Nitrogen-to-Carbon Single Atom Point Mutation of Pyridine *N*-Oxides

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ABSTRACT: Single-atom editing has emerged as a powerful process for altering molecular structures with precision. Within this growing class of transformations, reactions that replace one atom for another in heterocycles, while desirable, remain limited. We report the development of a transformation that achieves an N-to-C atom swap in pyridine *N*-oxides utilizing a sulfoxide-derived anion as a carbon source. This 'point mutation' exhibits good functional group tolerance and replaces the *N*-oxide moiety with either unsubstituted, substituted, or isotopically labeled carbon atoms in a single laboratory operation.

Single-atom skeletal editing has recently emerged as a powerful synthetic strategy, allowing precise and direct modification to the core skeleton of organic molecules. While broadly practical, the precision and efficiency provided by this tactic offers key enhancements to late-stage endeavors in drug discovery, as compounds bearing distinct—yet related—core scaffolds may otherwise require unique *de novo* syntheses and iterative optimization campaigns. Single-atom skeletal editing can be classified into three main types: (1) rearrangements, wherein the atom being edited is retained in the product of the reaction, (2) mutations, or the deletion or insertion of atoms directly into molecular skeletons, and (3) transmutations, which replace one atom in a scaffold with another.[1]

Pharmacological advancements leveraging the 'necessary nitrogen' effect have captivated the attention of medicinal and synthetic chemists alike and have driven a significant increase in methodological development for single-atom skeletal editing of heterocyclic compounds.[2] While Sarpong, Levin, and others have developed selective reagents and conditions to connect classes of aromatic compounds through mutations and rearrangements, the direct replacement of an atom within a heterocycle

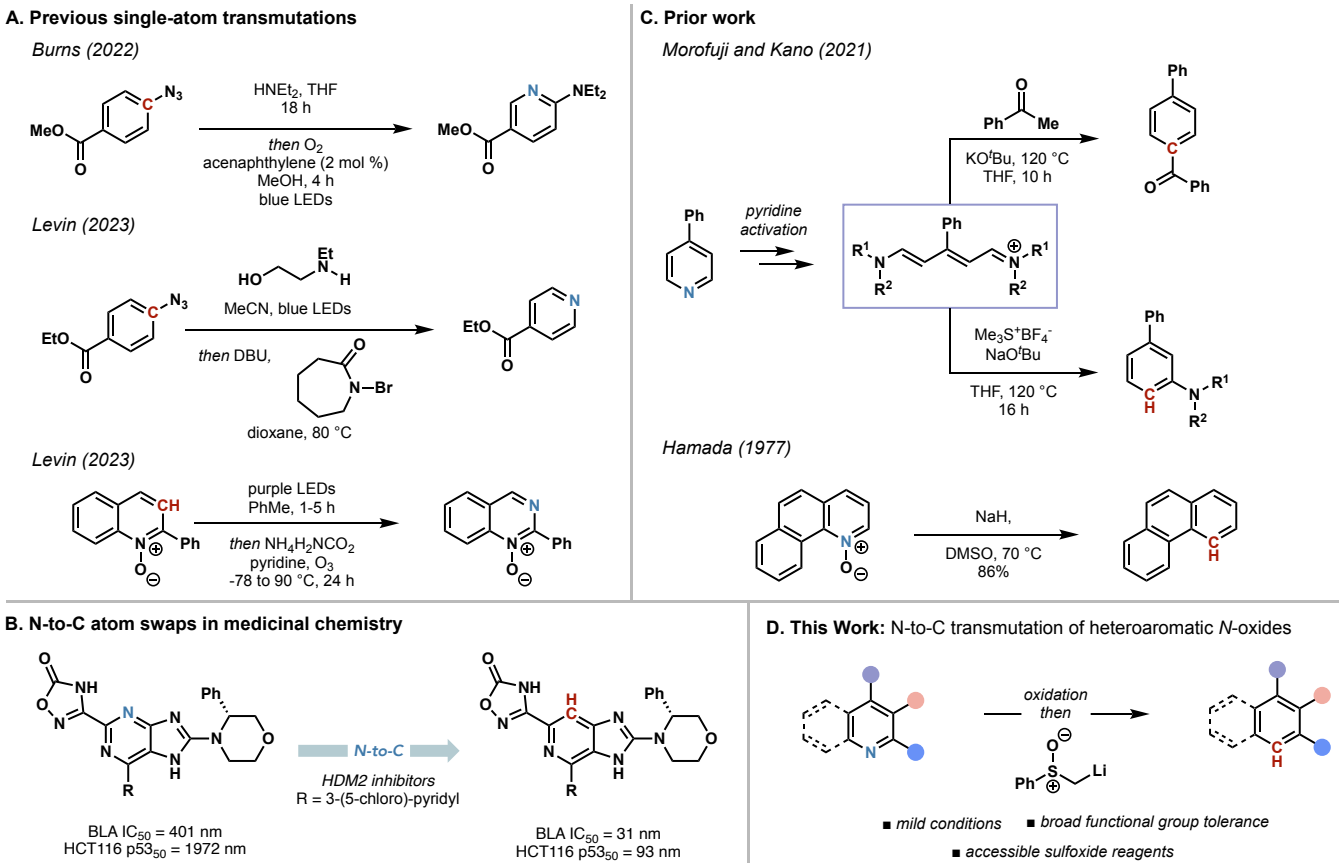


Figure 1. (A) Previously reported single-atom transmutations; (B) Previously reported N-to-C point mutations; (C) N-to-C atom swaps in medicinal chemistry; (D) This Work: N-to-C transmutation of azaarene *N*-oxides.

without peripheral modifications remains limited.[3–11] Recently, Burns and coworkers reported the conversion of aryl azides to aminopyridines via nitrene insertion and *meta*-carbon deletion (**Figure 1A**).[12] In a related study, Levin and coworkers disclosed a photochemical *ipso*-selective nitrene internalization of aryl azides to pyridines.[13] The Levin group also demonstrated C-to-N transmutations of quinolines to quinazolines via oxidative rearrangement of quinoline *N*-oxides.[14]

While C-to-N transmutations have dominated recent research in this area, the consequence of a single-atom swap on pharmacological activity may not always be predictable. For example, Reutershan and coworkers observed a remarkable increase in activity when performing an N-to-C swap in a purine core during their drug discovery campaign for an HDM2-p53 inhibitor (**Figure 1B**).[15] The ability to swap out an atom to transform one scaffold into another enables expedient access to diverse molecular scaffolds. Moreover, such single-atom swaps could have profound impact on a compound's pharmacological parameters that may be nonobvious.

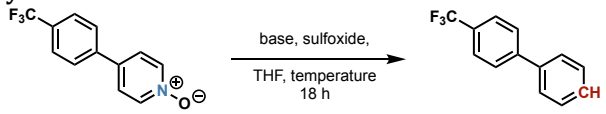
Pyridines represent a ubiquitous class of heterocycles in natural products, drug discovery, and organic synthesis. There has been a substantial body of research directed towards selective peripheral functionalization of pyridines (e.g., metalation, C–H functionalization, etc.).[16,17] However, few reports demonstrate the transformation of pyridine scaffolds into other classes of aromatic compounds.[18] Notably, during the preparation of this manuscript, Studer and coworkers disclosed the conversion of pyridines to benzenes through a CC to CN atom pair swap featuring a cycloaddition-retrocycloaddition strategy.[19]

We were drawn to the intrinsic challenge of transforming pyridines to diverse benzene derivatives through an N-to-C single-atom edit. In considering how to effect this 'point mutation', we drew inspiration from the Zincke aldehyde reaction, wherein an activation step followed by nucleophilic addition induces ring-opening to an unsaturated intermediate.[20] The Vanderwal and McNally laboratories recently leveraged this classical reactivity platform to achieve diverse transformations of pyridines.[21–23] Furthermore, Morofuji and Kano reported the conversion of pyridines to functionalized benzene derivatives by reacting Zincke intermediates with carbon-based nucleophiles (**Figure 1C**).[24,25] Though this transformation enables the conversion of pyridines to both anilines and benzophenones, it requires three steps and is limited in scope. To date, the direct conversion of pyridines to benzenes without peripheral alterations to the parent heterocycle remains underdeveloped.

In their efforts to react pyridine *N*-oxides with carbon-based nucleophiles, Hamada and Takeuchi discovered the conversion of benzo[*h*]quinoline *N*-oxide to anthracene with sodium hydride in dimethyl sulfoxide (DMSO) at elevated temperatures (**Figure 1C**).[26] The authors propose a nucleophilic addition, ring-opening, and ring-closing (ANRORC) mechanism analogous to that of the Zincke reaction (see **Supporting Information, Scheme S1**).[27–30] While this discovery represents an early example of an N-to-C transmutation, it remained limited to isolated examples of unsubstituted *N*-oxides. Herein, we report a general strategy for N-to-C transmutation of azaarene *N*-oxides to their corresponding benzene analogs (**Figure 1D**).

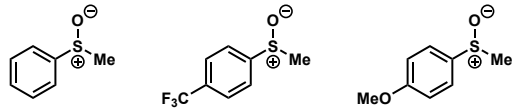
We began exploring reaction conditions for our desired N-to-C transmutation with pyridine *N*-oxide **1** (**Table 1**). First, subjecting **1** to slightly modified conditions to those of Hamada and Takeuchi using a large excess of nucleophile generated benzene analog **2** in 40% yield (entry 1). Increasing the reaction temperature to 60 ˚C led to a slight improvement, but reducing the equivalents of sodium dimsylate resulted in lower yields (entry 4). The use of lithium diisopropylamide (LDA) and *n*-butyllithium to facilitate nucleophile formation improved the yield to 46% and 59%, respectively (entries 5 and 6). After replacing the sulfoxide source with methyl phenyl sulfoxide (**3**), the product was obtained in 72% yield. Electron poor (**4**) and electron rich (**5**) aryl methyl sulfoxides did not improve the yield of the reaction. Finally, we discovered that the reaction could be performed with only a slight excess of sulfoxide **3** without significant reduction in reaction efficiency (for more details, see **Supporting Information**).

Table 1. Optimization for N-to-C Point Mutation of Pyridine *N*-Oxides[a]



1 2

Entry	Base (equiv.)	Sulfoxide (equiv.)	Temp. (˚C)	Yield (%)[b]
1[c]	NaH (10.0)	DMSO (xs)	40	40
2[c]	NaH (10.0)	DMSO (xs)	50	41
3[c]	NaH (10.0)	DMSO (xs)	60	47
4[c]	NaH (5.0)	DMSO (5.1)	60	25
5[d]	LDA (5.0)	DMSO (5.1)	60	46
6[d]	*n*BuLi (5.0)	DMSO (5.1)	60	59
7[d]	*n*BuLi (5.0)	PhSOMe (**3**) (5.1)	60	72
8[d]	*n*BuLi (5.0)	**4** (5.1)	60	72
9[d]	*n*BuLi (5.0)	**5** (5.1)	60	54
10[d]	*n*BuLi (4.0)	PhSOMe (**3**) (4.1)	60	73
11[d]	*n*BuLi (3.0)	PhSOMe (**3**) (3.1)	60	64



3 4 5

[a]Reactions were performed on a 0.1 mmol scale. [b]Yields were determined via ^{19}F NMR spectroscopic analysis of the crude reaction mixtures with 1-fluoronapthalene as an external standard. [c]Nucleophile formed at 60 ˚C. [d]Nucleophile formed at 0 ˚C.

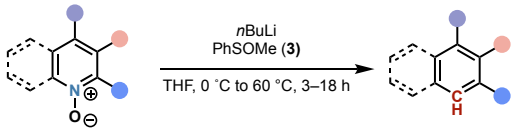
With the optimized conditions in hand, we examined the scope of pyridine *N*-oxides (**Table 2**). Within the class of 4-substituted pyridine *N*-oxides, various functional groups were tolerated under the reaction conditions, including ethers (**6**), halides (**9**), silyl ethers (**10**), alkenes (**11**), and protected benzylic alcohols (**12**). Compounds containing heterocyclic substituents performed well under the reaction conditions, such as thiophene (**14**), furan (**15**), and pyridine (**16**). Pyridine *N*-oxides substituted at the 3- and 2-positions could also undergo transmutation, albeit with

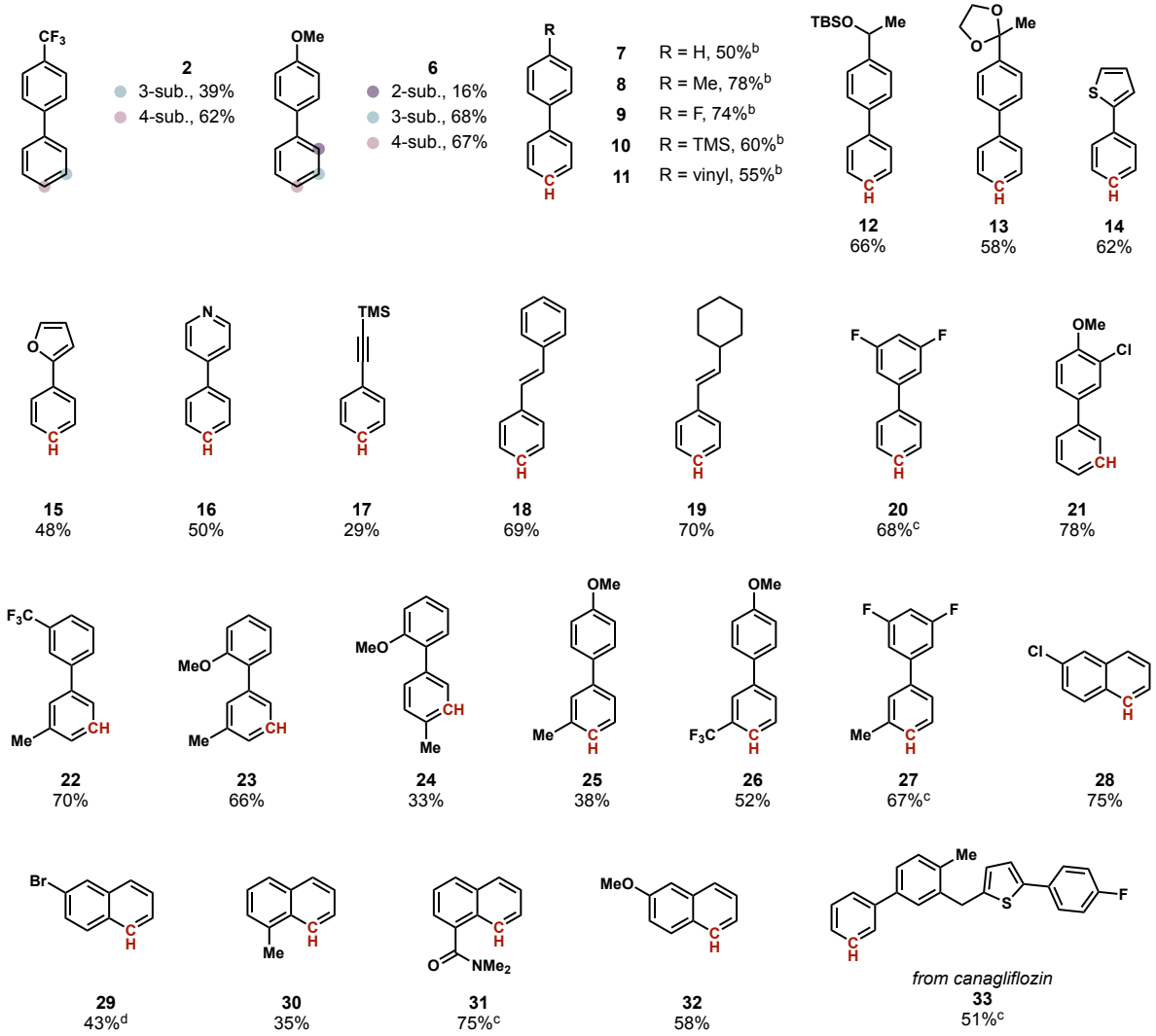
diminished yield in the case of 2-substitution. We attribute this to competing addition to the readily accessible 4-position of the pyridine *N*-oxide. At this time, substrates demonstrating highest reactivity bear a variety of stabilizing functional groups, such as substituted benzenes, alkenes, and heteroaromatics (see **Supporting Information**). Despite this limitation, substituted vinyl- and alkynyl- benzenes (**17**–**19**) were formed in synthetically useful yields. Disubstituted pyridine *N*-oxides with varying substitution patterns also afforded the desired benzene products (**22**–**27**). Notably, a pyridine *N*-oxide derivative of type 2 diabetes drug canagliflozin could also undergo an atom swap in 51% yield (**33**).

Next, we explored the scope of quinoline *N*-oxides. Halogenated quinolines gave the corresponding naphthalenes in good yields while preserving a functional handle for downstream functionalization (**28**, **29**). The reaction also tolerated electrophilic amides, providing **31** in excellent yield. Substrates containing more electrophilic ketones and esters failed to give the corresponding carbocyclic analogs (see **Supporting Information**).

After examining the scope of this transformation, we hypothesized that utilizing more complex sulfoxides could selectively introduce substituents at the newly introduced atom, thereby formally accomplishing a tandem atom-swap/*ipso*-functionalization. However, attempts to use simple phenyl alkyl sulfoxides failed to deliver the desired benzene derivatives, possibly due to a deleterious steric effect that prevents ring closure.

Table 2. Scope of N-to-C point mutation of azarene *N*-oxides[a]

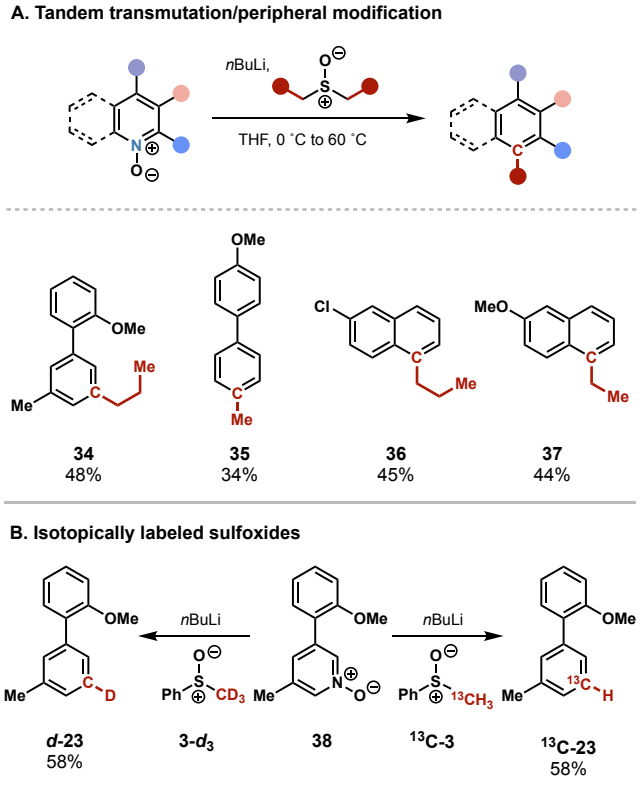




[a]Reactions were run on a 0.2 mmol scale with *N*-oxide (1.0 equiv.), *n*BuLi (4.0 equiv.), PhSOMe (4.1 equiv.), THF (0.1 M), 0 ˚C to 60 °C, 3–18 h. Yields are reported as isolated yields after column chromatography on silica gel. [b]Reactions were run as above, then $^{n}Bu_3P$ (6.2 equiv.) was added during workup. [c]The reaction was run for 3 hours. [d]The reaction was run for 6 hours.

Upon further investigation, we found that symmetrical dialkyl sulfoxides could effect the desired transformation (**Scheme 1A**). While linear alkyl groups were introduced to both pyridine and quinoline *N*-oxide substrates in synthetically useful yields (**34**–**37**), symmetrical sulfoxides with branched alkane substitution did not provide product. Efforts toward expanding the diversity of the sulfoxide reagent are ongoing.

Scheme 1. Substituted and isotopically labeled sulfoxides



[a]See Supporting Information for experimental details.

In addition to alkyl sulfoxides, we explored the application of isotopically labeled sulfoxides (**Scheme 1B**). Site-selective incorporation of isotopically labeled atoms into the core of a molecule remains underexplored.[31,32] Given the accessibility of the sulfoxide reagents and their derivatives, ^{2}H (**3-*d*$_3$**) and ^{13}C (**^{13}C-3**) analogs were readily prepared from isotopically labeled iodomethane. Indeed, subjecting *N*-oxide **38** to the optimized reaction conditions with **3-*d*$_3$** and **^{13}C-3** provided the corresponding labeled benzene derivatives ***d*-23** and **^{13}C-23**, respectively, in 58% yield. Overall, we anticipate that the ability of this methodology to precisely access ^{13}C-labeled cores will provide a valuable method to practitioners of medicinal chemistry, as ready access to core-labeled isotopologues possesses key advantages in the context of pharmacokinetic and radiochemical utility.

In conclusion, we developed a mild and convenient N-to-C transmutation to convert azaarene *N*-oxides to their respective benzene products. This reaction is both broadly functional group tolerant and efficient. This process enables a tandem transmutation/peripheral functionalization, while also providing access to isotopically labeled benzenes. Efforts to explore related edits on other classes of nitrogen-containing heterocycles as well as complex substituted sulfoxides are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge at http://pubs.acs.org.

Experimental procedures, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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