OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

C−H Pyridonation of (Hetero-)Arenes by Pyridinium Radical Cations

Julius Hillenbrand,[†,‡] Won Seok Ham,[†,§] and Tobias Ritter*[,†,‡,§]

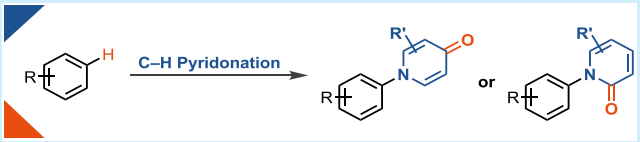
[†]Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany

[‡]Institute of Organic Chemistry, RWTH Aachen, Landoltweg 1, 52074 Aachen, Germany

[§]Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

Supporting Information

ABSTRACT: Pyridones are important heteroaromatic scaffolds found in natural products and pharmaceuticals and are, therefore, of major interest in organic synthetic chemistry. Here we report the first C−H pyridonation of unactivated (hetero-)arenes, providing a methodology to directly access *N*-aryl-2- and 4-pyridones. Generation of pyridinium radical cations through single-electron reduction allows for the synthesis of pyridones on structurally complex molecules.



Nitrogen heterocycles represent one of the most important structural scaffolds in pharmaceuticals and are found in 59% of all small-molecule drugs approved by the FDA.[1] Pyridine is the most commonly used aromatic heterocycle and has been extensively studied in terms of metabolism in vivo.[2,3] Oxidation or methylation pathways can produce highly toxic metabolites of pyridine.[2,3] *N*-Arylpyridones are less prone to oxidation or methylation pathways and are well recognized in medicinal chemistry for their diverse biological activities.[4−7] A large set of *N*-arylpyridone structures can be found in marketed drugs such as anti-inflammatory drug pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF).[8−11] However, significant challenges are encountered for installing pyridones in the presence of sensitive functional groups through traditional cross-coupling protocols. Due to the low nucleophilicity of 2- and 4-pyridones, forcing reaction conditions and an excess of the arene coupling partner are required.[12−15] C−H functionalization has been extensively used to functionalize pyridones via C−C bond formation (Figure 1),[16−25] but direct substitution of an aryl C−H bond with the nitrogen atom of a pyridone is unprecedented.

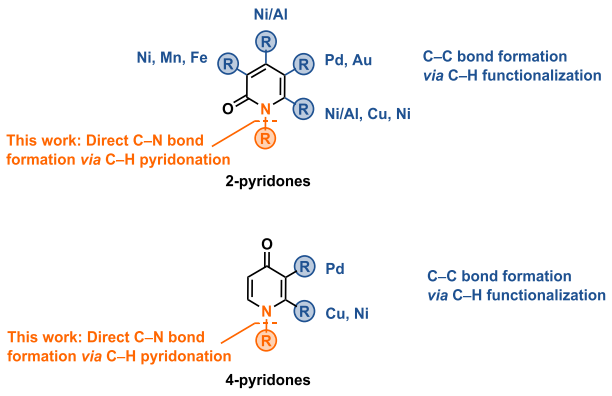


Figure 1. C−H functionalization on pyridones.

Here, we present the first direct C−H pyridonation reaction of (hetero-)arenes as the limiting reagent.

The traditional approach for the synthesis of *N*-arylpyridones involves copper-catalyzed coupling between 2- or 4-pyridones and a coupling partner such as an arylboronic acid,[12] an aryl stannane,[13] an aryl bismuth,[14] an aryl iodonium salt,[15] or an aryl halide.[26] However, due to the low nucleophilicity and the ambidentate nature of pyridones, such methods often require high temperatures[14,26] or excess of the arene coupling partner[12−15] or give mixtures of N-/O-arylated products.[14,15,26] *N*-Arylpyridones can also be prepared through ring construction including condensation reactions,[27,28] oxidative annulation,[29] metal-mediated cycloaddition,[30] or Vilsmeier−Haack cyclization.[31] Harsh reaction conditions and/or multistep procedures of the currently utilized methods limit the synthetic availability of *N*-arylpyridones.[27−31]

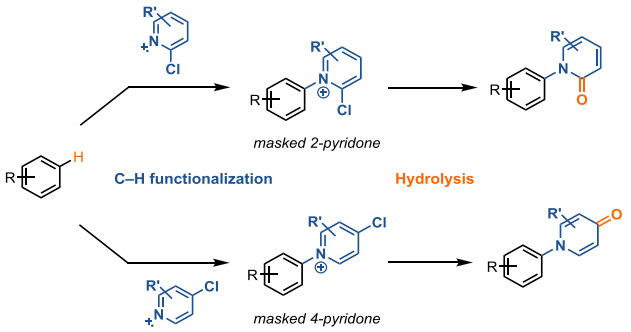
On the basis of our previous work on direct C−H amination of arenes,[32,33] we have evaluated different nitrogen electrophiles for addition to arenes. Earlier this year, Carreira and Togni as well as our laboratory have independently demonstrated the ability of pyridinium radical cations to react with arenes to afford *N*-arylpyridinium salts.[34,35] Here we show that 2- or 4-chloropyridinium radical cations can function as surrogates for the installation of 2- and 4-pyridones on (hetero-)arenes, respectively. Although we anticipated that chlorine-substituted pyridinium radical cations would display different spin density distributions when compared to the parent counterparts,[36] we identified novel reaction chemistry to access aryl chloropyridiniums, from which the corresponding *N*-aryl-2- or 4-pyridone compounds can be accessed upon hydrolysis (Scheme 1).[37,38] The method represents the first direct N-pyridonation of arenes.

We investigated the C−H functionalization step using 4-chloropyridine *N*-OTf under visible-light irradiation in the

Received: June 14, 2019

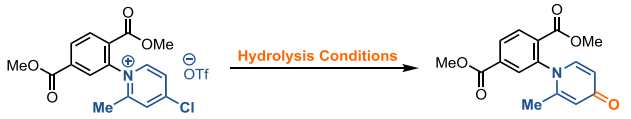
DOI: 10.1021/acs.orglett.9b02054
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. C−H Pyridonation to Access *N*-Aryl-2- and 4-Pyridones



presence of a photoredox catalyst. The pyridine-*N*-OTf reagent can be prepared in situ from commercially available 4-chloropyridine *N*-oxide and trifluoromethanesulfonic anhydride or synthesized on a multigram scale for isolation and storage under an inert atmosphere for at least six months. The optimum reaction condition for C−H functionalization of an arene as the limiting reagent requires 1.5 equiv of the *N*-OTf reagent and 5 mol % of $Ru(bpy)_3(PF_6)_2$ in acetonitrile at room temperature (Table S1). Irradiation with a 23 W household compact fluorescent lamp (CFL) led to complete substrate conversion within 24 h. Irradiation with a 70 W blue LED reduced the reaction time to 10 min but afforded the desired product in a lower yield (52%). Control experiments indicated that the photocatalyst and visible-light irradiation are crucial for the formation of the desired product. Subsequently, hydrolysis of the arylpyridinium salt to the desired *N*-aryl-4-pyridone can be accomplished (Table 1).[39]

Table 1. Optimization of the Hydrolysis Conditions for *N*-Aryl-4-pyridones

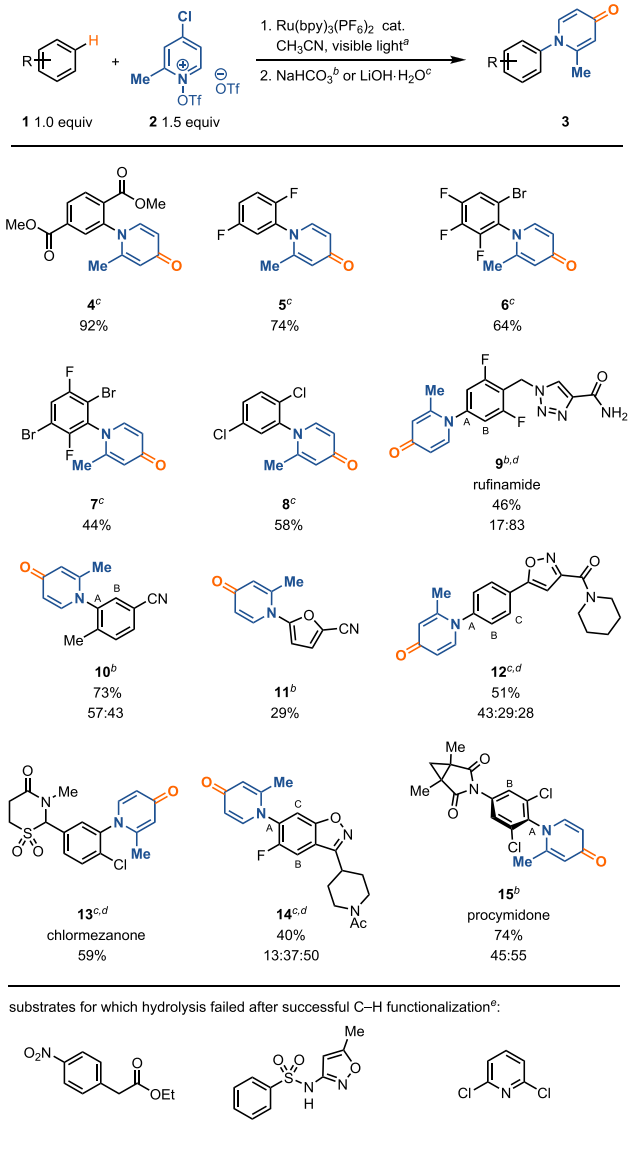


entry	reagents	equiv	solvent	T (°C)	time (h)	yield (%)
1	TMSOK	5	THF	23	4	–
2	KOH	10	MeOH	50	4	–
3	NaOH	10	CH_3CN:H_2O (1:1)	50	4	15
4	$NaHCO_3$	10	CH_3CN:H_2O (1:1)	50	4	30
5	$LiOH/H_2O_2$	5:10	THF:H_2O (3:1)	0-25	0.5	54
6	LiOH/*t*-BuOOH	5:10	THF:H_2O (3:1)	0-25	0.5	92
7	$NaHCO_3$/*t*-BuOOH	5:10	THF:H_2O (3:1)	0-25	4	90

In the subsequent hydrolysis, oxygen nucleophiles such as potassium trimethylsilanolate (TMSOK), KOH, NaOH, and $NaHCO_3$ resulted in either decomposition (entries 1 and 2) or low product yields (entries 3 and 4). As confirmed by LC-MS analysis, methyl esters are hydrolyzed under these reaction conditions, and competitive nucleophilic attack on the 2-position of the pyridinium salt provides the free aniline.[40,41] Inspired by the hydrolysis conditions for cleavage of chiral oxazolidone heterocycles (Evans auxiliaries), we used lithium hydroperoxide to provide the desired product in 54% yield (entry 5).[42,43] Substituting hydrogen peroxide with *tert*-butyl hydroperoxide gave the *N*-aryl-4-pyridone in 92% yield (entry 6).[44] Using $NaHCO_3$ instead of LiOH base increased the reaction time (4 h) but gave the product in comparable yield (90%) (entry 7). We reasoned that the bulky oxygen nucleophile allows for the regioselective attack on the less hindered γ-position of the pyridinium salt.

The optimized reaction conditions proved effective for introduction of the 4-pyridone motif on a range of diverse aromatics (Scheme 2, top), while the attempted hydrolysis reactions for certain substrates (Scheme 2, bottom) led to low conversion or compound decomposition. Disubstituted arenes afforded the corresponding *N*-aryl-4-pyridones **4**, **5**, **8**, and **10** in 58−92% yields. Highly electron-deficient aromatics (such as 1,4-dimethyl terephthalate) can be efficiently functionalized,

Scheme 2. C−H Pyridonation of 2-Methyl-4-pyridone with Various (Hetero-)arenes



[a]Reaction conditions: arene (0.4 mmol), $Ru(bpy)_3(PF_6)_2$ (5 mol %), 23 W CFL, CH_3CN (0.2 M), 23−25 °C, 24 h. [b]Hydrolysis conditions with $NaHCO_3$ (5−10 equiv), *t*-BuOOH (10 equiv), THF:H_2O (3:1), 0 to 25 °C. [c]Hydrolysis with $LiOH·H_2O$ (4−5 equiv) and *t*-BuOOH (10 equiv) in THF:H_2O (3:1), 0 to 25 °C. [d]TfOH (1.1 equiv). [e]See Supporting Information (S40−S46).

DOI: 10.1021/acs.orglett.9b02054
Org. Lett. XXXX, XXX, XXX−XXX

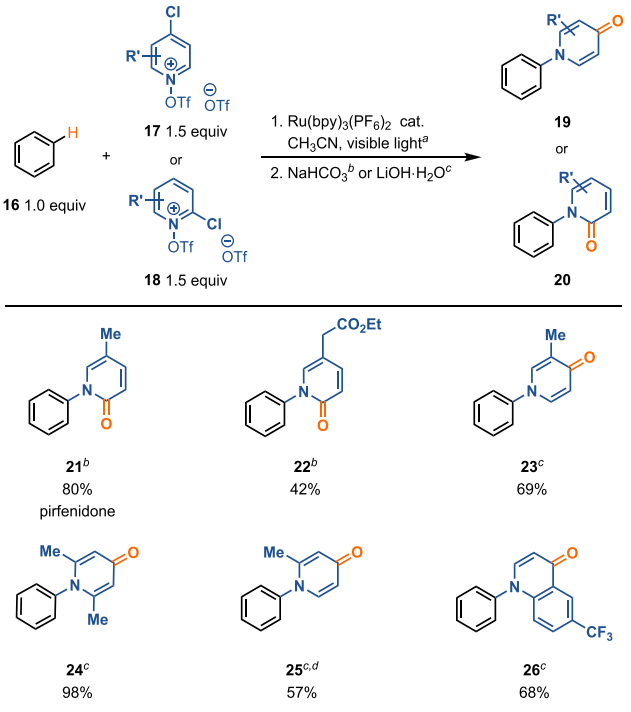
whereas many other modern C−H amination reactions can only functionalize electron-rich carboarenes.[45−59] Pyridonation of halogen-substituted arenes allowed efficient syntheses of **6** and **7**, the access to which would be challenging via traditional cross-coupling protocols. The reaction conditions also proved to be compatible with structurally complex substrates, such as rufinamide, procymidone, and chlormezanone, which are marketed drugs or agrochemicals. Late-stage functionalization of those molecules furnished the pyridone analogues **9**, **12**, **13**, **14**, and **15** in 40−74% yields, demonstrating that our methodology efficiently complements traditional pyridonation reactions.

Aryl C−H pyridonation of drug-like molecules that generates a broad range of constitutional isomers can be beneficial for drug discovery, and it allows for rapid exploration of structure−activity relationships.[60,61] Our reaction is capable of functionalizing all available aryl C−H bonds with the following exceptions: (1) Basic functional groups were protonated in situ with a stoichiometric amount of trifluoromethanesulfonic acid to suppress reagent decomposition. Therefore, basic N-heterocycles become deactivated toward functionalization (**9** and **12**). (2) Five-membered heteroarenes often exhibit a pronounced electronic bias favoring selective C5-functionalization (**11**). (3) Aryl C−H bonds *ortho* to substituents with high steric hindrance are not functionalized (**13**).

We then evaluated several 2- and 4-chloropyridine *N*-OTf reagents for C−H pyridonation reactions (Scheme 3). Hydrolysis of the corresponding *N*-phenyl-chloropyridinium salts can be achieved by simply adding $NaHCO_3$ (10 equiv) and H_2O (1 equiv) in a one-pot sequence. 5-Methyl-2-pyridonation of benzene afforded an antifibrotic agent pirfenidone (**21**) in 80% yield. An ester functionality tolerated the basic hydrolysis conditions for the synthesis of *N*-aryl-2-pyridone **22**. Mono- and dimethyl-substituted 4-pyridonation reagents generally proved efficient (**23**, **24**, and **25**). Extension of this methodology to install quinolones directly can be achieved with electron-deficient quinolinium reagents. The C−H functionalization provides the corresponding arylquinolinium salt, which upon hydrolysis furnishes the *N*-phenyl-4-quinolone **26** in 68% yield.[62,63] It is particularly noteworthy that our direct C−H pyridonation is a fragment coupling, in which both partners can be varied, enabling fast structural diversification.

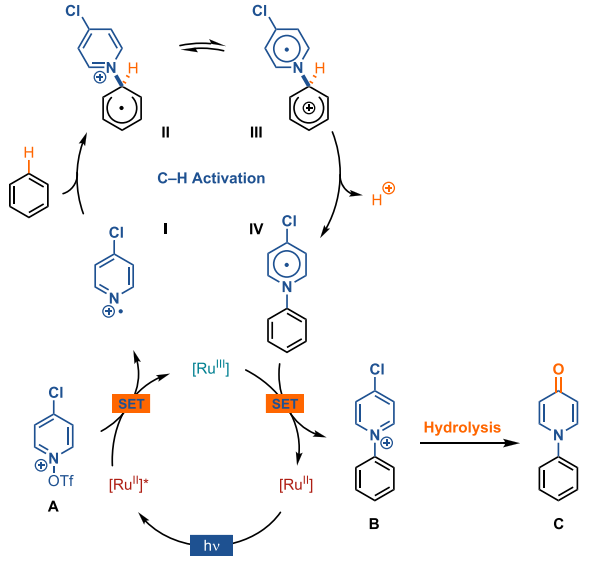
The proposed mechanism for the C−H pyridonation is outlined in Scheme 4.[34,35,64] Excitation of the photocatalyst

Scheme 3. C−H Pyridonation of Benzene with Various 2- and 4-Pyridones



[a]Reaction conditions: arene (0.4 mmol), $Ru(bpy)_3(PF_6)_2$ (5 mol %), 23 W CFL, CH_3CN (0.2 M), 23−25 °C, 24 h. [b]Hydrolysis with $NaHCO_3$ (10 equiv) in CH_3CN:H_2O (1:1), 50 °C. [c]Hydrolysis with $NaHCO_3$ (5−10 equiv) or $LiOH·H_2O$ (5 equiv) and *t*-BuOOH (10 equiv) in THF:H_2O (3:1), 0 to 25 °C. [d]1.0 mmol scale.

Scheme 4. Proposed Mechanism for C−H Pyridonation to Access *N*-Aryl-4-pyridones[a]



[a]Triflate (−OTf) anions were omitted for clarity.

$Ru(bpy)_3(PF_6)_2$ under visible-light irradiation produces a long-lived (1100 ns) photoexcited state, $[Ru^{II}]^*$.[65] Single-electron reduction of reagent **A** (onset reduction potential = 0.23 V vs saturated calomel electrode) is hypothesized to generate the pyridinium σ-radical cation (**I**) and $[Ru^{III}]$. C−N bond formation by the addition of the pyridinium radical cation (**I**) to an arene would afford the distonic radical **II** and/or **III**. Facile deprotonation and subsequent single-electron oxidation by the oxidized photocatalyst would then lead to the positively charged arylpyridinium salt **B**,[66] which upon hydrolysis can be converted into the corresponding *N*-arylpyridone **C**.

In summary, we have developed the first C−H pyridonation reaction that can introduce 2- or 4-pyridones to (hetero-)arenes. Generation of chloropyridinium radical cations through photoredox catalysis allows for the functionalization of structurally complex molecules and therefore renders our method useful for late-stage modification.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02054.

DOI: 10.1021/acs.orglett.9b02054
Org. Lett. XXXX, XXX, XXX−XXX

Detailed experimental procedures and spectroscopic characterization (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: ritter@mpi-muelheim.mpg.de.

ORCID

Won Seok Ham: 0000-0002-6239-5795

Tobias Ritter: 0000-0002-6957-450X

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank C. Farés, P. Philipps, and C. Wirtz (MPI KOFO) for assistance with NMR structural assignment, as well as S. Marcus and D. Kampen (MPI KOFO) for mass spectroscopy analysis. We thank Dr. Olaf Rüdiger (MPI for chemical energy conversion) for providing the electrochemical setup. We thank the Max-Planck-Institut für Kohlenforschung and UCB Pharma for funding. W.H. thanks the Kwanjeong Educational Foundation for funding.

REFERENCES

(1) 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 pharamceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(2) Carlson, G. P. Comparison of the effects of pyridine and its metabolites on rat liver and kidney. *Toxicol. Lett.* **1996**, *85*, 173−178.

(3) Pryde, D. C.; Dalvie, D.; Hu, Q.; Jones, P.; Obach, R. S.; Tran, T. D. Aldehyde Oxidase: An Enzyme of Emerging Importance in Drug Discovery. *J. Med. Chem.* **2010**, *53*, 8441−8460.

(4) Murray, K. J.; Eden, R. J.; Dolan, J. S.; Grimsditch, D. C.; Stutchbury, C. A.; Patel, B.; Knowles, A.; Worby, A.; Lynham, J. A.; Coates, W. J. Citation for: The effect of SK&F 95654, a novel phosphodiesterase inhibitor, on cardiovascular, respiratory and platelet function. *Br. J. Pharmacol.* **1992**, *107*, 463−470.

(5) Hanada, T.; Hashizume, Y.; Tokuhara, N.; Takenaka, O.; Kohmura, N.; Ogasawara, A.; Hatakeyama, S.; Ohgoh, M.; Ueno, M.; Nishizawa, Y. Perampanel: A novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. *Epilepsia* **2011**, *52*, 1331−1340.

(6) Hibi, S.; Ueno, K.; Nagato, S.; Kawano, K.; Ito, K.; Norimine, Y.; Takenaka, O.; Hanada, T.; Yonaga, M. Discovery of 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile (Perampanel): A Novel, Noncompetitive α-Amino-3-hydroxy-5-methyl-4-isoxazolepropanoic Acid (AMPA) Receptor Antagonist. *J. Med. Chem.* **2012**, *55*, 10584−10600.

(7) Harrison, S. T.; Poslusney, M. S.; Mulhearn, J. J.; Zhao, Z.; Kett, N. R.; Schubert, J. W.; Melamed, J. Y.; Allison, T. J.; Patel, S. B.; Sanders, J. M.; Sharma, S.; Smith, R. F.; Hall, D. L.; Robinson, R. G.; Sachs, N. A.; Hutson, P. H.; Wolkenberg, S. E.; Barrow, J. C. Synthesis and Evaluation of Heterocyclic Catechol Mimics as Inhibitors of Catechol-O-methyltransferase (COMT). *ACS Med. Chem. Lett.* **2015**, *6*, 318−323.

(8) Murray, K. J.; Eden, R. J.; Dolan, J. S.; Grimsditch, D. C.; Stutchbury, C. A.; Patel, B.; Knowles, A.; Worby, A.; Lynham, J. A.; Coates, W. J. The effect of SK&F 95654, a novel phosphodiesterase inhibitor, on cardiovascular, respiratory and platelet function. *Br. J. Pharmacol.* **1992**, *107*, 463−470.

(9) Raghu, G.; Johnson, W. C.; Lockhart, D.; Mageto, Y. Treatment of Idiopathic Pulmonary Fibrosis with a New Antifibrotic Agent, Pirfenidone. *Am. J. Respir. Crit. Care Med.* **1999**, *159*, 1061−1069.

(10) Selness, S. R.; Devraj, R. V.; Devadas, B.; Walker, J. K.; Boehm, T. L.; Durley, R. C.; Shieh, H.; Xing, L.; Rucker, P. V.; Jerome, K. D.; Benson, A. G.; Marrufo, L. D.; Madsen, H. M.; Hitchcock, J.; Owen, T. J.; Christie, L.; Promo, M. A.; Hickory, B. S.; Alvira, E.; Naing, W.; Blevis-Bal, R.; Messing, D.; Yang, J.; Mao, M. K.; Yalamanchili, G.; Vonder Embse, R.; Hirsch, J.; Saabye, M.; Bonar, S.; Webb, E.; Anderson, G.; Monahan, J. B. Discovery of PH-797804, a highly selective and potent inhibitor of p38 MAP kinase. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4066−4071.

(11) Richeldi, L.; Yasothan, U.; Kirkpatrick, P. Pirfenidone. *Nat. Rev. Drug Discovery* **2011**, *10*, 489−490.

(12) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *N*-aryl heterocycles via coupling reactions with arylboronic acids. *Tetrahedron* **1999**, *55*, 12757−12770.

(13) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. Copper-promoted C−N bond cross-coupling with phenylstannane. *Tetrahedron Lett.* **2002**, *43*, 3091−3094.

(14) Ikegai, K.; Nagata, Y.; Mukaiyama, T. N-Arylation of Pyridin-2(1H)-ones with Pentavalent Organobismuth Reagents under Copper-Free Conditions. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 761−767.

(15) Jung, S.-H.; Sung, D.-B.; Park, C.-H.; Kim, W.-S. Copper-Catalyzed N-Arylation of 2-Pyridones Employing Diaryliodonium Salts at Room Temperature. *J. Org. Chem.* **2016**, *81*, 7717−7724.

(16) Hirano, K.; Miura, M. A lesson for site-selective C-H functionalization on 2-pyridones: radical, organometallic, directing group and steric controls. *Chem. Sci.* **2018**, *9*, 22−32.

(17) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. Direct Alkenylation and Alkylation of Pyridone Derivatives by Ni/AlMe3 Catalysis. *J. Am. Chem. Soc.* **2009**, *131*, 15996−15997.

(18) Chen, Y.; Wang, F.; Jia, A.; Li, X. Palladium-catalyzed selective oxidative olefination and arylation of 2-pyridones. *Chem. Sci.* **2012**, *3*, 3231−3236.

(19) Chen, F.; Feng, Z.; He, C.-Y.; Wang, H.-Y.; Guo, Y.-l.; Zhang, X. Pd-Catalyzed Dehydrogenative Cross-Coupling of Polyfluoroarenes with Heteroatom-Substituted Enones. *Org. Lett.* **2012**, *14*, 1176−1179.

(20) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. Nickel-Catalyzed Direct Alkylation of Heterocycles with α-Bromo Carbonyl Compounds: C3-Selective Functionalization of 2-Pyridones. *Chem. - Eur. J.* **2013**, *19*, 7691−7695.

(21) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. Manganese-Mediated C3-Selective Direct Alkylation and Arylation of 2-Pyridones with Diethyl Malonates and Arylboronic Acids. *J. Org. Chem.* **2014**, *79*, 1377−1385.

(22) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. Copper-Mediated C6-Selective Dehydrogenative Heteroarylation of 2-Pyridones with 1,3-Azoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 10784−10788.

(23) Modak, A.; Rana, S.; Maiti, D. Iron-Catalyzed Regioselective Direct Arylation at the C-3 Position of *N*-Alkyl-2-pyridone. *J. Org. Chem.* **2015**, *80*, 296−303.

(24) Li, Y.; Xie, F.; Li, X. Formal Gold- and Rhodium-Catalyzed Regiodivergent C−H Alkynylation of 2-Pyridones. *J. Org. Chem.* **2016**, *81*, 715−722.

(25) Diesel, J.; Finogenova, A. M.; Cramer, N. Nickel-Catalyzed Enantioselective Pyridone C−H Functionalizations Enabled by a Bulky *N*-Heterocyclic Carbene Ligand. *J. Am. Chem. Soc.* **2018**, *140*, 4489−4493.

(26) Altman, R. A.; Buchwald, S. L. Cu-Catalyzed *N*- and *O*-Arylation of 2-, 3-, and 4-Hydroxypyridines and Hydroxyquinolines. *Org. Lett.* **2007**, *9*, 643−646.

(27) Smirnoff, A. P. Über die Konstitution von *N*-Arylderivaten des 4(γ)-Pyridons. *Helv. Chim. Acta* **1921**, *4*, 599−612.

(28) Tan, S.-F.; Ang, K.-P.; Jayachandran, H. Acetylpyran-2,6-diones: tautomeric enolic forms, spectral properties, and reactions with primary amines. *J. Chem. Soc., Perkin Trans. 2* **1986**, *2*, 973−979.

(29) Ackermann, L.; Lygin, A. V.; Hofmann, N. Ruthenium-Catalyzed Oxidative Synthesis of 2-Pyridones through C−H/N−H Bond Functionalizations. *Org. Lett.* **2011**, *13*, 3278−3281.

(30) Yamamoto, Y.; Takagishi, H.; Itoh, K. Ruthenium(II)-Catalyzed Cycloaddition of 1,6-Diynes with Isocyanates Leading to Bicyclic Pyridones. *Org. Lett.* **2001**, *3*, 2117−2119.

DOI: 10.1021/acs.orglett.9b02054
Org. Lett. XXXX, XXX, XXX−XXX

(31) Xiang, D.; Wang, K.; Liang, Y.; Zhou, G.; Dong, D. A Facile and Efficient Synthesis of Polyfunctionalized Pyridin-2(1*H*)-ones from *β*-Oxo Amides under Vilsmeier Conditions. *Org. Lett.* **2008**, *10*, 345−348.
(32) Boursalian, G. B.; Ngai, M.-Y.; Hojczyk, K. N.; Ritter, T. Pd-Catalyzed Aryl C−H Imidation with Arene as the Limiting Reagent. *J. Am. Chem. Soc.* **2013**, *135*, 13278−13281.
(33) Boursalian, G. B.; Ham, W. S.; Mazzotti, A. R.; Ritter, T. Charge-transfer-directed radical substitution enables para-selective C−H functionalization. *Nat. Chem.* **2016**, *8*, 810−815.
(34) Rössler, S. L.; Jelier, B. J.; Tripet, P. F.; Shemet, A.; Jeschke, G.; Togni, A.; Carreira, E. M. Pyridyl Radical Cation for C−H Amination of Arenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 526−531.
(35) Ham, W.; Hillenbrand, J.; Jacq, J.; Genicot, C.; Ritter, T. Divergent Late-Stage (Hetero)Aryl C−H Amination by the Pyridinium Radical Cation. *Angew. Chem., Int. Ed.* **2019**, *58*, 532−536.
(36) Rao, D. N. R.; Eastland, G. W.; Symons, M. C. R. Radical cations of substituted pyridines formed by radiolysis. An electron spin resonance study. *J. Chem. Soc., Faraday Trans. 1* **1984**, *80*, 2803−2815.
(37) Liveris, M.; Miller, J. 654. The S_N mechanism in aromatic compounds. Part XXVIII. Reactivity in the pyridine ring system. *J. Chem. Soc.* **1963**, 3486−3492.
(38) Johnson, R. M. Nucleophilic displacements in substituted pyridine *N*-oxides. Part I. Kinetics of the reactions between sodium ethoxide and 2- and 4-bromo-, 4-chloro-, 2-, 3-, and 4-nitro-, 4-chloro-3,5-dimethyl-, and 3,5-dimethyl-4-nitro-pyridine 1-oxide in anhydrous ethanol. *J. Chem. Soc. B* **1966**, 1058−1061.
(39) Cheung, P. K.; Horhant, D.; Bandy, L. E.; Zamiri, M.; Rabea, S. M.; Karagiosov, S. K.; Matloobi, M.; McArthur, S.; Harrigan, P. R.; Chabot, B.; Grierson, D. S. A Parallel Synthesis Approach to the Identification of Novel Diheteroarylamide-Based Compounds Blocking HIV Replication: Potential Inhibitors of HIV-1 Pre-mRNA Alternative Splicing. *J. Med. Chem.* **2016**, *59*, 1869−1879.
(40) Zincke, T.; Heuser, G.; Möller, W. I. Ueber Dinitrophenylpyridiniumchlorid und dessen Umwandlungsproducte. *Justus Liebigs Ann. Chem.* **1904**, *333*, 296−345.
(41) Li, J. J. *Name Reactions: A Collection of Detailed Reaction Mechanisms*; Springer: Berlin, Heidelberg, 2003; pp 10−10.
(42) Evans, D. A.; Britton, T. C.; Ellman, J. A. Contrasteric carboximide hydrolysis with lithium hydroperoxide. *Tetrahedron Lett.* **1987**, *28*, 6141−6144.
(43) Cantrell, W. R.; Bauta, W. E.; Engles, T. Hydrogen peroxide promoted hydroxylation of haloarenes and heteroarenes. *Tetrahedron Lett.* **2006**, *47*, 4249−4251.
(44) Makosza, M.; Sienkiewicz, K. Hydroxylation of nitroarenes with alkylhydroperoxide anions via vicarious nucleophilic substitution of hydrogen. *J. Org. Chem.* **1990**, *55*, 4979−4981.
(45) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147−1169.
(46) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. Intermolecular Oxidative C−N Bond Formation under Metal-Free Conditions: Control of Chemoselectivity between Aryl sp^2 and Benzylic sp^3 C−H Bond Imidation. *J. Am. Chem. Soc.* **2011**, *133*, 16382−16385.
(47) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. Metal-Free Intermolecular Oxidative C−N Bond Formation via Tandem C−H and N−H Bond Functionalization. *J. Am. Chem. Soc.* **2011**, *133*, 19960−19965.
(48) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C−H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788−802.
(49) Morofuji, T.; Shimizu, A.; Yoshida, J.-i. Electrochemical C−H Amination: Synthesis of Aromatic Primary Amines via *N*-Arylpyridinium Ions. *J. Am. Chem. Soc.* **2013**, *135*, 5000−5003.
(50) Foo, K.; Sella, E.; Thomé, I.; Eastgate, M. D.; Baran, P. S. A Mild, Ferrocene-Catalyzed C−H Imidation of (Hetero)Arenes. *J. Am. Chem. Soc.* **2014**, *136*, 5279−5282.
(51) Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. N-Acyloxyphthalimides as Nitrogen Radical Precursors in the Visible Light Photocatalyzed Room Temperature C−H Amination of Arenes and Heteroarenes. *J. Am. Chem. Soc.* **2014**, *136*, 5607−5610.
(52) Greulich, T. W.; Daniliuc, C. G.; Studer, A. N-Aminopyridinium Salts as Precursors for *N*-Centered Radicals − Direct Amidation of Arenes and Heteroarenes. *Org. Lett.* **2015**, *17*, 254−257.
(53) Kawakami, T.; Murakami, K.; Itami, K. Catalytic C−H Imidation of Aromatic Cores of Functional Molecules: Ligand-Accelerated Cu Catalysis and Application to Materials- and Biology-Oriented Aromatics. *J. Am. Chem. Soc.* **2015**, *137*, 2460−2463.
(54) 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.
(55) Davies, J.; Svejstrup, T. D.; Fernandez Reina, D.; Sheikh, N. S.; Leonori, D. Visible-Light-Mediated Synthesis of Amidyl Radicals: Transition-Metal-Free Hydroamination and *N*-Arylation Reactions. *J. Am. Chem. Soc.* **2016**, *138*, 8092−8095.
(56) Xie, W.; Yoon, J. H.; Chang, S. (NHC)Cu-Catalyzed Mild C−H Amidation of (Hetero)arenes with Deprotectable Carbamates: Scope and Mechanistic Studies. *J. Am. Chem. Soc.* **2016**, *138*, 12605−12614.
(57) Legnani, L.; Prina Cerai, G.; Morandi, B. Direct and Practical Synthesis of Primary Anilines through Iron-Catalyzed C−H Bond Amination. *ACS Catal.* **2016**, *6*, 8162−8165.
(58) Paudyal, M. P.; Adebesin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z.; Kürti, L.; Falck, J. R. Dirhodium-catalyzed C-H arene amination using hydroxylamines. *Science* **2016**, *353*, 1144−1147.
(59) Margrey, K. A.; Levens, A.; Nicewicz, D. A. Direct Aryl C−H Amination with Primary Amines Using Organic Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 15644−15648.
(60) Parsons, A. T.; Buchwald, S. L. A radical approach to diversity. *Nature* **2011**, *480*, 184−185.
(61) Nagib, D. A.; MacMillan, D. W. C. Trifluoromethylation of arenes and heteroarenes by means of photoredox catalysis. *Nature* **2011**, *480*, 224−228.
(62) Meth-Cohn, O.; Taylor, D. L. The reverse vilsmeier approach to the synthesis of quinolines, quinolinium salts and quinolones. *Tetrahedron* **1995**, *51*, 12869−12882.
(63) Seixas, R. S. G. R.; Silva, A. M. S.; Alkorta, I. An experimental NMR and computational study of 4-quinolones and related compounds. *Monatsh. Chem.* **2011**, *142*, 731−742.
(64) Jelier, B. J.; Tripet, P. F.; Pietrasiak, E.; Franzoni, I.; Jeschke, G.; Togni, A. Radical Trifluoromethoxylation of Arenes Triggered by a Visible-Light-Mediated N−O Bond Redox Fragmentation. *Angew. Chem., Int. Ed.* **2018**, *57*, 13784−13789.
(65) 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*, 5322−5363.
(66) The quantum yield of aryl C−H substitution by a chloropyridinium radical cation is below unity. Moreover, our reaction does not proceed in the dark after a short period of light irradiation, supporting against the presence of chain-transfer processes. See the Supporting Information.

DOI: 10.1021/acs.orglett.9b02054
Org. Lett. XXXX, XXX, XXX−XXX