulfur(VI) Fluorides. *Org. Lett.* **2018**, *20* (3), 812–815.