OL | Organic Letters

pubs.acs.org/OrgLett Letter

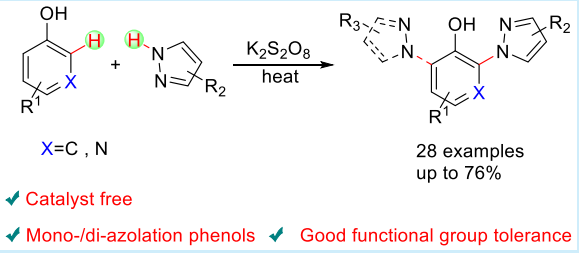
Oxidant-Induced Azolation of Electron-Rich Phenol Derivatives

Xiaoyu Wang,[§] Shengchun Wang,[§] Yiming Gao, He Sun, Xing'an Liang, Faxiang Bu, Takfaoui Abdelilah, and Aiwen Lei*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01796 Read Online

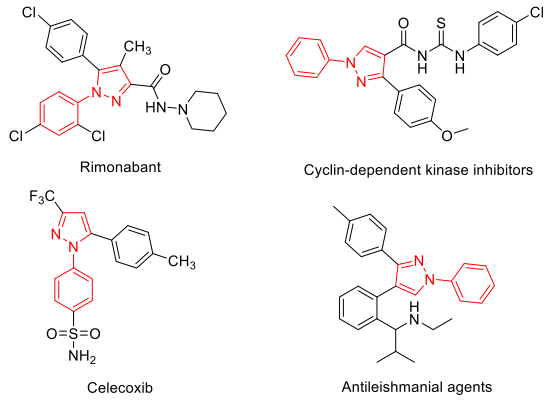
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Since *N*-arylazoles are widely present in natural products, pharmaceuticals, and functional materials, it is important to develop a simple and efficient synthetic method for the synthesis of *N*-arylazoles. Herein, an oxidant-induced intermolecular azolation of phenol derivatives was demonstrated under catalyst-free condition. Both monoazolation and diazolation of phenols can be successfully achieved via this practical and powerful method.



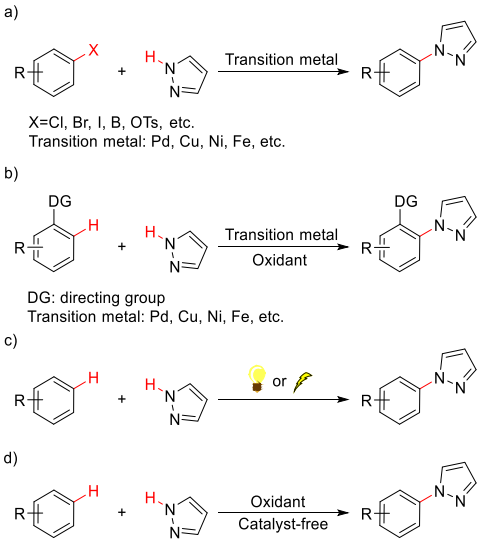
Amination of arenes has been recognized as one of the central issues in synthetic chemistry since the last century due to the unique physiological activity of arylamines.[1] Among these arylamines, *N*-arylazole scaffolds are ubiquitous structural units in biologically active molecules, agrochemicals, and drugs[2] such as rimonabant, celecoxib, and so on (Scheme 1),[3] whose synthesis drew much attention from chemists.

Scheme 1. Some Biologically Active Molecules with *N*-Arylazole Skeleton



The synthesis of *N*-arylazoles have been successfully realized by the transition-metal-catalyzed azolation reactions between azoles and aryl halides or aryl boronic acids (including Buchwald–Hartwig amination,[4] Ullmann-type amination,[5] and Chan–Evans–Lam reaction,[6] etc.) (Scheme 2a).[7] Assisted by a directing group, transition-metal-catalyzed dehydrogenative cross coupling has been developed over the past decades, avoiding the prefunctionalization of arenes (Scheme 2b).[8] Recently, the elegant photochemical and electrochemical studies have provided a novel strategy for arene azolation

Scheme 2. Synthesis of *N*-Arylazoles from Pyrazoles



facilitated by single-electron-transfer progress, where the radical cations of arene or *N*-centered radical usually serve as the key reactive intermediates (Scheme 2c).[9] Though there are several reports to synthesize *N*-arylazoles, an operationally simple method is still required. Herein, we present a simple and efficient synthetic protocol to construct *N*-arylazoles without catalyst (Scheme 2d).

Received: May 28, 2020

Inspired by oxidative-induced C−H bond activation strategies with simple synthetic operation,[10] we envisioned that the azolation of phenols can be realized through oxidant-induced activation of pyrazole with the corresponding radical of pyrazole as an intermediate. First, electron paramagnetic resonance (EPR) was used to gain important mechanistic information (Figure 1). To find a suitable oxidant that can

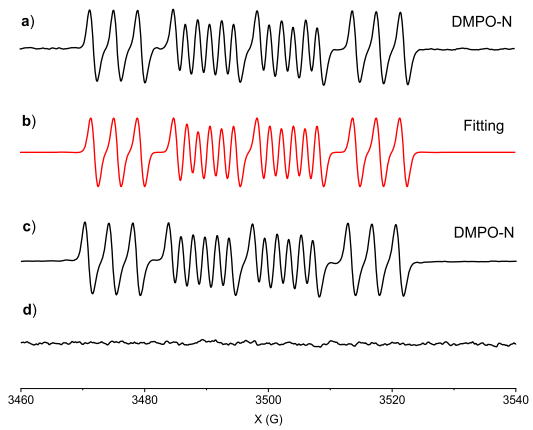


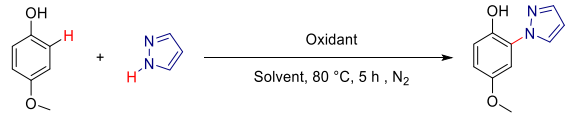
Figure 1. EPR experiment of $K_2S_2O_8$ and pyrazoles: (a) pyrazoles, $K_2S_2O_8$ and DMPO were added at 80 °C; (b) fitting result; (c) pyrazoles, 4-methoxyphenol, $K_2S_2O_8$ and DMPO were added at 80 °C; (d) pyrazoles, $K_2S_2O_8$ and DMPO were added at room temperature.

oxidize pyrazole to form a corresponding radical, different combinations of oxidants and pyrazoles were investigated (see details in Figure S3). When pyrazoles were treated with the cheap oxidant $K_2S_2O_8$ at 80 °C in MeCN, the *N*-centered radical trapped by 3,4-dihydro-2,2-dimethyl-2*H*-pyrrole 1-oxide (DMPO) was shown by EPR (Figure 1a, g = 2.0069, A_{N1} = 13.5 G, A_{N2} = 3.8 G, A_H = 15.5 G). The same radicals can be detected even with the addition of 4-methoxyphenol (Figure 1c). On the basis of these discoveries, a practical azolation of phenols under metal-free and catalyst-free condition is theoretically feasible.

Therefore, we chose 4-methoxyphenol and pyrazole as model substrates to investigate the reaction conditions using different oxidants, solvents, and loading of oxidants (Table 1). Gratifyingly, the azolation products were obtained in 75% yield with 2 equiv of $K_2S_2O_8$ at 80 °C in MeCN (entry 1). In accordance with the result of EPR study, the target product had not been detected at room temperature, which shows that the thermal activation of $K_2S_2O_8$ may be a start-up step (entry 2). In addition, other oxidants such as $(NH_4)_2S_2O_8$, selectfluor, DDQ, and TBHP (entry 3−6) were evidenced not as effective as $K_2S_2O_8$. Without oxidant, the azolation reaction cannot be achieved (entry 7). Subsequently various solvents were screened. Using DMF or DCE as solvents, no target product was detected. And trace azolation product was produced when EtOH or HFIP was selected as solvent (entries 8−11). When the amount of $K_2S_2O_8$ was increased to 2.5 equiv or decreased to 1.5 equiv, the reaction gave slightly worse results (entries 12 and 13). When an air atmosphere was used in place of nitrogen, a similar yield was observed (entry 14).

With the optimized conditions, the scope of the mono-azolation was explored among different functional groups substituted pyrazoles and phenols (Scheme 3). Various pyrazoles were satisfactory azolation reagents, providing the

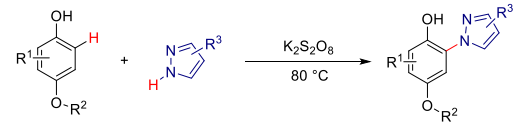
Table 1. Optimization of Reaction Conditions[a]

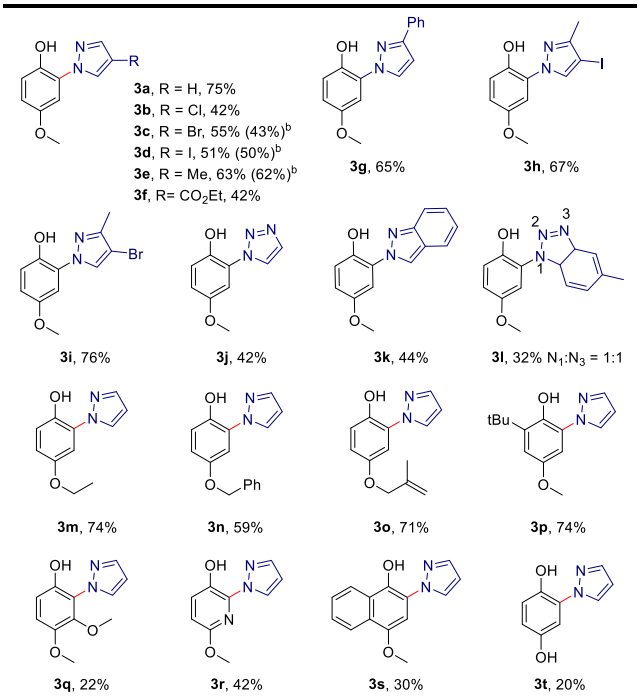


entry	solvent	oxidant	yield[b] (%)
1	MeCN	$K_2S_2O_8$	75
2[c]	MeCN	$K_2S_2O_8$	ND
3	MeCN	$(NH_4)_2S_2O_8$	31
4	MeCN	Selectfluor	32
5	MeCN	DDQ	30
6	MeCN	TBHP	ND
7	MeCN		ND
8	DMF	$K_2S_2O_8$	ND
9	EtOH	$K_2S_2O_8$	trace
10	DCE	$K_2S_2O_8$	ND
11	HFIP	$K_2S_2O_8$	trace
12[d]	MeCN	$K_2S_2O_8$	64
13[e]	MeCN	$K_2S_2O_8$	63
14[f]	MeCN	$K_2S_2O_8$	67

[a]Conditions: the reaction was carried out with 4-methoxyphenol **1a** (0.6 mmol), 1*H*-pyrazole **2a** (0.3 mmol), oxidant (0.6 mmol), 5 h, 3 mL of solvent, N_2. ND: not detected. [b]Isolated yield. [c]At room temperature. [d]1.5 equiv of oxidant was used. [e]2.5 equiv of oxidant was used. [f]The reaction was carried out under air.

Scheme 3. Scope of the Mono-azolation[a]





[a]Conditions: the reaction was carried out with phenols **1** (0.6 mmol), pyrazoles **2** (0.3 mmol), 5 h, 3 mL of MeCN, N_2. [b]Conditions: the reaction was carried out with phenols **1** (20 mmol), pyrazoles 2 (10 mmol), 5 h, 50 mL of MeCN, N_2.

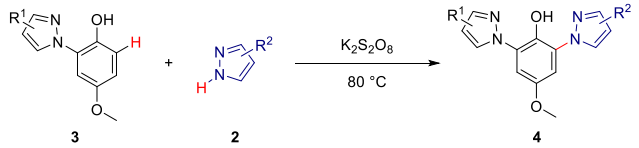
https://dx.doi.org/10.1021/acs.orglett.0c01796
Org. Lett. XXXX, XXX, XXX−XXX

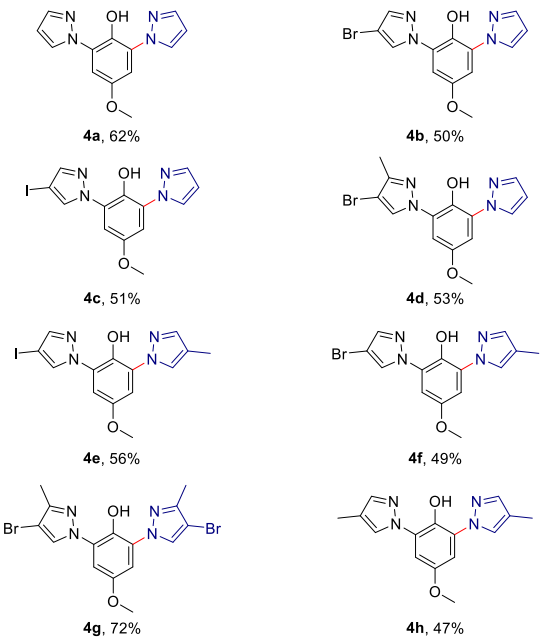
corresponding desired products (**3a**−**3i**) in good yields. In addition, triazole, indazole, and benzotriazole were compatible with this reaction system in moderate yields (**3j**−**3l**). Then different phenols were tested with the monoazolation reaction. Replacement of the 4-methoxy group with electron-donating substituents at the same position, such as ethoxy, benzyloxy, and (2-methylallyl)oxy, was tolerated in this reaction (**3m**−**3o**). Moreover, disubstituted phenols were investigated. The reaction of 2-*tert*-butyl-4-methoxyphenol reacted smoothly (**3p**), and 3,4-dimethoxyphenol proceeded in low yield and high site selectivity (**3q**). Remarkably, a good selective azolation of 6-methoxypyridin-3-ol **3r** was achieved. Besides phenols, 4-methoxy-1-naphthol was also suitable for achieving azolation (**3s**). Different from the previous reports,[9d] hydroquinone was tolerated in this oxidation-induced azolation reaction (**3t**). Furthermore, the gram-scale experiments were carried out, showing the utility of our protocol.

Interestingly, diazolation products were obtained when pyrazole was added in excess. However, the yield of diazolation phenol can only be isolated in 40% in one step (see details in Figure S4). In order to improve the reaction efficacy, the two-step synthesis method was used in which monoazolation products were selected as substrates to afford diazolation products under the standard reaction conditions (Scheme 4). With this method, both phenols disubstituted with the same pyrazole or different pyrazoles can be obtained smoothly (**4a**−**4h**).

To further explore the mechanism, preliminary kinetic studies were also carried out to determine the order of reaction components for the azolation reaction. As depicted in Figure 2a, the initial reaction rate depended on the concentration of

Scheme 4. Scope of the Di-azolation[a]





[a]Conditions: the reaction was carried out with **3** (0.6 mmol), **2** (0.3 mmol), 5 h, 3 mL of MeCN, N_2.

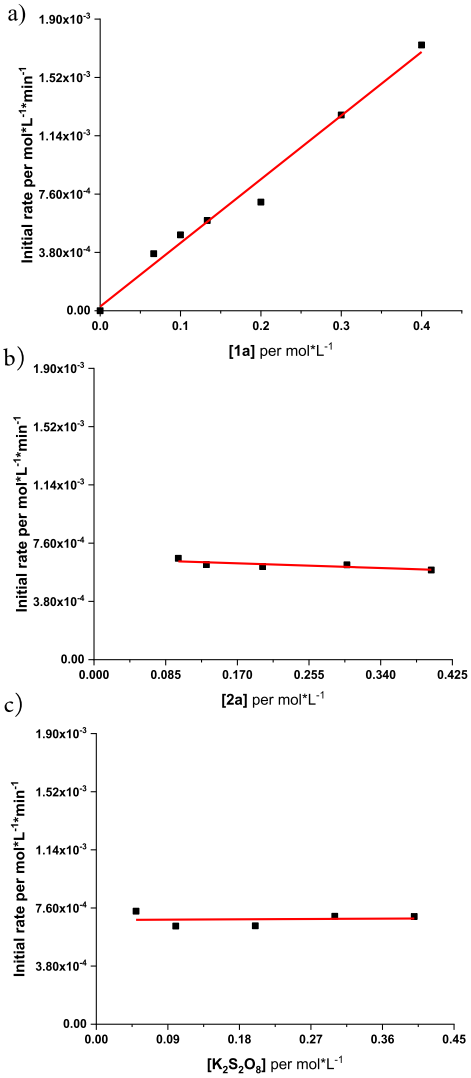
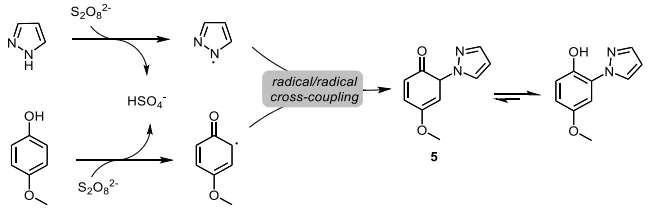


Figure 2. (a) Kinetic behavior of **1a**. (b) Kinetic behavior of **2a**. (c) Kinetic behavior of $K_2S_2O_8$.

the phenol, demonstrating first-order dependencies on phenol. Conversely, a zero-order reaction on pyrazole and $K_2S_2O_8$ is proved (Figure 2b,c). This result indicates that the activation of phenol is also critical to this reaction. In addition, initial EPR studies show that pyrazole can easily react with $K_2S_2O_8$ to produce the corresponding *N*-centered radical.

Based on the above-mentioned results, a possible mechanism of simultaneous activation of pyrazole and phenol is proposed (Scheme 5). Initially, $K_2S_2O_8$ thermally decomposes

Scheme 5. Proposed Mechanism



https://dx.doi.org/10.1021/acs.orglett.0c01796
Org. Lett. XXXX, XXX, XXX−XXX

to produce sulfate radical anion.[11] While sulfate radical anion oxidizes pyrazole to form the corresponding *N*-centered radical, it activates phenol to produce the corresponding *C*-centered radical. Then the intermediate **5** is obtained via a radical/radical cross-coupling and is further aromatized to form the final product.

In summary, we have developed an intermolecular azolation of phenol derivatives via oxidant-induced strategy under catalyst-free conditions. This method realizes mono-/diazolation of phenols, exhibiting a broad substrate scope and high functional group tolerance. This work provides an operationally simple strategy for achieving azolation reaction via oxidation-induced pyrazoles activation and shows potential as an alternative new avenue for further development of azolation transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01796.

Full experimental details and characterization data for all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Aiwen Lei − *National Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, P.R. China; Institute for Advanced Studies (IAS), College of Chemistry and Molecular Sciences Wuhan University, Wuhan 430072, P.R. China;* orcid.org/0000-0001-8417-3061; Email: aiwenlei@whu.edu.cn

Authors

Xiaoyu Wang − *National Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, P.R. China*

Shengchun Wang − *Institute for Advanced Studies (IAS), College of Chemistry and Molecular Sciences Wuhan University, Wuhan 430072, P.R. China*

Yiming Gao − *Institute for Advanced Studies (IAS), College of Chemistry and Molecular Sciences Wuhan University, Wuhan 430072, P.R. China*

He Sun − *Institute for Advanced Studies (IAS), College of Chemistry and Molecular Sciences Wuhan University, Wuhan 430072, P.R. China*

Xing'an Liang − *Institute for Advanced Studies (IAS), College of Chemistry and Molecular Sciences Wuhan University, Wuhan 430072, P.R. China*

Faxiang Bu − *Institute for Advanced Studies (IAS), College of Chemistry and Molecular Sciences Wuhan University, Wuhan 430072, P.R. China*

Takfaoui Abdelilah − *Institute for Advanced Studies (IAS), College of Chemistry and Molecular Sciences Wuhan University, Wuhan 430072, P.R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01796

Author Contributions

[§]X.W. and S.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21562026, 21762025, and 21702027) and the Natural Science Foundation of Jiangxi Province (20192ACBL20026).

■ REFERENCES

(1) Jiao, J.; Murakami, K.; Itami, K. Catalytic Methods for Aromatic C−H Amination: An Ideal Strategy for Nitrogen-Based Functional Molecules. *ACS Catal.* **2016**, *6*, 610−633.

(2) (a) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564−12649. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(3) Ansari, A.; Ali, A.; Asif, M. Shamsuzzaman, Review: biologically active pyrazole derivatives. *New J. Chem.* **2017**, *41*, 16−41.

(4) Hartwig, J. F. Carbon−Heteroatom Bond-Forming Reductive Eliminations of Amines, Ethers, and Sulfides. *Acc. Chem. Res.* **1998**, *31*, 852−860.

(5) (a) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Copper catalysed Ullmann type chemistry: from mechanistic aspects to modern development. *Chem. Soc. Rev.* **2014**, *43*, 3525−3550. (b) Monnier, F.; Taillefer, M. Catalytic C-C, C-N, and C-O Ullmann-type coupling reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954−6971.

(6) Hardouin Duparc, V.; Bano, G. L.; Schaper, F. Chan−Evans−Lam Couplings with Copper Iminoarylsulfonate Complexes: Scope and Mechanism. *ACS Catal.* **2018**, *8*, 7308−7325.

(7) (a) Okano, K.; Tokuyama, H.; Fukuyama, T. Copper-mediated aromatic amination reaction and its application to the total synthesis of natural products. *Chem. Commun.* **2014**, *50*, 13650−13663. (b) Taillefer, M.; Xia, N.; Ouali, A. Efficient iron/copper co-catalyzed arylation of nitrogen nucleophiles. *Angew. Chem., Int. Ed.* **2007**, *46*, 934−936. (c) Armstrong, A.; Collins, J. C. Direct azole amination: C-H functionalization as a new approach to biologically important heterocycles. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282−2285. (d) Buchwald, S. L.; Bolm, C. On the role of metal contaminants in catalyses with $FeCl_3$. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586−5587. (e) Carril, M.; SanMartin, R.; Dominguez, E. Palladium and copper-catalysed arylation reactions in the presence of water, with a focus on carbon-heteroatom bond formation. *Chem. Soc. Rev.* **2008**, *37*, 639−647. (f) Guo, D.; Huang, H.; Zhou, Y.; Xu, J.; Jiang, H.; Chen, K.; Liu, H. Ligand-free iron/copper cocatalyzed N-arylations of aryl halides with amines under microwave irradiation. *Green Chem.* **2010**, *12*, 276−281. (g) Ley, S. V.; Thomas, A. W. Modern synthetic methods for copper-mediated C(aryl)-O, C(aryl)-N, and C(aryl)-S bond formation. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449.

(8) (a) Li, Q.; Zhang, S. Y.; He, G.; Ai, Z.; Nack, W. A.; Chen, G. Copper-catalyzed carboxamide-directed ortho amination of anilines with alkylamines at room temperature. *Org. Lett.* **2014**, *16*, 1764−1767. (b) Henry, M. C.; McGrory, R.; Faggyas, R. J.; Mostafa, M. A. B.; Sutherland, A. One-pot ortho-amination of aryl C-H bonds using consecutive iron and copper catalysis. *Org. Biomol. Chem.* **2019**, *17*, 4629−4639. (c) Louillat, M. L.; Patureau, F. W. Oxidative C-H amination reactions. *Chem. Soc. Rev.* **2014**, *43*, 901−910. (d) Martinez, A. M.; Rodriguez, N.; Arrayas, R. G.; Carretero, J. C. Copper-catalyzed ortho-C-H amination of protected anilines with secondary amines. *Chem. Commun.* **2014**, *50*, 2801−2803. (e) Surry, D. S.; Buchwald, S. L. Biaryl phosphane ligands in palladium-catalyzed amination. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361.

(9) (a) Wang, J. H.; Lei, T.; Nan, X. L.; Wu, H. L.; Li, X. B.; Chen, B.; Tung, C. H.; Wu, L. Z. Regioselective Ortho Amination of an Aromatic C-H Bond by Trifluoroacetic Acid via Electrochemistry. *Org. Lett.* **2019**, *21*, 5581−5585. (b) Niu, L.; Yi, H.; Wang, S.; Liu, T.; Liu, J.; Lei, A. Photo-induced oxidant-free oxidative C-H/N-H cross-coupling between arenes and azoles. *Nat. Commun.* **2017**, *8*, 14226.

(c) Zhang, L.; Liardet, L.; Luo, J.; Ren, D.; Grätzel, M.; Hu, X. Photoelectrocatalytic arene C−H amination. *Nat. Catal.* **2019**, *2*, 366−373. (d) 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*, 8400−8404. (e) 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*, 426−433. (f) 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*, 10080−10083. (g) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. Site-selective arene C-H amination via photoredox catalysis. *Science* **2015**, *349*, 1326−1330. (h) Zhao, Y.; Huang, B.; Yang, C.; Xia, W. *Org. Lett.* **2016**, *18*, 3326−3329.

(10) (a) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent Advances in Radical C-H Activation/Radical Cross-Coupling. *Chem. Rev.* **2017**, *117*, 9016−9085. (b) Liu, Y.; Yi, H.; Lei, A. Oxidation-Induced C-H Functionalization: A Formal Way for C-H Activation. *Chin. J. Chem.* **2018**, *36*, 692−697. (c) Yi, H.; Tang, Z.; Bian, C.; Chen, H.; Qi, X.; Yue, X.; Lan, Y.; Lee, J. F.; Lei, A. Oxidation-induced C-H amination leads to a new avenue to build C-N bonds. *Chem. Commun.* **2017**, *53*, 8984−8987.

(11) Mandal, S.; Bera, T.; Dubey, G.; Saha, J.; Laha, J. K. Uses of $K_2S_2O_8$ in Metal-Catalyzed and Metal-Free Oxidative Transformations. *ACS Catal.* **2018**, *8*, 5085−5144.

https://dx.doi.org/10.1021/acs.orglett.0c01796
Org. Lett. XXXX, XXX, XXX−XXX