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Regioselective reactions of 3,4-pyridynes enabled by the aryne distortion model

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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 trisubstituted 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 were hampered by a lack of regiocontrol or the inability to later manipulate an adjacent directing group. The 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. After trapping of the pyridynes generated *in situ*, the neighbouring directing groups may be removed or exploited using versatile metal-catalysed cross-coupling reactions. This methodology now renders 3,4-pyridynes as 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 esomeprazole (Nexium) and loratadine (Claritin), in addition to the recently approved cancer therapeutic crizotinib (Xalkori) (Fig. 1a). Other drugs that contain the pyridine ring, or some derivative thereof, include the life-changing medicines montelukast sodium (Singulair, for asthma/allergies), pioglitazone (Actos, for diabetes), eszopiclone (Lunesta, for insomnia), imatinib mesylate (Gleevec, for various cancers), lansoprazole (Prevacid, for acid reflux/ulcers) and mirtazapine (for depression). As a result of the immense value of pyridines, for decades methods to access functionalized derivatives of this privileged heterocycle have been highly sought[1]. Several elegant methods were reported recently for the assembly of substituted pyridines[3–6].

A promising approach towards polyfunctionalized pyridines involves the use of highly reactive pyridyne intermediates[7–23], such as the isomeric hetarynes **1** and **2** (Fig. 1b), which are valued for their electrophilicity and high reactivity towards 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**) (ref. 7). Despite the many studies that followed over the subsequent 50 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 (for example, **2**), nucleophilic additions are known to occur without significant selectivity for attack at either C3 or C4 (refs 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 were met with promising results and can be summarized as follows (Fig. 1c–e):

- Snieckus and co-workers reported a single example using a C2 amido group to enhance nucleophilic addition to C4 of a 3,4-pyridyne intermediate (**3** → **4** → **5**) (ref. 18).
- Caubère and co-workers 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**.
- Guitián examined the influence of C2 halide substituents, which could be removed later, on the 3,4-pyridyne for use in a cycloaddition with substituted furans, which has applications in the synthesis of the natural product ellipticine[12,13]. Although bromide and fluoride groups did not significantly influence regioselectivity, some success was achieved using a C2 chlorosubstituent (**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 Fig. 1 demonstrate that substituent effects can modulate pyridyne regioselectivities, particularly for the favoured addition at C4. However, subsequently the ability to manipulate or remove the C2 amide-, oxygen- or nitrogen-directing groups of Snieckus' and Caubère's work is limited. Guitián's use of neighbouring 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, the most well-studied examples of regioselective 3,4-pyridyne reactions are restricted to the use of amine- or alcohol-based nucleophiles, and various 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:

- 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.

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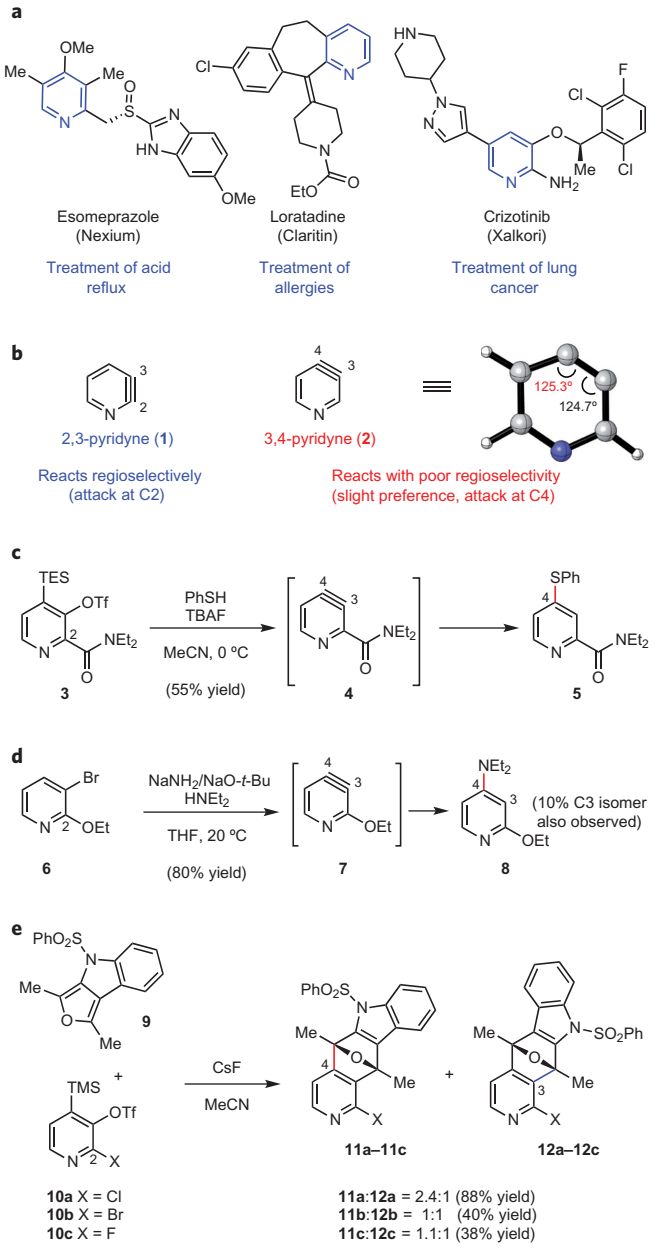


Figure 1 | Pyridine-containing drugs, pyridyne isomers and previous examples of pyridynes. a, Common pharmaceutical drugs that contain the pyridine scaffold. **b**, The structure of 2,3-pyridyne (**1**) and energy-minimized structure of 3,4-pyridyne (**2**) obtained using B3LYP/6-31G* calculations. The lack of unsymmetrical aryne distortion is responsible for the poor regioselectivity in the reactions of **2**. **c**, Snieckus' use of a C2 amide to direct an attack at 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 the effects of halides on pyridyne cycloadditions. TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TBAF = tetra-*N*-butylammonium fluoride, THF = tetrahydrofuran.

- A C5-bromide substituent is used to induce aryne distortion and direct nucleophilic additions to C3 of 3,4-pyridynes. Subsequently, the bromide may be manipulated using conventional Pd-catalysed reactions.
- By positioning a sulfamoyl group at C2 of the 3,4-pyridyne, aryne distortion is perturbed to favour 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-catalysed cross-couplings offer an effective new means to access functionalized pyridines.

The methodologies reported herein now render 3,4-pyridynes broadly useful as tools 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[26–28]. The geometry-optimized structure of **2** obtained from density functional theory (DFT) calculations (B3LYP/6-31G*) (ref. 29) is shown in Fig. 1b. Pyridyne **2** possesses only minor aryne distortion, as evidenced by the nearly identical internal angles at C3 and C4. We hypothesized that neighbouring electron-withdrawing substituents at C5 or C2 could increase the aryne distortion, and thus provide more 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 (Fig. 2; also see Supplementary Fig. S2). Parent pyridynes have been studied computationally[31], but no calculations that involve 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, because the methoxy group is well-known to govern regioselectivity in reactions of benzyne through significant aryne distortion[24].

As summarized in Fig. 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, which, according to the aryne distortion model, suggests this would be the preferred site of attack by nucleophiles[26]. Specifically, the more linear terminus of the aryne possesses a 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 $\geq 4^\circ$ should react with significant regioselectivities in nucleophilic addition and cycloaddition reations[26]. As the substituted 3,4-pyridynes shown in Fig. 2a all meet this criterion and their distortions are generally on par with those of methoxy-substituted pyridynes, we hypothesized that any of the halo- or sulfamoylpyridynes would prove useful. We envisioned accessing pyridynes from silyltriflate precursors, as aryne formation would be achieved readily using mild fluoride-based conditions. In addition, this general method (that is, 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 the synthesis of substituted pyridynes. With respect to the 5-substituted 3,4-pyridyne, bromopyridyne **13** was considered attractive because the bromide induced considerable pyridyne distortion and offered the most versatility for functionalization after pyridyne trapping. Furthermore, the presumed

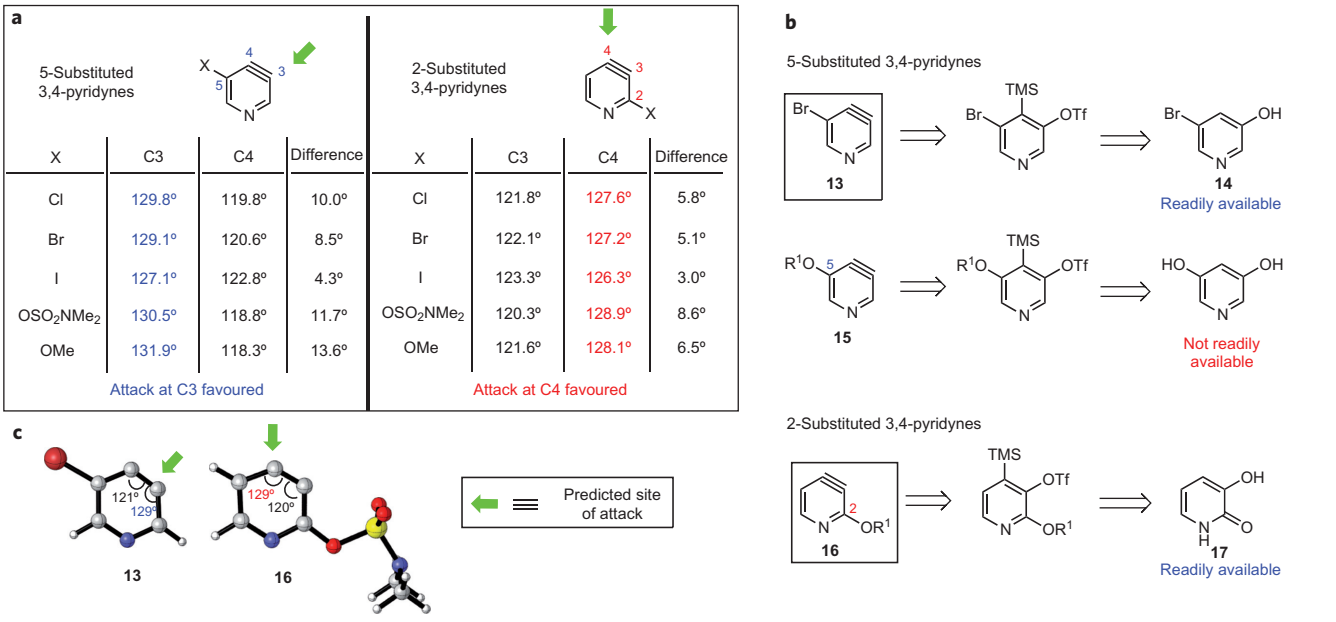


Figure 2 | Design of 3,4-pyridynes with controllable regioselectivity. a, Effect of substituents at either C2 or C5 on the distortion of 3,4-pyridyne. Inductively withdrawing substituents at C2 lead to a flattening at C4, but inductively withdrawing substituents at C5 lead to a flattening at C3. **b**, 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. $R^1 = SO_2NMe_2$.

silyltriflate precursor to **13** would probably be accessible from the commercially available bromohydroxypyridine **14**. 5-Sulfamoyl-3,4-pyridyne (**15**) was also attractive because computations suggested this species would be highly distorted. However, the presumed silyltriflate precursor to **15** did not appear readily accessible, because its probable predecessor, 3,5-dihydroxypyridine, is not obtained easily. Regarding 2-substituted 3,4-pyridynes, the sulfamate was predicted to induce the greatest degree of distortion. Coupled with the notion that it was plausible for an appropriate silyltriflate to be accessed from commercially available dihydroxypyridine **17**, 2-sulfamoylpyridyne **16** was deemed an appropriate target. Previously, sulfamates had not been used to direct aryne regioselectivities, but success with them would offer a valuable means to functionalize the pyridine ring after an aryne reaction by exploiting modern Ni-catalysed coupling methodologies[33]. Similarly, as demonstrated herein, the bromide of pyridyne adducts may be manipulated strategically using conventional Pd-mediated transformations. Geometry-optimized structures of pyridyne targets **13** and **16**, obtained using DFT methods, are shown in Fig. 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 (Fig. 3). Starting from commercially available 3-hydroxypyridine (**18**), carbamoylation followed by a C4-selective *o*-lithiation gave silylcarbamate **19** in 74% yield over two steps. A subsequent one-pot deprotection/triflation protocol[27] afforded silyltriflate **20**. This straightforward sequence provided 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 dependent on the isomer of silyltriflate employed[27,34–38], extensive efforts were made to synthesize the regioisomer of precursor **20**, in which the positions of the triflate and trimethylsilyl (TMS) 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 (for example, R = TMS, C(O)NH-*i*-Pr) (refs 40,41). Bromosilyltriflate **22** was synthesized using an analogous route starting from the commercially available bromohydroxypyridine **14**, although the conversion of **21** into **22** required the use of a highly optimized two-step procedure. Finally, silyltriflate **25** was synthesized from the known benzylether **23** (see Supplementary Information) using an efficient four-step sequence that involved 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

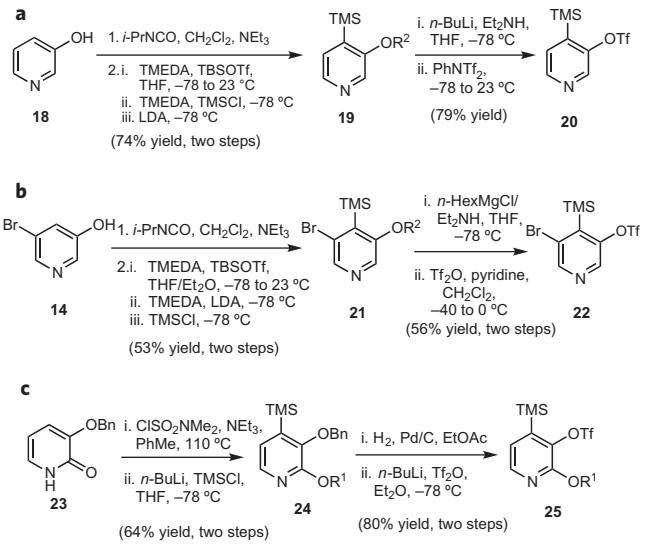


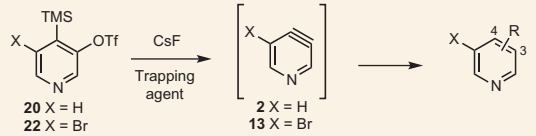
Figure 3 | Synthesis of silyltriflates 20, 22 and 25. a, Preparation of the 3,4-pyridyne precursor **20**. **b**, Preparation of the 5-bromo-3,4-pyridyne precursor **22**. **c**, Preparation of the 2-sulfamoyl-3,4-pyridyne precursor **25**. $R^1 = SO_2NMe_2$, $R^2 = C(O)NH$-*i*-Pr, *i*-PrNCO = isopropyl isocyanate, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine, TBS = *t*-butyldimethylsilyl, LDA = lithium diisopropylamide, Pd/C = palladium on carbon, Hex = hexyl.

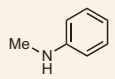
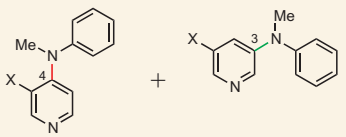
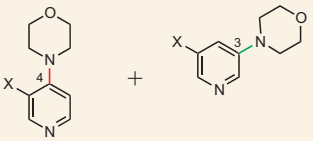
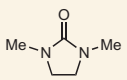
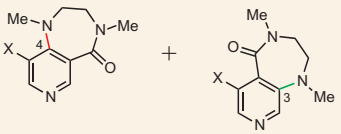
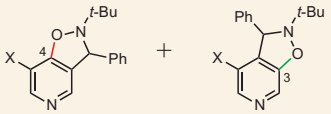
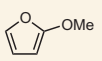
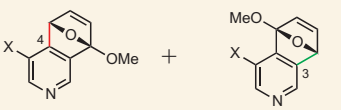
on 3,4-pyridyne regioselectivities, a comparative study that involved pyridynes **2** and **13** was undertaken (Table 1). Consistent with computations and previous studies of 3,4-pyridynes, reactions that involved **2** proceeded with modest regioselectivity across a range of nucleophilic trapping agents[42] and cycloaddition partners (entries 1, 3, 5, 7 and 9, Table 1). Nucleophilic addition at C4 was slightly favoured in all cases. In comparison, reactions of 5-bromo-3,4-pyridyne (**13**) uniformly gave improved degrees of regioselectivity with a reversal in selectivity that favoured the addition at C3. Use of *N*-methylaniline gave a mixture of C3 and C4 adducts in a 5.8:1 ratio (entry 2, Table 1). Similarly, a 2.9:1 ratio of adducts, which again favoured C3, was obtained when morpholine was employed as the trapping reagent (entry 4, Table 1). 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 that favoured C4 addition (entry 5, Table 1), the use of bromopyridyne **13** yielded exclusively the isomer indicative of an initial C3 addition (entry 6, Table 1). When *N*-*t*-butyl-α-phenylnitrone (entry 8, Table 1)[43,44] and 2-methoxyfuran (entry 10, Table 1) were used to trap **13**, ratios of the products obtained were 3.3:1 and 1.7:1, respectively, with C3 being favoured in both cases. 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 is thought to arise from electronic considerations rather than from steric factors.

To further probe this notion, we compared bromopyridyne **13** with its 5-chloro analogue. Despite a previous example in which 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*-*t*-butyl-α-phenylnitrone (see Supplementary Fig. S1). Selectivities were found to be more pronounced compared with those seen in reactions with bromopyridyne **13**, which is in agreement with the predictions shown in Fig. 2a based on the aryne distortion model.

Sulfamoylpyridyne **16** was next tested in nucleophilic additions and cycloaddition reactions (Table 2). In comparison with unsubstituted pyridyne **2**, sulfamate **16** was found to react with enhanced regioselectivity for addition to C4. For example, in the absence

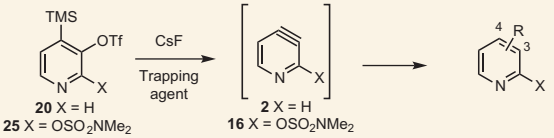
Table 1 | Regioselectivity studies of pyridynes 2 and 13.

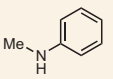
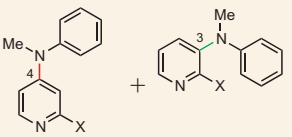
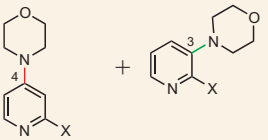
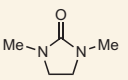
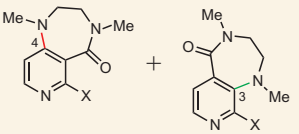
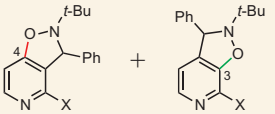
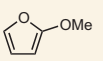
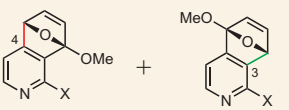


Entry	Trapping agent	Products	Ratio (yield)*
1			X = H 1.9:1 (77%)
2			X = Br 1:5.8 (64%)
3			X = H 1.3:1 (73%)
4			X = Br 1:2.9 (64%)
5			X = H 2.1:1 (68%)†
6			X = Br C3 only (72%)
7			X = H 1.9:1 (76%)
8			X = Br 1:3.3 (60%)
9			X = H 1.3:1 (64%)‡
10			X = Br 1:1.7 (68%)†

Reactions of silyltriflates **20** and **22** with CsF and trapping agents are shown (see the Supplementary Information for details). *Yields refer to isolated yields unless otherwise stated, and ratios refer to relative amounts of C4 to C3 adducts. †Yield determined by ^{1}H NMR spectroscopy using an external standard. ‡This Diels–Alder cycloadduct readily underwent isomerization to give the corresponding isoquinoline; the yield refers to the isolated yield of the isoquinoline (see the Supplementary Information for details).

Table 2 | Regioselectivity studies of pyridynes 2 and 16.



Entry	Trapping agent	Products	Ratio (yield)*
1			X = H 1.9:1 (77%)
2			X = OSO_2NMe_2 >15:1 (64%)
3			X = H 1.3:1 (73%)
4			X = OSO_2NMe_2 12:1 (64%)
5			X = H 2.1:1 (68%)†
6			X = OSO_2NMe_2 C4 only (79%)
7			X = H 1.9:1 (76%)
8			X = OSO_2NMe_2 10.7:1 (61%)
9			X = H 1.3:1 (64%)‡
10			X = OSO_2NMe_2 1.8:1 (60%)†

Reactions of silyltriflates **20** and **25** with CsF and trapping agents are shown (see the Supplementary Information for details). *Yields refer to isolated yields unless otherwise stated, and ratios refer to relative amounts of C4 to C3 adducts. †Yield determined by ^{1}H NMR spectroscopy using an external standard. ‡This Diels–Alder cycloadduct readily underwent isomerization to the corresponding isoquinoline; the yield refers to the isolated yield of the isoquinoline (see the Supplementary Information for details).

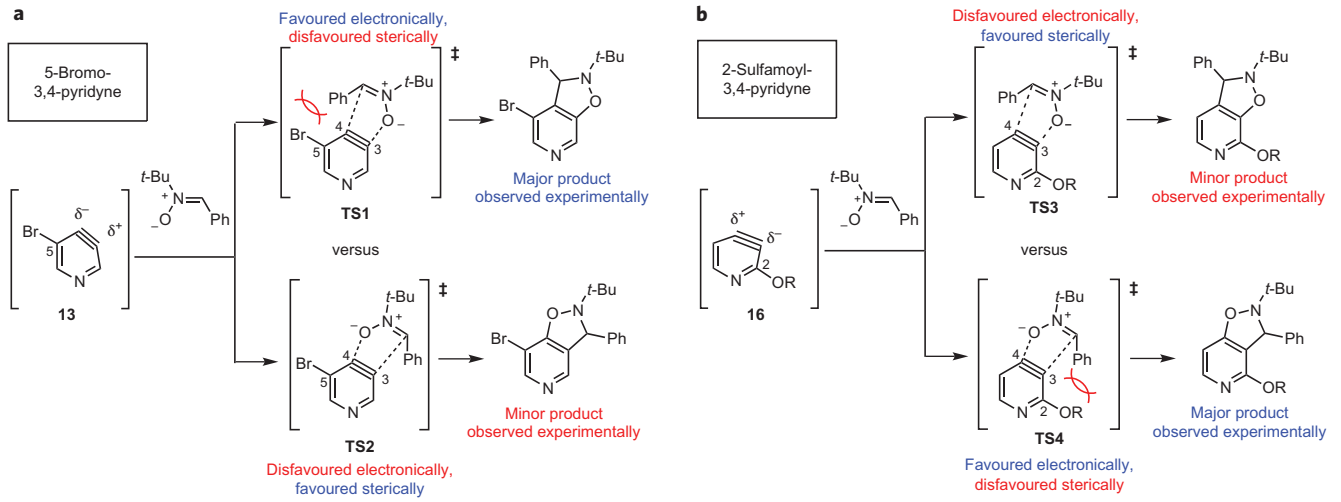


Figure 4 | Competition between steric interactions and electronic effects in transition states for nitrone cycloadditions. a, **TS1** shows the steric interaction between the C5 bromide and the large phenyl group of the nitrone, whereas this interaction is not present in **TS2**. However, the major product suggests that **TS1** is favoured because of electronic effects. **b**, **TS4** shows the steric interaction between the C2 sulfamate and the phenyl group on the nitrone, but the product arising from this transition state is favoured over the competing sterically favourable pathway, **TS3**.

of the C2 sulfamate, addition of *N*-methylaniline gave a 1.9:1 mixture of C4:C3 adducts (entry 1, Table 2), whereas the presence of the sulfamate led to an overwhelming preference for attack at C4 (entry 2, Table 2). Similar results were obtained for the addition of morpholine (entries 3 and 4, Table 2). When DMI was employed to trap sulfamate **16**, we obtained a single isomer in 79% yield, suggestive of an initial attack at C4 (entry 6, Table 2). For comparison, only a 2.1:1 ratio of products was observed using pyridyne **2** (entry 5, Table 2). *N*-*t*-butyl-α-phenylnitrone also displayed excellent selectivity for an initial attack at C4 (entry 8, Table 2), 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 an initial attack at C4 (entry 10, Table 2) compared with that for the parent pyridyne **2** (entry 9, Table 2).

Explanation for the observed regioselectivities in reactions of substituted pyridynes. Previously, it was 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 favour attack by nucleophiles at C3 and C4, respectively. The origin of distortion and regioselectivity is believed to stem from an inductive effect imparted by the electron-withdrawing substituents that can polarize the aryne triple bond in the manners suggested in Fig. 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 probable transition structures for the reactions between *N*-*t*-butyl-α-phenylnitrone and pyridynes **13** and **16**, respectively. In each case the major product arises from the electronically matched transition structures (that is, **TS1** and **TS4**), despite these being more sterically encumbered than **TS2** and **TS3**, respectively. Thus, although steric considerations should be considered and may impact ratios of products, the electronic nature of these substituents appears to be the guiding factor in reactions of substituted 3,4-pyridynes.

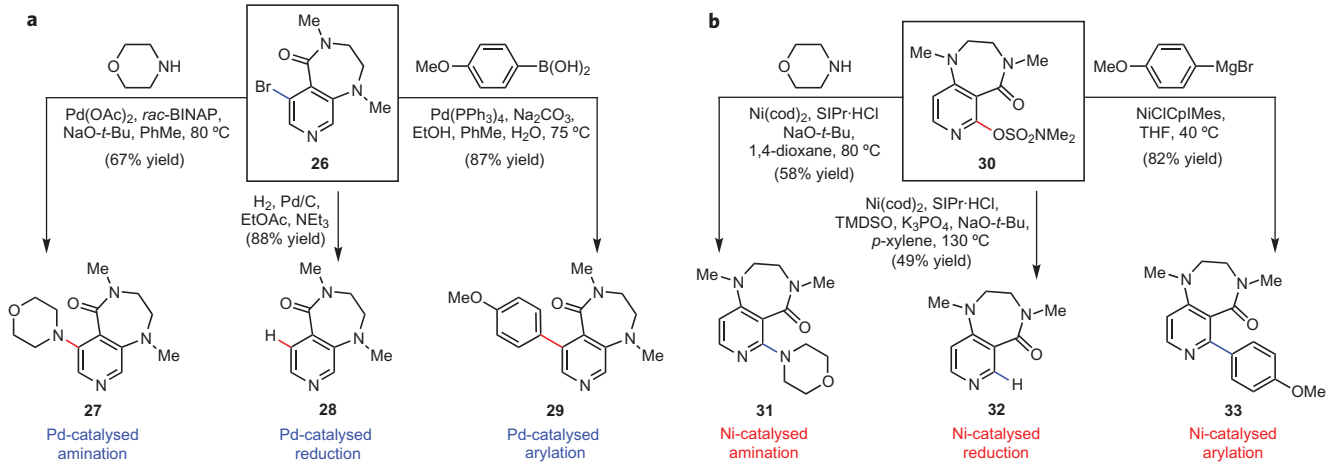


Figure 5 | Derivatization of adducts 26 and 30. a, Pd-catalysed amination, reduction and Suzuki coupling of pyridyl bromide **26**. **b**, Ni-catalysed amination, reduction and Kumada coupling of pyridyl sulfamate **30**. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, $Ni(cod)_2$ = bis(cyclooctadiene)nickel(0), SIPr·HCl = *N*,*N*′-(2,6-diisopropylphenyl)dihydroimidazolium chloride, TMDSO = tetramethyldisiloxane, NiClCpIMes = $(\eta^5\text{-}C_5H_5)$NiCl(1,3-dimesitylimidazol-2-ylidene).

Derivatization of pyridyne adducts using Pd or Ni catalysis. As shown in Fig. 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 entry 6, Table 1 and entry 6, Table 2, respectively), were selected as the substrates for these studies. Structures **26** and **30** are reminiscent of the medicinally important benzodiazepines[45] and, therefore, serve as an ideal testing ground for bromide- and sulfamate-based derivatizations of pyridyne adducts.

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

Also, we were delighted to find that sulfamate **30** could be functionalized readily using Ni catalysis (Fig. 5). Sulfamate amination provided aminopyridine **31** in 58% yield[46]. Furthermore, a Ni-catalysed Kumada–Corriu coupling[47] proceeded smoothly using the readily prepared, and bench-stable, (η^5-C_5H_5)NiCl(1,3-dimesityl-imidazol-2-ylidene) 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 (1) using this methodology diverse arrays of highly substituted pyridine derivatives are accessible in a highly controlled fashion, and (2) the aryl sulfamate group may be manipulated readily through modern Ni-catalysed 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 trisubstituted pyridine derivatives can be accessed with a 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.

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Author contributions

A.E.G. planned and carried out the experimental work. A.E.G. and N.K.G. conceived the project, co-wrote the manuscript and commented on the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to N.K.G.

Competing financial interests

The authors declare no competing financial interests.