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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c03537 • Publication Date (Web): 23 Apr 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

A Multifunctional Reagent Designed for the Site-Selective Amination of Pyridines

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Supporting Information Placeholder

ABSTRACT: We report the development of a multifunctional reagent for the direct conversion of pyridines to Boc-protected 2-aminopyridines with exquisite site- and chemoselectivity. The novel reagent was prepared on 200 gram-scale in a single step, reacts in the title reaction under mild conditions without precautions towards air or moisture, and is tolerant of nearly all common functionality. Experimental and *in-situ* spectroscopic monitoring techniques provide detailed insights and unexpected findings for the unique reaction mechanism.

Pyridines are privileged heterocycles as key components of hundreds of pharmaceuticals and agrochemicals, and thousands of natural products.[1] As such, several methods for the modification of pyridines have been developed that have expanded access to pyridine-containing compounds and their derivatives.[2] For example, Minisci-type radical addition reactions are commonplace for the introduction of carbon-bound fragments,[3,4] and numerous methods have been developed for installing carbon- or heteroatom-based fragments from pyridine *N*-oxides or related *N*-activated pyridinium species.[5,6] However, to avoid the strong oxidants and activating agents in pyridine *N*-oxide chemistry, and override inherent site-selectivity in radical reactions, we sought to develop a new approach for site-selective functionalization of pyridines.

Among the extensive pyridine-containing biologically active compounds known, 2-aminopyridines play a central role as privileged pharmacophores found in compounds across all therapeutic areas.[7a] *In fact, of the small-molecule-based therapeutics that were approved by the FDA in 2019, 8 of 32 (25%) contained a 2-aminopyridine (5 of 32) or 2-aminodiazine (3 of 32) motif* (for examples, see Figure 1).[7b] Thus, given the importance of 2-aminopyridines, the challenges associated with pyridine *N*-oxide and related chemistry,[8] and the extreme conditions and narrow utility of the Chichibabin reaction,[9] we aimed to develop conditions for the direct conversion of pyridines to 2-aminopyridines that would be applicable towards the functionalization of drug-like molecules. Specifically, the target reaction would need to occur with exquisite site-selectivity, work directly on pyridines without pre-activation, be tolerant of the protic and Lewis-basic functionalities found in drug-like molecules, be able to be conducted on the benchtop without special precautions towards air or moisture, generate minimal waste, allow for simple purification, and employ only simple and readily available reagents.[10]

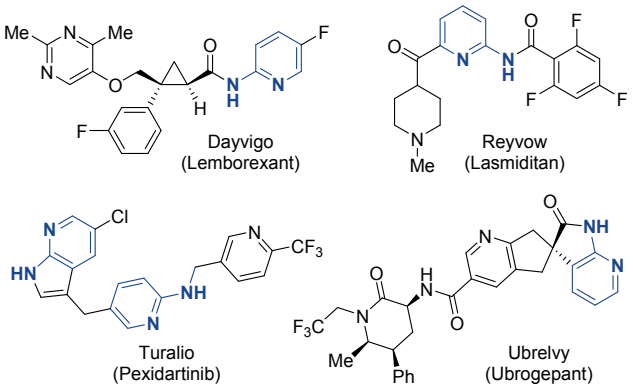


Figure 1. Selected Examples of Pharmaceuticals Containing 2-Aminopyridine Motifs that were Approved by the FDA in 2019.

With the above considerations in mind, we set out to develop a general method for the conversion of pyridines to 2-aminopyridines. Initially, we investigated reactions with our recently reported bifunctional reagent, **1**.[11] The bifunctional reagent acts as both an activator for the pyridine ring and as a mild two-electron oxidant through *N*-*O* bond cleavage. Though hundreds of reaction conditions were investigated with a diverse set of nitrogen-based nucleophiles and a library of bifunctional reagents, the targeted products were not detected in any instance. In general, attack of the nucleophile at the oxime carbon and/or ring-opening of putative aminal intermediates occurred (Figure 2A).[12] To circumvent these undesired pathways, we designed and tested several new reagents that would i) react with pyridine to form a reactive pyridinium salt, ii) provide *intramolecular* delivery of a nitrogen nucleophile, thereby iii) directing functionality exclusively to C-2, iv) prevent ring opening, and ultimately v) promote 2-electron oxidation/rearomatization through *N*-*O* bond cleavage.

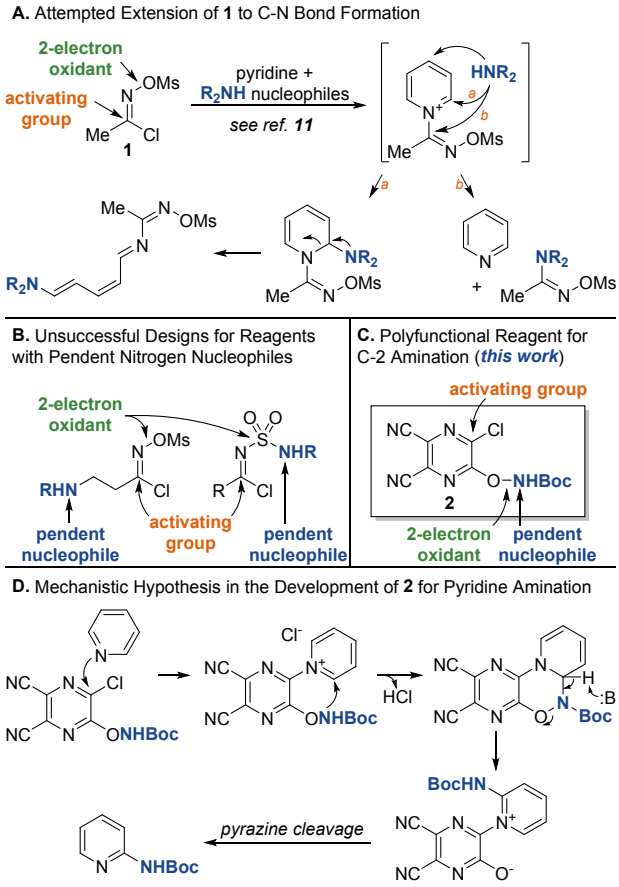
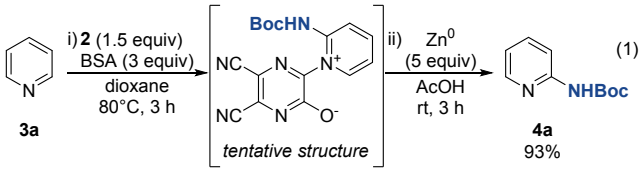


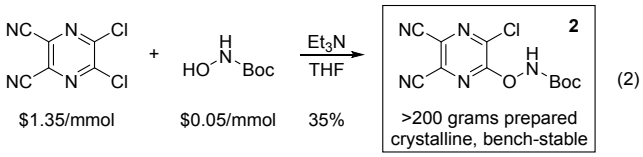
Figure 2. Pyridine Functionalization Strategies with Multifunctional Reagents

Several reagents based on the original bifunctional reagent design were prepared and tested (Figure 2B), but were either unstable, due to the presence of a nucleophile and electrophile in the same molecule, or did not promote the desired reaction. Finally, we evolved the design by changing the activating group from an oximoyl chloride to an electron-deficient chloropyrazine, and transposing the 2-electron oxidant to the nucleophilic nitrogen, ultimately leading to reagent **2** (Figure 2C).[13] The tentative mechanism that guided the reagent design and reaction development is shown in Figure 2D, consisting of pyridine activation, intramolecular delivery of the nitrogen nucleophile, rearomatization through *N-O* bond cleavage and tautomerization, and eventual cleavage of the pyrazine fragment.

With pyridine as a model substrate, conditions were investigated for C-2 amination by carrying out reactions of **2** in the presence of HCl scavengers. While typical inorganic or organic bases led to the decomposition of **2**, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) promoted the desired reaction by scavenging HCl through the generation of TMSCl. Reactions of pyridine with 1.5 equiv of **2** and 3 equiv of BSA in dioxane at 80°C formed the presumed (*vide infra*) pyrazine-bound product in nearly quantitative yield after 3 h. An extensive set of experiments were carried out to investigate cleavage of the adducts to reveal the 2-aminopyridine product. Initially, S_NAr reactions with a diverse set of nucleophiles were investigated, but were generally low-yielding. Acid-mediated hydrolysis could cleave the adducts with removal of the Boc group under forcing condition (6M HCl, reflux), but the harsh conditions were deemed impractical. Finally, we discovered that mild reducing conditions (Zn + AcOH) promote the cleavage at ambient temperature to reveal the 2-NHBoc pyridine product in high yield (eq 1).

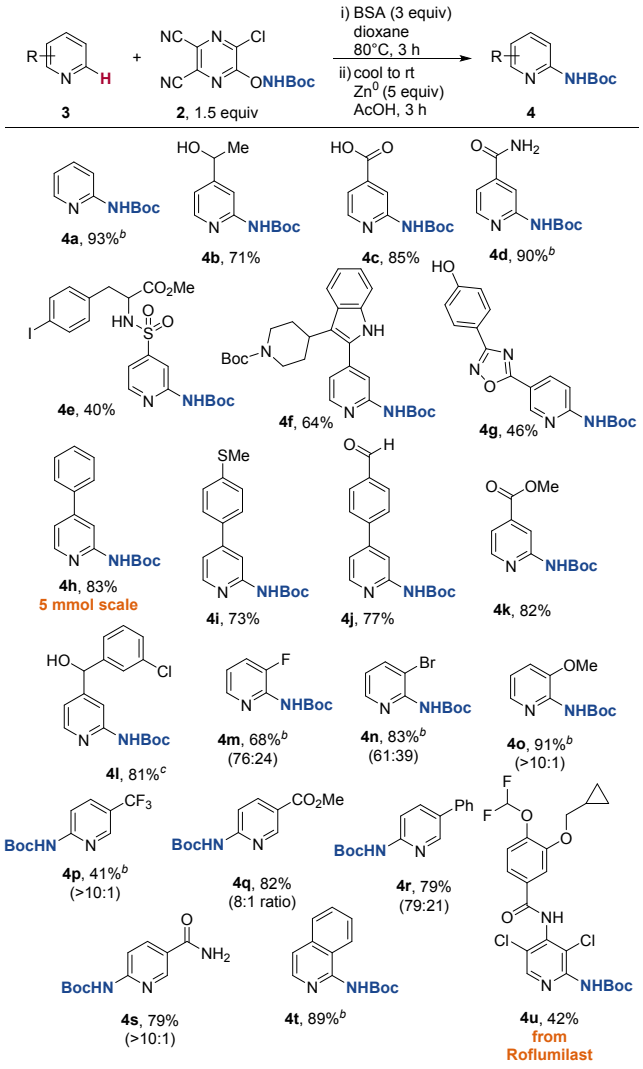


Having demonstrated the ability of reagent **2** to convert pyridine to 2-NHBoc pyridine, 200 grams of the reagent were prepared in a single step (eq 2) from commercially available 5,6-dichloropyrazine-2,3-dicarbonitrile ($1.35/mmol) and *N*-Boc hydroxylamine ($0.05/mmol).[14] Purified **2** is crystalline, indefinitely stable in air, not shock-sensitive, and is thermally stable in the solid state to 126 °C based on DSC analysis.[15]



With bulk quantities of reagent **2**, the substrate scope was investigated with respect to the electronic properties of the substrates and the tolerance of common functional groups (Scheme 1). The reaction sequence allows for the direct functionalization of pyridines spanning a range of electronically disparate substrates. The functional group tolerance encompasses protic and nucleophilic functionality such as alcohols, carboxylic acids, N-H bearing sulfonamides, amides and indoles, and unprotected phenols. This is significant, as such functional groups are reactive towards activating agents used in many pyridine functionalization methods. The tolerance of such functional groups in this work may be attributed, in part, to the capping action of the BSA, masking the functionality as inert silyl derivatives. By design, as a relatively inert *N-O* bond is used as the terminal oxidant, the reaction is tolerant of thioethers and aldehydes, functional groups that are reactive towards the oxidants used in pyridine *N*-oxide chemistry.

Scheme 1. Representative Substrate Scope with Multifunctional Reagent **2**[a]

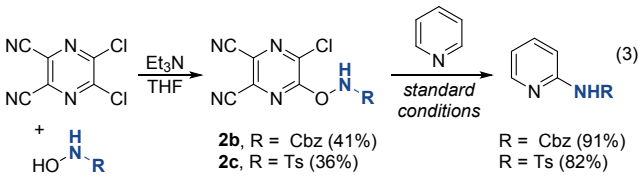


[a]Isolated yields shown for reactions carried out with 0.5 mmol of **3** unless otherwise noted. Ratios in brackets refer to the ratio of the major product (drawn) and the minor isomeric product at the end of the reaction. [b]The yield was determined with a UPLC instrument calibrated against authentic standards. [c]The ketone group of **3** was reduced to the secondary alcohol in quantitative yield in the second step.

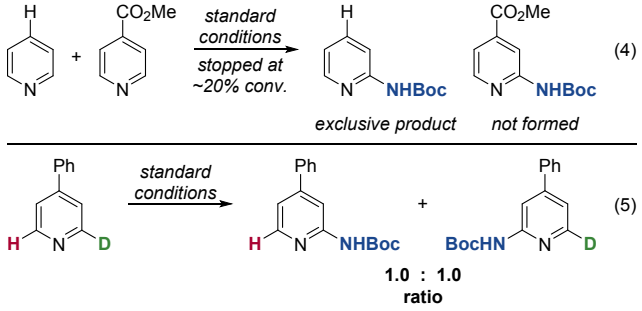
During the investigation of the scope for the pyridine amination reaction with **2**, some limitations became evident that we would like to disclose. First, 2-substituted pyridines reacted in low yield due to their significantly reduced nucleophilicity compared to analogous 3- or 4-substituted pyridines. Similarly, diazine substrates reacted to form less than 10% of the target products; attempts to force the reaction were unsuccessful. While the mild reducing conditions used to cleave the pyrazine-containing product adducts generally showed broad generality and tolerated aldehyde, aryl iodide, and 1,2,4-oxadiazole groups, the diaryl ketone in substrate **4l** was reduced to the secondary alcohol in quantitative yield during the reduction step.

Reactions carried out with 3-substituted pyridines revealed that functionalization can occur with selectivity to form either the 2,3- or 2,5-disubstituted products. Pyridine substrates bearing 3-fluoro, 3-bromo, or 3-methoxy substituents formed the 2,3-disubsituted products preferentially. Larger functional groups such as (hetero)aryl, methoxycarbonyl, and trifluoromethyl directed functionalization primarily to the less-hindered carbon. Quinoline reacted to form 1-NHBoc quinoline exclusively. These selectivity trends are analogous to known pyridine C-2 functionalization reactions, including those with pyridine *N*-oxides,[3] cyanation reactions with **1**,[11] and fluorination with AgF_2.[16] Contrasteric reactions that form the more hindered product may be rationalized by the increased reactivity of the C-2 carbon relative to the C-6 carbon from inductive or resonance effects, and the relief of eclipsing interactions during rehybridization in the nucleophilic addition step.

In most cases, reactions were carried out with 0.5 mmol of the pyridine substrate. The reaction carried out with 4-phenylpyridine formed the product in the same yield and with the same reaction profile on both 0.5 and 5.0 mmol scales, in line with expectations for a homogeneous, air- and moisture-tolerant, thermally-driven reaction that forms stable products. Furthermore, variants of reagent **2** containing Cbz or Ts groups in place of Boc were also prepared on gram-scale and promoted C-2 functionalization of pyridine under the standard conditions in high yields (eq 3).



To gain additional insight into the reaction mechanism, mechanistic and spectroscopic experiments were carried out. First, a competition reaction was conducted between pyridine and 4-CO_2Me pyridine. Analyzing the reaction after approximately 20% conversion revealed that only pyridine had reacted with **2** to form the pyridine-pyrazine adduct, with none of the product formed from 4-CO_2Me pyridine (eq 4). This observation is consistent with the fact that poorly nucleophilic pyridines react slower than more nucleophilic pyridines. Next, a reaction with 2-deuterio-4-phenylpyridine was carried out under the standard conditions to measure the intramolecular KIE (eq 5). At the end of the reaction, equimolar amounts of the product resulting from C-H and C-D functionalization were observed.[17]



To build on the experimental results, a series of NMR spectroscopy experiments were carried in dioxane-d_8 out to observe and characterize the intermediates that are formed throughout the reaction. First, the reaction was monitored at ambient temperature to observe short-lived reaction intermediates. Within the first 10 minutes, the originally proposed dihydropyridine species **5** was observed as a major species in the reaction mixture (COSY, HSQC, HMBC), along with unreacted pyridine. The pyridinium adduct that results from displacement of the chloride in **2** by pyridine (Figure 2D) was not observed, consistent with rapid intramolecular attack of the pendent NHBoc group at the electrophilic C-2 position occurring as the pyridinium adduct forms. At room temperature, dihydropyridine **5** reacted further through base-mediated cleavage of the *N-O* bond, reaching full conversion after approximately 90 minutes. The originally proposed zwitterionic structure was found

to be incorrect, with the actual structure (**6**) containing an OTMS group and a deprotonated N-H Boc group on the pyridine. The structure was unambiguously assigned through COSY, HSQC, HMBC, LR-HSQMBC,[19] NOESY, and $^{1}H/^{15}N$ HMBC experiments.

In a separate experiment, the final species formed under the standard reaction conditions after 3 h at 80°C was characterized and determined to be different than the final species, **6**, formed at room temperature.[18] LC/MS analysis of reactions carried out at room temperature and 80°C clearly showed that the species formed prior to Zn-mediated reduction were different, suggesting that isomerization occurs at elevated temperatures. Indeed, the species observed after heating at 80°C was found to be an isomer of **6** that results from a net displacement of the pyridine nitrogen with the Boc-protected nitrogen, forming **7**.[20] The structure was unambiguously assigned through COSY, HSQC, HMBC, LR-HSQMBC,[19] NOESY, and $^{1}H/^{15}N$ HMBC experiments. The isomerization process was unexpected, and demonstrates the value of detailed 2D NMR spectroscopy experiments, inculding LR-HSQMBC[19] that provided key long-range correlations of the proton-deficient molecules, as the structural assignments of **6** and **7** were ambiguous based on typical ^{1}H and ^{13}C experiments and mass spectrometry.

Finally, the reaction mixture was subjected to the Zn-mediated reduction step in acetic acid-d_4. After reduction, the reaction mixture contained **4a** as the only observable pyridine-derived compound by NMR spectroscopy.[21] The structure of the pyrazine fragment was characterized by the above-mentiond 2D NMR spectroscopy experiments, including LR-HSQMBC, and determined to be compound **8**.

The combination of experimental observations and characterization of intermediates allows for a detailed mechanism to be proposed. The attack of the pyridine substrates at the chloropyrazine is product determining (eq 4) and the adduct is quickly trapped by the pendent NHBoc group. The HCl that is formally generated in this step reacts with BSA to generate TMSCl and AcNHTMS (characterized *in situ*). Based on the results shown in eq 5, dihydropyridine formation is irreversible. The *N-O* bond cleavage occurs with rapid silylation of the liberated oxygen anion, and the initially formed species undergoes an isomerization to generate a more stable intermediate. The Zn-mediated reduction likely proceeds by donation of electrons to the electrophilic pyrazine, with extrusion of the Boc-protected aminopyridine as from a putative aminal intermediate, followed by further reduction to **8**.

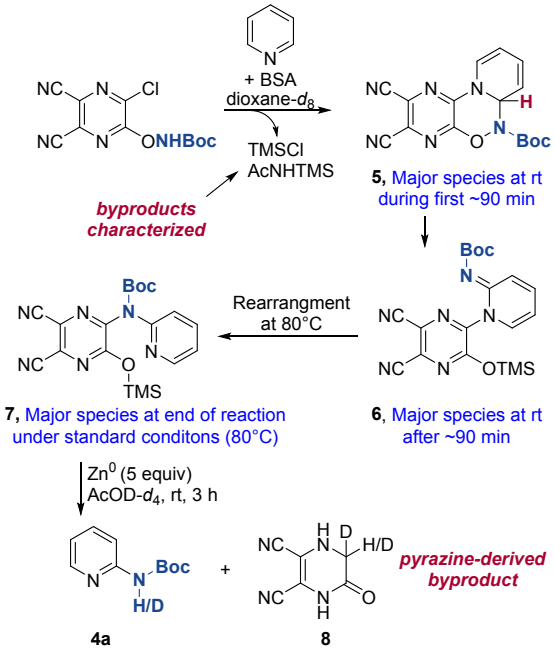


Figure 3. Reaction Monitoring by NMR Spectroscopy

In summary, we have developed a novel, multifunctional reagent for the conversion of pyridines to Boc-protected 2-aminopyridines. A series of mechanistic and spectroscopic experiments demonstrate that the multifunctional reagent effects the C-2 amination of pyridines by activating pyridine as a pyridinium salt, directing the rapid intramolecular delivery of a nitrogen nucleophile, rearomatizing an intermediate dihydropyridine through *N-O* bond cleavage, which is then thermally isomerized to a more stable product before Zn-mediated reduction. Given the utility and scope of the reaction, the availability of the reagent in bulk quantities in a single step, and the straightforward reaction set-up, we are confident this new method will be valuable for pyridine functionalization. Building upon the concepts and observations reported here, the invention of new multifunctional reagents to carry-out synthetically useful reactions is the focus of several ongoing projects in our lab.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We would like to thank our Merck colleagues L.C. Campeau, Ben Sherry, and Kevin Maloney for their helpful feedback. We thank Ralph Zhao and Don Bachert of Merck for carrying out the physical safety assessment of **2**. S.K. would like to thank the Merck & Co., Inc., Rahway, NJ, USA internship program.

REFERENCES

(1) (a) 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. (b) Substructure search of pyridine, Dictionary of Natural Products; Taylor & Francis Group.

(2) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley, 2010. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 3rd ed.; Wiley-VCH, 2012.

(3) (a) Minisci, F.; Vismara, E.; Fontana, F. Recent Developments of Free-Radical Substitutions of Heteroaromatic Bases. *Heterocycles* **1989**, *28*, 489–519. (b) Duncton, M. A. Minisci reactions: Versatile CH-functionalizations for medicinal chemists. *Med. Chem. Commun.* **2011**, *2*, 1135–1161. (c) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. Practical and innate carbon–hydrogen functionalization of heterocycles. *Nature* **2012**, *492*, 95–99. (d) Ma, X.; Dang, H.; Rose, J. A.; Rablen, P.; Herzon, S. B. Hydroheteroarylation of Unactivated Alkenes Using N-Methoxyheteroarenium Salts. *J. Am. Chem. Soc.* **2017**, *139*, 5998–6007.

(4) For Minisci-type reactions with aryl or nitrogen radicals, see: (a) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. Direct C–H Arylation of Electron-Deficient Heterocycles with Arylboronic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196. (b) Foo, K.; Sella, E.; Thome, 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. (c) 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. (d) Kim, H.; Kim, T.; Lee, D. G.; Roh, S. W.; Lee, C. Nitrogen-centered radical-mediated C–H imidation of arenes and heteroarenes via visible light induced photocatalysis. *Chem. Commun.* **2014**, *50*, 9273–9276.

(5) (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. Synthesis of Pyridine and Dihydropyridine Derivatives by Regio- and Stereoselective Addition to N-Activated Pyridines. *Chem. Rev.* **2012**, 2642–2713. For representative examples, see: (b) Farrell, R. P.; Elipe, M. V. S.; Bartberger, M. D.; Tedrow, J. S.; Vounatsos, F. An Efficient, Regioselective Amination of 3,5-Disubstituted Pyridine N-Oxides Using Saccharin as an Ammonium Surrogate. *Org. Lett.* **2013**, *15*, 168–171. (c) Keith, J. M. One Step Conversion of Heteroaromatic-N-Oxides to Imidazolo-Heteroarenes *J. Org. Chem.* **2008**, *73*, 327–330. (d) Yin, J. J.; Xiang, B. P.; Huffman, M. A.; Raab, C. E.; Davies, I. W. A General and Efficient 2-Amination of Pyridines and Quinolines. *J. Org. Chem.* **2007**, *72*, 4554–4557. (e) Londregan, A. T.; Jennings, S.; Wei, L. Q. Mild Addition of Nucleophiles to Pyridine-N-Oxides. *Org. Lett.* **2011**, *13*, 1840–1843. (f) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. Regioselective Bromination of Fused Heterocyclic N-Oxides. *Org. Lett.* **2013**, *15*, 792–795.

(6) (a) Hilton, M. C.; Dolewski, R. D.; McNally, A. Selective Functionalization of Pyridines via Heterocyclic Phosphonium Salts. *J. Am. Chem. Soc.* **2016**, *138*, 13806–13809. (b) Patel, C.; Mohnike, M.; Hilton, M. C.; McNally, A. A Strategy to Aminate Pyridines, Diazines, and Pharmaceuticals via Heterocyclic Phosphonium Salts. *Org. Lett.* **2018**, *20*, 2607–2610. (c) Alberico, D.; Scott, M. E.; Lautens, M. Aryl−Aryl Bond Formation by Transition-Metal-Catalyzed Direct Arylation. *Chem. Rev.* **2007**, *107*, 174–238. (d) Seregin, I. V.; Gevorgyan, V. Direct transition metal-catalyzed functionalization of heteroaromatic compounds. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (e) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. C–H Functionalization of Azines. *Chem. Rev.* **2017**, *117*, 9302–9332.

(7) 2-aminopyridines are often utilized as stable, non-genotoxic isosteres of anilines. For a review of 2-aminopyridines, see: (a) Marinescu, M. 2-Aminopyridine – A Classic and Trendy Pharmacophore. *Int. J. Pharm. Bio. Sci.* **2017**, *8*, 338–335. For 2-aminopyridine motifs in recently approved pharmaceuticals, see: (b) https://cen.acs.org/sections/drugs-approved-in-2019.html

(8) Katritzky, A. R.; Lam, J. N. Heterocyclic N-Oxides and N-Imides. *Heterocycles* **1992**, *33*, 1011–1049.

(9) (a) Chichibabin, A. E.; Zeide, O. A. New Reaction for Compounds Containing the Pyridine Nucleus. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 1216–1236. (b) Pang, J. H.; Kaga, A.; Roediger, S.; Lin, M. H.; Chiba, S. Revisiting the Chichibabin Reaction: C2 Amination of Pyridines with a NaH-Iodide Composite. *Asian J. Org. Chem.* **2019**, *8*, 1058–1060.

(10) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachalb, P.; Krska, S. W. The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016**, *45*, 546–576.

(11) Fier, P. S. A Bifunctional Reagent Designed for the Mild, Nucleophilic Functionalization of Pyridines *J. Am. Chem. Soc*. **2017**, *139*, 9499−9502.

(12) Van der Plas, H. C. The Sn(ANRORC) Mechanism: A New Mechanism for Nucleophilic Substitution. *Acc. Chem. Res.* **1978**, *11*, 462–468.

(13) (a) Pratt, E. F.; Keresztesy, J. C. Syntheses of Indolizino- and Dihydroindolizinoquinoxalines. *J. Org. Chem.* **1967**, *32*, 49–53. (b) Guimond, N.l; Gorelsky, S. I.; Fagnou, K. Rhodium(III)-Catalyzed Heterocycle Synthesis Using an Internal Oxidant: Improved Reactivity and Mechanistic Studies. *J. Am. Chem. Soc.* **2011**, *133*, 6449–6457.

(14) Prices based on Combi-blocks online catalog at the time of submission.

(15) No decomposition or loss of activity was observed over 6 months for reagent **2** that was stored and handled on the benchtop without precautions towards air or moisture. For additional details on the thermal stability and safety assessment of **2**, see the Supporting Information.

(16) (a) Fier, P. S.; Hartwig, J. F. Selective C-H Fluorination of Pyridines and Diazines Inspired by a Classic Amination Reaction. *Science* **2013**, *342* 956–960. (b) Fier, P. S.; Hartwig, J. F. Synthesis and Late-Stage Functionalization of Complex Molecules through C–H Fluorination and Nucleophilic Aromatic Substitution. *J. Am. Chem. Soc.* **2014**, *136*, 10139–10147.

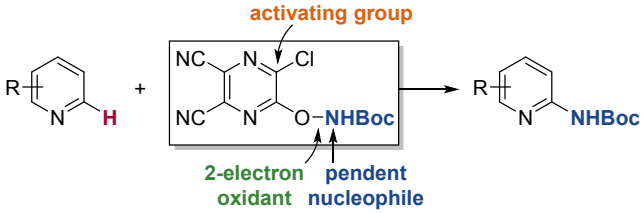
(17) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C–H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066 – 3072.

(18) Although pyridine reacts with **2** at room temperature, electron-deficient substrates require elevated temperatures to react with **2** at appreciable rates.

(19) Williamson, R.T.; Buevich, A.V.; Martin, G.E.; Parella, T. LR-HSQMBC: A Sensitive NMR Technique to Probe Very Long-Range Heteronuclear Coupling Pathways. *J. Org. Chem.* **2014**, *79*, 3887 – 3894.

(20) A possible mechanism for the rearrangment may be one that is analogous to the Newman-Kwart reaction (a) Miyazaki, K. The Thermal Rearrangement of Thionocarbamates to Thiolcarbamates. *Tetrahedron Lett.* **1968**, *23*, 2793–2798. (b) Kwart, H.; Evans, R. E. The Vapor Phase Rearrangement of Thioncarbonates and Thioncarbamates. *J. Org. Chem.* **1966**, *31*, 410–413. (c) Newman, M. S.; Karnes, H. A. The Conversion of Phenols to Thiophenols via Dialkylthiocarbamates. *J. Org. Chem.* **1966**, *31*, 3980–3984.

(21) Intermediate **6** also reacts with Zn + AcOH to form product **4a**.


activating group
R
N
H
+
NC
N
Cl
NC
N
O
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2-electron
oxidant
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nucleophile
R
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NHBoc