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A Simple Strategy to Aminate Pyridines, Diazines and Pharmaceuticals via Heterocyclic Phosphonium Salts

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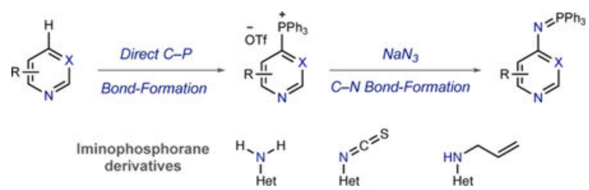
Abstract

A straightforward process to aminate pyridines and diazines is presented by reacting phosphonium salt derivatives with sodium azide. The iminophosphorane products are versatile precursors to several nitrogen-containing functional groups, and the process can be applied to building block heterocycles, drug-like fragments and for late-stage functionalization of complex pharmaceuticals. Appealing features of this strategy include using C–H bonds as precursors, precise regioselectivity, and a distinct scope from other amination methods, particularly those relying on halogenated azaarenes.

Graphical Abstract



Extensive efforts have been dedicated towards aminating aromatic rings over the past several decades due to the wide-spread occurrence of aryl amines in pharmaceuticals, agro-chemicals, natural products and materials.[1] The most widely applied methods are metal-catalyzed C–N cross-coupling reactions but several other distinct strategies have emerged including radical-based methods, reactions with nitrogen electrophiles, nitroarene reduction processes and C–H amination reactions (eq 1).[2–6] We became interested in this field after noticing that: a) aminopyridines and diazines are prominent in drug compounds (eq 2) and b) the number of broadly effective methods to aminate these heterocycles are considerably narrower than for benzene derivatives.[7–10] The classic Chichibabin reaction forms 2-aminopyridines from C–H precursors lacks generality due to the excessive reactivity of NaNH2.[11] Most methods rely on prehalogenated substrates such as Buchwald-Hartwig reactions, recent Ni-catalyzed cross-couplings and SNAr reactions.[2a,2f,13] While these are powerful approaches, they can be limited by the lack of methods that can selectively install

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Supporting Information
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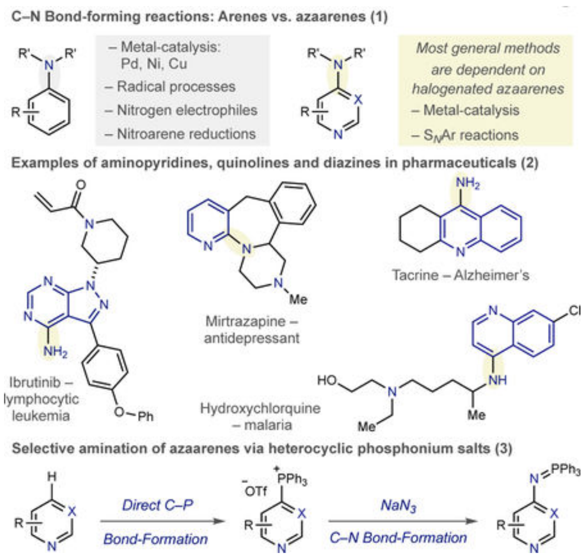
Experimental procedures and spectral data (PDF)

halides on more complex pyridines and diazines. As such, an alternative approach that produces a distinct set of aminated products would be valuable to medicinal chemists.

We are engaged in a program aimed at selectively transforming pyridine and diazine C–H bonds into phosphonium ions and then exploiting the reactivity of the C–P bond to make useful heterocyclic derivatives. Ourselves and Anders reported a single example of transforming the C–$^{+}$PPh3 group into an iminophosphorane using NaN3 as a nucleophile, however, we did not know if this strategy would be general across a range of pyridines and diazines.[14,15] We were therefore compelled to investigate this process further as phosphonium salts can be formed on azaarenes that are often outside of the scope



of current halogenation methods (eq 3). For example, Hartwig's AgF2-mediated pyridine fluorination reaction can be used to introduce amines at the 2-position,[16] whereas phosphonium salt formation is selective for the 4-position of the scaffold. We herein report that this phosphorus-mediated strategy can be broadly applied to selectively aminate building block heterocycles, drug-like fragments and complex pharmaceuticals. Iminophosphoranes are also versatile functional groups that can be transformed into valuable nitrogen-containing derivatives.

Our first priority was to build on the preliminary result by investigating reaction parameters to obtain a standard amination protocol. We found that heating 2-phenyl phosphonium salt in the presence of sodium azide in DMSO at 120 ^{0}C was optimal in terms of temperature and that increasing the concentration of the reaction to 1.5 M also increased the yield of the reaction. Although it is possible to use solvents other than DMSO as the reaction medium, reaction efficiency suffers (see ESI for further details). Small amounts of the corresponding C–H heterocyclic precursor are obtained in the reaction that can be separated via column chromatography.

With an optimized amination reaction in hand, we began exploring the generality of this amination process. Starting with pyridines, we selected scaffolds displaying a variety of substitution patterns and functional groups. In all cases, phosphonium salt formation and subsequent amination is exclusively selective for the 4-position (Table 1A). Tetrahydroquinoline, bearing a 2,3-susbtitution pattern is smoothly aminated using this protocol

(**2a**). Similarly, 2,5-disubstituted pyridines bearing substituents including trifluoromethyl, thiomethyl, cyano groups and aryl ethers are effective (**2b–2d**). Sterically hindered 3,5-disubstituted pyridines also see C–N bond formation selectively occur at the 4-position (**2e** & **2f**). If the 4-position is blocked, then the 2-position is aminated instead, as shown for pyridine **2g** and quinoline **2h**. Diazines are also compatible with this approach; aminopyrazine **2i** and aminoquinoxaline **2j** are obtained in reasonable yields. Pyrimidines **2k** and **2l** work particularly well in the C–N bond-forming step and although the synthesis of pyrrolopyrimidine **2m** was less efficient, it still gives access to a motif found in drugs such as tofacitinib (Scheme 1B).

Our attention turned to drug-like fragments with pyridines and diazines in their structures.[17] These types of molecules are abundant in pharmaceutical compound collections, and applying the amination protocol would result in important amino derivatives. However, their structures are often complex with other functional groups and basic nitrogen atoms present making C–N bond-formation challenging. Table 1B shows that a diverse set of representative drug fragments can be converted into iminophosphoranes using this two-step process. Iminophosphorane **2n**, containing a tri(hetero)aryl methane motif is formed in good overall yield. Similarly, benzhydryl stereocenters are accommodated in pyridine **2o**, without interference from the piperidine moiety. Distinct pyrimidine-containing fragments, such as **2p** and **2q**, are particularly effective in this strategy. Finally, tri(hetero)aryl systems **2r** and **2s** are noteworthy due to the potential isomeric mixtures of iminophosphoranes between the different pyridine rings; a single regio- and site-selective outcome was observed in each case.

Late-stage functionalization of pharmaceuticals is being intensively investigated at present, although strategies to aminate complex pyridines and diazines are limited.[18] Outside of Hartwig's 2-fluorination reaction, Iridium-catalyzed borylation is the most promising strategy for aminating azaarenes as the C–B bond can be used as a coupling handle to introduce an amine.[16,19] Our previous studies have shown that complex pharmaceuticals can be converted into phosphonium salts with excellent regio and site-selectivity;[14a,b] successfully applying the subsequent azide coupling reaction would therefore represent an important method for late-stage amination. Table 1C shows that the two-step sequence is straightforward to apply to a set of structurally diverse pharmaceuticals. Chlorphenamine, a common antihistamine, is converted into iminophosphorane **2t** with exclusive regioselectivity over two steps. The C–N bond-forming step for loratadine occurs with lower yield but in quantities that would be usable for medicinal chemists (**2u**). Benzyl protected varenicline (**2v**), containing a quinoxaline ring, can also be aminated via this strategy. The site-selectivity issues in etoricoxib and imatinib are overcome using this phosphorus mediated approach; the

C–P bond is formed exclusively at the 4-position of the 2,5-disubstituted pyridine in etoricoxib and with 20:1 selectivity for pyridine versus pyrimidine in imatinib. Subsequent iminophosphorane formation proceeds efficiently resulting in etoricoxib derivative **2w**. When the corresponding gleevec salt was aminated, we observed that appreciable amounts of the iminophosphorane hydrolyzes under the reaction conditions. After consumption of the salt, water was added to the reaction mixture and stirring at room temperature results in aniline derivative **2x**. In general hydrolysis under the reaction conditions is a minor pathway in a small number of cases in this study; we believe that the adjacent aminopyrimidine ring in gleevec and conformation effects are responsible for this outcome.

We next derivatized the iminophosphorane within **2a** to show that this versatile functional group can give access to useful nitrogen-containing products (Scheme 1). Hydrolysis to the heteroaryl aniline, **3aa**, occurs by heating under neutral aqueous conditions.[20] Stirring the iminophosphorane in carbon disulfide forms isothiocyanate **3ab** in reasonable yield and is another versatile functional group that can be used to access carbonyl derivatives and heterocycles.[21] Finally, combining the iminophosphoranes with alkyl halides followed by stirring in acidic protic media is a simple protocol to obtain alkylated derivatives (**3ac**).[22]

Two mechanisms can be envisioned to form the iminophosphorane products that both proceed via an organoazide intermediate followed by a Staudinger reaction (Scheme 2A). First, sodium azide adds to the phosphonium ion and the resulting phosphorane undergoes ligand coupling to form the C–N bond.[23] Second, a S*N*Ar reaction where the azide reacts at the *ipso* carbon forming a Meisenheimer complex that then decomposes to release PPh3. We favour an S*N*Ar process given that polar solvents are most suitable and that the reaction is most effective on pyridines with electron-withdrawing substituents and diazine systems.[24] Scheme 2B provides evidence of a discrete organoazide intermediate. When 2-phenyl phosphonium salt was subjected to standard conditions in the presence of one equivalent of PTol3, a mixture of two iminophosphoranes are observed in the crude LCMS and ^{31}P NMR indicating that the organoazide intermediate can be intercepted by an external nucleophile.

In summary, we have developed a simple and broadly applicable strategy to aminate pyridines and diazines. The heterocycle is first converted into a phosphonium salt and then heated with sodium azide to form useful iminophosphorane derivatives. The reaction is exclusively regioselective in almost every case and can be applied on drug-like fragments and as a tool for late-stage functionalization of pharmaceuticals. The iminophosphorane is a versatile handle providing access to other important nitrogen-containing molecules making this strategy particularly valuable for medicinal chemists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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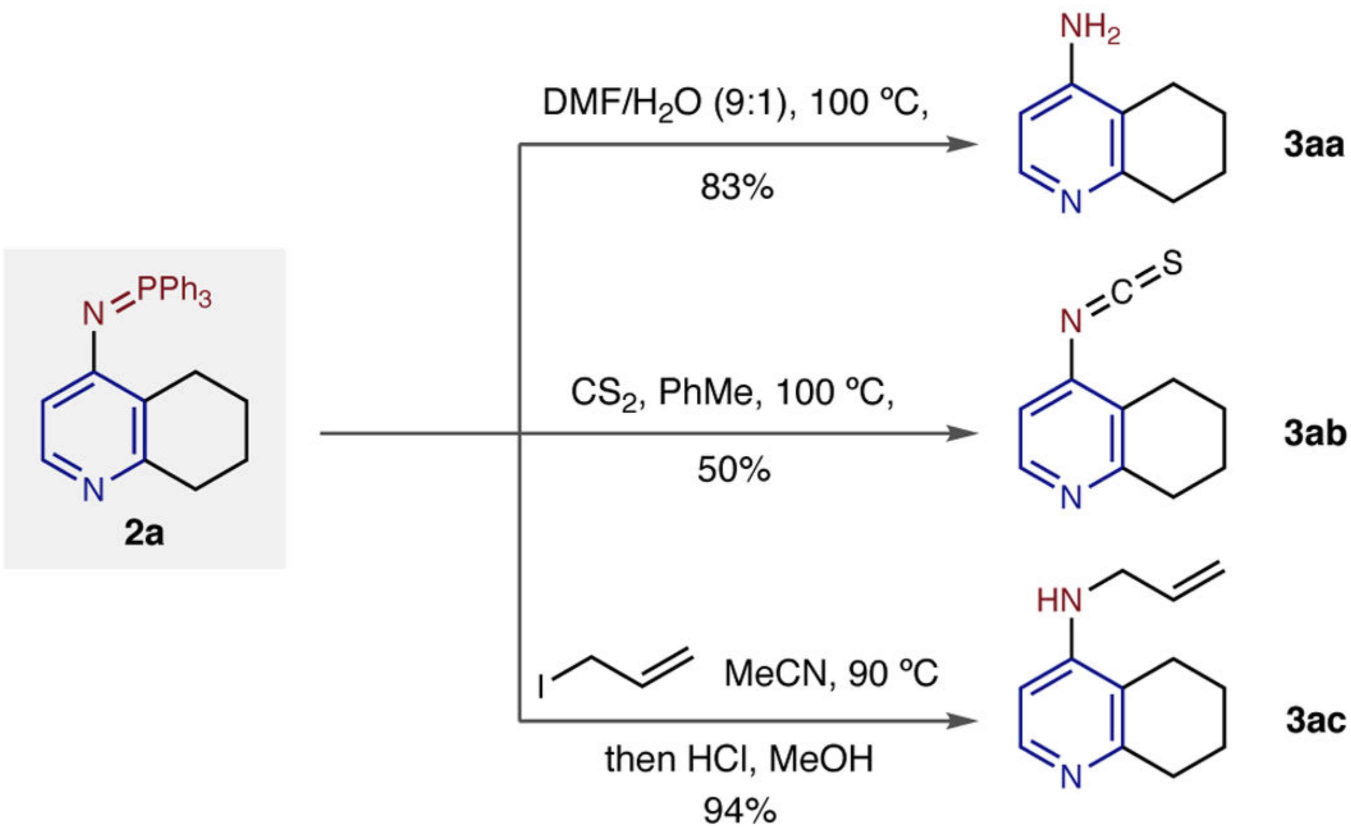
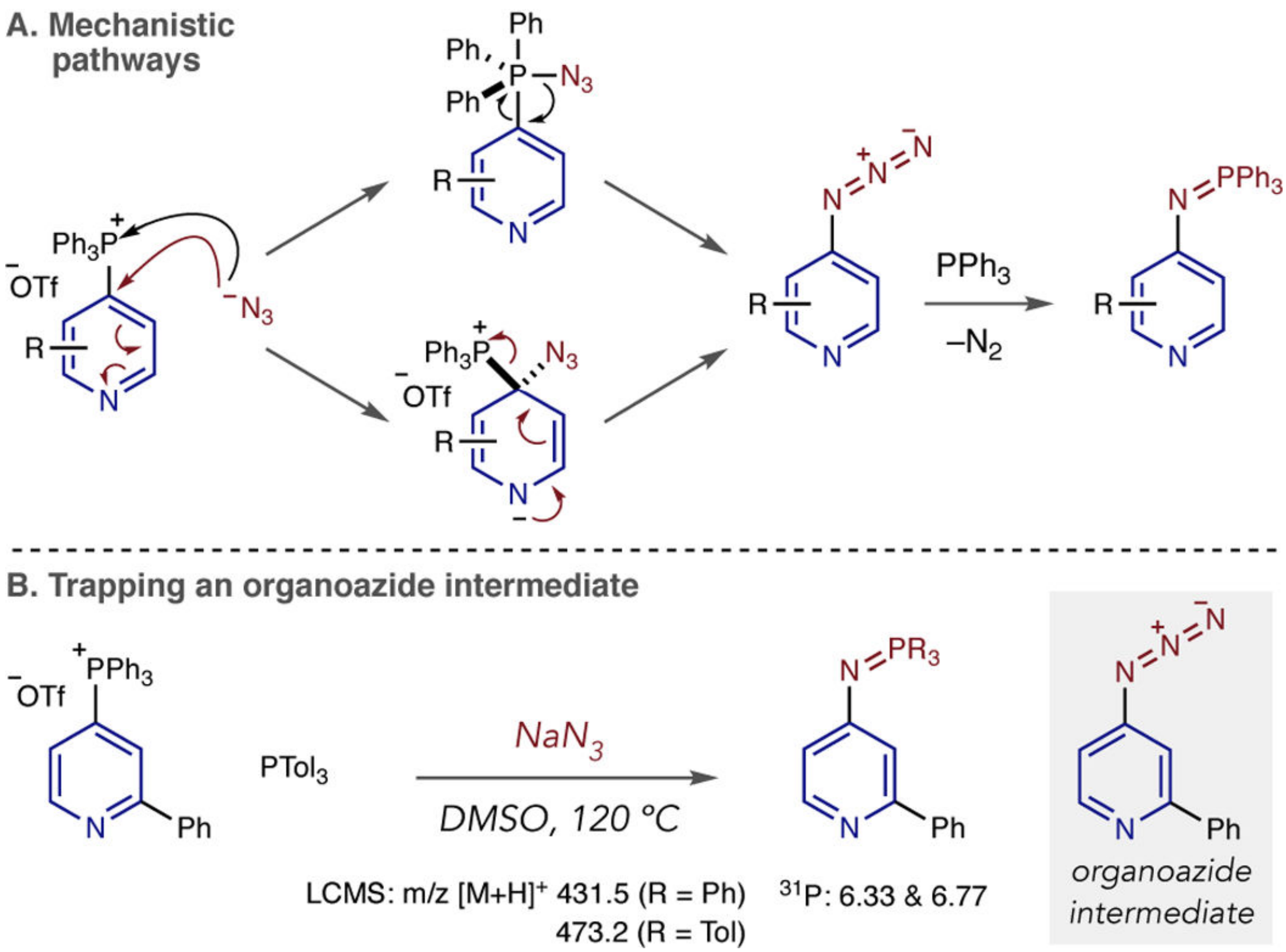


[a]Isolated yields of products are shown.

Scheme 1.
Derivatizations of iminophosphoranes

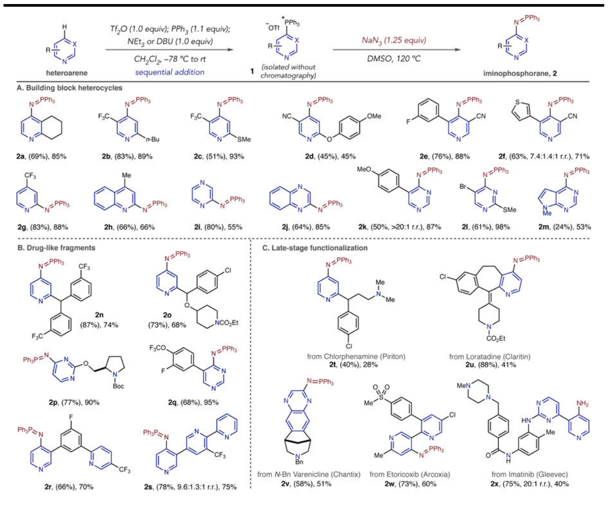


Scheme 2.

Mechanistic pathways and evidence of an organoazide intermediate.

Table 1.

Scope of the phosphorus-mediated amination process[a]



[a]Isolated yields of products are shown with yields of phosphonium salts in parentheses.