Selective Halogenation of Pyridines Using Designed Phosphine Reagents

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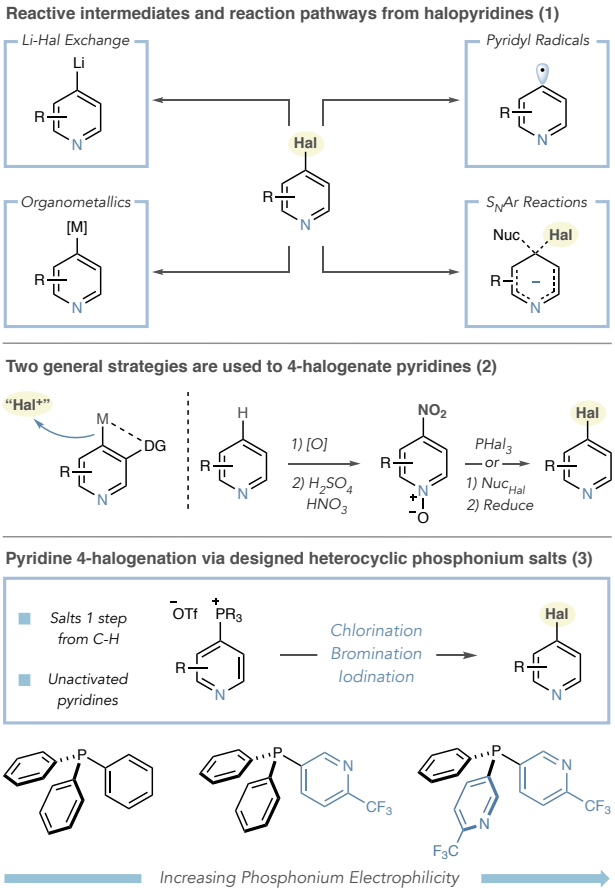
ABSTRACT: Halopyridines are key building blocks for synthesizing pharmaceuticals, agrochemicals, and ligands for metal complexes, but strategies to selectively halogenate pyridine C–H precursors are lacking. We designed a set of heterocyclic phosphines that are selectively installed at the 4-position of pyridines as phosphonium salts and then displaced with halide nucleophiles. A broad range of unactivated pyridines can be halogenated, and the method is viable for late-stage halogenation of complex pharmaceuticals. The study concludes that both tuning the phosphonium electrophilicity and pyridine substitution patterns influence the efficiency of the carbon-halogen bond-forming step.

INTRODUCTION

Haloarenes are fundamental building block compounds that enable access to an array of derivatives with precise regiocontrol (eq 1).[1] Furthermore, haloarenes are inherently valuable in functional molecules and frequently occur in pharmaceuticals and agrochemicals.[2] Halogenation methods are historically important in synthetic chemistry; numerous seminal advances in synthetic methodology use the carbon-halogen bond as a platform, and haloarene synthesis by electrophilic aromatic substitution (EAS) reactions is central to our understanding of aromatic reactivity.[3] In EAS processes, reaction of the arene π-system with electrophilic halides forms the carbon-halogen bond. However, this reactivity principle typically limits halogenation to electron-rich and electron-neutral aromatics. Electron-deficient π-systems, such as pyridines and diazines, are electronically mismatched for EAS processes, and therefore halogenation reactions require harsh conditions and are significantly more limited in scope.[4] As haloazines are essential synthetic intermediates and present in biologically active molecules, new halogenation methods can potentially address the current limitations in accessing these compounds.[5]

Positional selectivity is a useful way to classify azine halogenation reactions. For pyridines, EAS processes are 3-selective and often require strong mineral acids as solvents or Lewis acid promotion with elevated temperatures and elemental halides.[6] Lower temperatures and alternate electrophiles can be used to halogenate pyridines, but electron-donating groups are typically present.[7] 2-Selective halogenation reactions use pyridine *N*-oxides, and Hartwig reported that AgF_2 directly 2-fluorinates pyridines.[8,9] To halogenate pyridines at the 4-position, practitioners generally use two strategies (eq 2). First, metalation-trapping sequences exploit directing groups such as carbonyls and halides.[10] Second, sequences that convert pyridines into *N*-oxides followed by 4-selective nitration and then treatment with $PHal_3$ or $P(O)Hal_3$ reagents form halopyridines. Alternatively, the nitropyridine *N*-oxide can be subjected to halide nucleophiles and subsequently reduced.[11,12] Pre-installed functional groups, strong bases, oxidants, and highly acidic media



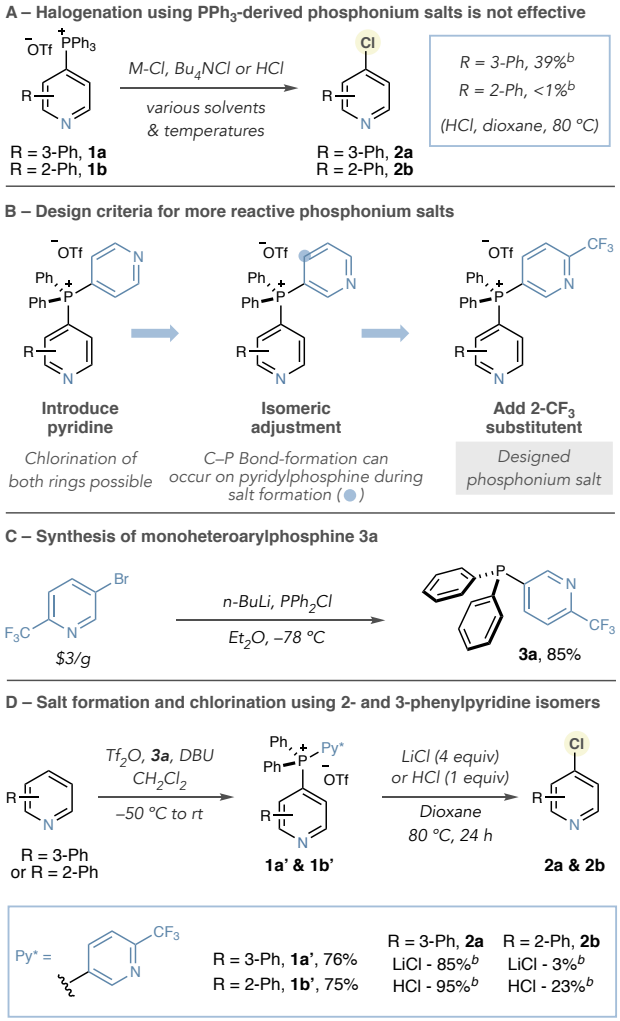
are factors in these two approaches that limit their applicability.[13] As a result, there are considerably fewer commercial 4-halopyridines than other isomers, and those available can be prohibitively expensive. Our goal was to develop a general strategy to halogenate pyridines at the 4-position that tolerates a range of functional groups as well as steric and electronic variance.[14] Herein, we present a two-step approach that hinges on designing heterocyclic phosphine reagents (eq 3). The process

uses metal halides, or halogen acids, to displace electrophilic phosphonium ions, applies to other azines, and functions on complex substrates including late-stage halogenation of pharmaceuticals.

RESULTS AND DISCUSSION

Phosphonium salts can be selectively formed at the 4-position of pyridines and displaced by nucleophiles.[15] We envisioned two mechanistic pathways for C–Hal bond formation using halide nucleophiles: halide addition to the phosphonium ion to form a P(V) intermediate followed by ligand-coupling or an S_NAr pathway with PPh_3 as a leaving group. In either case, we envisioned that the halide counterion would activate the pyridine nitrogen and promote the reaction. Therefore, we tested a set of

Scheme 1. Design of Heteroarylphosphines[a,b]

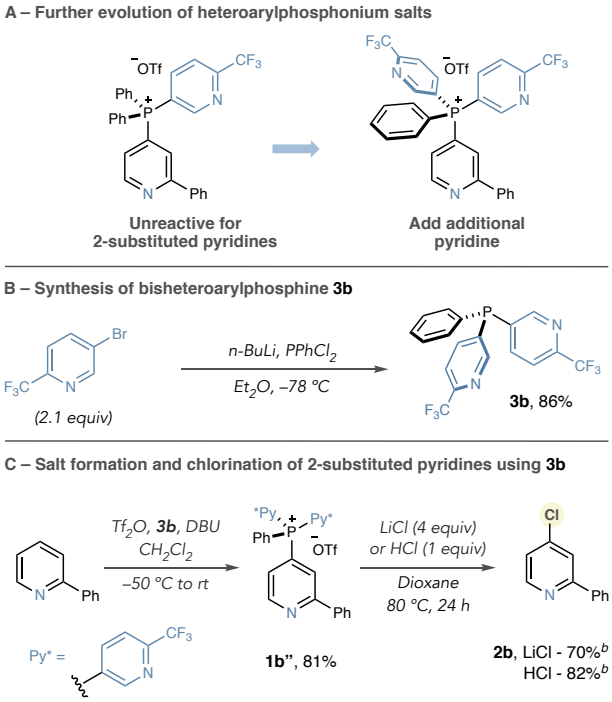


[a]Isolated yields shown (unless otherwise stated). [b]Yields calculated by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

of nucleophilic chloride sources with isomeric salts **1a** and **1b** (Scheme 1A). Despite investigating a range of reaction conditions, only low yields of **2a** and **2b** could be obtained using HCl in dioxane at 80 ºC. Given that these PPh_3-derived phosphonium salts did not react efficiently with chloride nucleophiles, we considered that more electrophilic versions were required. Therefore, we implemented a set of criteria to design salts, as shown in Scheme 1B. First, introducing a pyridyl ligand would increase the electrophilicity of the resulting phosphonium salt, where two pyridines, rather than one, could be activated by Lewis or Brønsted acids.[16] Second, we altered the C–P bond substitution pattern in the pyridine component to ensure the pyridine of interest was selectively chlorinated; both ligand-coupling processes and S_NAr reactions are unfavorable at the 3-position of pyridines. Third, installing a 2-CF_3 group would prevent reaction with Tf_2O during the salt-forming stage and ensure C–P bond formation occurs on the pyridine of interest, rather than on the phosphine reagent.[17] Importantly, preparing phosphine **3a** is straightforward in one step from diphenylphosphine and 2-trifluoromethyl-5-bromopyridine (Scheme 1C).

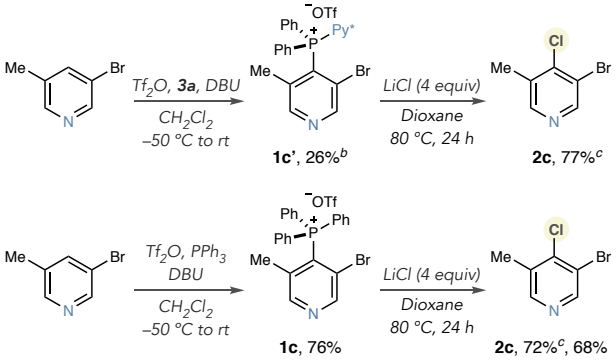
To test the hypothesis that more electrophilic phosphonium salts are viable for chlorination, we selected 2-phenylpyridine and 3-phenylpyridine as test substrates (Scheme 1D). We synthesized the corresponding phosphonium salts **1a'** and **1b'** in good yields and then subjected them to a range of metal chlorides or HCl and examined a range of reaction parameters (see the Supporting Information for full details). The results showed that 3-substituted isomer **2a** was obtained in high yields using LiCl or HCl, but significantly lower amounts of the 2-substituted isomer **2b** formed. Notably, we did not detect any chlorination of the 2-CF_3 pyridine group in the crude reaction mixtures. Our hypothesis that phosphonium electrophilicity can influence reactivity appeared valid, however, as

Scheme 2. Chlorination of 2-Substituted Pyridines[a,b]



[a]Isolated yields shown (unless otherwise stated). [b]Yield calculated by ^1H NMR or GC analysis using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3. Chlorination of 3,5-Disubstituted Pyridines[a,b,c]



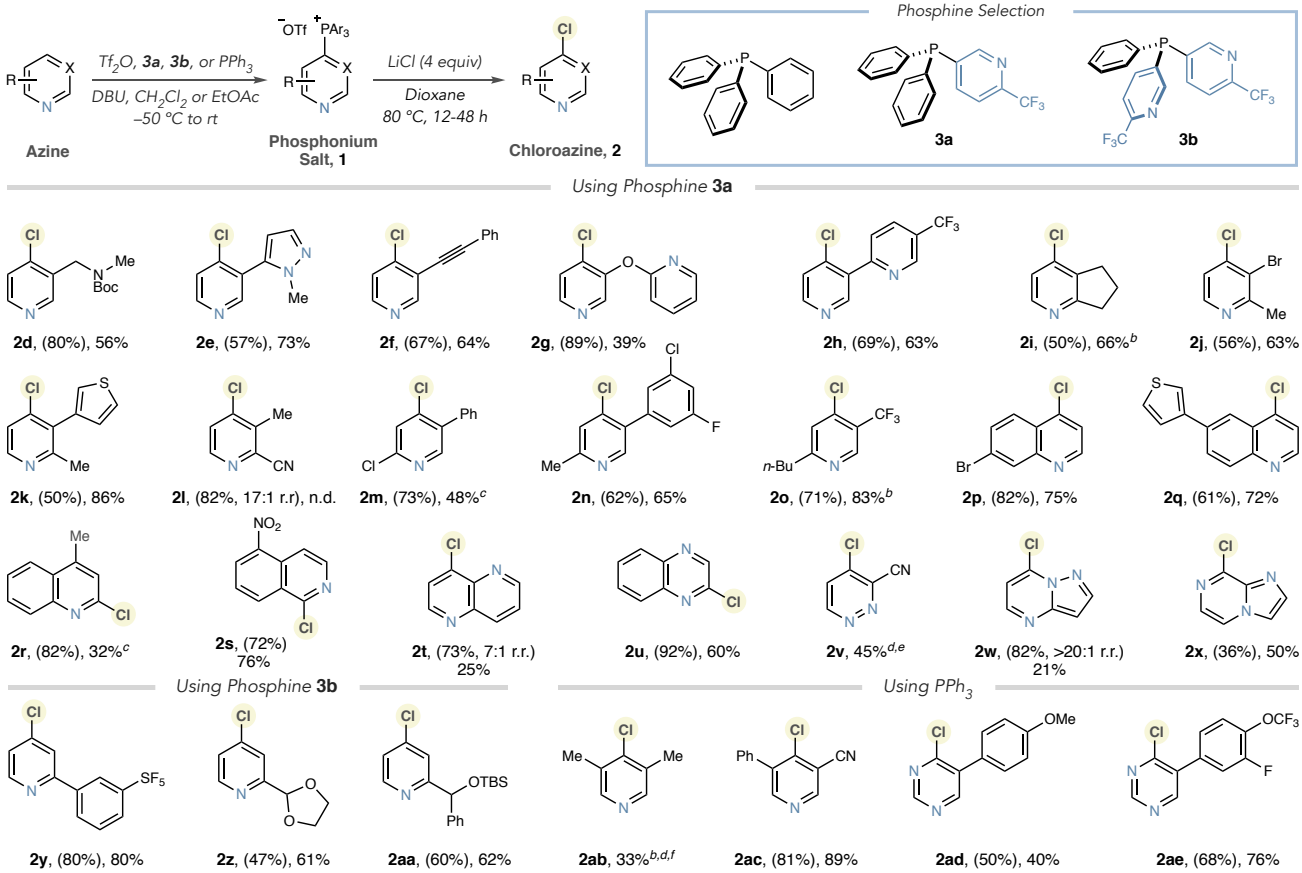
[a]Isolated yields shown (unless otherwise stated). [b]Salt isolated with 5% of an unknown impurity. [c]Yields calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

2-substituted salt **1b'** was less reactive, we suspected that steric destabilization from the 3-phenyl substituent in **1a'** was also a significant factor. Therefore, to chlorinate 2-substituted pyridines, we speculated that more electrophilic phosphonium salts were required (Scheme 2A) and synthesized modified phosphine **3b**, possessing two pyridyl groups (Scheme 2B). In line with this approach, salt **1b''** was prepared in good yield, and heating in dioxane at 80 ºC with four equivalents of LiCl, or one equivalent of HCl, efficiently formed chlorinated product **2b** (Scheme 2C).

A 3,5-disubstituted pyridine presented a further opportunity to examine the effects of steric destabilization on the reactivity phosphonium salts with chloride nucleophiles (Scheme 3). Based on the observations in Scheme 1, the significant steric hindrance in these systems was expected to result in more facile chlorination. Forming salt **1c'** proved challenging using phosphine **3a**, although the subsequent chlorination reaction was effective. In contrast, we obtained PPh_3-derived salt **1c** in a much higher yield and then **2c** in comparable yield. The conclusion from this study was that steric destabilization in 3,5-disubstituted systems outweighs the requirement for electron-deficient phosphoniums, making designed phosphines **3a** and **3b** replaceable with PPh_3.

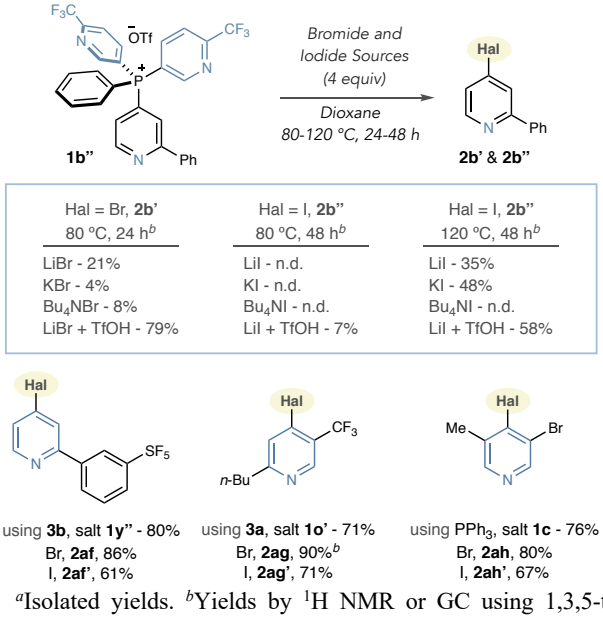
After identifying a set of phosphines, we explored the substrate scope of the pyridines and related azines amenable to the chlorination process (Table 3). Based on the substitution pattern, we matched pyridines with one of three phosphines **3a**, **3b**, and PPh_3. For pyridines possessing a 3- or 5-substituent (but not both), monoheterocyclic phosphine **3a** is most appropriate. From Scheme 1, both HCl or LiCl are effective chlorination reagents, but we proceeded with LiCl because of the likelihood of a broader substrate scope and compatibility with acid-sensitive groups, such as Boc-protected amines. As a typical case, chloropyridine **2d** was obtained in 56% yield using LiCl, without evidence of Boc-deprotection. Using HCl as a reagent, the corresponding secondary amine observed in the reaction mixture

Table 1. Chlorination of Pyridine, Quinoline and Diazine Building Blocks[a,b,c,d,e,f]



[a]Isolated yields of single regioisomers (unless stated) shown with yields of phosphonium salts in parentheses. [b]Yields calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene or triphenylmethane as an internal standard. [c]Run for 72 hours. [d]Chlorination was performed directly on the crude phosphonium salt and yield for two steps is reported. [e]Run for 5 hours. [f]Run using HCl in 1,4-dioxane (1.0 equiv) instead of LiCl.

Scheme 4. Pyridine Bromination and Iodination[a,b]

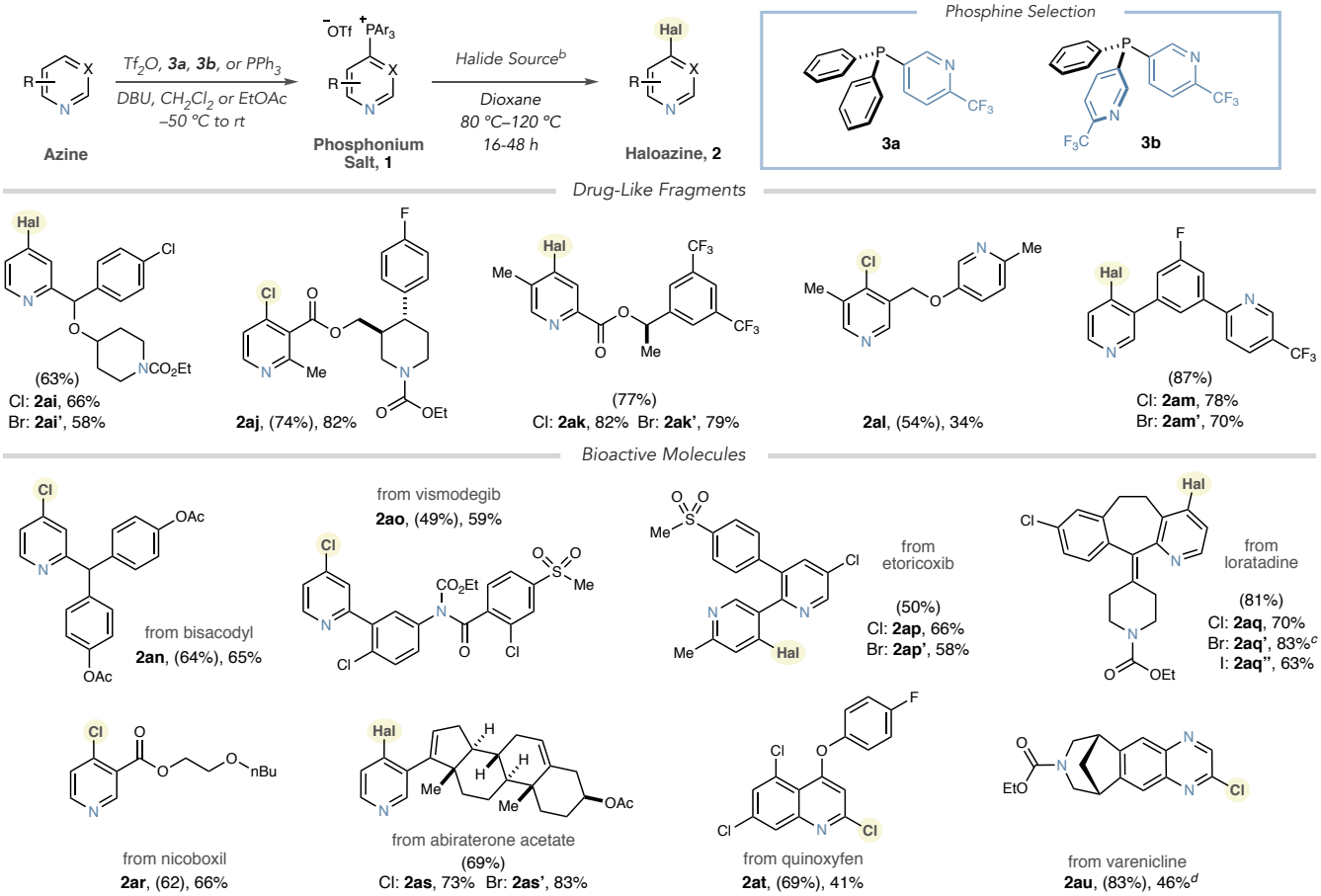


[a]Isolated yields. [b]Yields by ^{1}H NMR or GC using 1,3,5-trimethoxybenzene triphenylmethane as internal standards.

using LCMS analysis. The chlorination step tolerated 3-substituents such as pyrazoles, alkynes, and other substituted pyridines (**2e-2h**). The two-step process also chlorinated 2,3- and 2,5-disubstituted pyridines in moderate to good yields for each stage (**2i-2o**). In this set, chlorinating a 2-cyanopyridine was unsuccessful using LiCl or HCl, and the starting phosphonium salt was largely unreacted (**2l**). On the other hand, 2-chloro substituents can be present, although the reaction requires 72 hours to reach completion (**2m**). From these results, the chlorination reaction tolerates certain 2-position withdrawing groups, but cyano groups appear to prevent activation of the pyridine nitrogen sufficiently by the lithium counterion or proton. Phosphine **3a** is also a suitable reagent for quinolines and isoquinolines, and we obtained isomeric chlorinated products **2p-2s** with complete control of regioselectivity. Diazines **2t-2v** were successfully chlorinated, as were fused triazines **2w** and **2x**.

Phosphine **3b** and PPh_3 were then used to chlorinate 2- and 3,5-substituted pyridines. Using the former, we obtained an SF_5-aryl derivative **2y** without difficulty. The acid-sensitive groups in chlorides **2z** and **2aa** were again preserved using LiCl; we observed TBS deprotection by LCMS analysis using HCl as a chloride source. Forming chlorides **2ab** and **2ac** is viable using PPh_3-derived salts, and as pyrimidines undergo facile S_NAr reactions, we proposed that this attribute would also enable chlorination using PPh_3 as a reagent. Using this approach, we obtained aryl-substituted chloropyrimidines **2ad** and **2ae** in moderate yields.

Table 2. Halogenation of Pyridine-Containing Fragments and Pharmaceuticals[a,b,c,d]

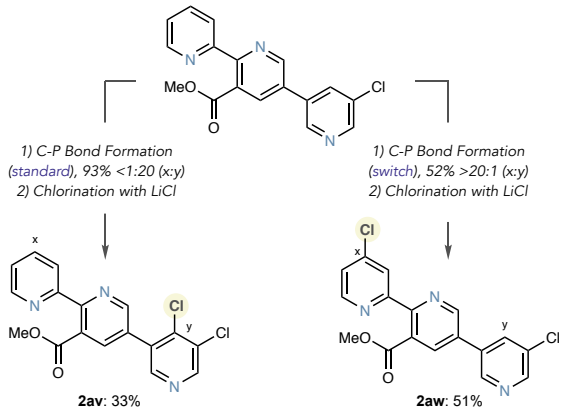


[a]Isolated yields of single regioisomers (unless stated) shown with yields of phosphonium salts in parentheses. [b]Chlorination: LiCl (4.0 equiv), 80 ºC. Bromination: LiBr (4.0 equiv), TfOH (1.0 equiv), 80 ºC. Iodination: LiI (4.0 equiv), TfOH (1.0 equiv), 120 ºC. [c]Run without TfOH. [d]Run for 72 hours.

Next, we developed protocols to install halides other than chlorides using phosphonium salt **1b''** as a test substrate (Scheme 4). For bromination, low yields of product **2b'** were obtained using LiBr, KBr or Bu_4NBr as nucleophiles at 80 ºC. However, when we combined four equivalents of LiBr with one equivalent of TfOH, bromination occurred in good yield. Using the equivalent iodide salts, either no reaction or low yields of pyridyl iodide **2b''** was observed at 80 ºC; heating the reactions at 120 ºC and prolonging the reaction times to 48 hours did result in iodination and, again, combining LiI with TfOH was optimal. Using these conditions, we chose a selection of substrates from Table 1 to examine bromination and iodination (Scheme 4). The reaction conditions translated well to halogenate a 2-aryl-SF_5 derivative (**2af** & **2af'**). Phosphonium salts derived from **3b** and PPh_3 also required acid for bromination and iodination with products **3ag-3ah'** obtained in moderate to good yields. When we examined fluoride nucleophiles or HF sources, phosphonium salts predominately cleaved to the parent C–H compounds and no fluorinated products formed using these protocols. Efforts are currently ongoing in our laboratory to improve this fluorination process.

Diversifying complex azine-containing structures is valuable for medicinal chemistry, and selective halogenation represents a means to access multiple analogs by subsequently transforming the C–Hal bond. We first tested compounds representative of drug fragments or lead compounds (Table 2). Using phosphine **3a**, a precursor to the antihistamine Bepotastine was chlorinated and brominated (**2ai** & **2ai'**). Halogenation of two isomeric ester-containing structures proceeded in good overall yields for the two-step process and ester C–O bonds were not cleaved during the process (**2aj-2ak'**). Site-selective halogenation is a valuable attribute of this protocol; we obtained bispyridyl halides **2al-2am'** with exclusive selectivity favoring the pyridine without 2- or 6-substitution in each case. Table 2 also shows late-stage halogenation of pyridine- and diazine-containing pharmaceuticals. The 2-substituted pyridines in Bisacodyl and a Vismodegib derivative were chlorinated to form **2an** & **2ao** using phosphine **3b**. Monoheterocyclic phosphine **3a** was used to generate a variety of halide derivatives of Etoricoxib, Loratadine, Nicoboxil and Abiraterone Acetate, with exclusive 4-selectivity in all cases (**2ap-2as**). With the 4-position in the pesticide Quinoxyfen blocked, the 2-position of the quinoline was chlorinated (**2at**). Finally, the two-step process was effective at chlorinating the quinoxaline core within a protected version of Varenicline in moderate yield (**2au**).

Scheme 5. Site-Selective Chlorination[a]



[a]Isolated yields are shown. Standard C–P bond formation: Heterocycle (1.0 equiv), Tf_2O (1.0 equiv), PPh_3 (1.1 equiv), DBU, (1.0 equiv), CH_2Cl_2. Switch C–P bond formation: Heterocycle (1.0 equiv), Tf_2O (2.0 equiv), Phosphine **3b** (2.0 equiv), NMe_2Cy (2.0 equiv) CH_2Cl_2.

To further emphasize that diverse libraries of analogs could be generated using this halogenation strategy, we tested our previously reported site-selective switching protocol on a MK-1064 precursor (Scheme 5).[18] Using phosphine **3a**, salt formation, and subsequent chlorination occurred on the 2,6-unsubstituted ring to form chloride **2av**, in line with the kinetically preferred reaction with Tf_2O. Although the yield of the subsequent chlorination was low, only one isomer formed. Applying the base-switch protocol allowed us to synthesize isomeric pyridyl chloride **2aw** with excellent control of regio- and site-selectivity. Numerous transformations then apply to **2av** and **2aw** to synthesize libraries of isomeric compounds.

CONCLUSIONS

In summary, we have developed a set of designed phosphine reagents that enable 4-selective halogenation of pyridines. The key design element was to incorporate electron-deficient pyridine ligands on the phosphine reagents so that the corresponding phosphonium salts are more reactive towards halide nucleophiles. Pyridines with a variety of substitution patterns and variations in steric and electronic properties are amenable to this two-step strategy, which is also effective for late-stage halogenation of complex pharmaceuticals. Given the deficiency in existing methods to produce these halogenated products, we anticipate the protocol will be useful in medicinal chemistry. Current efforts are focusing on elucidating the mechanism of the carbon-halogen bond-forming step and will be reported in due course.

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