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J Am Chem Soc. Author manuscript; available in PMC 2020 September 30.

Published in final edited form as:

J Am Chem Soc. 2020 June 24; 142(25): 11295–11305. doi:10.1021/jacs.0c04674.

Selective Halogenation of Pyridines Using Designed Phosphine Reagents

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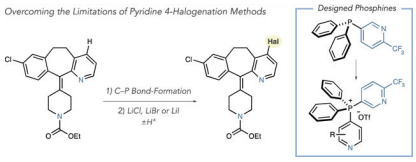
Abstract

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 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. Computational studies indicate that C–halogen bond formation occurs via an S_NAr pathway, and phosphine elimination is the rate-determining step. Steric interactions during C–P bond cleavage account for differences in reactivity between 2- and 3-substituted pyridines.

Graphical Abstract



INTRODUCTION

Haloarenes are fundamental building block compounds in which the carbon–halogen bond enables 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 understanding aromatic reactivity.[3] In EAS processes, reaction

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The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c04674.

Experimental procedures, spectral data and details of the computational methods (PDF)

Molecular coordinates and thermochemistry data (ZIP)

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of the arene π-system with an electrophilic halogen source forms the carbon– halogen bond. However, this reactivity principle typically favors halogenation of electron-rich and electron-neutral aromatics. Electron-deficient π-systems, such as pyridines, are electronically mismatched toward EAS processes; their halogenation reactions require harsh conditions and are significantly more limited in scope.[4] Developing broadly applicable pyridine halogenation methods will address current limitations in accessing essential synthetic halopyridine intermediates and biologically relevant molecules.[5]

Positional selectivity is a useful way to classify pyridine halogenation reactions. 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 required.[7] 2-Selective halogenation reactions use pyridine *N*-oxides, and Hartwig reported that AgF_2 directly 2-fluorinates pyridines.[8,9] Two strategies are generally used to halogenate pyridines at the 4-position (eq 2). First, metalation-trapping sequences exploit directing groups such as carbonyls and halides.[10] Second, sequences that convert pyridines into *N*-oxides are followed by 4-selective nitration. Halopyridines are then formed directly by treatment with $PHal_3$ or $P(O)Hal_3$ reagents, or by displacing the nitro group with a nucleophilic halide and then reducing the *N*-oxide.[11,12] Requiring preinstalled functional groups, strong bases, oxidants, and highly acidic media limits the applicability of these approaches.[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.

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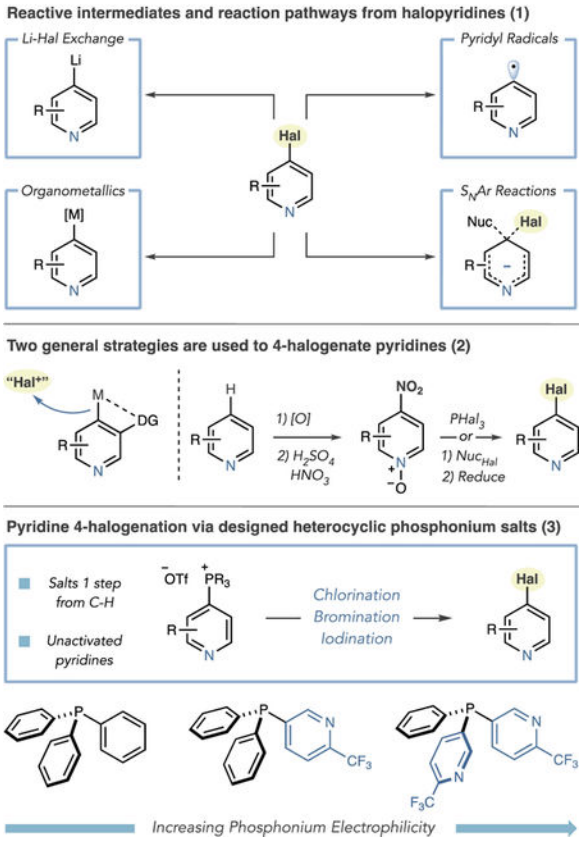

RESULTS AND DISCUSSION

Phosphonium salts can be selectively formed at the 4-position of pyridines and displaced by nucleophiles.[15] We envisioned that nucleophilic halides could displace the phosphonium group and considered two mechanistic pathways at the outset: 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.[16] As there are no reports of C–Hal bond formation via phosphorus ligand–ligand coupling reactions, we strongly preferred an S_NAr mechanism, and in either case, we suspected the halide countercation would play an important role in coordinating to the pyridine N-atom.

We tested a set of nucleophilic chloride sources with isomeric salts **1** and **2** (Scheme 1A). Despite investigating a range of reaction conditions, only low yields of **3** and **4** could be obtained using HCl in dioxane at 80 °C. Given that these PPh_3-derived phosphonium salts did not react efficiently with chloride nucleophiles, we considered that more electrophilic analogs were required. Therefore, we implemented a set of criteria to prepare more reactive phosphonium 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.[17] Second, we altered the C–P bond substitution pattern in the pyridine component to ensure the pyridine of interest was

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selectively chlorinated; both ligand-coupling processes and S_NAr reactions are unfavorable at the 3-position of pyridines.[16–18] 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.[19] Importantly, preparing phosphine **I** 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 **5** and **6** 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 (SI) for full details). The results showed that 3-substituted isomer 3 was obtained in high yields using LiCl or HCl, but significantly lower amounts of the 2-substituted isomer **4** 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 2-substituted salt **6** was less reactive, we suspected that steric destabilization from the 3-phenyl substituent in **5** 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 **II**, possessing two pyridyl groups (Scheme 2B). In line with this approach, salt **7** was prepared in good yield, and heating in dioxane at 80 °C with 4 equiv of LiCl, or 1 equiv of HCl, efficiently formed chlorinated product **4** (Scheme 2C). An increase in electrophilicity of phosphonium salts is predicted computationally at both the 4-position and the P-atom in the order of salts derived from PPh_3, **I**, and **II** (Figure S2). A one-pot salt-formation–halogenation reaction is possible, but significant decreases in yield and reversion of the phosphonium salt to the parent C–H compound are observed (Table S6).

A 3,5-disubstituted pyridine presented further opportunity to examine the effects of steric destabilization on the of 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 **8** proved challenging using phosphine **I**, although the subsequent chlorination reaction was effective (**9**). In contrast, we obtained PPh_3-derived salt **10** in a much higher yield, and **9** formed in comparable yield. The greater steric destabilization present in these systems outweighs the requirement for electron-deficient phosphoniums such that designed phosphines **I** and **II** are replaceable with PPh_3 for the reactions of 3,5-disubstituted substrates.

After identifying a set of phosphines, we explored the substrate scope of the pyridines and related azines amenable to the chlorination process (Table 1). Based on the substitution pattern, we matched pyridines with one of three phosphines **I**, **II**, and PPh_3. For pyridines possessing a 3- or 5-substituent (but not both), monoheterocyclic phosphine **I** is most appropriate. From Scheme 1, both HCl and 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 **11** was obtained in 56% yield using LiCl, without evidence of Boc-deprotection. Using HCl as a reagent, the corresponding secondary amine was observed in the reaction mixture using

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LCMS analysis. The chlorination step tolerated 3-substituents such as pyrazoles, alkynes, and other substituted pyridines (**12**–**15**). The two-step process also chlorinated 2,3- and 2,5-disubstituted pyridines in moderate to good yields for each stage (**16**–**22**). In this set, chlorinating a 2-cyanopyridine was unsuccessful using LiCl or HCl, and the starting phosphonium salt was largely unreacted (**19**). On the other hand, 2-chloro substituents can be present, although the reaction requires 72 h to reach completion (**20**). We hypothesized that the cyano group prevents pyridine activation by the Lewis or Brønsted acid. Phosphine I is also a suitable reagent for quinolines and isoquinolines for which we obtained isomeric chlorinated products **23**–**26** with complete control of regioselectivity. Diazines **27**–**29** were successfully chlorinated, as were fused triazines **30** and **31**.

Phosphine **II** and PPh_3 were then used to chlorinate 2- and 3,5-substituted pyridines. Using the former, we obtained an SF_5-aryl derivative **32** without difficulty. The acid-sensitive groups in chlorides **33** and **34** were again preserved using LiCl; we observed TBS deprotection by LCMS analysis using HCl as a chloride source. Forming chlorides **35** and **36** 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 **37** and **38** in moderate yields.

Next, we developed protocols to install halides other than chlorides using phosphonium salt **7** as a test substrate (Scheme 4). For bromination, low yields of product **39** were obtained using LiBr, KBr, or Bu_4NBr as nucleophiles at 80 °C. However, when we combined 4 equiv of LiBr with 1 equiv of TfOH, bromination occurred in good yield, presumably because protonation generates a more reactive pyridinium salt. Using the analogous iodide salts, either no reaction or low yields of pyridyl iodide **40** were observed at 80 °C; heating the reactions at 120 °C and prolonging the reaction times to 48 h 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 (**42** and **43**). Phosphonium salts derived from **II** and PPh_3 also required acid for bromination and iodination with products **45**–**48** 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 pyridine-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 **I**, a precursor to the antihistamine Bepotastine was chlorinated and brominated (**49** and **50**). 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 (**51**–**53**). Site-selective halogenation is a valuable attribute of this protocol; we obtained bis-pyridyl halides **54**–**56** with exclusive selectivity favoring the pyridine without 2- or 6-substitution in each case. Table 2 also shows late-stage halogenation of pyridine-containing pharmaceuticals. The 2-substituted pyridines in

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Bisacodyl and a Vismodegib derivative were chlorinated to form **57** and **58** using phosphine **II**. Monoheterocyclic phosphine **I** was used to generate a variety of halide derivatives of Etoricoxib, Loratadine, Nicoboxil, and Abiraterone Acetate, with exclusive 4-selectivity in all cases (**59**–**66**). With the 4-position in the pesticide Quinoxyfen blocked, the 2-position of the quinoline was chlorinated (**67**). Finally, the two-step process was effective at chlorinating the quinoxaline core within a protected version of Varenicline in moderate yield (**68**).

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 an MK-1064 precursor (Scheme 5).[20] Using phosphine PPh_3 and DBU as a base, salt formation and subsequent chlorination occurred on the 2,6-unsubstituted ring to form chloride **69**, 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, using NMe_2Cy as well as 2 equiv of Tf_2O and **II**, allowed us to synthesize isomeric pyridyl chloride **70** with excellent control of regioselectivity and site selectivity. This result aligns with the rationale where the phosphine adds to the Tf-activated 2- and 3,5-disubstituted pyridine rings to form dearomatized adducts. Steric interactions between the 3- and 5-substituents and the trialkylamine base prevent rearomatization, whereas these effects are absent in the 2-substituted pyridine. Numerous transformations then apply to **69** and **70** to synthesize libraries of isomeric compounds.

COMPUTATIONAL STUDIES

We turned to quantum chemical calculations to model the mechanism of carbon–halogen bond formation, using density functional theory (DFT)[21] with the SMD solvation model (1,4-dioxane)[22] to study these reactions. Results are presented at the ωB97X-D/def2-QZVPP//ωB97X-D/def2-SVP level of theory. The presence of anionic nucleophiles and hypervalent P(V) species present potential challenges for computation,[23] and benchmarking studies were carried out. The use of larger basis sets and additional diffuse basis functions during geometry optimizations and single-point energy calculations, including Def2-TZVPP, Def2-TZVPPD, and Def2-QZVPPD, were examined, and very similar results were obtained with these different protocols (see the Studies using larger basis sets with diffuse functions section of the SI). We selected 3-Ph and 2-Ph phosphonium salts **5** and **6**, respectively, as the substrates for the computational study. We included the triflate counteranion in all calculations unless otherwise stated, since the calculated energy of the dissociated ions in dioxane is considerably larger than that of the ion pair (19.0 kcal/mol). However, the overall mechanism is qualitatively unaffected by omitting this counterion (Figure S7).

First, we address the question of whether hypervalent P(V) intermediates are formed prior to C–X bond formation. Figure 1 shows the calculated Wiberg Bond Orders (WBOs)[24] and bond distances of P–X bonds for the optimized geometries of **6** with the different halides used experimentally. Chloro-, bromo-, and iodophosphoranes do not form stable pentavalent geometries and instead prefer phosphonium halide ion-pair structures. Fluorophosphoranes, on the other hand, form stable P(V) intermediate structures as illustrated in Figure 1B. These DFT results are consistent with tabulated P–X bond strengths (P–Br: 267, P–Cl 289, P–F

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439 kJ/mol).[25] Excluding fluorination, these results implicate the direct attack of the halide at carbon (i.e., an S_NAr pathway) rather than via phosphorus ligand-coupling.

Figure 2A shows the overall Gibbs energy profile for the formation of chloropyridines **3** and **4**. The computed transition structures (TSs) indicate an S_NAr-type mechanism takes place.[26] A relatively flat potential energy surface exists, across which two discrete steps occur: addition of chloride at the 4-position of an activated pyridinium (here modeled by HCl protonation) in **TS-I**, and the subsequent cleavage of the C–P bond in **TS-II**. The intervening Meisenheimer complex, **Int-III**, is a stable intermediate structure, although this lies very close in energy with the first TS. The second TS, forming products **3** and **4** and phosphine byproduct, lies highest in energy and is the rate-limiting step. Figure 2B highlights the critical role of a Brønsted or Lewis acid additive (either HCl or LiCl), as the activation barrier is raised prohibitively high (42.5 kcal/mol for salt 6) in their absence, via a concerted mechanism.[27] The calculations also clarify why reagents such as Bu_4NCl are not effective due to the relatively weak Lewis acidity of the ammonium counterions with pyridine Lewis bases. The differential reactivity of 2- and 3-substituted pyridines results from steric interactions that are enhanced as the phosphine departs in **TS-II** (Figure 2C). Compared to **TS-I**, the phosphine lies further out of the aromatic plane, bringing it closer of the ring substituents. As seen in the NCI plots, the P-aryl groups make contact with the 3-Ph substituent of salt **5** while these interactions are less significant with the more remote 2-Ph group in salt **6**. The computed $\Delta\Delta G^{\ddagger}$ of 2.8 kcal/mol is indicative of around a 50-fold increase in reactivity of **5** over **6**. Computations suggest that this energy difference is due to sterics, rather than arising from differences in pyridine electronics, since similarly sized but electronically distinct groups are predicted to behave in the same way (Figure S6). This finding reinforces the role of sterics over electronic effects, and we believe the hypothesis is generalizable to a reasonable extent based on the substrates examined in this study.

The computed activation barrier obtained in 1,4-dioxane (20–22 kcal/mol) would be indicative of room temperature sreactivity,[28] whereas experimentally we required heating to 80 °C. We attribute this in part to the heterogeneous nature of the reaction, and potential solubility effects, that were not modeled computationally. Qualitative conclusions concerning the C– Hal bond-forming process and the differences in reactivity between 2- and 3-substituted pyridines, which are consistent with experiment, are unaffected by these differences.[29,30]

Finally, we considered the failure of phosphonium salt fluorination to occur under these the same conditions, and the return of the parent C–H bond as the major outcome. As described above, a mechanistic switch vs other halogens is expected, involving the intermediacy of a P(V) fluorophosphorane. In the optimized geometry of this intermediate, the axial $P–C_{pyr}$ bond is lengthened, and therefore weakened, considerably relative to its equatorial counterpart (1.96 and 1.91 vs 1.84 Å, Figure 1C), and can potentially decompose in the same manner as when pyridine phosphonium salts react with carbonates, hydroxides, and alkoxides.[31] Elongation of the axial $P–C_{pyr}$ bond can occur relatively easily (computationally, stretching by 0.2 Å costs just 3.9 kcal/mol), such that reaction of this pyridyl group with an external proton source at the 4-position is possible; we have not

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identified the nature of the proton source at this point in our studies and have observed the same result with rigorously dried reaction reagents and solvents.

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 toward 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. Computational studies indicate that C–Hal bond formation occurs via a stepwise S_NAr pathway that requires *N*-activation of the pyridyl group. Phosphine elimination is the rate-determining step. Steric interactions between the departing phosphine and pyridyl substituents are most pronounced during C–P bond cleavage and account for differences in reactivity between 2-and 3-substituted pyridines. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by The National Institutes of Health (NIGMS) under Award Number R01 GM124094. Further support came from startup funds from Colorado State University and partial support from the National Science Foundation under Grant No. (1753087). We acknowledge the RMACC Summit supercomputer, supported by the NSF (ACI-1532235 and ACI1532236), and the Extreme Science and Engineering Discovery Environment (XSEDE) allocations TG-CHE180056 and TG-CHE190111.

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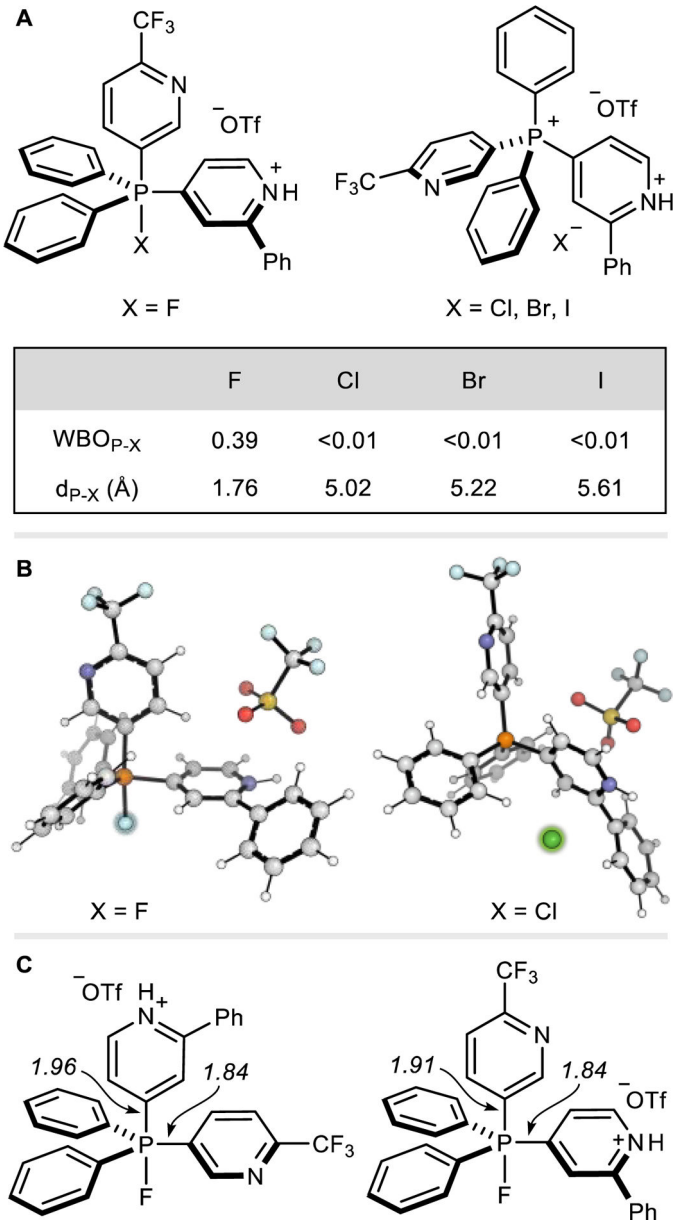

	F	Cl	Br	I
WBO_{P-X}	0.39	<0.01	<0.01	<0.01
d_{P-X} (Å)	1.76	5.02	5.22	5.61

Figure 1.

(A) WBO and distances of P–X bonds of the different species formed with phosphonium salts and different halogen anions. (B) Representation of the most stable conformers when using F and Cl atoms. (C) Lengths of axial and equatorial P–C bonds, in Å, in multiple conformations of the fluorophosphorane studied.

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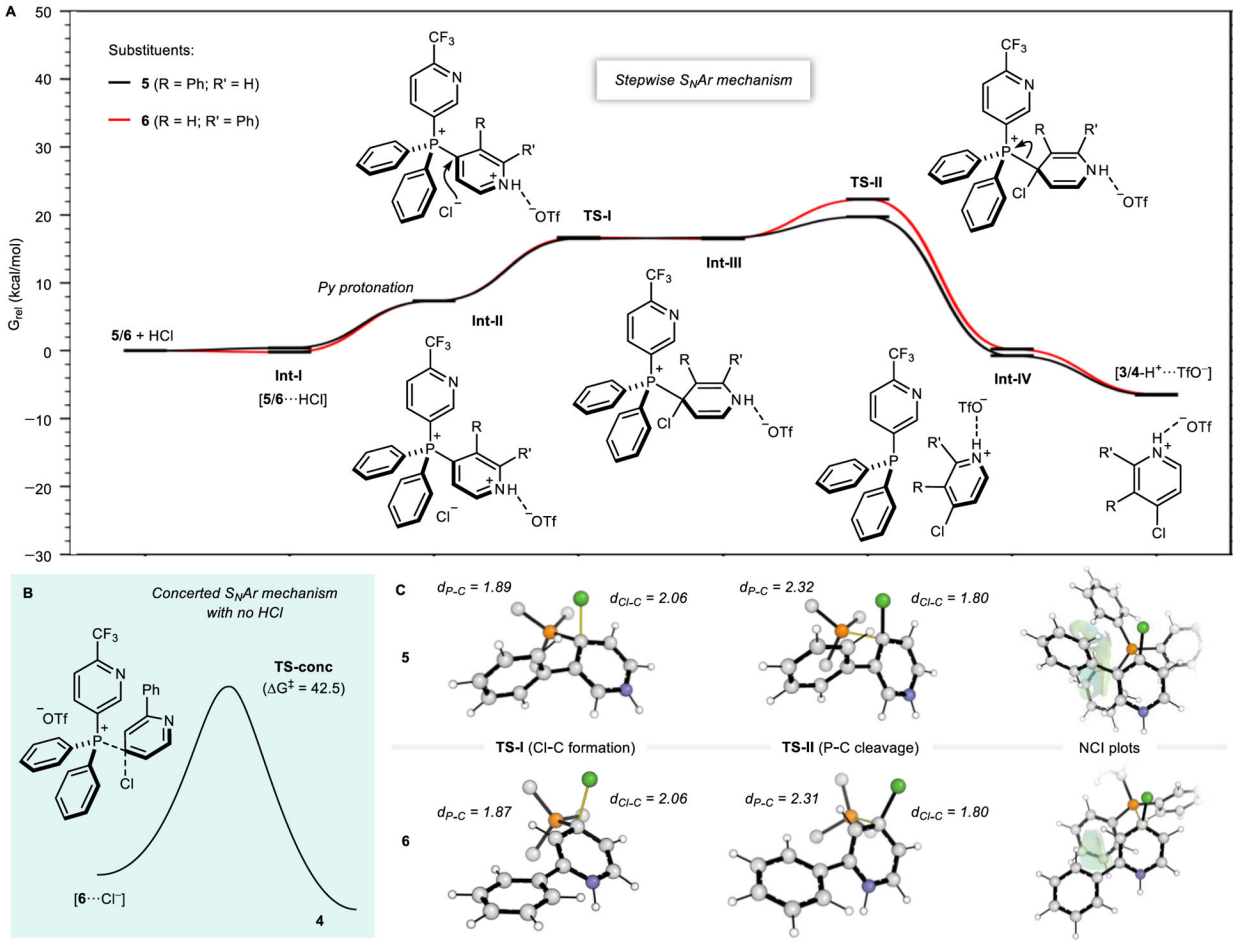

Figure 2.

(A) Boltzmann weighted relative *G* in kcal/mol during the formation of products **3** (3-Ph substituent, black line) and **4** (2-Ph substituent, red line) at 80 °C (*ω*B97X-D/Def2-QZVPP//*ω*B97X-D/Def2-SVP, SMD with 1,4-dioxane). (B) Reaction coordinate to form **4** when using Cl^- instead of HCl. $\Delta G^{\ddagger}$ is shown in kcal/mol. (C) Representations of the most favorable **TS-I** and **TS-II** steps with P–C and Cl–C bond distances (in Å) when using 5 and 6, along with NCIPlot[32] surfaces of the corresponding **TS-II** steps. Bonds involved in the TSs are represented as yellow lines. Phosphorus substituents and the TfO^- counteranion are omitted for clarity in some cases.

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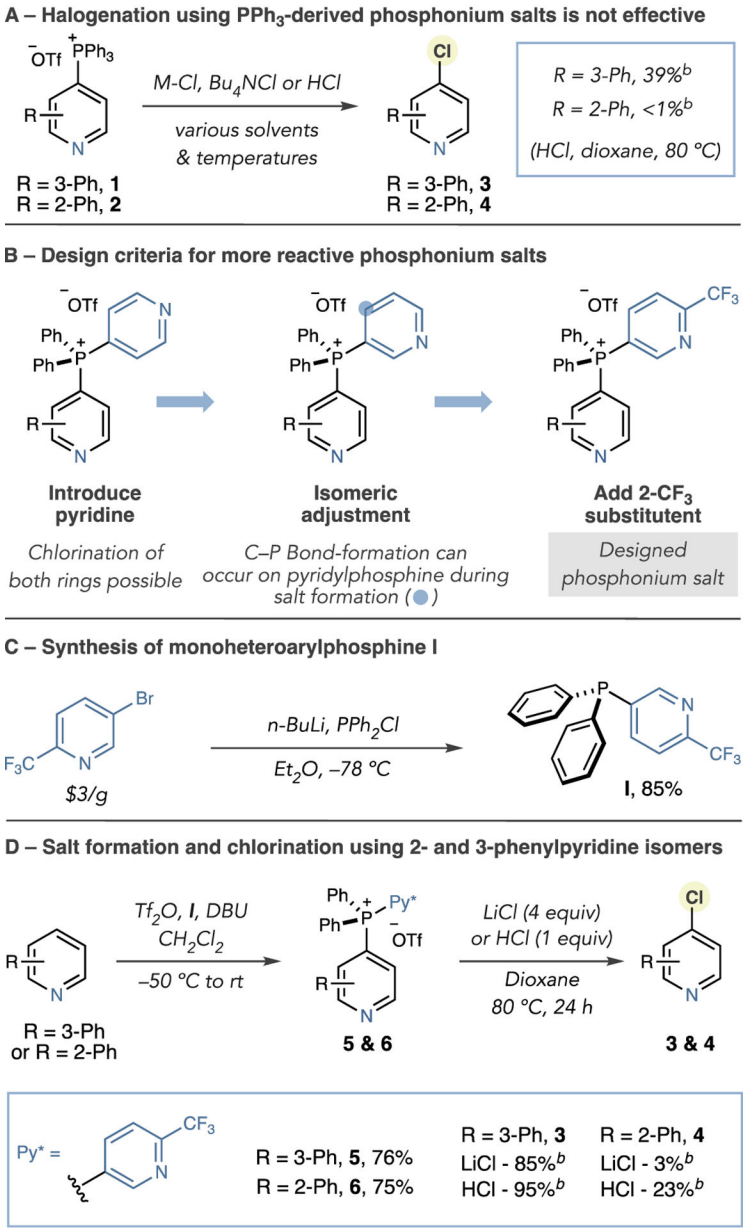

Scheme 1. Design of Heteroarylphosphines[a,b]

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

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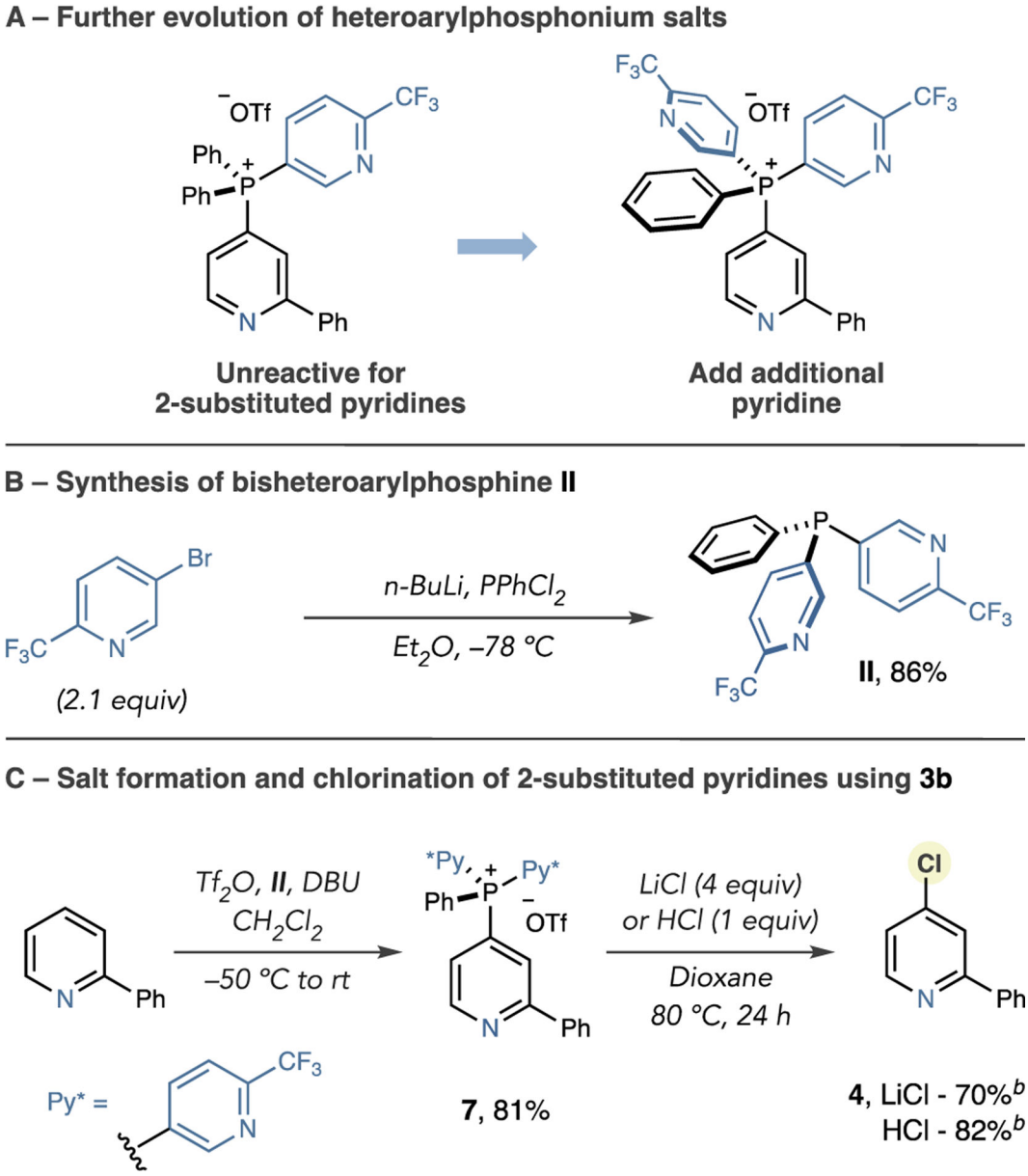

Scheme 2. Chlorination of 2-Substituted Pyridines[a,b]

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

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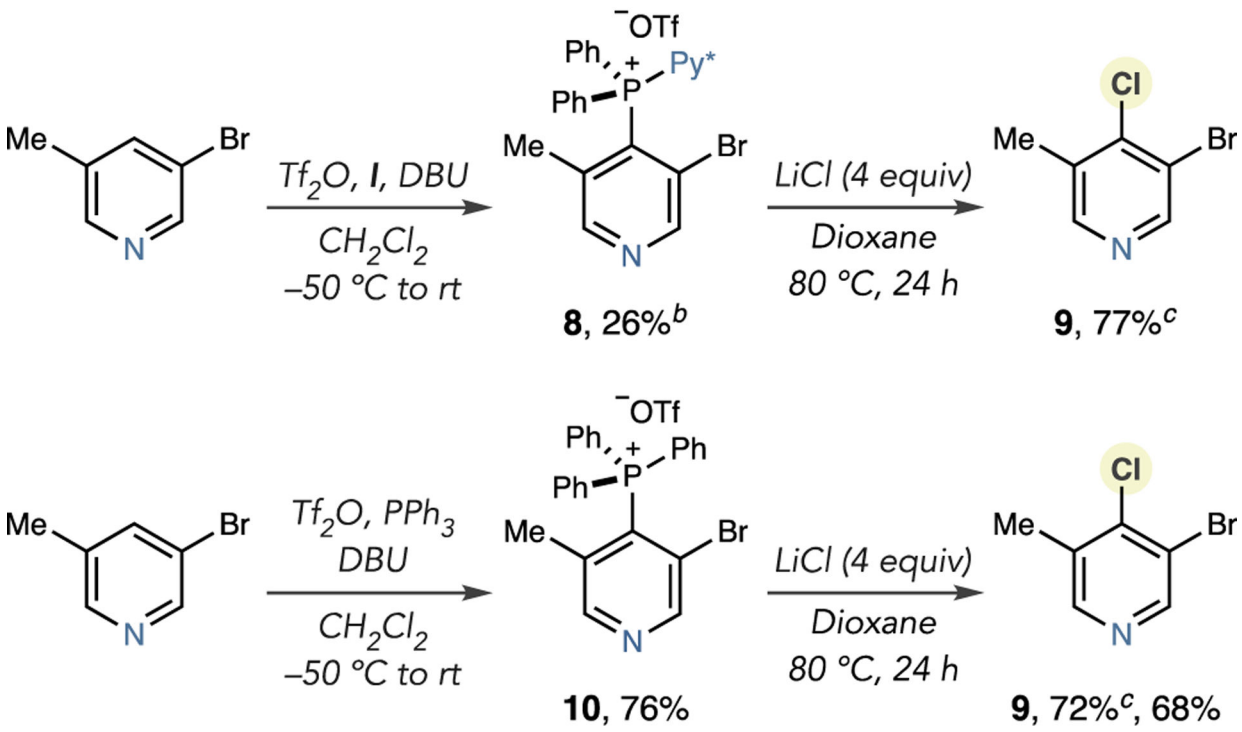

Scheme 3. Chlorination of 3,5-Disubstituted Pyridines[a,b,c]

[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.

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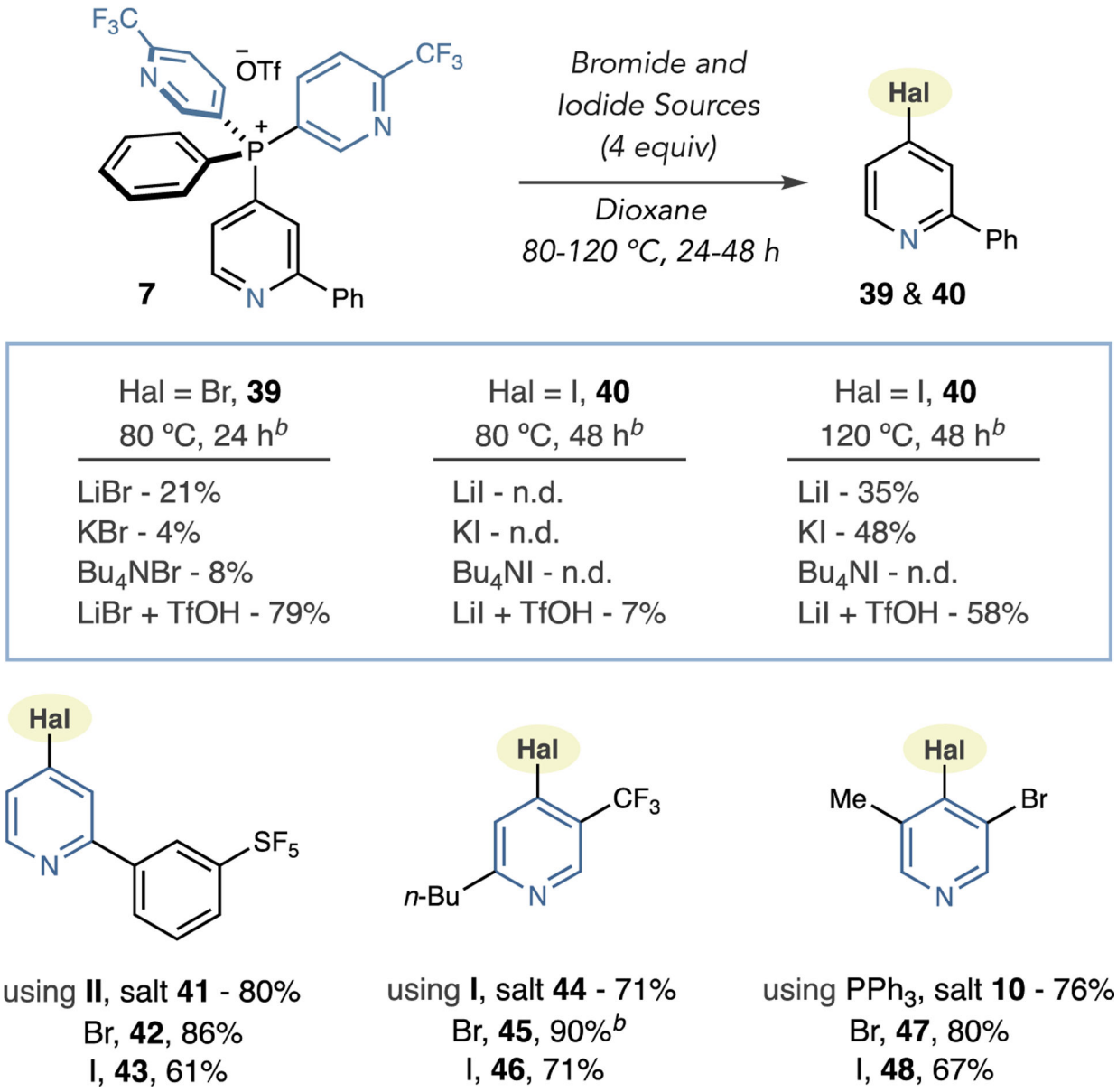

Scheme 4. Pyridine Bromination and Iodination[a,b]

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

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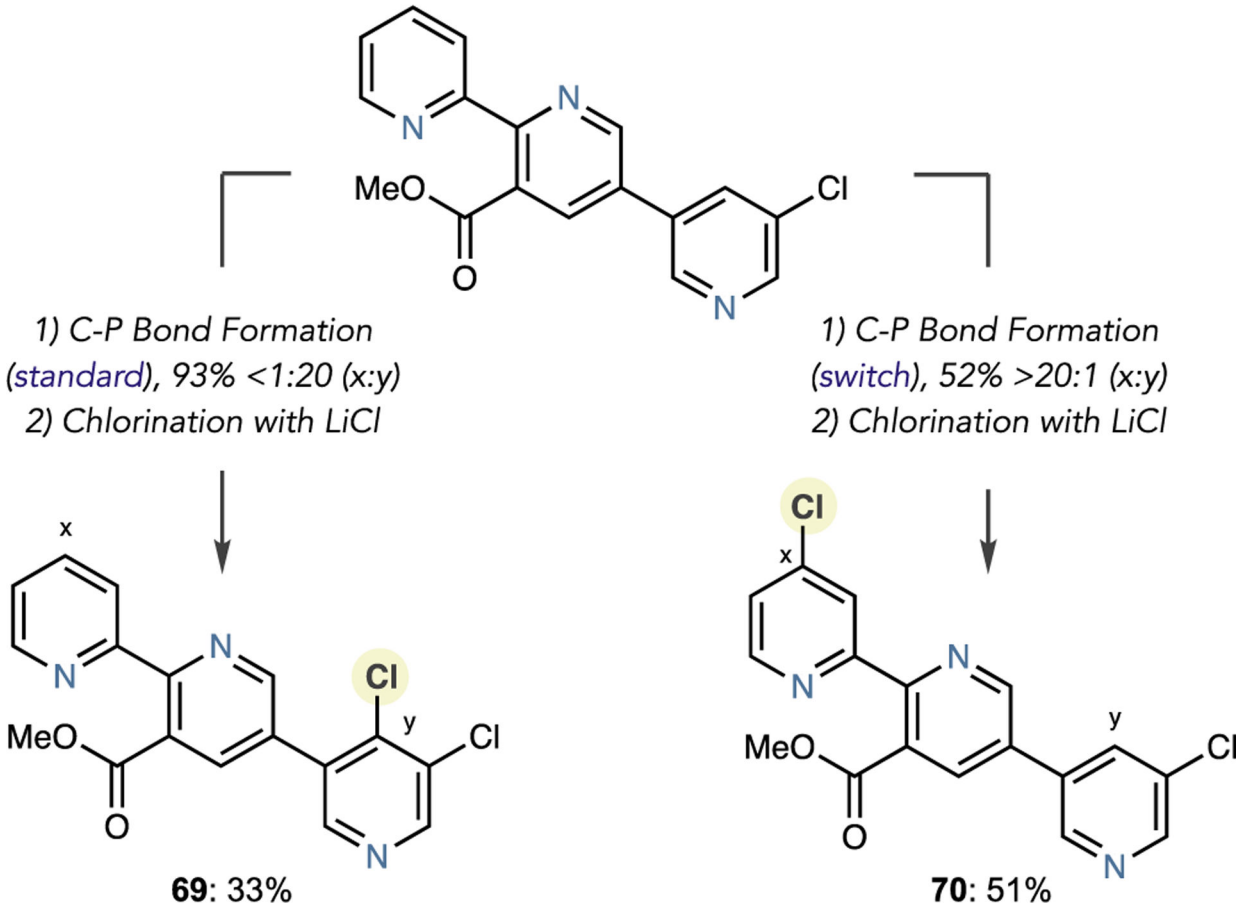

Scheme 5. Site-Selective Chlorination[a]

[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 **II** (2.0 equiv), NMe_2Cy (2.0 equiv), CH_2Cl_2.

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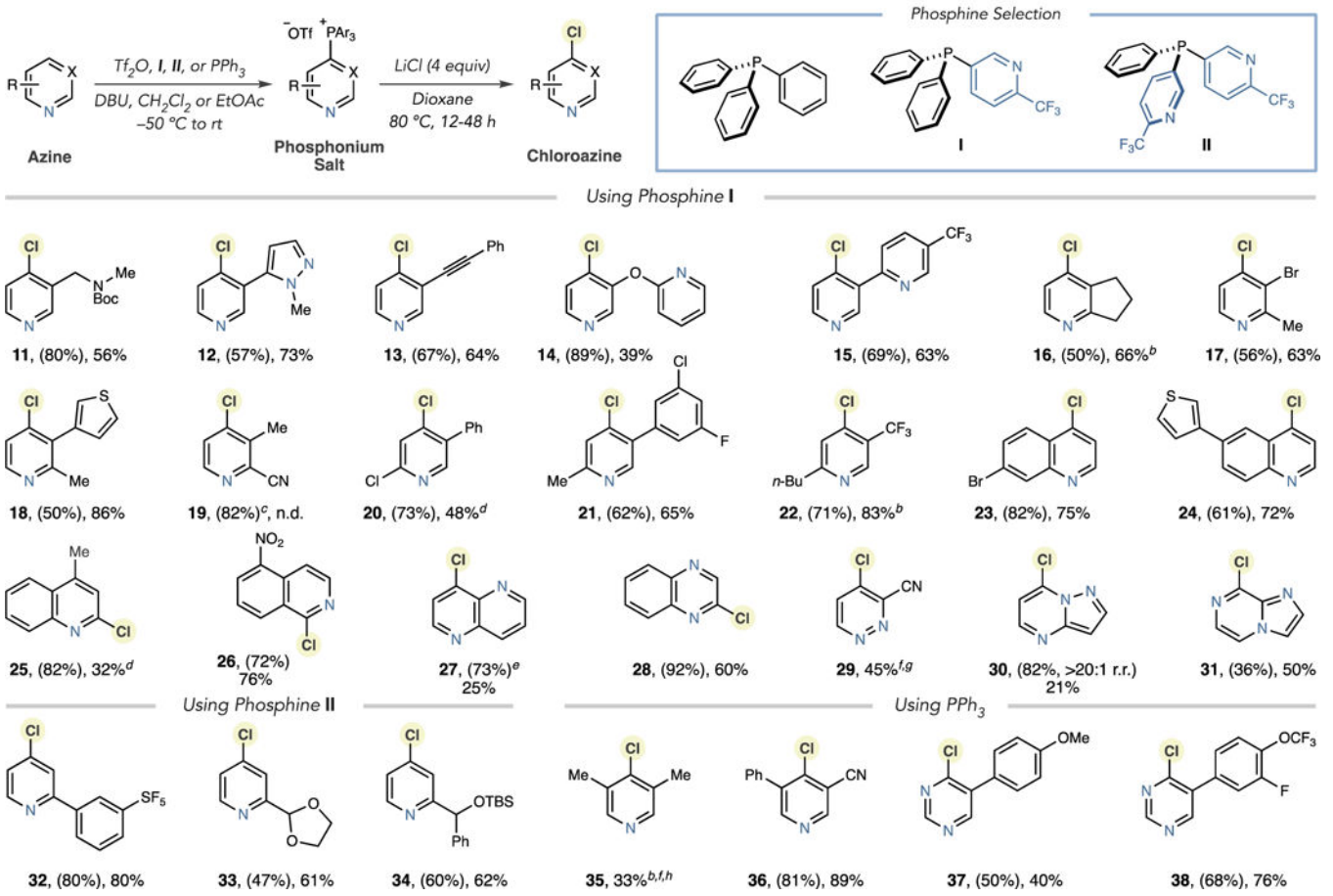
Table 1.

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] Isolated as an inseparable 17:1 mixture with an impurity.

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[d] Run for 72 h.

[e] Isolated as an inseparable 7:1 mixture with an impurity.

[f] Chlorination was performed directly on the crude phosphonium salt and yield for two steps is reported.

[g] Run for 5 h.

[h] Run using HCl in 1,4-dioxane (1.0 equiv) instead of LiCl.

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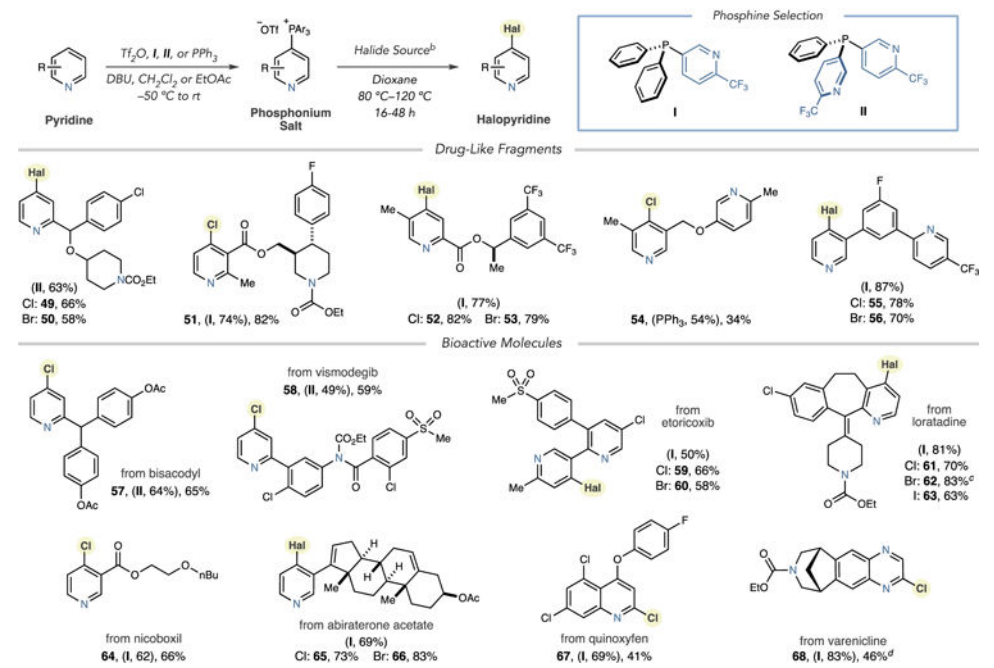
Table 2.

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 from **I**, **II**, or PPh3.

[b] Chlorination: LiCl (4.0 equiv), 80 °C. Bromination: LiBr (4.0 equiv), TfOH (1.0 equiv), 80 °C. Iodination: LiI (4.0 equiv), TfOH (1.0 equiv), 120 °C.

[c] Run without TfOH.

[d] Run for 72 h.