A Broadly Applicable Strategy to Aminate Azines Enabled by Electronically Tuned Phosphine Reagents.

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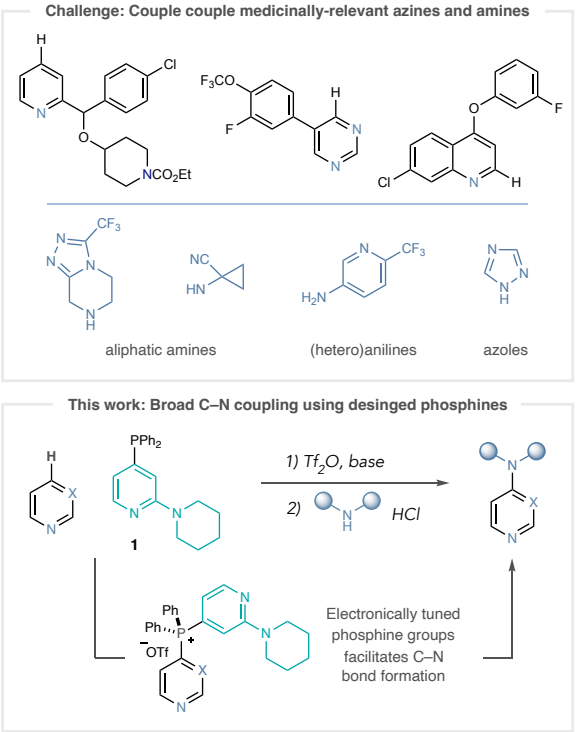
KEYWORDS. Pyridines, Amination, Phosphonium salts, Late-stage functionalization, S_NAr reaction.

ABSTRACT: We describe a strategy for aminating pyridines and other azines via phosphonium salt intermediates. Precisely tuning the electronic properties of the phosphonium ion was key for C–N bond formation via an S_NAr-halogenation, S_NAr-amination sequence. The process accommodates a wide range of amine classes and pyridine coupling partners and is viable for applications such as late-stage amination of complex pharmaceuticals and fragment-fragment coupling reactions. The capacity to rapidly modify the structure of the phosphine reagent was decisive and is a valuable feature in pseudohalide design.

Practitioners in the pharmaceutical and agrochemical industries frequently couple azines and amines due to the prevalence of aminated heterocycles in candidate compounds and marketed products.[1-8] Metal-catalyzed cross-couplings and S_NAr reactions are the two most common processes for these C–N couplings and significant progress has occurred using these reaction classes.[9-12] A remaining challenge is to develop approaches that commence from azine C–H precursors and allow the amine component to vary substantially (Scheme 1). Practitioner could then sample from vast collections of azines and amines in pharmaceutical compound collections to construct aminoazine libraries as well as other endeavors in drug development, such as late-stage amination and convergent coupling reactions.[13-15] For pyridines, there are approaches that can aminate the 2-position,[16-23] however, 4-amination strategies are less common, particularly under the above constraints. Recent two-step processes exploiting azine C–H pyridination reactions are an advance, although the scope of complex azines is narrow, and they cannot subsequently couple with aliphatic amines.[24-28] Here, we present an approach using an electronically tuned phosphine reagent (**1**), and intermediate phosphonium salts. The capacity to alter the reagent structure in response to deleterious reaction pathways was crucial for C–N coupling and is a valuable attribute of phosphonium ion intermediates compared to other pseudohalides.

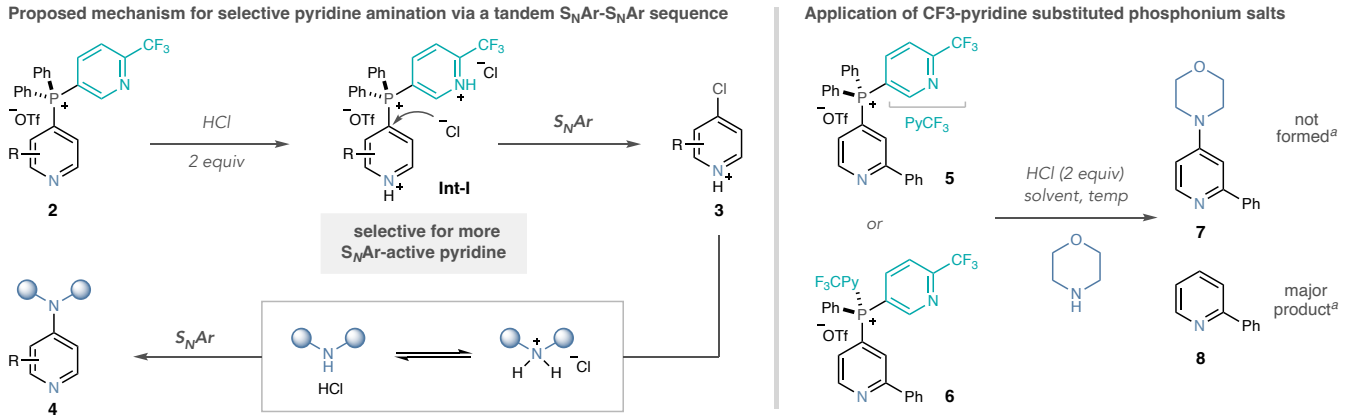
Previously, we have shown examples of pyridine C4-amination reactions with PPh_3-derived azine phosphonium salts and encountered several restrictions.[29, 30] C–N coupling requires anionic nucleophiles that limit the process to certain anilines, azoles, and azides as partners and narrows the range of applicable azine salts. Furthermore, aliphatic amines were uniformly unsuccessful as coupling partners, and decomposed the phosphonium salts to the parent C–H compound. Therefore, we turned our attention to an S_NAr-halogenation, S_NAr-amination sequence as an alternative strategy (Scheme 2). We reported that designed phosphines bearing CF_3-substituted pyridines could form azine phosphonium salts (**2**) and facilitate selective S_NAr reactions with halides via **Int-I** under acidic conditions (**3**).[31]

Scheme 1. Challenges for Azine Amination Reactions and an Approach via Designed Phosphonium Salts.



Bis protonated salt **Int-I**, enables the reaction with halides, and is selective for the pyridine of interest. Here, we propose that a second S_NAr reaction will occur in the presence of amines, resulting in 4-aminated products **4**. However, when we tested salts **5** or **6** with morpholine as a nucleophile, we did not observe the desired product **7** and observed significant amounts of parent pyridine **8**.

Scheme 2. Design Plan for a Phosphine-Mediated Amination and Initial Results.

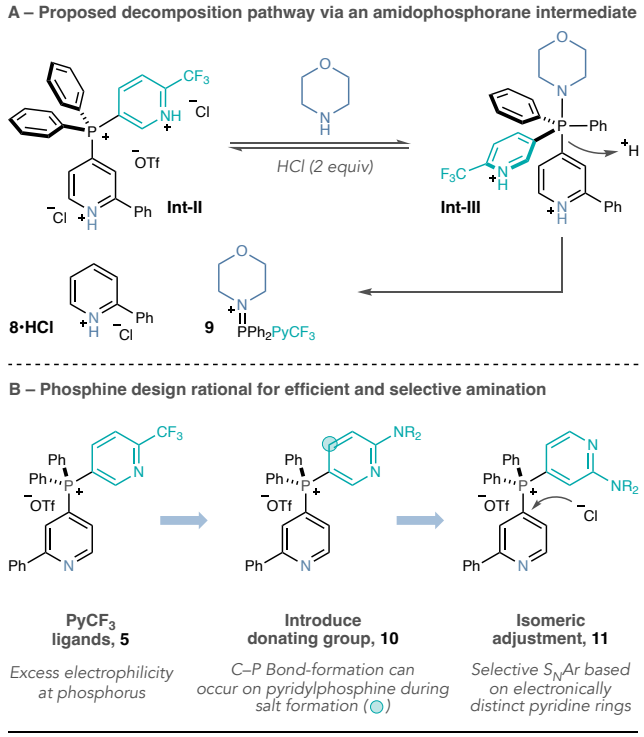


[a]Reaction outcome determined by ^{1}H NMR analysis of the crude reaction mixtures.

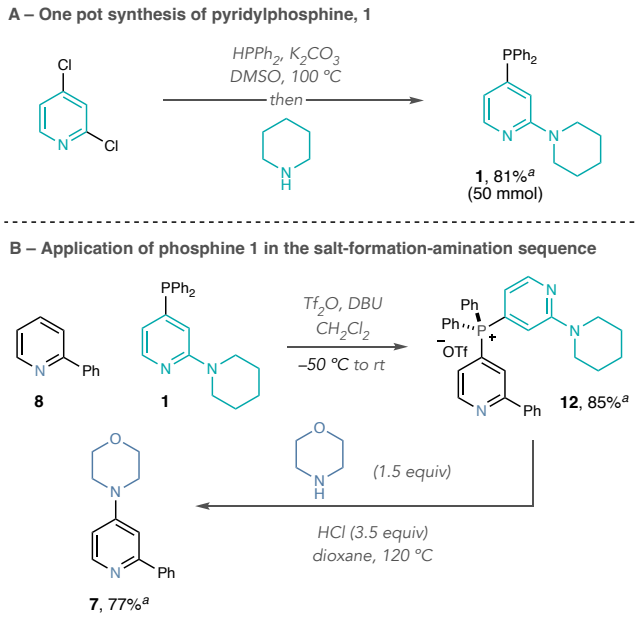
Scheme 3 shows our rationale for a new phosphine design that led to a successful amination process. We propose that salts **5** and **6** decompose via the mechanism described in Scheme 3A. The amine attacks the phosphonium ion **Int-II** to form P(V)-aminophosphorane intermediate **Int-III** and undergoes protiodephosphination resulting in protonated 2 phenylpyridine (**8·HCl**) and **9**.[32-34] To address this problem, we reasoned that reducing the electrophilicity of the phosphonium ion while still maintaining the capacity for S_NAr halogenation, would mitigate this unwanted reaction pathway. Therefore, we maintained a second pyridine ring to ensure bis protonation but replaced the trifluoromethyl group with an amine (**10**, Scheme 3B). While the amine substituent should decrease reactivity, this alteration introduces a potential complication during phosphonium salt formation. 2-CF_3 pyridines do not form salts due to poor reactivity with Tf_2O; however, 2-aminopyridines are competent substrates, and C–P bond-formation could potentially occur on this heterocycle.[35] To prevent this outcome, we made an isomeric adjustment to block the 4-position of the aminopyridine group (**11**). Although C–P bond-formation can occur at the 2-position of pyridines if the 4-position is blocked, this site is significantly less reactive, particularly when electron-donating groups are present. Selective S_NAr reactions between the two pyridines in salt **11** should occur based on the relative difference in the electronics of each ring.

We tested the hypothesis in Scheme 3B, via a scalable synthesis of phosphine **1** (Scheme 4). Using a 2,4-dichloropyridine as an abundant and inexpensive starting material, we synthesized pyridylphosphine **1** via a one-pot process (Scheme 4A). Diphenylphosphine selectively adds to the 4-position when conducted in DMSO with K_2CO_3. Piperidine then reacts at the 2-chloro site forming **1** in good yield on a multigram scale. We then used **1** to form phosphonium salt **12** from 2-phenylpyridine and did not observe any evidence of isomeric products. Gratifyingly, subjecting **12** to morpholine under acidic conditions resulted in 4-aminopyridine product **7**, with only trace amounts of 2-phenylpyridine **8** observed in the crude reaction mixture.

Scheme 3. Revised Phosphine Design.

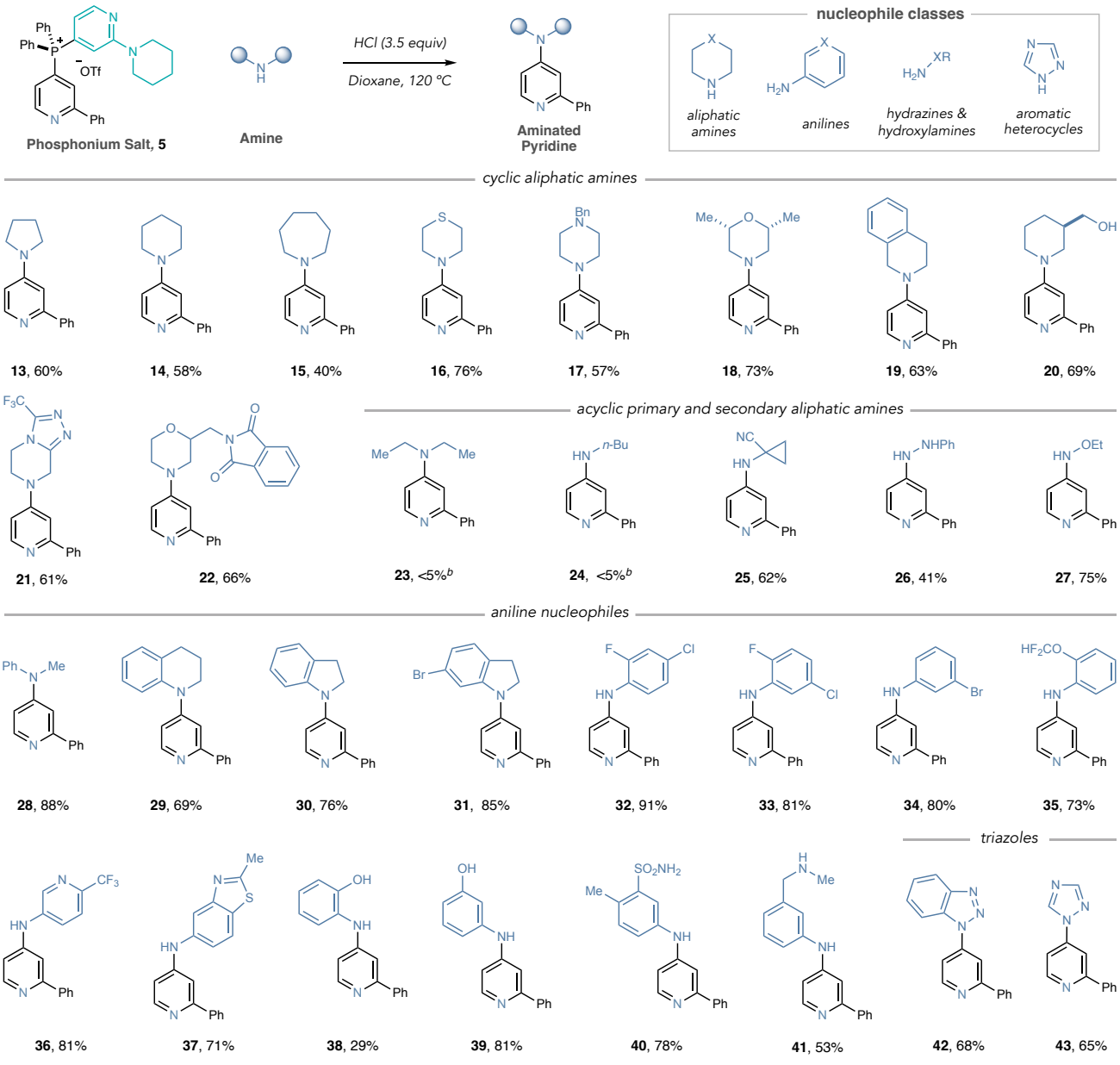


Scheme 4. Synthesis of Phosphine 1 and It's Application in Pyridine Amination.



[a]Isolated yields are shown.

Table 1. Scope of Amines and Nitrogen Heteroaromatics in the Azine Amination Process[a]

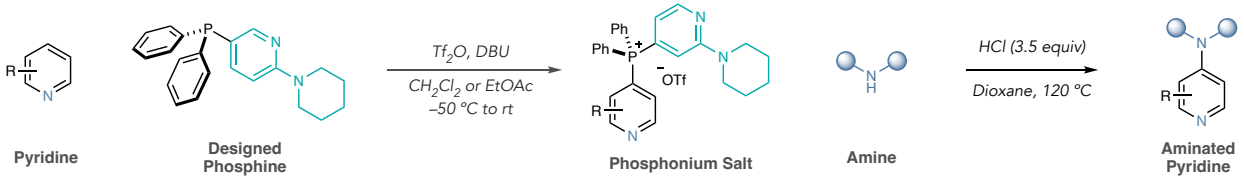


[b]Yields determined by analysis of the crude ^{1}H NMR spectra.

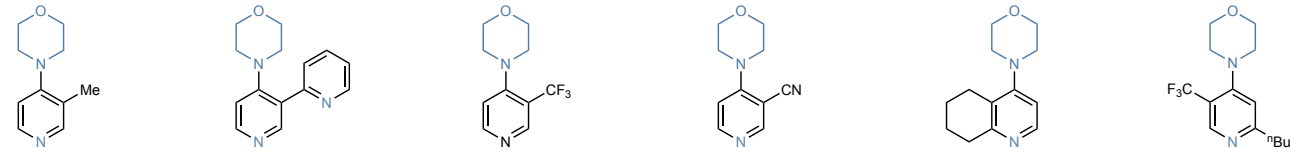
With a protocol in hand for pyridine C4-amination, we then explored the scope of amines and nitrogen-containing heterocycles. Cyclic aliphatic amines with different ring sizes are competent nucleophiles (**13-19**). The C–N coupling step tolerates free alcohols and more complex amines resulting in aminopyridines **20-22**. On the other hand, acyclic primary and secondary aliphatic amines perform poorly in the amination step (**23** & **24**). We attribute this limitation to the small equilibrium content of free amines under the acidic conditions and the lower nucleophilicity of acyclic relative to cyclic aliphatic amines. Aminopyridine **25**, derived from a cyano-substituted aminocyclopropane, indicates that less basic aliphatic amines can be competent. Similarly, the reaction tolerates hydrazines and hydroxylamine derivatives (**26** & **27**).

We then found that a series of anilines are competent in the amination step. Acyclic and cyclic secondary anilines performed well, as did four examples of substituted primary systems (**28-35**). Heteroarylanilines are also suitable substrates, resulting in **36** and **37**. Chemoselective aminations using aminophenols and sulfonamide-substituted anilines are viable under these conditions (**38-40**), and we also observed that anilines preferentially react over aliphatic amines (**41**). The latter example indicates that a higher concentration of the free aniline portion under the acidic conditions likely dictates selective C–N bond formation, in line with the arguments above. Finally, two triazoles were effective as nucleophiles forming **42** and **43** in moderate yields.

Table 2. Scope of Azine Building Blocks, Complex Structures, and Fragment-Fragment Couplings[a]



azine building blocks



44, (62%), 42%

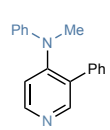
45, (79%), 73%

46, (57%), 44%

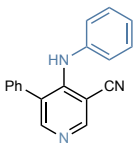
47, (76%), 78%

48, (51%), 50%

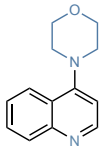
49, (83%), 53%



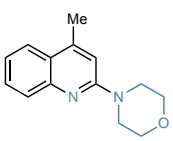
50, (65%), 44%



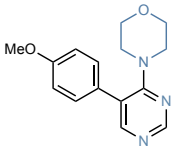
51, (91%), 80%



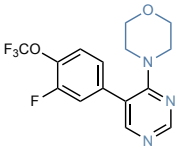
52, (76%), 79%



53, (64%), 64%

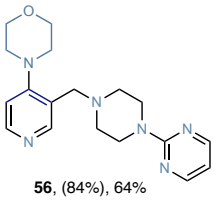


54, (50%, >20:1 r.r.), 85%

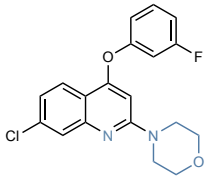


55, (68%), 63%

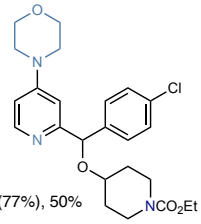
amination of drug-like fragements and pharmaceuticals



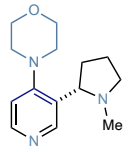
56, (84%), 64%



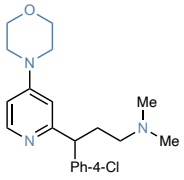
57, (76%), 60%



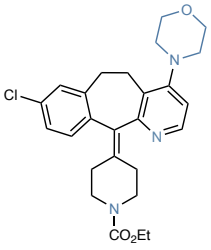
58, (77%), 50%



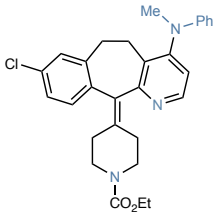
from nicotine
59, (74%), 82%



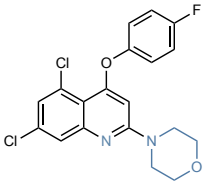
from chlorphenamine
60, (47%), 66%



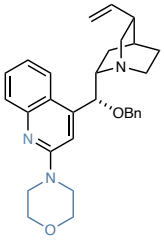
from loratadine
61, (85%), 62%



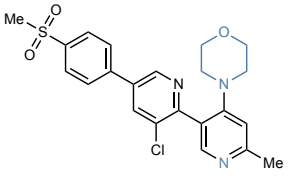
from loratadine
62, (85%), 71%



from quinoxyfen
63, (62%), 56%

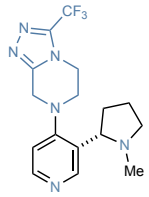


from OBn-cinchonidine
64, (36%), 31%

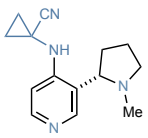


From etoricoxib
65, (71%), 84%

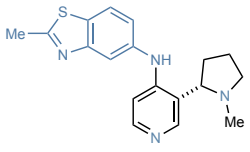
fragment-fragment couplings



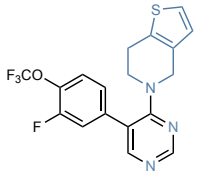
66, (74%), 52%



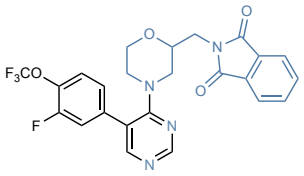
67, (74%), 72%



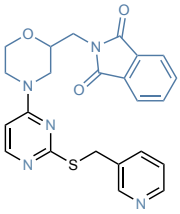
68, (74%), 71%



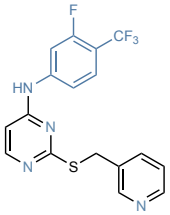
69, (68%), 43%



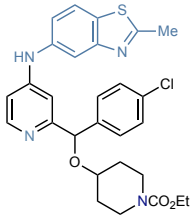
70, (68%), 56%



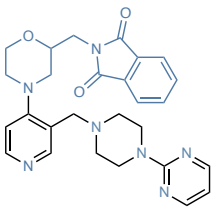
71, (83%), 48%



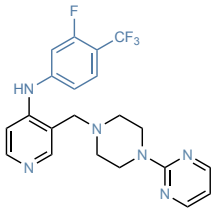
72, (83%), 74%



73, (77%), 51%



74, (84%), 50%



75, (84%), 64%

[a]Isolated yields are shown. Numbers in parentheses refer to isolated yields of phosphonium salts.

Next, we examined the scope of azines in the amination process (Table 2). Monosubstituted, 2,3- and 2,5-disubstituted pyridines were competent for salt formation and animation using morpholine as a representative nucleophile (**44-49**). Examples **50** and **51**, derived from anilines, show that the amine class can also change as the pyridine varies (*vide infra*). The process functions on quinolines (**52**), and C–N bond formation occurs at C2 when the 4-position is blocked (**53**). Pyrimidines are also competent substrates, as shown by examples **54** & **55**. Note in these last two cases, PPh_3-derived phosphonium salts were sufficient to promote C–N bond formation.

We then tested the amination reaction in applications relevant to pharmaceutical and agrochemical discovery. First, we examined whether C–N bond formation was viable on drug-like fragments and pharmaceuticals. These molecules are significantly more complex with multiple reactive sites and Lewis basic atoms. In these cases, selective amination is challenging for contemporary methods, particularly using C–H bond precursors as inputs. Nevertheless, using this two-step approach, it was straightforward to form aminated fragments **56-58**. We also synthesized aminated derivatives of nicotine, chlorphenamine, loratadine, and the agrochemical quinoxyfen (**59-63**). It is also possible to aminate the 2-position site of the quinoline ring in a cinchonidine derivative (**64**) and execute site- and regioselective C–N bond formation on etoricoxib (**65**). Second, we tested whether fragment-fragment coupling reactions were viable. These reactions show that the amination strategy is viable for convergent couplings that are important in synthetic route design and for library construction, where it is necessary to vary both coupling partners considerably. As shown in Table 2, we produced a diverse set of aminated azines in reasonable overall yields from C–H precursors (**66-75**).

In summary, we designed a phosphine reagent that enables a 4-selective pyridine amination via a tandem S_NAr-halogenation-S_NAr-amination sequence. The capacity to judiciously modify the electronic properties of the phosphine substituents was a crucial factor in promoting C–N bond formation. The reaction tolerates a broad scope of pyridines and extends to other azines. Several distinct classes of amines are viable coupling partners, and the strategy is appropriate for late-stage amination of complex pharmaceuticals and fragment-fragment coupling of drug-like intermediates. We are currently exploring additional phosphine designs for reactions to facilitate other valuable coupling reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reported compounds.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript

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Notes

Any additional relevant notes should be placed here.

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ABBREVIATIONS

SAR, structure activity relationship.

REFERENCES

(1) Torborg, C.; Beller, M. Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemical Industries. *Adv. Synth. Catal.* **2009**, *351*, 3027-3043. DOI:10.1002/adsc.200900587

(2) Corbet, J. P.; Mignani, G. Selected Patented Cross-Coupling Reaction Technologies. *Chem. Rev.* **2006**, *106*, 2651-2710. DOI:10.1021/cr0505268

(3) Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K. K.; Jonnalagadda, S. B. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules* **2020**, *25*, 1909. DOI:10.3390/molecules25081909

(4) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among US FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257-10274. DOI:10.1021/jm501100b

(5) Baumann, M.; Baxendale, I. R. An Overview of the Synthetic Routes to the Best Selling Drugs Containing 6-Membered Heterocycles. *Beilstein J. Org. Chem.* **2013**, *9*, 2265-2319. DOI:10.3762/bjoc.9.265

(6) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic Synthesis Provides Opportunities to Transform Drug Discovery. *Nat. Chem.* **2018**, *10*, 383-394. DOI:10.1038/s41557-018-0021-z

(7) De, S.; Kumar, S. K. A.; Shah, S. K.; Kazi, S.; Sarkar, N.; Banerjee, S.; Dey, S. Pyridine: The Scaffolds With Significant Clinical Diversity. *RSC Adv.* **2022**, *12*, 15385-15406. DOI:10.1039/d2ra01571d

(8) Zakharychev, V. V.; Kuzenkov, A. V.; Martsynkevich, A. M. Good Pyridine Hunting: A Biomimic Compound, a Modifier and a Unique Pharmacophore in Agrochemicals. *Chem. Heterocycl. Compd.* **2020**, *56*, 1491–1516.

(9) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564-12649. DOI:10.1021/acs.chemrev.6b00512

(10) Evano, G.; Blanchard, N.; Toumi, M. Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis. *Chem. Rev.* **2008**, *108*, 3054-3131. DOI:10.1021/cr8002505

(11) Beletskaya, I. P.; Cheprakov, A. V. The Complementary Competitors: Palladium and Copper in C–N Cross-Coupling Reactions. *Organometallics* **2012**, *31*, 7753-7808. DOI:10.1021/om300683c

(12) Fischer, C.; Koenig, B. Palladium- and Copper-Mediated N-aryl Bond Formation Reactions for the Synthesis of Biological Active Compounds. *Beilstein J. Org. Chem.* **2011**, *7*, 59-74. DOI:10.3762/bjoc.7.10

(13) Josephitis, C. M.; Nguyen, H. M. H.; McNally, A. Late-Stage C–H Functionalization of Azines. *Chem. Rev.* **2023**, *123*, 7655-7691. DOI:10.1021/acs.chemrev.2c00881

(14) Zhang, L.; Ritter, T. A Perspective on Late-Stage Aromatic C–H Bond Functionalization. *J. Am. Chem. Soc.* **2022**, *144*, 2399-2414. DOI:10.1021/jacs.1c10783

(15) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-Like Molecules. *Chem. Soc. Rev.* **2016**, *45*, 546-576. DOI:10.1039/c5cs00628g

(16) Yin, J. J.; Xiang, B. P.; Huffman, M. A.; Raab, C. E.; Davies, I. W. A General and Efficient 2-Amination of Pyridines and Quinolines. *J. Org. Chem.* **2007**, *72*, 4554-4557. DOI:10.1021/jo070189y

(17) Londregan, A. T.; Jennings, S.; Wei, L. Q. General and Mild Preparation of 2-Aminopyridines. *Org. Lett.* **2010**, *12*, 5254-5257. DOI:10.1021/ol102301u

(18) Velavan, A.; Mondal, D.; Survase, S. Metal Free Quick Introduction of Azole in to Azine Nucleus: Acid Catalyzed Reissert-Henze Reaction. *B Korean Chem Soc* **2013**, *34*, 3459-3462. DOI:10.5012/bkcs.2013.34.11.3459

(19) Bugaenko, D. I.; Yurovskaya, M. A.; Karchava, A. V. Quaternary *N*-(2-Pyridyl)-DABCO Salts: One-Pot in Situ Formation from Pyridine-*N*-oxides and Reactions with Nucleophiles: A Mild and Selective Route to Substituted *N*-(2-Pyridyl)-*N*′-ethylpiperazines. *J. Org. Chem.* **2017**, *82*, 2136-2149. DOI:10.1021/acs.joc.6b02952

(20) Pang, J. H.; Kaga, A.; Roediger, S.; Lin, M. H.; Chiba, S. Revisiting the Chichibabin Reaction: C2 Amination of Pyridines with a NaH-Iodide Composite. *Asian. J. Org. Chem.* **2019**, *8*, 1058-1060. DOI:10.1002/ajoc.201900094

(21) Bugaenko, D. I.; Yurovskaya, M. A.; Karchava, A. V. Reaction of Pyridine-*N*-Oxides with Tertiary sp^2-*N*-Nucleophiles: An Efficient Synthesis of Precursors for *N*-(Pyrid-2-yl)-Substituted *N*-Heterocyclic Carbenes. *Adv. Synth. Catal.* **2020**, *362*, 5777-5782. DOI:10.1002/adsc.202001063

(22) Fier, P. S.; Kim, S.; Cohen, R. D. A Multifunctional Reagent Designed for the Site-Selective Amination of Pyridines. *J. Am. Chem. Soc.* **2020**, *142*, 8614-8618. DOI:10.1021/jacs.0c03537

(23) Lipshultz, J. M.; Radosevich, A. T. Uniting Amide Synthesis and Activation by P^{III}/P^{V}-Catalyzed Serial Condensation: Three-Component Assembly of 2-Amidopyridines. *J. Am. Chem. Soc.* **2021**, *143*, 14487-14494. DOI:10.1021/jacs.1c07608

(24) Rossler, S. L.; Jelier, B. J.; Tripet, P. F.; Shemet, A.; Jeschke, G.; Togni, A.; Carreira, E. M. Pyridyl Radical Cation for C-H Amination of Arenes. *Angew. Chem. Int. Ed.* **2019**, *58*, 526-531. DOI:10.1002/anie.201810261

(25) Ham, W. S.; Hillenbrand, J.; Jacq, J.; Genicot, C.; Ritter, T. Divergent Late-Stage (Hetero)aryl C-H Amination by the Pyridinium Radical Cation. *Angew. Chem. Int. Ed.* **2019**, *58*, 532-536. DOI:10.1002/anie.201810262

(26) Choi, H.; Ham, W. S.; van Bonn, P.; Zhang, J. B.; Kim, D.; Chang, S. Mechanistic Approach Toward the C4-Selective Amination of Pyridines via Nucleophilic Substitution of Hydrogen. *Angew. Chem. Int. Ed.* **2024**, *63*, e202401388. DOI:10.1002/anie.202401388

(27) Ham, W. S.; Choi, H.; Zhang, J.; Kim, D.; Chang, S. C2-Selective, Functional-Group-Divergent Amination of Pyrimidines by Enthalpy-Controlled Nucleophilic Functionalization. *J. Am. Chem. Soc.* **2022**, *144*, 2885-2892. DOI:10.1021/jacs.1c13373

(28) Motsch, B. J.; Quach, A. H.; Dutton, J. L.; Wilson, D. J.; Wengryniuk, S. E. Direct C4- and C2 C–H Amination of Heteroarenes Using I(III) Reagents via a Cross Azine Coupling. *ChemRxiv. Cambridge: Cambridge Open Engage* **2024**. DOI:10.26434/chemrxiv-2024-n14xq

(29) Anderson, R. G.; Jett, B. M.; McNally, A. A Unified Approach to Couple Aromatic Heteronucleophiles to Azines and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2018**, *57*, 12514-12518. DOI:10.1002/anie.201807322

(30) Patel, C.; Mohnike, M.; Hilton, M. C.; McNally, A. A Strategy to Aminate Pyridines, Diazines, and Pharmaceuticals via Heterocyclic Phosphonium Salts. *Org. Lett.* **2018**, *20*, 2607-2610. DOI:10.1021/acs.orglett.8b00813

(31) Levy, J. N.; Alegre-Requena, J. V.; Liu, R. R.; Paton, R. S.; McNally, A. Selective Halogenation of Pyridines Using Designed Phosphine Reagents. *J. Am. Chem. Soc.* **2020**, *142*, 11295-11305. DOI:10.1021/jacs.0c04674

(32) Finet, J.-P. *Ligand Coupling Reactions with Heteroatomic Compounds*; Pergamon; New York, 1998.

(33) Deng, Z. Y.; Lin, J. H.; Xiao, J. C. Nucleophilic Arylation with Tetraarylphosphonium Salts. *Nat. Commun.* **2016**, *7*. DOI:10.1038/ncomms10337

(34) Koniarczyk, J. L.; Hesk, D.; Overgard, A.; Davies, I. W.; McNally, A. A General Strategy for Site-Selective Incorporation of Deuterium and Tritium into Pyridines, Diazines, and Pharmaceuticals. *J. Am. Chem. Soc.* **2018**, *140*, 1990-1993. DOI:10.1021/jacs.7b11710

(35) Hilton, M. C.; Dolewski, R. D.; McNally, A. Selective Functionalization of Pyridines via Heterocyclic Phosphonium Salts. *J. Am. Chem. Soc.* **2016**, *138*, 13806-13809. DOI:10.1021/jacs.6b08662