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Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model

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Abstract

The pyridine heterocycle continues to play a vital role in the development of human medicines. More than 100 currently-marketed drugs contain this privileged unit, which remains highly sought after synthetically. We report an efficient means to access di- and tri-substituted pyridines in an efficient and highly controlled manner using transient 3,4-pyridyne intermediates. Previous efforts to employ 3,4-pyridynes for the construction of substituted pyridines have been hampered by a lack of regiocontrol or the inability to later manipulate an adjacent directing group. The newly developed strategy relies on the use of proximal halide or sulfamate substituents to perturb pyridyne distortion, which in turn governs regioselectivities in nucleophilic addition and cycloaddition reactions. Following trapping of in situ-generated pyridynes, the neighboring directing groups may be removed or exploited using versatile metal-catalyzed cross-coupling reactions. This methodology now renders 3,4-pyridynes useful synthetic building blocks for the creation of highly decorated derivatives of the medicinally privileged pyridine heterocycle.

The pyridine ring is one of the most important heterocycles in drug discovery.[1,2] It is present in more than 100 currently marketed drugs, including the blockbuster drugs Nexium® and Claritin®, in addition to the recently approved cancer therapeutic Xalkori® (Figure 1a). Additional drugs that contain the pyridine ring, or some derivative there of, include the life-changing medicines Singulair® (asthma/allergies), Actos® (diabetes), Lunesta® (insomnia), Gleevec® (various cancers), Prevacid® (acid reflux/ulcers), and Mirtazapine (depression). Because of the immense value of pyridines, methods to access functionalized derivatives of this privileged heterocycle have remained highly sought after for decades.[1] Several elegant methods have recently been reported for the assembly of substituted pyridines.[3,4,5,6]

A promising approach toward polyfunctionalized pyridines involves the use of highly reactive pyridyne intermediates,[7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23] such as isomeric hetarynes **1** and **2** (Figure 1b), which are valued for their electrophilicity and high reactivity

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toward nucleophiles and cycloaddition partners.[24,25] The first pyridyne studies were reported in 1955, with Levine and Leake's seminal discovery of 3,4-pyridyne (**2**).[7] Despite the many studies that followed over the next fifty years, pyridynes have yet to mature into a widely used tool for the assembly of functionalized pyridine scaffolds. The 2,3-pyridyne (**1**) reacts with excellent degrees of regioselectivity to give 2-substituted pyridines or related cycloadducts;[20,21] however, other methods for C2 functionalization of pyridines are available and are often preferred.[1] In the case of 3,4-pyridynes (e.g., **2**), nucleophilic additions are known to occur without significant selectivity for attack at either C3 or C4.[9–19] If the regioselectivity in reactions of 3,4-pyridynes could be controlled, these intermediates could serve as valuable building blocks for the synthesis of substituted pyridines that are otherwise difficult to access.

Prior efforts to modulate regioselectivities of 3,4-pyridynes using substituent effects have been met with promising results and can be summarized as follows (Figure 1c–e): (a) Snieckus reported a single example using a C2 amido group to enhance nucleophilic addition to C4 of a 3,4-pyridyne intermediate (**3**→**4**→**5**).[18] (b) Caubère found that oxygen and nitrogen substituents positioned in close proximity to the 3,4-pyridyne could also lead to enhanced selectivity for the addition of amines.[19] For example, treatment of halopyridine **6** with diethylamine under $NaNH_2$/NaO*t*-Bu conditions gave **8** in 80% yield, along with 10% of the C3 isomer, both presumably arising via pyridyne **7**. (c) Guitián has examined the influence of C2 halide substituents, which would later be removable, on the 3,4-pyridyne for applications in a cycloaddition with substituted furans with applications in the synthesis of the natural product ellipticine.[12,13] Although bromide or fluoride groups did not significantly influence regioselectivity, some success was seen using a C2 chloro substituent (**9**+**10**→**11**+**12**). Interestingly, the authors reported that the presence of a chloride at C5 of the 3,4-pyridyne gave an equimolar mixture of cycloadducts using furan **9**.

The studies highlighted in Figure 1 demonstrate that substituent effects can modulate pyridyne regioselectivities, particularly for the favored addition at C4. However, the ability to subsequently manipulate or remove the C2 amide, oxygen, or nitrogen directing groups in Snieckus' and Caubère's reports is limited. Guitián's use of neighboring halides to modulate 3,4-pyridyne regioselectivity gave mixed results, with a C2 chloride being the most promising directing group for the specific cycloaddition examined. Moreover, most known examples of regioselective 3,4-pyridyne reactions are restricted to the use of amine- or alcohol-based nucleophiles, whereas a variety of other trapping agents have yet to be explored.

Herein, we report the design and synthesis of substituted 3,4-pyridynes that react with significant regioselectivities. Our strategy renders 3,4-pyridynes synthetically useful for the assembly of highly functionalized pyridine scaffolds and features several key design elements: (a) The pyridynes are accessed from pyridylsilyltriflate precursors using mild fluoride-based reaction conditions. This allows for a broad range of trapping agents (nucleophiles and cycloaddition partners) to be employed, which in turn, delivers a more diverse collection of polysubstituted pyridine derivatives. (b) A C5-bromide substituent is used to induce aryne distortion and direct nucleophilic additions to C3 of 3,4-pyridynes. The bromide may subsequently be manipulated using conventional Pd-catalyzed reactions. (c)

By positioning a sulfamoyl group at C2 of the 3,4-pyridyne, aryne distortion is perturbed to favor attack at C4 of 3,4-pyridynes. Sulfamoyl groups have not been used previously to govern pyridyne or aryne regioselectivities, but when used in conjunction with modern Ni-catalyzed cross-couplings, offer an effective new means to access functionalized pyridines. The methodologies reported herein now render 3,4-pyridynes broadly useful as a tool for the construction of polysubstituted pyridines. We expect our findings will promote the use of 3,4-pyridynes and other heterocyclic arynes in the synthesis of medicinally privileged molecular scaffolds.

Results and Discussion

Design and Synthesis of Pyridyne Precursors

The observation that 3,4-pyridyne **2** reacts with poor regioselectivity can be explained by consideration of the aryne distortion model.[26,27,28] The geometry-optimized structure of **2** obtained from DFT calculations (B3LYP/6-31G*)[29] is shown in Figure 1b. Pyridyne **2** possesses only minor aryne distortion, as evidenced by the internal angles at C3 and C4 being nearly identical. We hypothesized that neighboring electron-withdrawing substituents at C5 or C2 could increase aryne distortion, thus providing greater degrees of regioselectivity.

Bearing in mind the seminal findings of Guitián,[12,13] and that aryne distortion and subsequent regioselectivities may be perturbed by inductively electron-withdrawing substituents,[24,30] we evaluated a series of 2- and 5-substituted 3,4-pyridynes using computational methods (Figure 2, also see Supplementary Figure S2). Parent pyridynes have been studied computationally;[31] however, no calculations involving C2- or C5-substituted derivatives are available in the literature. We considered chloride, bromide, iodide, and sulfamate substituents to be particularly attractive pyridyne substituents as each could plausibly serve as a handle for further elaboration after being used to modulate pyridyne regioselectivity. Although less useful synthetically, the methoxy substituent was also evaluated as a point of comparison, since methoxy is well-known to govern regioselectivity in reactions of benzyne due to significant aryne distortion.[24]

As summarized in Figure 2, computations predict that a variety of electron-withdrawing substituents could be used to induce 3,4-pyridyne distortion. In the case of 5-substituted pyridynes, the inductively withdrawing substituents cause a flattening at C3, suggesting this would be the preferred site of attack by nucleophiles according to the aryne distortion model.[26] Specifically, the more linear terminus of the aryne possesses greater p character and is therefore more electropositive. A similar effect was seen in our studies of 2-substituted 3,4-pyridynes. In all cases, the electron-withdrawing substituents lead to a flattening at C4, which is in turn predicted to be the preferred site of attack by nucleophiles.

The aryne distortion model suggests that arynes with internal angle differences ≥ 4° are likely to react with significant regioselectivities in nucleophilic addition and cycloaddition reations.[26] As the substituted 3,4-pyridynes shown in Figure 2a all meet this criterion and their distortions are generally on par with that of methoxy-substituted pyridynes, we hypothesized that any of the halo- or sulfamoyl pyridynes would prove useful. We

envisioned accessing pyridynes from silyltriflate precursors, as aryne formation would be readily achieved using mild fluoride-based conditions. In addition, this general method (i.e., the Kobayashi approach to aryne generation)[32] was expected to be highly tolerant of an array of functional groups and trapping agents, and therefore could be used in a range of aryne trapping processes.[24]

Figure 2b summarizes several key aspects of pyridyne design that were considered prior to synthesizing substituted pyridynes. With respect to the 5-substituted 3,4-pyridyne, bromopyridyne **13** was considered attractive since the bromide induced considerable pyridyne distortion and offered the most versatility for functionalization after pyridyne trapping. Furthermore, the presumed silyltriflate precursor to **13** would likely be accessible from commercially available bromohydroxypyridine **14**. The 5-sulfamoyl-3,4-pyridyne **15** was also attractive since computations suggested this species would be highly distorted. However, the presumed silyltriflate precursor to **15** did not appear readily accessible since its likely predecessor, 3,5-dihydroxypyridine, is not easily obtained. Regarding 2-substituted 3,4-pyridynes, the sulfamate was predicted to induce the greatest degree of distortion. Coupled with the notion that an appropriate silyltriflate could plausibly be accessed from commercially available dihydroxypyridine **17**, 2-sulfamoyl-pyridyne **16** was deemed an appropriate target. It should be emphasized that sulfamates have not previously been used to direct aryne regioselectivities, but if successful, would offer a valuable means to functionalize the pyridine ring after an aryne reaction by exploiting modern Ni-catalyzed coupling methodologies.[33] Likewise, as demonstrated herein, the bromide of pyridyne adducts may be strategically manipulated using conventional Pd-mediated transformations. Geometry-optimized structures of pyridyne targets **13** and **16**, obtained using DFT methods, are shown in Figure 2c.

Robust syntheses of pyridylsilyltriflates **20**, **22**, and **25** were developed, as these compounds were expected to function as appropriate precursors to pyridynes **2**, **13**, and **16**, respectively (Figure 3). Starting from commercially available 3-hydroxypyridine (**18**), carbamoylation followed by a C4-selective *o*-lithiation gave silylcarbamate **19** in 74% yield over 2 steps. A subsequent one-pot deprotection/triflation protocol[27] afforded silyltriflate **20**. This straightforward sequence provides the desired precursor to 3,4-pyridyne (**2**) in three steps and in >50% overall yield. Although regioselectivities in reactions of unsymmetrical arynes are not thought to be dependant upon the isomer of silyltriflate employed,[27,34,35,36,37,38] extensive efforts were made to synthesize the regioisomer of precursor **20**, where the positions of the triflate and trimethylsilyl groups are reversed. However, in accord with a previous report, we were unable to prepare this compound, presumably because of its instability[39] and the lability of C4-OR derivatives needed in our routes (e.g., R=TMS, C(O)NH*i*Pr).[40,41] Bromosilyltriflate **22** was synthesized using an analogous route starting from the commercially available bromohydroxypyridine **20**, although the conversion of **21** to **22** requires the use of a highly optimized two-step procedure. Finally, silyltriflate **25** was synthesized from known benzylether **23** (see Supporting Information) using an efficient four-step sequence involving sulfamoylation and C4 silylation (**23**→**24**), followed by deprotection and triflation (**24**→**25**). Using these practical routes, gram quantities of silyltriflates **20**, **22**, and **25** are readily accessible.

Nucleophilic Additions and Cycloaddition Reactions of 3,4-Pyridynes

To assess the influence of the C5 bromide substituent on 3,4-pyridyne regioselectivities, a comparative study involving pyridynes **2** and **13** was undertaken (Table 1). Consistent with computations and previous studies of 3,4-pyridynes, reactions involving **2** proceeded with modest regioselectivity across a range of nucleophilic trapping agents[42] and cycloaddition partners (entries 1, 3, 5, 7, and 9). Nucleophilic addition at C4 was slightly favored in all cases. In comparison, reactions of the 5-bromo-3,4-pyridyne (**13**) uniformly gave improved degrees of regioselectivity with a reversal in selectivity favoring addition at C3. Use of *N*-methylaniline gave a mixture of C3 and C4 adducts in a 5.8:1 ratio (entry 2). Similarly, a 2.9:1 ratio of adducts, again favoring C3, was obtained when morpholine was employed as the trapping reagent (entry 4). Several formal cycloadditions were also tested. Whereas unsubstituted pyridyne **2** reacted with 1,3-dimethyl-2-imidazolidinone (DMI)[36] to give a 2.1:1 mixture of isomeric products favoring C4 addition (entry 5), the use of bromopyridyne **13** exclusively yielded the isomer indicative of initial C3 addition (entry 6). When *N-tert*-butyl-α-phenylnitrone (entry 8)[43,44] and 2-methoxyfuran (entry 10) were used to trap **13**, 3.3:1 and 1.7:1 ratios of product were obtained, respectively, with C3 being favored in both cases. It should be noted that in the latter two cycloaddition reactions, the major products presumably arise from transition states that possess significant steric encumbrances. Consequently, the bromine's influence on aryne distortion and regioselectivity likely arises from electronic considerations, rather than from steric factors.

To further probe this notion, we compared bromopyridyne **13** to its 5-chloro analogue. Despite a previous example where a 5-Cl substituent minimally perturbed regioselectivity in a 3,4-pyridyne cycloaddition,[13] we found that the chloride governed regioselectivities in reactions with morpholine and *N-tert*-butyl-α-phenylnitrone (see Supplementary Figure S1). Selectivities were found to be more pronounced compared to those seen in reactions with bromopyridyne **13**, which is in agreement with the predictions shown in Figure 2a based on the aryne distortion model.

Sulfamoylpyridyne **16** was next tested in nucleophilic additions and cycloaddition reactions (Table 2). In comparison to unsubstituted pyridyne **2**, sulfamate **16** was found to react with enhanced regioselectivity for addition to C4. For example, in the absence of the C2 sulfamate, addition of *N*-Me-aniline gave a 1.9:1 mixture of C4:C3 adducts (entry 1), whereas the presence of the sulfamate led to an overwhelming preference for attack at C4 (entry 2). Similar results were seen in the addition of morpholine (entries 3 and 4). When DMI was employed to trap sulfamate **16**, we obtained a single isomer in 79% yield suggestive of initial attack at C4 (entry 6). For comparison, only a 2.1:1 ratio of products was observed using pyridyne **2** (entry 5). *N-tert*-butyl-α-phenylnitrone also displayed excellent selectivity for initial attack at C4 (entry 8), despite the steric burden encountered in the assumed transition state. Finally, the use of 2-methoxyfuran to trap sulfamoylpyridyne **16** led to a modest improvement in the preference for initial attack at C4 (entry 10), compared to the parent pyridyne **2** (entry 9).

Explanation for the Observed Regioselectivities in Reactions of Substituted Pyridynes

It has previously been suggested that aryne distortion governs regioselectivity in reactions of unsymmetrical arynes.[26] We surmise that this notion also holds for substituted 3,4-pyridynes, and that 5-bromo and 2-sulfamoyl substituents induce aryne distortion to favor attack by nucleophiles at C3 and C4, respectively. The origin of distortion and regioselectivity likely stems from an inductive effect imparted by the electron-withdrawing substituents that can polarize the aryne triple bond in the manners suggested in Figure 4.

Although steric factors may contribute to the regioselectivities observed in nucleophilic additions to substituted 3,4-pyridynes, experimental results emphasize the importance of electronic considerations. Figure 4 shows the likely transition structures for the reactions between *N-tert*-butyl-α-phenylnitrone and pyridynes **13** and **16**, respectively. In each case, the major product arises from the electronically matched transition structures (i.e., **TS1** and **TS4**), despite these being more sterically encumbered in comparison to **TS2** and **TS3**, respectively. Thus, although steric considerations should be considered and may impact ratios of products, the electronic nature of these substiuents appears to be the guiding factor in reactions of substituted 3,4- pyridynes.

Derivatization of Pyridyne Adducts Using Pd- or Ni-Catalysis

As shown in Figure 5, the halide and sulfamoyl substituents can be removed or used as functional group handles for further elaboration. Bromide **26** and sulfamate **30**, each of which was accessed as a single regioisomer from its corresponding pyridyne precursor (see Table 1, entry 6 and Table 2, entry 6, respectively), were selected as the substrates for these studies. Of note, structures **26** and **30** are reminiscent of medicinally important benzodiazepines[45] and, therefore, serve as an ideal testing ground for bromide and sulfamate-based derivatization of pyridyne adducts.

Bromide **26** underwent smooth reaction using Pd catalysis to afford various analogues (Figure 5). Buchwald–Hartwig amination gave amine derivative **27** in 67% yield, whereas Suzuki–Miyaura coupling furnished arylated product **29** in 87% yield. Additionally, it was found that the bromide could be removed under Pd-catalyzed hydrogenolysis conditions to deliver **28** in high yield.

We were also delighted to find that sulfamate **30** could be readily functionalized using Ni catalysis (Figure 5). Sulfamate amination provided aminopyridine **31** in 58% yield.[46] Furthermore, a Ni-catalyzed Kumada–Corriu coupling[47] proceeded smoothly using the readily prepared, and bench-stable NiClCpIMes complex to give biaryl **33** in 82% yield. Finally, we found that the sulfamate could be removed under reductive conditions[48,49] to afford **32**, which marks the first example of reductive sulfamate cleavage. The straightforward manipulations of **26** and **30** demonstrate that: (a) diverse arrays of highly substituted pyridine derivatives are accessible from this methodology in a highly controlled fashion, and (b) the aryl sulfamate group may be readily manipulated through modern Ni-catalyzed coupling reactions, even when adorned with a complex heterocyclic system.

In summary, we have developed the first general method to govern 3,4-pyridyne regioselectivities. Our approach relies on the strategic use of bromide and sulfamate directing groups that can be removed or exploited as synthetic handles for further elaboration using transition metal catalysis. Using this methodology, unique di- and tri-substituted pyridine derivatives can be accessed with significant control of regiochemistry. These studies further validate the aryne distortion model and its predictive capabilities in gauging aryne regioselectivities. We expect our findings will promote the use of 3,4-pyridynes and other heterocyclic arynes in the synthesis of medicinally privileged molecular scaffolds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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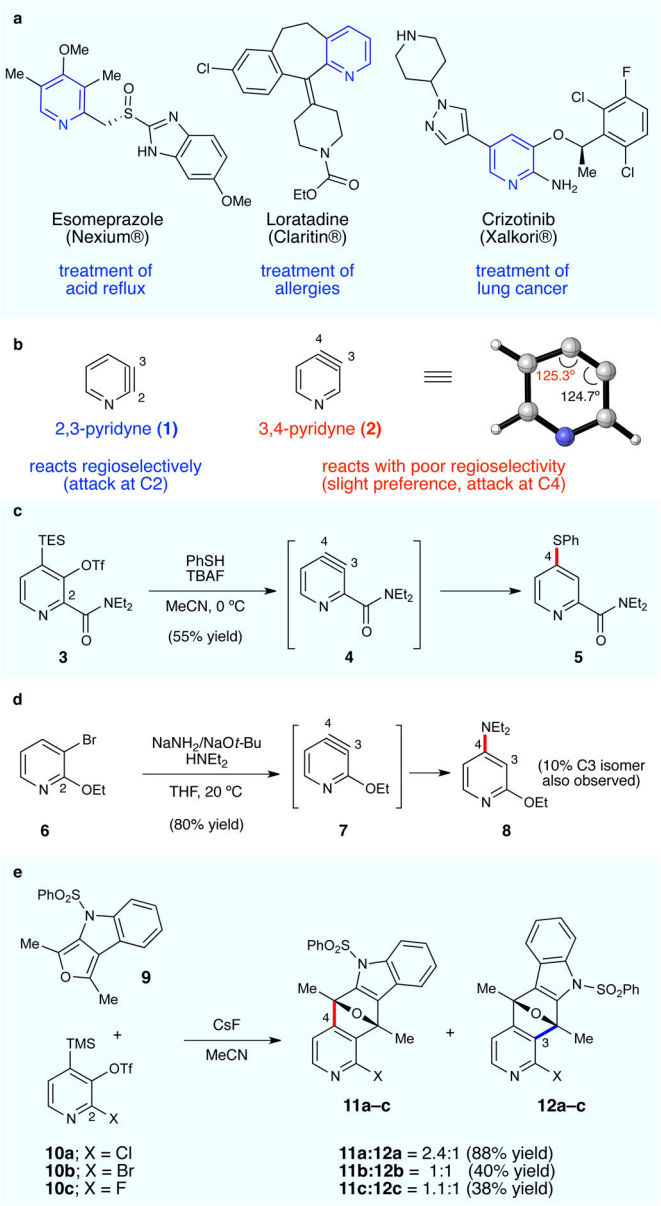


Figure 1. Pyridine-containing drugs, pyridyne isomers, and previous examples of pyridynes

a, Common pharmaceutical drugs containing the pyridine scaffold. **b**, The structure of the 2,3-pyridyne (**1**) and energy-minimized structure of the 3,4-pyridyne (**2**) obtained using B3LYP/6-31G* calculations. The lack of unsymmetrical aryne distortion is responsible for the poor regioselectivity in reactions of **2. c**, Snieckus' use of a C2 amide to direct attack to C4 of pyridyne **4. d**, Caubère's use of a C2-oxygen substituent in the dehydrohalogenation approach to pyridyne **7. e**, Guitián's examination of halide effects on pyridyne cycloadditions. TES, triethylsilyl; Tf, trifluoromethansulfonyl; TBAF, tetra-*N*-buylammonium fluoride; THF, tetrahydrofuran; TMS, trimethylsilyl.

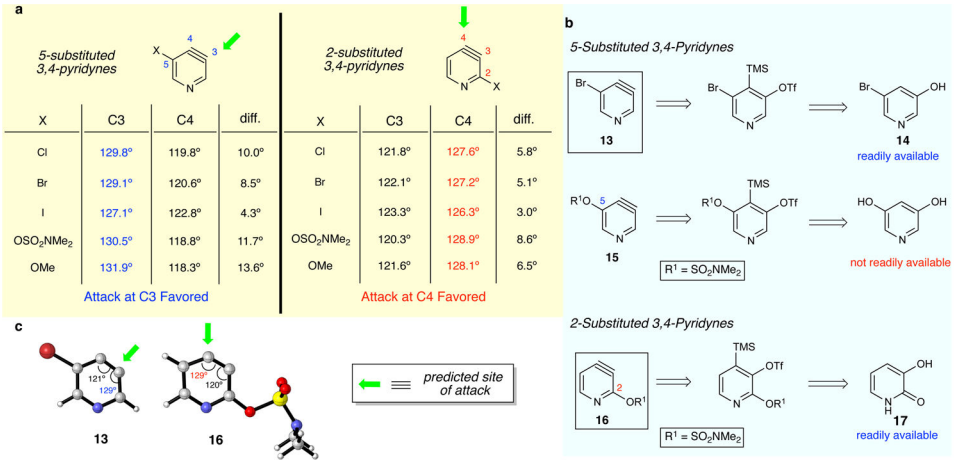


Figure 2. Design of 3,4-pyridynes with controllable regioselectivity

a, Effect of substituents at either C2 or C5 on the distorion of 3,4-pyridyne. Inductively withdrawing substituents at C2 lead to a flattening at C4, while inductively withdrawing substituents at C5 lead to a flattening at C3. **b**, Selection of pyridyne targets based on retrosynthetic analysis. **c**, Geometry-optimized structures of pyridynes **13** and **16** using B3LYP/6-31G* calculations and their predicted site of attack based on the calculated angles.

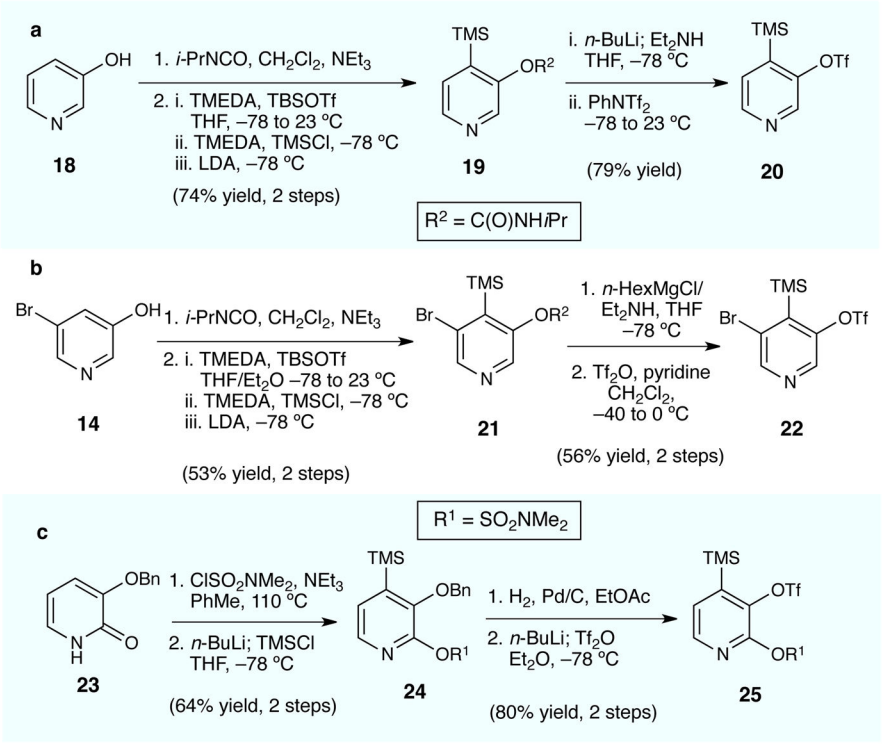


Figure 3. Synthesis of silyltriflates 20, 22, and 25

a, preparation of 3,4-pyridyne precursor **20. b**, preparation of 5-bromo-3,4-pyridyne precursor **22. c**, preparation of 2-sulfamoyl-3,4-pyridyne precursor **25**. *i*-PrNCO, isopropyl isocyanate; TMEDA, *N*,*N*,*N*,*N*-tetramethylethane-1,2-diamine; TBS, *tert*-butyldimethylsilyl; LDA, lithium diisopropylamide; Pd/C, palladium on carbon.

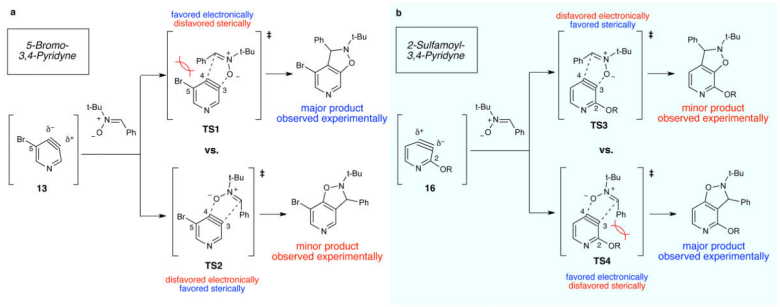


Figure 4. Competition between sterics and electronics in transition states for nitrone cycloadditions

a, **TS1** shows the steric interaction between the C5 bromide and the large phenyl group of the nitrone, whereas this interaction is not present in **TS2**. However, the major product suggests that **TS1** is favored due to electronic effects. **b**, **TS4** shows the steric interaction between the C2 sulfamate and the phenyl group on the nitrone, however, the product arising from this transition state is favored over the competing sterically favorable pathway, **TS3**.

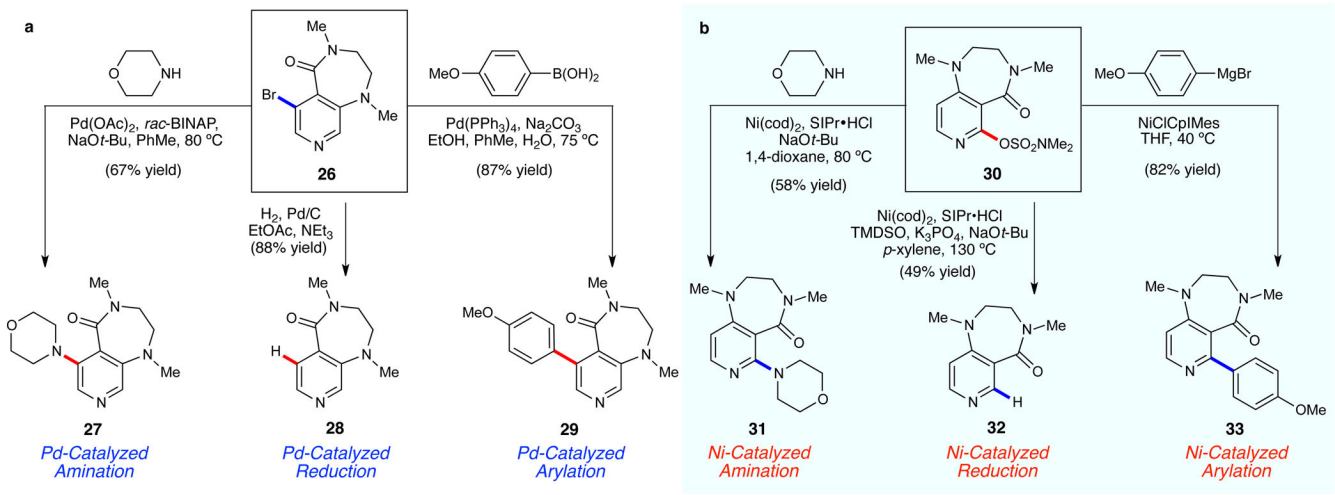
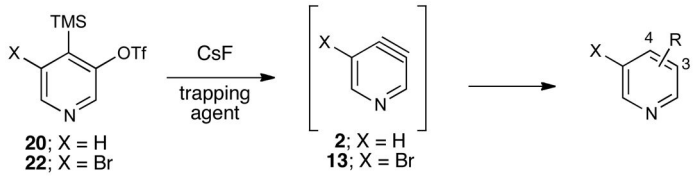


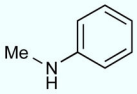
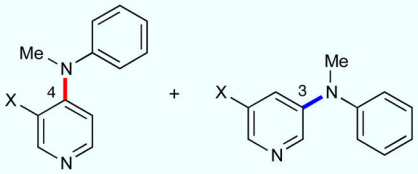
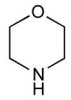
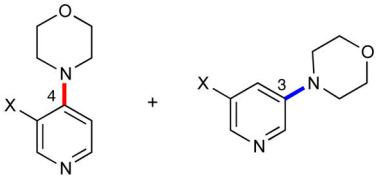
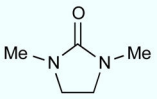
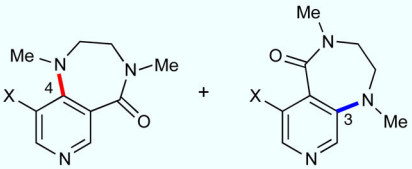
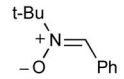
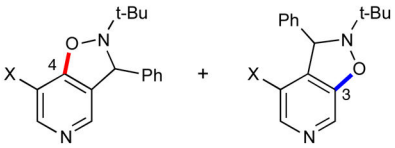
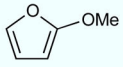
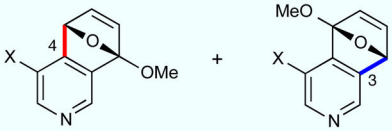
Figure 5. Derivatization of adducts 26 and 30

a, Pd-catalyzed amination, reduction, and Suzuki-coupling of pyridyl bromide **26. b**, Ni-catalyzed amination, reduction, and Kumada-coupling of pyridyl sulfamate **30**. BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; $Ni(cod)_2$, bis(cyclooctadiene)nickel (0); SIPr·HCl, *N*,*N*′-(2,6-Diisopropylphenyl)dihydroimidazolium chloride; TMDSO, tetramethyldisiloxane; NiClCpIMes, (η^5-C_5H_5)NiCl(1,3-dimesitylimidazol-2-ylidene).

Table 1

Regioselectivity studies of pyridynes **2** and **13**.[a]



entry	trapping agent	products	ratio (yield)[b]
1 2			X = H 1.9 : 1 (77% yield) X = Br 1 : 5.8 (64% yield)
3 4			X = H 1.3 : 1 (73% yield) X = Br 1 : 2.9 (64% yield)
5 6			X = H 2.1 : 1 (68% yield)[c] X = Br C3 only (72% yield)
7 8			X = H 1.9 : 1 (76% yield) X = Br 1 : 3.3 (60% yield)
9 10			X = H 1.3 : 1 (64% yield)[d] X = Br 1 : 1.7 (68% yield)[c]

[a] Reactions of silyltriflates **20** and **22** with CsF and trapping agents shown; see the SI for details.

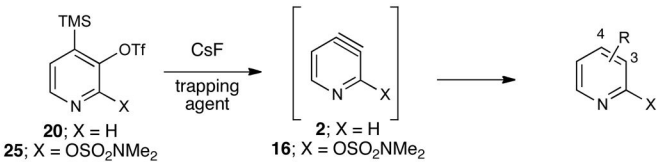
[b] Yields refer to isolated yield unless otherwise noted; ratios refer to relative amounts of C4 to C3 adducts.

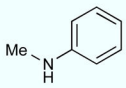
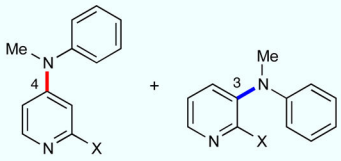
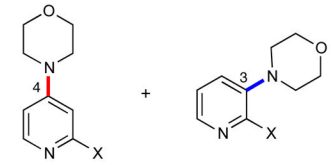
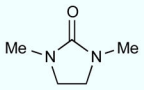
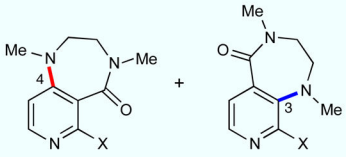
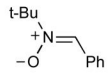
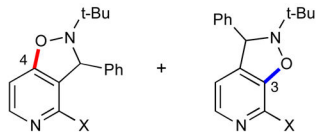
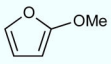
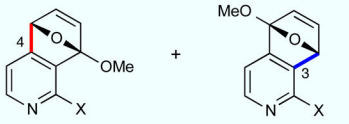
[c] Yield determined by ^{1}H NMR using an external standard.

[d]This Diels–Alder cycloadduct readily underwent isomerization to the corresponding isoquinoline; yield refers to the isolated yield of the isoquinoline (see the SI for details).

Table 2

Regioselectivity studies of pyridynes **2** and **16**.[a]



entry	trapping agent	products	ratio (yield)[b]
1			X = H 1.9 : 1 (77% yield)
2			X = OSO_2NMe_2 >15 : 1 (64% yield)
3			X = H 1.3 : 1 (73% yield)
4			X = OSO_2NMe_2 12 : 1 (64% yield)
5			X = H 2.1 : 1 (68% yield)[c]
6			X = OSO_2NMe_2 C4 only (79% yield)
7			X = H 1.9 : 1 (76% yield)
8			X = OSO_2NMe_2 10.7:1 (61% yield)
9			X = H 1.3 : 1 (64% yield)[d]
10			X = OSO_2NMe_2 1.8 : 1 (60% yield)[c]

[a] Reactions of silyltriflates **20** and **25** with CsF and trapping agents shown; see the SI for details.

[b] Yields refer to isolated yield unless otherwise noted; ratios refer to relative amounts of C4 to C3 adducts.

[c] Yield determined by ^{1}H NMR using an external standard.

[d] This Diels–Alder cycloadduct readily underwent isomerization to the corresponding isoquinoline; yield refers to the isolated yield of the isoquinoline (see the SI for details).