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Selective Functionalization of Pyridines via Heterocyclic Phosphonium Salts

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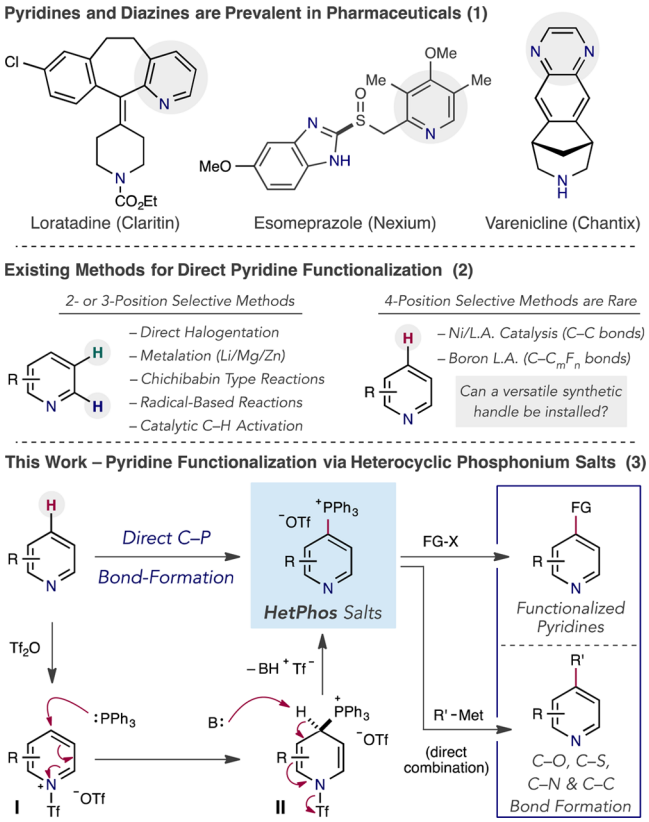
Supporting Information

ABSTRACT: Methods that directly functionalize pyridines are in high demand due to their presence in pharmaceuticals, agrochemicals, and materials. A reaction that selectively transforms the 4-position C−H bonds in pyridines into C−PPh_3^+ groups that are subsequently converted into heteroaryl ethers is presented. The two step sequence is effective on complex pyridines, pharmaceutical molecules, and other classes of heterocycles. Initial studies show that C−C, C−N, and C−S bond formations are also amenable.

Electron-deficient heteroarenes are ubiquitous structural features in small molecule therapeutics, and six-membered ring nitrogen-containing variants are particularly common (eq 1).[1] Within this class of compounds, pyridines are the most widespread heteroarene found in FDA approved drugs that contain a nitrogen heterocycle.[2] They are also key motifs in agrochemicals, functional materials, and ligands for metal catalysts.[3−5] As a result of this importance, direct methods that selectively functionalize pyridine scaffolds are in high demand in the pharmaceutical sciences and beyond.

Traditional electrophilic aromatic substitution reactions on pyridines, such as halogenation, require strong Brønsted or Lewis acids at elevated temperatures, produce regiomeric mixtures, and are limited in scope (eq 2).[6] Classical metalation-trapping sequences usually require strong lithium or magnesium bases and often rely on directing groups.[7] The Chichibabin amination and Hartwig's related fluorination reaction are examples of 2-selective processes.[8,9] Other strategies to functionalize pyridines include radical-based Minisci-type reactions that can form C−C bonds but often lack control between the 2- and 4-positions.[10,11] More recently, transition metal catalyzed C−H activation approaches have witnessed a series of 2- and 3-position selective reactions.[12] Conversely, 4-selective pyridine functionalization methods are comparatively rare. Synergistic Ni/Lewis acid catalysis enables C−C bond formation, $SOCl_2$ mediates pyridine dimerizations, and Kanai recently demonstrated a bulky borane Lewis acid facilitates 4-selective perfluoroalkylations.[13]



Herein, we show a facile method for C4-pyridine functionalization by conversion into heterocyclic phosphonium salts and subsequent transformation. Phosphonium groups can be installed with broad tolerance of sterics and electronics, the reaction can function on quinolines and diazines and, in general, is completely regioselective (eq 3). In this study we show that C−PPh_3^+ groups can be converted into C−OR motifs and preliminary examples of C−S, C−N, and C−C bond formation. This two-step sequence can generate products currently inaccessible by current methods including derivatives of complex pharmaceuticals. As such, we believe that heterocyclic phosphonium salts will be valuable reagents for medicinal chemists.

Our strategy for pyridine functionalization centered on addition of a nucleophile to an activated pyridinium salt followed by rearomatization (eq 3).[14] The identity of the nucleophile is critical as it must be installed in high efficiency and selectivity while also serving as a versatile functional group. Alongside our

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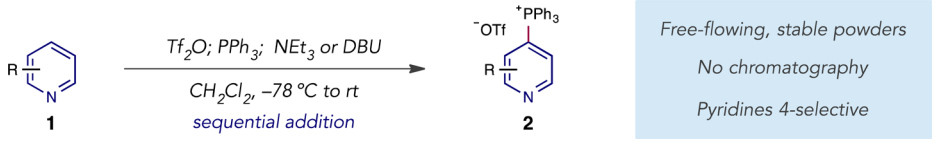
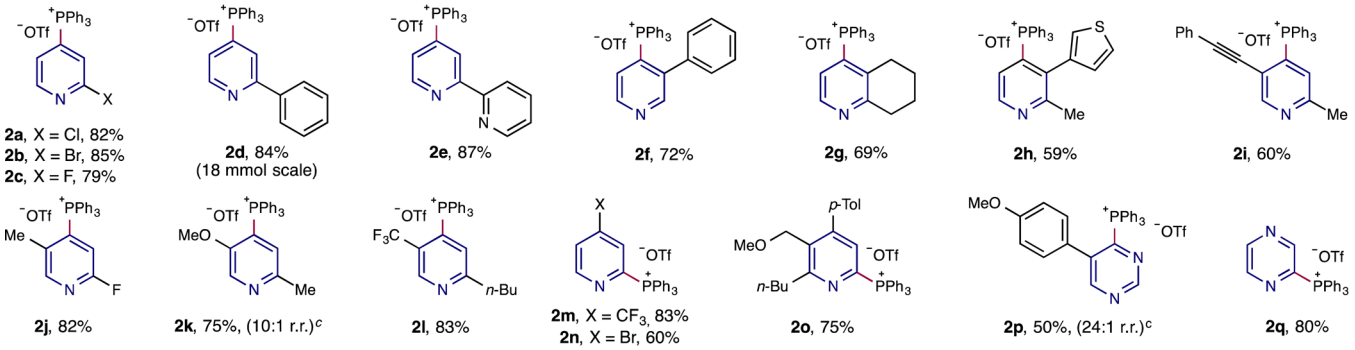
Table 1. Heterocyclic Phosphonium Salt Scope[a,b,c]





[a]Typical reaction stoichiometry: heteroaromatic (1.0 equiv), Tf_2O (1.0 equiv), PPh_3 (1.1 equiv), organic base (1.0 equiv). [b]Isolated yields of single regioisomers (unless stated) are shown. [c]r.r. = regiomeric ratio. For **2k** and **2p**, the minor product is the 2-phosphonium salt isomer and the crude ^1H NMR ratios are 10:1 and 20:1, respectively.

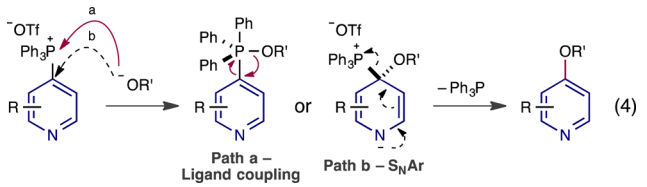
investigations, we were inspired by a report from Anders in which pyridine could be transformed into a heterocyclic phosphonium salt through sequential addition of Tf_2O, PPh_3, and NEt_3 at low temperature.[15] After initially forming a triflyl salt, attack of PPh_3 results in a dearomatized intermediate (eq 3, **I**). Base-mediated elimination (**II**) forms the heteroarylphosphonium salt and an ammonium salt byproduct. Investigations into the scope of this process have been limited.[16] Furthermore, we believe that the unique reactivity of the phosphonium ion can enable multiple new transformations and potentially provides a general platform to obtain functionalized pyridines.

In addition to simple substituted pyridines, we selected a set of pyridines where a conventional functional group, such as a halide, had limited or no commercial availability, or would be challenging to prepare using existing methods. Table 1 shows that phosphonium salts can be formed with functional groups and substitution patterns that are typically found in medicinal chemistry building blocks. The identity of the organic base (NEt_3 or DBU) and control of temperature are key to the success of this protocol, and the salts are isolated via a simple precipitation process as free-flowing powders. Furthermore, apart from two cases (**2k** and **2p**), we isolate the salts exclusively as the 4-substituted product with only traces of other phosphorus species observed in the crude reaction mixtures. We believe that the exceptional regioselectivity results from an enhanced orbital interaction at the 4-position rather than steric encumbrance at the 2-position from the trifyl group.[17] 2-Halo pyridines are excellent substrates and we do not observe any products resulting from halogen substitution (**2a**–**2c**). Other mono as well as disubstituted pyridines, containing carbocycles, heterocycles, methoxy, and trifluoromethyl groups, work well in this process (**2d**–**2l**). 4-Substituted pyridines result in phosphorus addition at the 2-position (**2m**–**2o**); pyrimidines and pyrazines are also competent heterocycles (**2p** and **2q**).

With a variety of phosphonium salts in hand, we envisioned constructing C–O bonds by adding alkoxide nucleophiles. Heteroaryl ethers are widely found in pharmaceutical compounds including Esomeprazole (the number one selling drug in 2012, eq 1) that contains a 4-methoxy pyridine subunit. In practice, deprotonation of an alcohol at 0 °C in THF followed by addition of the phosphonium salt and stirring at room temperature is a reliable procedure. Table 2 shows that primary alkoxides including benzyl, pyridyl, trifluoromethyl, and alkynyl substituents (**3da**–**3de**) are competent nucleophiles. Secondary and tertiary alcohols also form heteroaryl ether products in good yields (**3df**–**3di**). We next examined the set of phosphonium salts from Table 1. Notably, 2-halo salts undergo the reaction without competitive displacement of the halide via an S_NAr reaction for **3aa** and **3ba** with only minor amounts of fluoride substitution products detected in the case of **3ca**.

The reaction can effectively form other di-, tri-, and tetrasubstituted pyridines (**3ea**–**3oa**) and heteroaryl ethers derived from pyrimidine and pyrazine salts (**3pa** and **3qa**). Typical methods to form heteroaryl ethers rely on haloaromatics for metal-catalyzed cross coupling or S_NAr processes.[18] This protocol has greater scope and can access complex pyridines where the corresponding halide cannot be easily prepared but relies on preformed alkoxides and has a higher overall waste footprint.

A proposed mechanism involves forming an alkoxyphosphorane intermediate followed by ligand coupling to construct the C–O bond (eq 4, path a).[19] This pathway has been implicated for



tetraphenylphosphonium alkoxides at high temperatures where C–O bonds are also formed.[20] We do not observe any O–Ph coupling implying that O-heteroaryl coupling is intrinsically more favored although we cannot rule out an S_NAr process at this stage (eq 4, path b).[21] A minor component of these reactions is the

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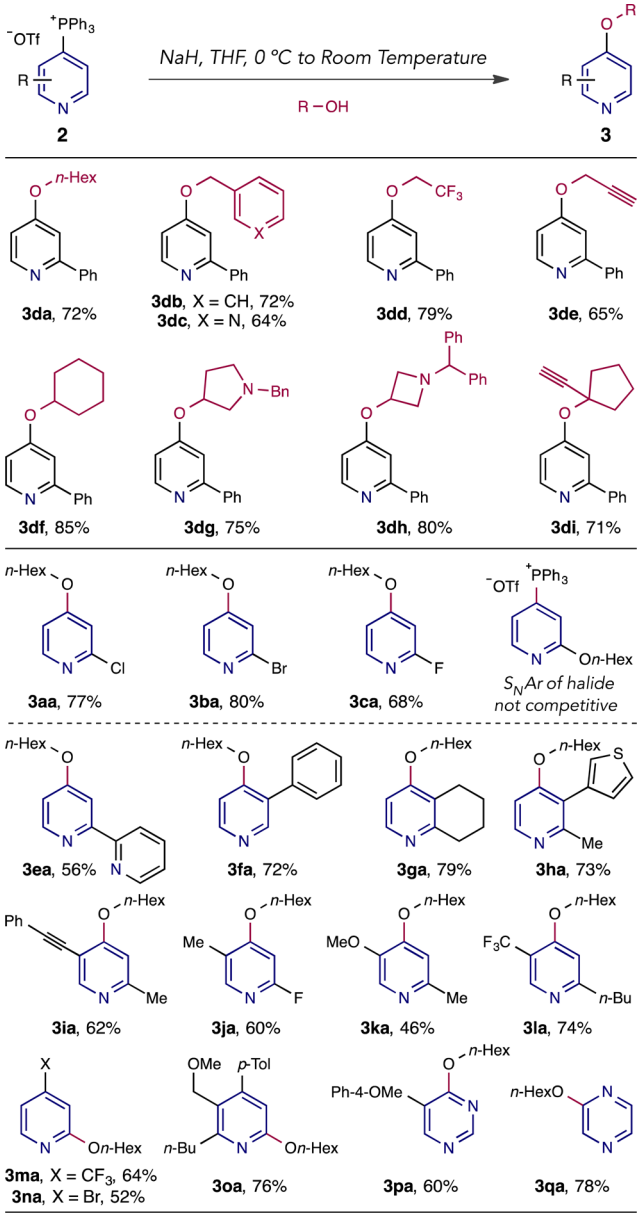
Table 2. C−O Bond Formation: Alcohol and Salt Scope[a]



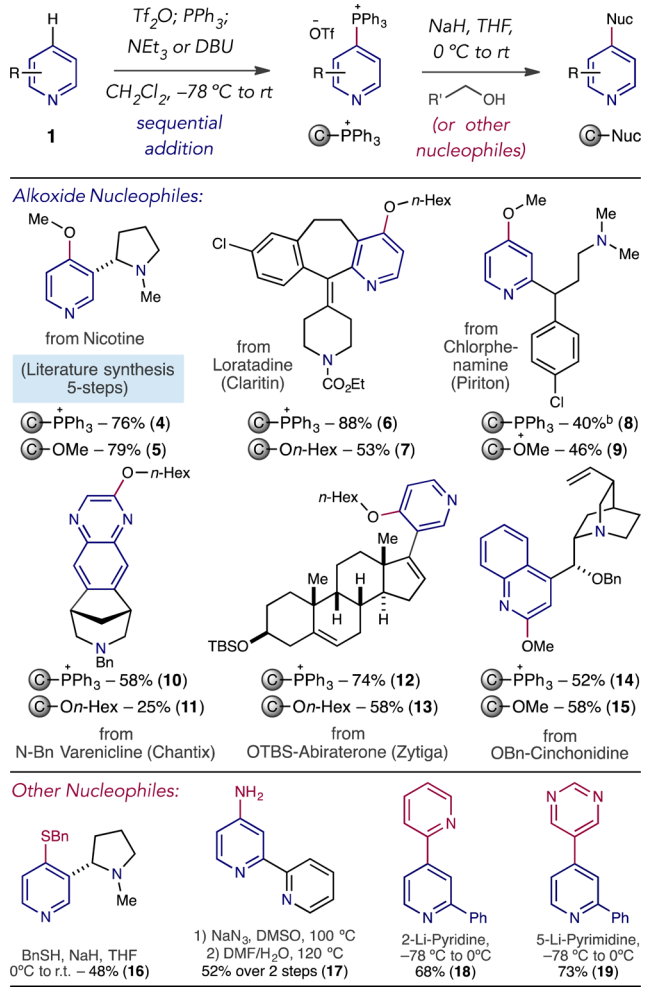
[a]Isolated yields are shown.

corresponding C−H product; studies into the reaction mechanism are ongoing in our laboratory.

We selected a number of pharmaceuticals to demonstrate late-stage functionalization (Table 3).[22] Nicotine, despite containing a tertiary aliphatic amine, is an excellent substrate for salt formation and C−O bond construction (**4**−**5**). This example is also representative of the step-economy of this protocol over conventional methods; the reported synthesis of **5** takes five steps from Cotinine.[23,24] Loratadine and Chlorphenamine can proceed through the two-step process (**6**−**9**) without difficulty. Protected versions of Varenicline, Abiraterone, and Chinchonidine are also amenable to heteroaryl ether formation in reasonable levels of efficiency (**10**−**15**).

Initial studies indicate that other readily available nucleophiles can promote bond formation. Thiolates result in C−S bonds such as in nicotine derivative **16**. Reaction with sodium azide forms iminophosphoranes after an in situ Staudinger reaction;[15,16b] deprotection under neutral conditions gives heteroaryl aniline

Table 3. Late Stage Application and Other Nucleophiles[a,b]



[a]Isolated yields are shown. [b]TfOH salt of starting material used.

(**17**). Finally, C−C bonds can be formed by adding lithiated heterocycles as in heterobiaryls **18** and **19**; LCMS analysis indicates intermediate phosphoranes are present during these reactions. At present, anionic amine, amide, or halide nucleophiles give little or no product.

In summary, pyridines and diazines can be converted into phosphonium salts that serve as reagents for subsequent C−O bond-forming reactions. Salts can be formed where traditional functionalizations would be extremely challenging using current methods. The protocol is applicable to complex bioactive molecules, and initial studies indicate C−S, C−N, and C−C bond formations are feasible. The simplicity and broad applicability of this strategy will be valuable for medicinal chemists. Currently, we are expanding the scope of phosphonium salts and range of subsequent bond-forming reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08662.

Experimental procedures and spectral data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(24) For comparative literature synthesis of **5** and analogues of **3ea** and **3ga**, see Supporting Information.

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